5. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE AND ACUTE DIETARY INTAKE FOR HUMANS, MAXIMUM RESIDUE LEVELS AND SUPERVISED TRIALS MEDIAN RESIDUE VALUES

5.1 BIFENAZATE (219)

RESIDUE AND ANALYTICAL ASPECTS

Bifenazate was first evaluated by the 2006 JMPR when an ADI of 0–0.01 mg/kg bw was established and an acute reference dose was considered unnecessary. The 2006 Meeting recommended maximum and median residue levels for a number of commodities. The residue was defined for the purposes of undertaking enforcement and dietary intake calculations as the s*um of bifenazate and bifenazate-diazene (diazenecarboxylic acid, 2-(4-methoxy-[1,1'-biphenyl-3-yl] 1-methylethyl ester), expressed as bifenazate.* The residue is considered fat-soluble. The current Meeting evaluated results of supervised trials for certain berry fruit, tropical fruit, legume vegetables and pulses.

Metabolism in animals and plants

The Meeting did not received additional metabolism studies, however those studies evaluated by the 2006 Meeting were deemed sufficient to cover the additional commodities.

Analytical methods

The analytical methods used in the supervised trials presented for evaluation by the present meeting are all based on the method previously reviewed by JMPR in 2006. The individual recoveries for residue concentration of 0.01–1 mg/kg ranged between 70 and 117% for lychee, papaya, succulent bean seeds, beans in pods, succulent peas, and peas in pods with relative standard deviations of 6–19%.

Stability of residues in samples stored under deep-frozen conditions was evaluated by the 2006 JMPR.

The maximum period of storage prior to analysis of samples evaluated by the present Meeting was less than 30 days except for lychee. Therefore no storage stability studies were conducted for these crops according to current guidelines. As the lychee samples were stored over 300 days, a storage stability study was carried out with the fortification of aliquots of un-homogenized samples to more accurately reflect application of bifenazate to whole fruit. The residues corrected for concurrent recoveries remained after the storage interval of one week and 10 months ranged between 59 to 64%. The results indicate a rapid decline during the first week and remained stable afterwards.

Results of supervised trials on crops

Supervised trial reports on cane berries, lychee, papaya, sugar apple, guava, legume vegetables, pulses were submitted for evaluation by the present Meeting.

Cane berries subgroup

The US GAP specifies one application at maximum 0.56 kg ai/ha with a PHI of 1 day.

Eight supervised trials on cane berries were conducted in the United States and Canada during the 2004–2005 growing season. Six of the trials were on raspberries and two on blackberries.

Two applications were made with maximum GAP dosage rate at 29–35 days apart. Residues in samples were collected at day 0 were: 1.4, 1.5, 1.7, 2.2, 2.3, 2.6, 3.3 and 4.6 mg/kg.

The Meeting considered the rate of degradation of bifenazate between 7 and 28 days in grape, apple, pear in supervised trials evaluated by the 2006 JMPR and noted that the half-lives of the compound on grape, apple and pear were about 12.2, 10.9 and 13 days, respectively. Considering that the residue is mainly on the surface of the fruits, the similarity in the size of grape berries and raspberries, and the comparable rate of decline on several crops, the Meting assumed that the first treatment performed 29–35 days before the second one did not probably contribute more than 10–15% to the initial residue.

The Meeting estimated maximum residue level, STMR of 7 mg/kg, and 2.25 mg/kg for cane berries.

Lychee

The US GAP specifies one application at maximum 0.56 kg ai/ha with a PHI of 1 day. Three trials were performed at the same site with two pesticide treatments with maximum GAP dosage rate 20–21 days apart. The plots were treated on different days within a short period of time.

The residue levels in/on lychee fruits, corrected for loss during storage, one day after the 2nd application were 2.9, 3.3, and 3.7 mg/kg.

As the trials could not be considered independent and trial conditions did not match the GAP and the instability of residues in stored samples, the residue data available were not sufficient for estimation of residue levels.

Papaya

The US GAP specifies one application at maximum 0.56 kg ai/ha with a PHI of 1 day. Three field trials were conducted on papaya in Florida and Hawaii in the United States during the 2003 growing season. Two pesticide treatments were performed with maximum GAP dosage rate 21–22 days apart. All harvested samples were cut into fractions (1/8 to 1/2) on the fields to reduce sample size. This practice may lead to contamination of the samples and it is against provisions of the Codex Standards on Recommended method of sampling for the determination of pesticide residues for compliance with MRLs, and the Good Laboratory Practice in Residue Analysis as well as the FAO Manual

The residues 1 day after the 2nd pesticide application were: 0.14, 0.81 and 1.9 mg/kg.

Taking into account the uncertainties derived for sample size reduction in the field and the limited data, the Meeting could not recommend residue limits for papaya.

Sugar apple

The US GAP specifies one application at max 0.56 kg ai/ha with a PHI of 1 day. Three field trials performing 2 treatments with maximum GAP dosage rate at 21 days apart were conducted on sugar apple in the United States during the 2006 growing season. The trials were performed at the same site applying the pesticide with the same equipment on different days. These trials could not be considered independent.

The analyses of samples were repeated 6 days later due to the outlier concurrent recoveries in the first run. The relative difference of the results of repeated measurements ranged between 21 and 143% indicating very low reproducibility of the analysis and making the results questionable.

The higher of the replicated residue values in samples taken 1 day after the 2nd application were 0.21, 0.23 and 0.99 mg/kg.

Taking into account the trials were not independent and the large uncertainty of the results the Meeting considered the residue data unsuitable for estimation of residue levels for sugar apple.

Assorted tropical and sub-tropical fruits – edible Peel

Guava

The US GAP specifies one application at max 0.56 kg ai/ha with a PHI of 1 day. Three field trials were conducted on guava with two treatments with maximum GAP dosage rate at 21–27 days apart in the United States during the 2004 growing season. The trials were performed at the same site applying the pesticide with the same equipment on different days.

Residues 1 day after the second application were 0.18, 0.21 and 0.30 mg/kg.

As the trials could not be considered independent, the residue data available were not sufficient for estimation of residue levels.

Legume vegetables

The US GAP specifies two application at 0.56–0.84 kg ai/ha (0.30–0.45 kg ai/hL) with a PHI of 3 days.

Eleven supervised field trials on beans were conducted in the United States during the 2002 growing season according the US GAP. Five field trials were conducted on succulent-shelled beans and six on beans with edible pod. Two additional trials on lima beans were conducted during the 2003 growing season. These trials were performed at the same site with different varieties.

The samples of beans in pod collected 3 days after 2nd pesticide treatment contained residues: of 0.58, 0.7, 1.3 and 1.8 mg/kg. The residues in samples taken at day 2 and 4 were 2 mg/kg and 0.24 mg/kg, respectively.

Succulent shelled bean samples collected 3 days after 2nd pesticide treatment contained residues of: 0.02, 0.07 and 0.15 mg/kg, while the samples collected 2 days after 2nd pesticide application contained residues of 0.13, 0.18 and 0.26 mg/kg. Sample taken at day 4 contained residue of 0.09 mg/kg

Eleven supervised field trials on peas were conducted in the United States during the 2002 growing season according the US GAP. Six field trials were conducted on succulent-shelled peas and five on peas with pod. Only one sample, containing 1.4 mg/kg bifenazate residues, was taken from peas in pod at the registered PHI of 3 days. The residue content of samples of peas in pod taken at day 2 was 1.5, 2.2 and 3.7 mg/kg. The residue in a sample taken at day 4 was 3.4 mg/kg.

The residue content of shelled pea samples taken at 2 days after the 2nd pesticide treatment were: 0.03, 0.03, 0.08, 0.09 and 0.17 mg/kg. The day 4 sample contained residue of 0.04 mg/kg

As the decline of residues is moderate and the residue values in samples taken between 2 and 4 days were in the same range, all residue values were taken into account. The residues in beans and peas were similar and could be considered together.

The residues in samples of beans and peas in pod taken between 2 and 4 days after the second pesticide treatments were 0.58, 0.7, 1.3, 1.4, 1.5, 1.8, 2.2, 3.4 and 3.7 mg/kg.

Taking into account the mutual support, the Meeting estimated maximum residue and STMR values of 7 mg/kg and 1.5 mg/kg, respectively, for legume vegetables.

Pulses

The US GAP specifies two application at 0.56–0.84 kg ai/ha (0.30–0.45 kg ai/hL) with a PHI of 8 days. Eleven supervised field trials on beans (shelled, dry) were conducted in the United States during the 2004–2005 growing season. Samples collected 7–8 days after 2nd pesticide treatment contained residues of: < 0.01 (3), 0.01 (3), 0.02, 0.02, 0.04, 0.09 and 0.2 mg/kg.

The Meeting estimated maximum residue level, and STMR values of 0.3 mg/kg, and 0.01 mg/kg for beans, dry, respectively.

Residues in animal commodities

The 2006 JMPR evaluated a lactating dairy cow feeding study and estimated maximum and median residue levels in animal tissues and milk from residues in the animal diet.

Livestock dietary burden

The 2006 Meeting estimated the dietary burden of bifenazate in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual1st ed. The estimated maximum and mean intakes were for beef (4.4 mg/kg and 1.02 mg/kg) and dairy cattle (4.24 mg/kg and 0.86 mg/kg), respectively.

Of the commodities evaluated by the present Meeting, only dry bean seeds can be considered as animal feedstuff Highest residue is 0.2 mg/kg, median residue 0.01 mg/kg. Dry bean seeds may be fed to cattle and poultry. Based on the new OECD feed table (FAO Manual 2nd ed. Appendix IX) the dietary burden calculations based also on the feed items considered by the 2006 JMPR for beef cattle, dairy cattle and poultry are provided in Annex 6. The Japanese animal dietary burden was 0 for the four animal groups and is therefore not included in the summary below.

	Livestock dietary burden, bifenazate, ppm of dry matter diet					
	US/CAN		EU		Australia	
	max	mean	max	mean	max	mean
Beef cattle	0.07	0.07	0.21	0.16	0.83 [a]	0.73 [b]
Dairy cattle	0.64	0.64	0.13	0.08	0.67	0.64 [c]
Poultry, broilers	0.00	0.00	0.05	0.00	0.16 [d]	0.01 [e]
Poultry, layers	0.00	0.00	0.05	0.00	0.16	0.01

[a] Highest maximum beef or dairy cattle burden suitable for MRL estimates for mammalian meat

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

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

[d] Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat, edible offal and eggs.

[e] Highest mean poultry dietary burden suitable for STMR estimates for poultry meat, edible offal and eggs.

Even with the addition of dry bean seeds, the resulting maximum dietary burdens for beef and dairy cattle are lower than those estimated in 2006 (4.4 ppm and 4.24 ppm, respectively), because a different animal feeds table was used then and the percent contribution of feed items in the diet has changed. Similarly, the mean dietary burdens are also lower than the previous estimates (1.02 ppm and 0.86 ppm for beef and dairy cattle, respectively). Therefore, the additional use of bifenazate on dry bean seeds will not affect the current MRLs for milk, milk fats, meat, and edible offal.

The dietary burden for poultry is very low. According to the poultry metabolism study, residues in poultry tissues and eggs are at very low levels even for a dietary burden of 10 ppm. Additional use of bifenazate on dry bean seed is not expected to result in residues in poultry tissues and eggs.

Based on the new dietary burden calculation, the Meeting confirmed its previous estimates for residues in animal commodities.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of bifenazate resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated, including data from the 2006 JMPR Report, for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the thirteen Cluster Diets, based on estimated STMRs were 3–20 % of the maximum ADI (0.01 mg/kg bw). The Meeting concluded that the long-term intake of residues of difenoconazole from uses that have been considered by the JMPR is unlikely to present a public health concern.

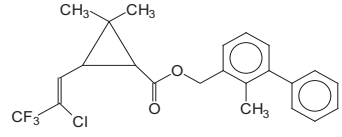
Short-term intake

As the establishment of an ARfD was previously considered unnecessary, the Meeting concluded that the short-term intake of bifenazate residues is unlikely to present a public health concern.

5.2 BIFENTHRIN (178)

RESIDUE AND ANALYTICAL ASPECTS

Bifenthrin is a pyrethroid insecticide and miticide. It was first evaluated by the 1992 JMPR (T, R) and subsequently for residues a number of times. The pesticide was evaluated for toxicology by the 2009 JMPR within the periodic review programme of the CCPR. The periodic review for residues was scheduled at the Forty-first Session of the CCPR for the 2010 JMPR.



Bifenthrin is a mixture of the E- and the Z-isomer with a Z/E-ratio of 99.67% Z-bifenthrin : 0.33% E-bifenthrin and can be present as a cis-isomer and a trans-isomer. The ratio of cis- to trans-isomers is typically 98.65 : 1.35 (specification = 97% cis minimum : 3% trans maximum).

List of metabolites

4'Hydroxy-bifenthrin	3-(4'hydroxyphenyl)-2-methylphenyl-methyl-cis,trans-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropane-carboxylate
Hydroxy-methyl-bifenthrin	2-methyl-[1,1'biphenyl]-3-yl)-methyl-cis-3-(2-chloro- 3,3,3-trifluoro-1-propenyl) trans-2-hydroxy-methyl-2-methyl-cyclopropane-carboxylate
TFP acid	cis-trans-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropane- carboxylic acid
Acetyl-cyclopropane-carboxylic acid	cis-trans-3-acetyl-2,2-dimethyl-cyclopropane-carboxylic acid
Biphenyl alcohol (BP alcohol)	2-methyl-3-phenylbenzyl alcohol
Biphenyl acid (BP acid)	2-methyl-3-phenylbenzoic acid

Animal metabolism

The Meeting received studies on lactating goats and laying hens dosed with either acid cyclopropyl-[^{14}C]-bifenthrin (CP label) or phenyl-^{14}C-bifenthrin (PH label). Studies on rats were reviewed by JMPR during toxicological evaluation in 2009.

Four lactating goats were orally dosed with [^{14}C]-bifenthrin daily for 7 consecutive days at a body weight level of 2.3 mg/kg/day - equivalent to a dietary level of 79 ppm. TRR in milk, liver, fat, kidneys and heart ranged from 0.7–1.5, 1.6-3.9, 1.8–2.8, 0.3–1.0 and 0.4–0.6 mg/kg [^{14}C]-bifenthrin equivalents, respectively. TRR in muscle were relatively lower and amounted to a range of 0.2–0.4 mg/kg. Analysis of ^{14}C in excreta showed that 40–52% and 7.7–17% of the total administered dose was recovered in faeces and urine, respectively.

Bifenthrin was the major product in milk (72–82% of TRR, 0.7–1.1 mg/kg), fat (78–80% of TRR, 1.6–1.8 mg/kg) and muscle (74–88% of TRR, 0.2–0.3 mg/kg). Parent chemical was also found to be a significant residue in kidney and liver tissue, amount to 16–22% of TRR (0.082–0.12 mg/kg) and 19–44% (0.7–0.9 mg/kg), respectively. Biphenyl acid was a significant product identified in kidney and liver tissue (35% of TRR, 0.14 mg/kg and 29% of TRR, 0.5 mg/kg, respectively). Biphenyl alcohol was detected at lower levels relative to parent chemical in milk (13% of TRR) and fat (10% of TRR). TFP acid was detected as a significant metabolite in milk (8.8% of TRR), liver

(4% of TRR) and kidney (14% of TRR). Other metabolites including 4'-hydroxy-bifenthrin, hydroxyl-methyl-TFP acid and biphenyl aldehyde were detected in minor amounts (< 5% of TRR).

Laying hens were dosed by [^{14}C]-bifenthrin for ten days at a body weight level of 1.55 mg/kg/day - equivalent to a dietary level of 31 ppm. The results (values as bifenthrin equivalents) indicated:

- orally administered ^{14}C-bifenthrin is eliminated primarily *via* the excreta (> 90% of the applied radioactivity);
- measurable levels of residues are transferred to tissues of the body, concentrating mostly in the fat (2.1–2.2 mg/kg) and liver (1.4–1.9 mg/kg), the activity in all tissues accounted for less than 0.4% of the applied dose;
- residues in the egg yolk were < 0.8% (max. 3.3 mg/kg) and in egg white < 0.03% (max. 0.05 mg/kg) of the applied radioactivity.

Metabolism of bifenthrin in hens occurred primarily on the cyclopropyl (acid) moiety of the molecule. Hydroxylation on the gem-dimethyl system was followed by formation of organosoluble conjugates with either palmitic or oleic acid. Bifenthrin and these fatty acid conjugates were the major compounds observed in all tissues studied. In egg yolk from the 10 days interval, approximately 40% of TRR (1.4 mg/kg bifenthrin equivalents) was present as bifenthrin. An additional 35% (1.1–1.3 mg/kg) was represented by a mixture of fatty acid conjugates. Unconjugated hydroxyl-methyl-bifenthrin made up another 3.5–4.6% (0.12–0.15 mg/kg) of the residue. Fragmentation products of bifenthrin (or conjugates) were observed as biphenyl alcohol to the extent of 4.2% of TRR (0.15 mg/kg) from hens treated with alcohol (phenyl)-^{14}C-bifenthrin.

In rats, goats and hens, excreta, faeces and urine were shown to be the major route of elimination of bifenthrin and its degradation products. Total radioactivity in excreta amounted in all animals to approximately 92–98 % of all recovered radioactivity. Unchanged bifenthrin was the major residue in the milk and tissues of goat, in the egg yolk and tissues of poultry. Exceptions were goat kidney, where biphenyl acid was the major metabolite with unchanged bifenthrin second and poultry liver, where the TFP acid and fatty acid conjugates of hydroxyl-methyl-bifenthrin were the major residues.

The major routes of metabolism appear to consist in oxidation of one of the gem-dimethyl groups on the cyclopropyl ring to give OH-methyl derivatives, either before or after hydrolysis to TFP acid and biphenyl alcohol and/or oxidation of the biphenyl group. Some of the oxidized or acid derivatives become conjugated.

Although there are qualitative similarities, there appear to be differences, primarily quantitative, between rat, goat and poultry metabolism. In rats and goats the major metabolites result from biphenyl ring oxidation. In poultry the oxidation of the dimethyl-cyclopropane group followed by the formation of fatty acid conjugates with oleic or palmitic acid is the major metabolic pathway which is different from the findings in rats and goats.

Plant metabolism

The metabolism of bifenthrin has been studied on apple (treatment of leaves and fruit surface), potato (treatment of soil, leaves), cotton (treatment of seeds, leaves, soil) and maize (treatment of leaves, husks, soil).

Apple fruits treated with [^{14}C]-bifenthrin (CP label) at a rate equivalent to approximately 24 g ai/hL were harvested and analysed 0, 7, 14 and 21 days following treatment. Most of the residue (> 85%) remained on the peel with little present in the pulp (2–16%, possibly due to contamination during peeling). At 21 days, 93% of the TRR in the whole apple (pulp and peel) was parent bifenthrin.

Apple leaves treated with [^{14}C]-bifenthrin (CP and PH label) were harvested and analysed 29 days following treatment. Bifenthrin accounted for 84–88% of the TRR, and biphenyl acid (2.6%) was detected as a metabolite from the PH label.

Bifenthrin metabolism in potato was studied using [^{14}C]-bifenthrin (CP and PH label). It was applied to soil in-furrow at planting and twice foliar to greenhouse-grown potatoes. The application regimen was designed to simulate a field-like application where the soil was treated at the rate of about 0.34 kg ai/ha at the time of planting followed by two foliar applications each at about 0.11 kg ai/ha at 28 and 14 days pre-harvest interval for a total of 0.56 kg ai/ha. The TRR in the mature foliage for CP and PH labels was 2.7 and 1.94 mg/kg, respectively. The TRR in the tubers from the CP and PH labels was very low, < 0.05 mg/kg at 0.047 and 0.038 mg/kg, respectively, indicating radioactivity in the tubers was not significant. Levels of bifenthrin in tubers were negligible from both labels and ranged between 0.031 mg/kg to 0.034 mg/kg for both labels. It also showed very negligible residues of bifenthrin plant metabolites including 4'-OH-bifenthrin, TFP acid, biphenyl alcohol, biphenyl acid, and biphenyl aldehyde none of which reached 0.001 mg/kg. It was concluded that when bifenthrin is applied foliar to leaves or in furrows, very limited translocation of bifenthrin from either leaf or soil to tubers took place. Parent bifenthrin was the major residue in tubers (73–81% of TRR) and was below 0.035 mg/kg.

Three-week old cotton plants were treated with [^{14}C]-bifenthrin (PH label) either by soil application or by treatment of individual leaves. In all cases essentially no radiocarbon was present in untreated leaves, stems, boll husks, lint and seeds. This indicates that there is essentially no translocation of bifenthrin or metabolite from soil or treated leaves into other portions of the plant through maturity. The metabolite profile indicated that biphenyl alcohol, biphenyl acid and TFP acid account individually for less than 1% of the TRR. Six unidentified metabolites were detected with no single metabolite exceeding 5% of the total residue.

In a second study cotton plants were treated individually with [^{14}C]-bifenthrin (PH label) at a rate of 1.3 µg/seed. Parent bifenthrin made was the main product identified (approximately 83–95% the total ^{14}C-residue). In the 28-day sample, 9% of the residue was not extractable. Other metabolites (up to six minor products) had reached 8% of the total residue in the 28-day sample. ^{14}C-residues in untreated bolls from the treated plants were negligible (not detected in lint, seed, stem, 0.08% in bolls, 0.07% in leaves) indicating that bifenthrin does not translocate from treated cottonseeds to other parts of the plant.

The metabolism study on maize demonstrates that bifenthrin is essentially non-systemic when applied either post-emergence to the soil or when applied as a dilute formulation to the leaves and husks of young maize plants. Bifenthrin on treated leaves degrades only to a minor extent. The major metabolite is 4'-hydroxy-bifenthrin, which comprises 11% of the TRR one month after foliar treatment.

In summary, the results of the different bifenthrin plant metabolism studies are consistent: unchanged and unconjugated bifenthrin was shown to be the predominant residue in plants. No cis- to trans-isomerisation was observed in the course of the studies. Studies on apple fruits and leaves, or either by soil application or by treatment of individual leaves on potatoes, cotton and maize show that bifenthrin is essentially non-systemic. Only little translocation from treated soils or plant parts to untreated parts of the plant was observed.

Environmental fate in soil

The Meeting received information on soil aerobic metabolism, soil photolysis, hydrolysis and crop rotation properties of bifenthrin.

In a series of aerobic soil metabolism studies at 25 °C with [^{14}C]-bifenthrin (CP- and PH-label), the percentage parent remaining after 120–180 days was 28–55% of dose (n = 8). The half-lives ranged for CP-^{14}C-bifenthrin from 50 to 205 days and for PH-^{14}C-bifenthrin from 69 to 135 days, depending on soil type. It can be concluded, that parent compound is the only relevant residue

for quantification in soil. The main metabolite, 4'-OH-bifenthrin, is always found in amounts generally lower than 10% of TRR, other metabolites such as TFP acid, biphenyl alcohol or biphenyl acid mostly occurred in traces only.

The measured half-lives for bifenthrin in two soil surface photolysis studies were 84 and 124 days. No major metabolite was formed, TFP acid reflecting the most predominant identifiable minor metabolite peaking at 3.8% on day 30.

Because of the highly insoluble nature of bifenthrin in water, no hydrolysis of the compound occurred at any of the pH tested (5.05, 7.08, 8.97).

In a confined rotational crop study with lettuce, sugar beet and wheat, soil was spiked with [^{14}C]-bifenthrin (CP- and PH-label), at the equivalent of 0.56 kg ai/ha. The crops were sown at 30, 60 and 120 days later. The maximum TRR (as bifenthrin equivalents) were 0.029 mg/kg in lettuce, 0.065 mg/kg in sugar beets (whole plant) and 0.053 mg/kg in wheat (whole plant). In wheat grain, TRR up to 0.049 mg/kg were determined. In wheat straw, higher TRR up to 0.31 mg/kg were detected.

In a second confined rotational study, only wheat was sowed 30 days, 120 days, 7 months and 12 months following application of [^{14}C]-bifenthrin (CP- and PH-label) at the equivalent of 0.56 kg ai/ha to the soil. Bifenthrin was present in the 30-day straw at 0.064–0.12 mg/kg. The 120 day straw samples had levels of 0.022 mg/kg bifenthrin, and even lower values were found from the 7 and 12 month sowings. The results of those studies are comparable and demonstrated that the translocation of bifenthrin residues is very low.

The residue data from a field crop rotation study showed that wheat planted 30 to 32 days after harvest of a primary crop (cotton, maize or sweet corn) treated with total 0.56 kg ai/ha yielded no bifenthrin residues. This adequately supports the fact that residues in soils resulting from recommended uses should not contribute to the residues in succeeding crops.

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for residues of bifenthrin in plant and animal commodities.

Residue analytical methods for bifenthrin rely on GC-ECD and GC-MSD. Typical LOQs achieved for plant and animal commodities fall in the range of 0.01–0.05 mg/kg. Methods have been subjected to independent laboratory validation.

Stability of residues in stored analytical samples

Information was received on the freezer storage stability of bifenthrin residues in plant and animal commodities. Residues were apparently stable at freezer temperature for the intervals tested.

Definition of the residue

The parent compound bifenthrin is the dominant component of the residue in plant commodities.

Unchanged bifenthrin was the major residue in the milk and tissues of goat, in the egg yolk and tissues of poultry. Exceptions were goat kidney, where biphenyl acid was the major metabolite with unchanged bifenthrin second and poultry liver, where the TFP acid and fatty acid conjugates of hydroxyl-methyl-bifenthrin were the major residues. The Meeting noted that the only compound of toxicological relevance in animal commodities is bifenthrin.

Therefore, from the metabolism studies on plants and animals presented, the proposed definition of the residue is parent bifenthrin only.

In animal metabolism and feeding studies, bifenthrin displays the properties of a fat-soluble compound.

Definition of the residue (for compliance with the MRL and for estimation of dietary intake) for plant and animal commodities: *bifenthrin (sum of isomers)*.

The residue is fat soluble.

Results of supervised trials on crops

Supervised trials were available on the following crops: oranges, grapefruit, lemons, raspberries, blackberries, bananas, mangos, papaya, Brussels sprouts, head cabbage, cauliflower, egg plant, peppers, okra, sweet corn, tomatoes, mustard greens, green beans, peas, beans (pulses), peas (pulses), soya beans (pulses), carrots, potatoes, radish, sugar beet, barley, maize, oats, triticale, wheat, tree nuts, cotton, rape, hops and tea.

The NAFTA calculator was used as a tool in the estimation of the maximum residue level 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 using expert judgement. 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 provided. Some common factors that may lead to rejection of the statistical estimate include those situations where the number of data points is less than 15 or where there are too many values below LOQ.

Citrus fruits

Supervised trials were available for lemon, oranges and grapefruit from Brazil and the USA. Furthermore, residue data were submitted from Italy and Spain, but currently no registered use exists in the European Union.

In Brazil, bifenthrin is registered for foliar spray use on citrus fruits at an application rate of 0.014–0.036 kg ai/ha with a PHI of 7 days. One trial each on lemon and oranges is matching the maximum GAP (0.038 kg ai/ha, 7 days PHI). The residues were < 0.05 and 0.05 mg/kg.

In the USA, bifenthrin is registered by ground application to bare soil beneath citrus trees at a rate of 0.11–0.56 kg ai/ha and a PHI of 1 day. In 36 US trials in line with GAP, seven on lemon, 21 on oranges and eight on grapefruit, the residues were: < 0.005, 0.0082, < 0.05 mg/kg (34).

The Meeting estimated a maximum residue level, an STMR and an HR of 0.05 mg/kg for citrus fruits. The previous recommendation of 0.05* mg/kg for grapefruit, lemon and oranges is withdrawn.

Statistical calculations were not possible, since most of the values are below the LOQ.

Pear

Bifenthrin is registered for foliar spray treatment on pears in Australia with 0.0025–0.004 kg ai/hL (PHI 14 days) and in Japan with 0.001–0.002 kg ai/hL (PHI 1 day). No residue data for pears were submitted.

The Meeting withdrew the previous recommendation of 0.5 mg/kg for pear.

Berries and other small fruits

Supervised trials were available for raspberries, blackberries and strawberries from the USA. Furthermore, residue data on strawberries were submitted from Belgium, France, Italy, the Netherlands, Poland, Spain and the UK, but currently no registered use exists in the European Union.

Caneberries

In the USA, bifenthrin may be used as foliar spray on caneberries (blackberry, dewberry, loganberry and raspberry) with an application rate of 2 × 0.056–0.11 kg ai/ha and a PHI of 3 days.

Five US trials (four on raspberries, one on blackberries) were carried out according to GAP. The residues in ranked order were: < 0.05, 0.25, 0.29, 0.34 and 0.51 mg/kg.

The Meeting estimated a maximum residue level, an STMR and an HR for bifenthrin in blackberries, dewberries (including boysenberry and loganberry) and raspberries (red, black) of 1 mg/kg, 0.29 mg/kg and 0.51 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.81 mg/kg, which when rounded up, was in agreement with the Meeting's estimation.

Strawberry

Bifenthrin is registered in the USA for foliar spray use on strawberries at an application rate of 0.045–0.22 kg ai/ha, maximum 0.56 kg ai/ha per season (PHI not specified).

One US trial was conducted with 2 spray applications (interval 14 days) of 0.22 kg ai/ha resulting in a residue of 0.59 mg/kg at the day of the treatment.

Eighteen US trials were carried out with 4 spray treatments (interval 14 days) of 0.22 kg ai/ha. The maximum application rate of 0.56 kg ai/ha per season was exceeded (0.88 kg ai/ha). Samples were taken at 0, 1, 3 and 5 days. Because no PHI is specified, the highest value of each trial from all sampling days was selected.

The Meeting noted that the number of applications is not relevant because of the large treatment interval of 14 days and used all US trials for the evaluation. The residues, in ranked order, were (n = 19): 0.27, 0.30, 0.31, 0.33, 0.33, 0.34, 0.34, 0.36, 0.41, 0.46, 0.46, 0.48, 0.51, 0.59, 0.86, 0.86, 0.88, 2.1 and 2.3 mg/kg.

The Meeting estimated a maximum residue level for bifenthrin in strawberries of 3 mg/kg to replace the previous recommendation of 1 mg/kg. The Meeting estimated an STMR of 0.46 mg/kg and an HR of 2.3 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 2.39 mg/kg, which when rounded up, was in agreement with the Meeting's estimation.

The Meeting noted that the ARfD is exceeded for children (430%) and the general population (230%) by the dietary intake calculation. No alternative GAP is available.

Assorted tropical and sub-tropical fruits – inedible peel

Supervised trials were available for banana from France, Puerto Rico, Spain and the USA. Data for mango and papaya were submitted as part of the field trials conducted within the Pesticide Initiative Programme aiming to provide data for establishing import MRLs in the European Union.

Banana

In Central America (Columbia, Costa Rica, Ecuador, Guatemala, Honduras, Panama), tree bags with 1% bifenthrin are placed over the banana bunch before flower stalk shows first hand until harvest.

Four trials from France (Martinique) and two from Spain (Canary Islands) in line with Central American GAP showed from 1–132 days no residues in the pulp (< 0.01 mg/kg, n = 6); data on whole fruit were not submitted.

Samples were taken after 43–112 days in six trials from Puerto Rico and three from the USA. No residues were detected in the pulp (< 0.01 mg/kg, n = 9). In the whole fruits, the residues were: < 0.05 (7), 0.057 and 0.074 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg for bifenthrin in banana. Based on data on pulp, the Meeting estimated an STMR and an HR of 0.01 mg/kg.

Statistical calculations were not possible, as the majority of the values were below the LOQ.

Mango

Bifenthrin was applied as foliar spray treatment with 0.05 kg ai/ha and a PHI of 7 days in two trials each in Mali and Senegal. The application conditions were based on the requirement of appropriate control of diseases of mango, but they were not supported by label or official declaration of approved use.

The residues in whole fruit were: 0.066, 0.13, 0.15 and 0.23 mg/kg. In two trials, peel and pulp from day 7 an 14 were analysed separately. No residues were found in flesh (< 0.01 mg/kg).

The Meeting estimated a maximum residue level for bifenthrin in mango of 0.5 mg/kg. The estimated STMR and HR values were 0.01 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.44 mg/kg, which when rounded up, was in agreement with the Meeting's estimation.

Papaya

Bifenthrin was applied as foliar spray treatment with 4 × 0.05 kg ai/ha and a PHI of 3 days in eight trials carried out in Ghana and the Ivory Cost. The application conditions were apparently based on the requirement to achieve appropriate disease control in papaya. However, the data provided was not supported by a label or official declaration indicating the use had regulatory approval.

The residues in whole fruit were (n = 8): 0.095, 0.13, 0.13, 0.14, 0.16, 0.17, 0.20 and 0.30 mg/kg.

No residue data for the edible portion were available. Nevertheless, taking into account the results of the apple fruit metabolism study showing that more than 85% of the residue remained on the peel and that no residues were found in supervised residue trials in pulp of banana and mango, the Meeting concluded that no residues higher than 0.01 mg/kg are expected in papaya edible portion.

The Meeting estimated for bifenthrin in papaya a maximum residue level of 0.4 mg/kg and STMR and an HR of 0.0.1 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.35 mg/kg, which when rounded up, was in agreement with the Meeting's estimation.

Brassica vegetables

Supervised trials were available for head cabbage and cauliflower from Japan and the USA. Furthermore, residue data on Brussels sprouts, head cabbage and cauliflower were submitted from France, Germany, Italy, the Netherlands, Poland and the UK, but currently no registered use exists in the European Union.

The registered use of bifenthrin in brassica vegetables in the USA is foliar spray treatment of 5 × 0.034–0.11 kg ai/ha and a PHI of 7 days or as soil treatment in-furrow at seeding or at transplant with 0.06–0.11 kg ai/ha.

Trials on head cabbage were carried out in the USA, three of them were in line with the US GAP (5 × 0.11 kg ai/ha, PHI 7 days). The treatment interval was 7 days. Two further trials had the same treatment rate and PHI, but higher application numbers of 8 and 11. In these trials, cool, wet weather resulted in much slower growth of the plants than expected. In order to collect mature-sized cabbages and to maintain a PHI of 7 days, spraying at weekly intervals was continued. The Meeting noted that the earlier sprays do not influence the terminal residues and considered these trials also as being in GAP. The residues were < 0.04, < 0.04, < 0.04, < 0.05 and 0.19 mg/kg in cabbage without

wrapper leaves. In cabbage with wrapper leaves the residues were 0.70, 0.82, 1.5, 2.3 and 3.1 mg/kg which are relevant for animal dietary burden estimation.

Ten trials on cauliflower were carried out in the USA, four of them were in line with the US GAP (5 × 0.11 kg ai/ha, PHI 7 days). The residues were < 0.05, 0.09, 0.14 and 0.19 mg/kg.

Based on the data for cauliflower, the Meeting estimated a maximum residue level, an STMR and an HR of 0.4, 0.115 and 0.19 mg/kg for brassica vegetables.

Based on the data for head cabbage with wrapper leaves, an STMR of 1.5 mg/kg and a highest residue of 3.1 mg/kg were estimated for animal dietary burden calculation.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.4 mg/kg, which was in agreement with the Meeting's estimation.

Fruiting vegetables, other than Cucurbits

Supervised trials were available for egg plant, peppers, sweet corn and tomato from the USA and European countries as well as for okra from Ivory Coast. No GAP exists currently in the European Union for the use of bifenthrin in fruiting vegetables.

Peppers

The registered use of bifenthrin in peppers in the USA is foliar spray treatment 0.022–0.11 kg ai/ha and a PHI of 7 days. Eleven US trials in line with US GAP were available. The residues were in rank order (n = 11) were: < 0.055, 0.07, 0.09, 0.10, 0.11, 0.14, 0.17, 0.21, 0.23, 0.24 and 0.31 mg/kg.

The Meeting estimated for bifenthrin residues in peppers a maximum residue level, an STMR and an HR of 0.5 mg/kg, 0.14 mg/kg and 0.31 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.5 mg/kg, which was in agreement with the Meeting's estimation.

Okra

As part of the field trials conducted within the Pesticide Initiative Programme aiming to provide data for establishing import MRLs in the European Union, bifenthrin was applied as foliar spray treatment with 2 × 0.05 kg ai/ha and a PHI of 2 days in four trials in Ivory Cost. The application conditions were based on the requirement of appropriate control of diseases of okra, but they were not supported by label or official declaration of approved use. The residues were 0.04, 0.05, 0.09 and 0.11 mg/kg.

The Meeting estimated for bifenthrin residues in okra a maximum residue level, an STMR and an HR of 0.2 mg/kg, 0.07 mg/kg and 0.11 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.2 mg/kg, which was in agreement with the Meeting's estimation.

Sweet corn

The registered use of bifenthrin in sweet corn in the USA is foliar treatment with 0.036–0.11 kg ai/ha (max. 0.34 kg ai/ha per season) and a PHI of 1 day. Thirteen US trials treated with 0.09, 0.09 and 0.04 kg ai/ha showed residues of < 0.05 mg/kg at one day after the last application, but did not match the critical GAP.

The Meeting was not able to estimate a maximum residue level for bifenthrin residues in sweet corn.

Tomato

The registered use of bifenthrin in tomato in the USA is foliar spray treatment 0.022–0.11 kg ai/ha and a PHI of 1 day. None of the 22 US trials submitted was in line with critical US GAP because the samples were taken later than the PHI of 1 day.

In Mexico, bifenthrin is registered as foliar spray treatment of 0.06 kg ai/ha and a PHI of 1 day. Seven outdoor trials according to GAP were received. The residues were 0.03, 0.04, 0.06, 0.06, 0.09, 0.15 and 0.15 mg/kg.

The Meeting estimated a maximum residue level, an STMR and an HR of 0.3 mg/kg, 0.06 mg/kg and 0.15 mg/kg, respectively, for bifenthrin residues in tomatoes.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.3 mg/kg, which was in agreement with the Meeting's estimation.

Egg plant

The registered use of bifenthrin in eggplant in the USA is foliar spray treatment 0.034–0.11 kg ai/ha and a PHI of 7 days. Three US trials in line with US GAP were available. The residues were < 0.05 mg/kg (3). The Meeting noted that three trials are not sufficient to estimate a maximum residue level.

Six trials from the USA on tomato were available carried out about according to the GAP for eggplant (4 × 0.09 kg ai/ha, PHI 6–7 days). The residues in tomatoes were: < 0.05 (4), 0.07 and 0.10 mg/kg.

The Meeting concluded to use the trials on tomatoes to estimate a maximum residue level, an STMR and an HR of 0.3 mg/kg, 0.05 mg/kg and 0.10 mg/kg, respectively, for bifenthrin residues in eggplant.

Statistical calculations were not possible, since most of the values are below the LOQ.

Leafy vegetables (incl. brassica leafy vegetables)

Supervised trials on leafy vegetables were available for mustard greens and radish leaves and tops from the USA.

The registered use of bifenthrin in brassica leafy vegetables in the USA is foliar spray treatment of 0.037–0.11 kg ai/ha and a PHI of 7 days.

Eight US trials on mustards greens in line with US GAP were available. The residues were in rank order (n = 8): 0.08, 0.19, 0.85, 0.91, 1.4, 1.9, 1.9 and 2.1 mg/kg.

The Meeting estimated for bifenthrin residues in mustard greens a maximum residue level, an STMR and an HR of 4 mg/kg, 1.16 mg/kg and 2.1 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 3.52 mg/kg (mean +3SD), which when rounded up, was in agreement with the Meeting's estimation.

Six US trials on radish leaves and tops in line with US GAP for leafy vegetables were available. The residues were in rank order (n = 6): 0.69, 1.2, 1.7, 1.8, 2.0 and 2.3 mg/kg.

The Meeting estimated for bifenthrin residues in radish leaves and tops a maximum residue level, an STMR and an HR of 4 mg/kg, 1.75 mg/kg and 2.3 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 4.19 mg/kg, which was in agreement with the Meeting's estimation.

Legume vegetables

Supervised trials on legume vegetables were available for green beans and peas from European countries and the USA. None of the trials submitted was in line with the GAP.

The Meeting was not able to estimate a maximum residue level for bifenthrin in legume vegetables.

Pulses

Supervised trials on pulses were available for dry beans and soya beans from the USA as well as for dry peas from Denmark, France, Germany, Poland, Sweden and the UK, but currently no registered use exists in the European Union.

Bifenthrin is registered on beans and peas in the USA with 0.028–0.11 kg ai/ha and a PHI of 14 days. Nine US trials matching the GAP showed residues in dried beans of < 0.05 (6), 0.07, 0.10 and 0.10 mg/kg. Residues in dried peas were < 0.05 mg/kg (6) in six US trials matching the GAP.

For soya beans, the US GAP is 0.028–0.11 kg ai/ha and a PHI of 18 days. The residues were in 15 US trials in line with US GAP (n = 15): < 0.05 (13), 0.07 and 0.18 mg/kg.

Based on the soya bean data, the Meeting estimated for bifenthrin residues in pulses a maximum residue level and an STMR of 0.3 mg/kg and 0.05 mg/kg, respectively.

Statistical calculations were not possible, since 13 from 15 residue values are below the LOQ.

Root and tuber vegetables

Supervised trials on root and tuber vegetables were available for carrots from European countries and the USA; for potatoes from Brazil, European countries and the USA; for radish from the USA and for sugar beet from France. Currently no registered use exists in the European Union.

The US GAP allows the foliar spray treatment of 0.09–0.11 kg ai/ha with a PHI of 21 days on root and tuber vegetables. In ten US trials on carrots matching US foliar spray GAP, the residues were in roots < 0.05 mg/kg (10).

In 17 US trials on potatoes matching US foliar spray GAP for root and tuber vegetables, the residues were in tubers < 0.05 mg/kg (17).

Bifenthrin is registered on potatoes in Brazil for soil treatment with 0.1 kg ai/ha and a PHI of 35 days. Three residue supervised trials each were carried out with 0.15 and 0.30 kg ai/ha (PHI 35 days). In all trials the residues were lower than the LOQ: < 0.02 mg/kg (6).

The Meeting estimated a maximum residue level, an STMR and an HR of for bifenthrin in root and tuber vegetables of 0.05 mg/kg.

Statistical calculations were not possible, since all levels are below the LOQ.

Cereals

Supervised trials on cereal grains were available for maize from the USA, for wheat after treatment at storage from the European countries and Brazil as well as for barley, oat, triticale and wheat after foliar spray application from European countries, but currently no registered uses exist in the European Union.

The previous recommendation for bifenthrin on barley of 0.05* mg/kg was withdrawn.

Wheat – storage treatment

The registered GAP on stored wheat grain in Brazil is 0.0004 kg ai/ton (withholding period 30 days). One Brazilian trial was in GAP and shows residues of 0.2 mg/kg.

The Meeting received 11 trials from Belgium, France and the UK treated with 0.0003 kg ai/ton (withholding period 30 days). The residues were 0.19, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.28 and 0.29 mg/kg. In one further trial from the UK treated with 0.0005 kg ai/ton the residues were 0.40 mg/kg.

The Meeting noted that the storage treatment of the European trials was in line with the Brazilian GAP (±25%) and could be used for the evaluation. The residues of one Brazilian and

twelve European trials, in ranked order, were (n = 13): 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.28, 0.28, 0.29 and 0.40 mg/kg.

Based on the European data and Brazilian GAP for stored wheat grain, the Meeting estimated a maximum residue level of 0.5 mg/kg Po for wheat and confirmed the previous recommendation. The STMR and the HR were 0.25 mg/kg and 0.40 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.39 mg/kg. However, in order to cover residues in wheat after post harvest use, a higher maximum residue level was necessary.

Maize

Bifenthrin is registered on maize in the USA as foliar spray treatment with 0.11 kg ai/ha and a PHI of 30 days. The Meeting received the following residue data from US trials:

- Seven trials treated with 5 × 0.11 kg ai/ha, PHI 29–38 days: < 0.05 mg/kg (7)
- 18 trials treated with 5 × 0.11, kg ai/ha, PHI 39–68 days: < 0.05 mg/kg (18)
- Five overdosed trials treated 4 × 0.11 and 1 × 1.1 kg ai/ha, PHI 31, 33, 39, 54, 65 days: < 0.05 mg/kg (5).

The Meeting estimated a maximum residue level of 0.05* mg/kg for bifenthrin residues in maize and confirmed its previous recommendation. An STMR of 0 mg/kg was derived.

Statistical calculations were not possible, since all levels are below the LOQ.

Tree nuts

Supervised trials on tree nuts were available from the USA. The registered GAP on tree nuts in the USA is foliar spray treatment with 0.056–0.22 kg ai/ha. The PHI is 21 days for pecans and 7 days for others. The Meeting received 30 US trials treated 3 - 8 times with 0.22 kg ai/ha:

- 12 trials on walnuts, PHI 7 days, residues in meat: < 0.05 mg/kg (12)
- Six trials on filberts, PHI 14 days, residues in meat: < 0.05 mg/kg (6)
- 12 trials on pecans, PHI 21–23 days, residues in meat: < 0.05 mg/kg (12).

The Meeting estimated a maximum residue level, an STMR and an HR for tree nuts of 0.05 mg/kg.

Statistical calculations were not possible, since all levels are below the LOQ.

Oilseed

Supervised trials on oil seed were available from Brazil, Canada and the USA with data on cotton seed and rape seed. Furthermore, for cotton seed data from Greece and Spain as well as for rape seed from Germany, Poland and the UK were submitted, but currently no registered use exists in the European Union.

Cotton seed

Bifenthrin is registered in Brazil on cotton with 5 × 0.03 - 0.1 kg a/ha and a PHI of 15 days. Two Brazilian trials were matching the critical GAP. The residues were 0.02 and 0.07 mg/kg.

In the USA, Bifenthrin is registered with 0.11 kg ai/ha (maximum 0.56 kg ai/ha per season) and a PHI of 14 days. The Meeting received US trials treated with 0.1–0.11 kg ai/ha and a PHI of 14 days. Different application numbers in an interval of 7 days were used. The residues were after 3–11 treatments with 0.1–0.11 kg ai/ha (n = 21): < 0.05 (14), 0.06, 0.06, 0.07, 0.07, 0.13, 0.17 and 0.37 mg/kg.

The Meeting estimated a maximum residue level and an STMR for bifenthrin in cotton seed of 0.5 mg/kg and 0.05 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator (after MLE[28]) was 0.34 mg/kg. However, in order to cover residues in cotton seed, a higher maximum residue level was necessary. The number of < LOQ values (13 in 21 trials, > 50%) reduces the reliability of the calculated result.

Rape seed

In the USA, bifenthrin may be used as foliar spray treatment with 0.036–0.045 kg ai/ha and a PHI of 35 days. Four US and two Canadian trials treated with 0.04 kg ai/ha and PHIs of 20–29 days were received. The residues were < 0.05 mg/kg (6).

The Meeting estimated a maximum residue level and an STMR for bifenthrin in rape seed of 0.05 mg/kg.

Statistical calculations were not possible, since all levels are below the LOQ.

Hops, dry

Supervised trials on hops were available from Germany, the UK and the USA. No GAP exists currently in the European Union.

In USA, bifenthrin is registered for use on hops at 0.056–0.11 kg ai/ha and a PHI of 14 days. Three US trials in line with GAP were submitted. The residues were in dried hops 0.85, 1.9 and 5.4 mg/kg.

The Meeting estimated for bifenthrin residues in hops, dry a maximum residue level of 20 mg/kg and an STMR of 1.9 mg/kg. The pervious recommendation of 10 mg/kg was withdrawn.

Statistical calculations for only three data points were not adequate.

Tea, green and black

Supervised trials on green and black tea (dry) were available from China, India, Indonesia and Japan.

In China, the registered use for bifenthrin in tea is foliar spray treatment at 0.0075–0.053 kg ai/ha and a PHI of 7 days. The Meeting received ten Chinese trials treated with 2 × 0.045–0.048 kg ai/ha and a PHI of 7 days which were considered still consistent with Chinese GAP. The residues were in dried tea in ranked order (n = 10): 0.04, 0.07, 0.08, 0.08, 0.08, 0.09, 0.09, 0.11, 1.2 and 4.3 mg/kg.

Three trials from India treated with 0.06 kg ai/ha and a PHI of 7 days were submitted. The application rate was in the limit of ± 25% of Chinese GAP. The residues were in dried tea 0.42, 5.1 and 5.9 mg/kg.

The GAP in Japan is 2 × 0.08 kg ai/ha and a PHI of 14 days. Three Japanese trials according to GAP were submitted. The residues were in dried tea 1.3, 5.2 and 18 mg/kg.

One Indian (1 × 0.08 kg ai/ha, PHI 14 days) and one Indonesian trial (0.06 and 0.10 kg ai/ha, PHI 10 days) were considered still consistent with Japanese GAP. The residues were in dried tea 0.47 and 4.6 mg/kg.

The Meeting agreed to use the Japanese trials supported by the results of the Indian and Indonesian trials to estimate a maximum residue level.

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[28] Note: MLE (Maximum Likelihood Estimate) is the NAFTA process that adjusts the data below LOQ to a lognormal distribution, by applying the distribution based on values at or above the LOQ

The Meeting estimated a maximum residue level and an STMR for bifenthrin in tea, green and black, of 30 mg/kg and 5.2 mg/kg, respectively.

Statistical calculations for only three data points were not adequate.

Primary animal feed commodities

Legume animal feeds

Supervised trials on peas were available from Germany and the UK with data on fodder and forage but no GAP was submitted.

Straw and fodder (dry) of cereal grains (except maize)

Supervised trials on cereals as barley, oats, triticale and wheat were available from European countries with data on straw but no GAP was available.

The Meeting decided to withdraw the previous recommendation for barley straw and fodder, dry and wheat straw and fodder, dry of 0.5 mg/kg.

Forage of cereal grains (except maize)

Supervised trials on cereals as barley, oats, triticale and wheat were available from European countries with data on forage but no GAP was available.

Maize fodder and forage

Supervised trials on maize were available from the USA with data on fodder and forage.

Bifenthrin is registered on maize in the USA as foliar spray treatment with 0.11 kg ai/ha and a PHI of 30 days.

The Meeting received eight US trials treated with 5 × 0.11 kg ai/ha, PHI 29–39 days. The residues in maize straw (fresh weight) were (n = 8): 0.2, < 0.5, 1.3, 1.7, 1.9, 2.0, 2.7 and 4.6 mg/kg.

Based on 83% dry matter (FAO Manual, Table IX.2), the Meeting estimated a maximum residue level for maize fodder of 15 mg/kg (dry weight) to replace the previous recommendation of 0.2 mg/kg. The estimated STMR value was 2.2 mg/kg and the high residue level 5.5 mg/kg, respectively, based on dry weight.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 12.37 mg/kg (fresh weight) or 14.9 mg/kg (dry weight) which was in agreement with the Meeting's estimation.

The Meeting received 24 US trials on maize forage treated with 5 × 0.11 kg ai/ha, samples were taken 10–42 days after the last treatment. The residues in maize forage (fresh weight) were (n = 24): < 0.1, 0.14, 0.16, 0.23, 0.23, 0.29, 0.29, 0.39, 0.49, 0.49, 0.55, 0.57, 0.60, 0.60, 0.76, 0.85, 0.97, 0.97, 1.2, 1.3, 1.4, 1.5, 1.6 and 2.0 mg/kg.

The Meeting estimated STMR and highest residue values for maize forage (fresh weight) of 0.585 mg/kg and 2.0 mg/kg, respectively.

Almond hulls

Supervised trials on almond hulls were available from the USA.

The registered GAP on tree nuts in the USA is foliar spray treatment with 0.056–0.22 kg ai/ha. The Meeting received five US trials where the last treatment was with 0.06–0.11 kg ai/ha. The trials did not match the critical US GAP.

The trials could not used to support recommendations.

Fate of residues during processing

A nature of the residue under simulated processing conditions study was received. The hydrolysis of ^{14}C[phenyl ring] bifenthrin was studied at 90, 100, and 120 °C in sterile buffers. The radio labelled compound was applied to pH 4, 5, and 6 sterile aqueous buffer solutions at an application rate of 0.005 mg/L. The samples were incubated for 20 to 60 minutes at 90, 100, and 120 °C in the dark. The mean material balance was 100.3, 97.6, and 81.3% of the applied radioactivity for the pH 4, 5, and 6 tests, respectively. Under the sterile hydrolysis conditions of the study, bifenthrin was found to be hydrolytically stable at those pH levels.

The Meeting received information on the fate of bifenthrin residues during the processing of tomatoes to paste and puree; of maize to meal, flour, oil and wet milling starch; of soya beans to meal and oil; of cotton seed to oil and of hops to beer. Information is available on processing of wheat to flour, bred, bran and germ and of tea to tea water extract. A potato processing studies could not be used to derive processing factors, as the RAC contained no residues above LOQ and the processed fraction residues were below the LOQ.

The processing factors and the derived STMR-P values are summarized as follows:

RAC	Processed commodity	Calculated processing factors	PF (median or best estimate)	RAC STMR (HR)	STMR-P (HR-P)
Tomato	Paste	< 0.63, < 0.71	< 0.67 (mean)	0.06	0.04
	Puree	< 0.63, < 0.71	< 0.67 (mean)		0.04
Maize	Coarse meal	0.32	0.32	0	0
	Flour	1.1	1.1		0
	Grits	< 0.15	< 0.15		0
	Crude oil	0.77, 1.9	1.9 (highest)		0
	Refined oil	0.92, 2.3	2.3 (highest)		0
	Germ	0.29, 0.52	0.52 (highest)		0
	Hulls	2.9, 1.5	2.9 (highest)		0
	Starch	< 0.15	< 0.15		0
Soya bean	Hulls	1.2, 1.4	≥ 1.3		0.065
	Aspirated grain	140, 240	≥ 190 (mean)		9.5
Wheat	Bran	2.5, 2.6, 2.7, 2.7, 2.7, 2.9, 3.0, 3.0, 3.0, 3.1, 3.1, 3.2, 3.3, 3.3, 3.5, 3.5, 4.4, 4.6, 4.6, 5.0, 5.0, 5.1	3.15 (median, n = 22)	0.25 (0.40)	0.79 (1.26)
	Whole meal flour	0.29, 0.32, 0.37, 0.59, 0.63, 0.64, 0.68, 0.68, 0.69, 0.69, 0.70, 0.71, 0.73, 0.76, 0.76, 0.77, 0.77, 0.78, 0.79, 0.81, 0.81, 0.87, 0.88, 0.92, 0.95, 1.0, 1.0, 1.1, 1.1, 1.1	0.765 (median, n = 30)		0.19 (0.306)
	Whole meal bread	0.11, 0.11, 0.14, 0.15, 0.15, 0.18, 0.19, 0.19, 0.60, 0.69, 0.73, 0.76, 0.76, 0.81, 0.83, 0.85, 0.86, 0.87, 0.88, 0.88, 0.89, 0.97	0.75 (median, n = 22)		0.19 (0.3)
	White flour	0.038, 0.038, 0.071, 0.077, 0.21, 0.21, 0.24, 0.26, < 0.3, 0.3, 0.3, 0.32, 0.32, 0.32, 0.33, 0.34, 0.35, 0.39, 0.42, 0.47, 0.51, 0.52	0.31 (median, n=22)		0.078 (0.124)
	White flour bread	0.036, 0.037, 0.038, 0.038, 0.069, 0.071, 0.074, 0.077, 0.20, 0.24, 0.24, 0.25, 0.25, 0.25, 0.27, 0.28, < 0.29, < 0.30, 0.30, 0.31, < 0.32, 0.32	0.245 (median, n=22)		0.061 (0.098)
	Germ	1.1, 1.2, 1.5, 1.6, 2.0, 2.2, 2.5, 2.7	1.8 (median, n=8)		0.45 (0.72)

RAC	Processed commodity	Calculated processing factors	PF (median or best estimate)	RAC STMR (HR)	STMR-P (HR-P)
Cotton seed	Linters	4.5, 4.2	4.4 (mean)	0.05	0.22
	Hulls	0.27, 0.40	0.34 (mean)		0.017
	Meal	< 0.058, < 0.053	< 0.06 (highest)		0.003
	Refined oil	0.10, 0.084	0.1 (highest)		0.005
Rape seed	Meal	0.54	0.54	0.05	0.027
	Refined oil	1.6	1.6		0.08
Hops	Beer	< 0.0055, < 0.0057	< 0.006	1.9	0.011
Tea	Water extract	0.001, 0.0018, 0.002, 0.002, 0.0021, 0.0023, 0.0023, 0.0025, 0.0026, 0.0027, 0.0027, 0.003, 0.0035, 0.0043, < 0.005, 0.0062, < 0.007, 0.0077, < 0.011, 0.014, < 0.019, < 0.024	0.003 (median, n=22)	5.2	0.0156

On processing, bifenthrin concentrated in maize oil, rape seed oil, wheat germ, wheat bran and in milled by-products as hulls and aspirated grain fractions. The Meeting decided to estimate the following maximum residue levels, STMR-P and HR-P values for processed commodities:

Based on the STMR of 0.05 mg/kg for rape seed and a processing factor of 1.6, the Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR-P of 0.08 mg/kg for rape seed oil, edible.

Based on an HR for wheat of 0.4 mg/kg Po, an STMR of 0.25 mg/kg Po and a processing factor of 1.8, the Meeting estimated a maximum residue level of 1 mg/kg PoP, a STMR-P of 0.45 mg/kg PoP and an HR-P of 0.72 mg/kg PoP for wheat germ.

Based on an HR for wheat of 0.4 mg/kg Po, an STMR of 0.25 mg/kg Po, an HR and a processing factor of 3.15, the Meeting estimated a maximum residue level of 2 mg/kg PoP, an STMR-P of 0.79 mg/kg PoP and an HR-P of 1.26 mg/kg PoP for wheat bran, unprocessed. The previous recommendation was confirmed.

The Meeting was aware that bifenthrin residues concentrated during processing of maize to maize oil. Because the STMR in maize grain is 0 mg/kg, residues in maize oil are not expected above the maximum residue level of 0.05* mg/kg for maize grain. The Meeting estimated an STMR of 0 for maize oil, edible and maize oil, crude, maize flour, maize grits and maize starch.

The Meeting also decided to estimate a maximum residue for chilli pepper (dried) of 5 mg/kg following application of a default dehydration factor of 10 to the estimated maximum residue level of 0.5 mg/kg for sweet pepper (10 × 0.5 = 5 mg/kg). The STMR for residues of bifenthrin in chilli peppers (dry) is estimated to be 10 × 0.14 = 1.4 mg/kg.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of bifenthrin in farm animals on the basis of the diets listed in Appendix X of the FAO Manual (OECD Feedstuffs Derived from Field Crops). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6.

	Livestock dietary burden, bifenthrin, ppm of dry matter diet							
	US/CAN		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle	1.85	1.35	**8.26** [a]	**3.35** [b]	5.2	1.76	0.57	0.57
Dairy cattle	2.68	1.12	**7.41** [c]	**3.21** [d]	5.2	1.76	2.92	1.15
Poultry - broiler	0.59	0.59	0.43	0.43	0.38	0.38	0.11	0.11
Poultry - layer	0.59	0.59	**1.97** [e]	**1.10** [f]	0.35	0.35	0.28	0.28

[a] Highest maximum beef or dairy cattle burden suitable for MRL 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 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.

Farm animal feeding studies

The Meeting received information on the residue levels arising in animal tissues and milk when dairy cows were dosed daily with bifenthrin for 28 days at the equivalent of 0.5, 5, 15 and 50 ppm in the diet. Average residues of bifenthrin in milk for the 5, 15 and 50 ppm dose group were 0.082, 0.15 and 0.65 mg/kg, respectively. Residues in tissues were:

- In the 5 ppm dose group, no residues of bifenthrin above the LOQ of 0.1 mg/kg were detected in muscle, kidney and liver; in fat, the highest residue was 1.7 mg/kg and the mean 0.865 mg/kg.
- In the 15 ppm dose group, the highest residues in muscle, liver, kidney and fat were 0.24, < 0.1, 0.19, and 2.2 mg/kg, respectively. The mean residues in muscle, liver, kidney and fat were 0.154, < 0.1, 0.185 and 1.325 mg/kg.
- In the 50 ppm dose group, the highest residues in muscle, liver, kidney and fat were 0.88, < 0.1, 0.49 and 5.8 mg/kg, respectively. The mean residues in muscle, liver, kidney and fat were 0.37, < 0.1, 0.465 and 3.45 mg/kg.

In a second study, dairy cows were dosed with bifenthrin at levels of 5 and 50 ppm per day for 28 consecutive days. Milk fat was analysed for parent bifenthrin. Additional, milk and tissues were analysed for biphenyl alcohol and tissues for biphenyl acid. The results were:

- Bifenthrin mean residues in milk fat were 0.765 mg/kg in the 5 ppm dose group and 8.81 mg/kg in the 50 ppm dose group.
- Residues of the metabolite biphenyl alcohol were in milk < 0.02 mg/kg of the 50 ppm dose group.
- In tissues, in the 5 ppm dose group, the highest residues of biphenyl alcohol in muscle, liver and kidney were < 0.05 mg/kg and in fat 0.11 mg/kg. The mean residues in muscle, liver, kidney were < 0.05 mg/kg and 0.067 mg/kg in fat.
- In tissues, in the 50 ppm dose group, the highest residues of biphenyl alcohol in muscle, liver, kidney and fat were 0.07, < 0.05, < 0.05 and 1.1 mg/kg, respectively. The mean residues in muscle, liver, kidney were < 0.05 mg/kg and 0.067 mg/kg in fat.
- Residues of the metabolite biphenyl acid were at the 50 ppm feeding level in muscle and fat < 0.05 mg/kg. Highest residues were in liver 0.05 mg/kg and in kidney 0.14 mg/kg. Mean residues were in liver 0.045 mg/kg and in kidney 0.09 mg/kg.

In a third study, dairy cows were dosed with bifenthrin at levels of 5 and 50 ppm per day for 28 consecutive days. Tissue samples of peritoneal fat and subcutaneous fat were analysed for 4'-hydroxy-bifenthrin. No detectable (< 0.01 mg/kg) 4'-hydroxy-bifenthrin residue was found in any of the cow fat samples analysed.

The Meeting also received information on the residue levels arising in tissues and eggs when laying hens were dosed with bifenthrin for 28 days at levels equivalent to 0.0025, 0.025 and 0.25 ppm in the diet. At the high dose residues of bifenthrin and 4'-hydroxy-bifenthrin in eggs were below the LOQ of 0.01 mg/kg. No bifenthrin residues were found in any of the tissue samples of the 0.25 ppm dosing group (< 0.02 muscle, < 0.05 mg/kg liver, fat, gizzard). Biphenyl alcohol could only be detected in subcutaneous fat of the 0.25 ppm dosing group, but was always below LOQ of 0.05 mg/kg. It was not detected at the lower dosing level of 0.025 ppm. No TFP acid residues were found in any of the liver samples of the 0.25 ppm dosing group (< 0.05 mg/kg).

Animal commodity maximum residue level estimation

Cattle

The dietary burdens for the estimation of maximum residue levels for bifenthrin in animal commodities are 8.3 ppm for beef cattle and 7.41 ppm for dairy cattle. The dietary burdens for the estimation of STMR values are 3.35 ppm for beef cattle and 3.21 for dairy 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]	Milk	Milk fat	Muscle	Liver	Kidney	Fat
MRL	mean	highest	highest	highest	highest	highest
Beef cattle (8.26) [5/15]			0.104 mg/kg [< 0.1/0.24]	< 0.165 mg/kg [< 0.1/0.1]	0.108 mg/kg [0.1/0.19]	1.902 mg/kg [1.7/2.2]
Dairy cattle (7.41) [5/15]	0.088 mg/kg [0.082/0.15]	2.371 mg/kg [1.6/-]				
STMR	mean	mean	mean	mean	mean	mean
Beef cattle (3.4) [0/5]			< 0.068 mg/kg [< 0.1]	< 0.068 mg/kg [< 0.1]	< 0.068 mg/kg [< 0.1]	0.588 mg/kg [0.865]
Dairy cattle (3.21) [0/5]	0.053 mg/kg [0.082]	0.491 mg/kg [0.765]				

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

The Meeting estimated STMR values of 0.07 mg/kg for mammalian muscle and 0.59 mg/kg for mammalian fat, and a maximum residue level of 3 (fat) for mammalian meat. The HRs were 0.104 and 1.9 mg/kg for muscle and fat, respectively.

The Meeting estimated an STMR value of 0.07 mg/kg and a maximum residue level of 0.2 mg/kg for mammalian edible offal, based on liver and kidney data. The HR was 0.165 mg/kg.

The Meeting estimated an STMR value of 0.053 mg/kg and a maximum residue level of 0.2 mg/kg for milks.

The Meeting estimated an STMR value of 0.49 mg/kg and for milk fat. The Meeting estimated a maximum residue level of 3 mg/kg for milk fat.

Previous recommendations for cattle meat (fat) (0.5 mg/kg), cattle liver (0.05* mg/kg), cattle kidney (0.05* mg/kg), cattle fat (0.5 mg/kg) and cattle milk (0.05* mg/kg) were withdrawn.

Poultry

The dietary burdens for the estimation of maximum residue levels and STMR values for bifenthrin in poultry commodities are 1.79 ppm and 1.1 ppm, respectively.

An extrapolation from the highest dose level of 0.25 ppm in the laying hen feeding study to the estimated dietary burdens was not made because of the big distance.

The laying hen feeding study submitted is not adequate to estimate maximum residue levels, STMR and HR values for poultry tissues and eggs.

Previous recommendations for chicken eggs (0.01* mg/kg), chicken fat (0.05* mg/kg), chicken meat (fat) (0.05* mg/kg) and chicken, edible offal of (0.05* mg/kg) are withdrawn.

FURTHER WORK OR INFORMATION

The Meeting identified the following data gaps:

An adequate poultry feeding study at the dose level matching the animal dietary burden.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) of bifenthrin were calculated for the 13 GEMS/Food cluster diets using STMRs and STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.01 mg/kg bw and the calculated IEDIs were 8–20% of the maximum ADI. The Meeting concluded that the long-term intake of residues of bifenthrin resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term intake

The International Estimated Short Term Intake (IESTI) for bifenthrin was calculated for food commodities and their processed fractions for which maximum residue levels were estimated and for which consumption data were available. The results are shown in Annex 4.

For strawberries, the IESTI represented 230% of the ARfD of 0.01 mg/kg bw for the general population and 430 % of the ARfD for children. The information provided to the JMPR precludes an estimate that the short-term intake of residue of bifenthrin from the consumption of strawberries will below the ARfD. The Meeting noticed that an alternative GAP for strawberries was not available.

For the other commodities considered by the JMPR, the IESTI represented 0–50 % of the ARfD for the general population and 0–90% of the ARfD for children. The Meeting concluded that the short-term intake of residues of bifenthrin, when used in ways that have been considered by the JMPR (except strawberry), is unlikely to present a public health concern.

A concern form regarding the ARfD established by the JMPR in 2009 was received immediately prior to the current Meeting, long after the agreed CCPR deadline (see 3.1). The Meeting decided to defer this item to the next JMPR.

5.3 BOSCALID (221)

RESIDUE AND ANALYTICAL ASPECTS

Boscalid was evaluated for the first time for toxicology and residues by the JMPR in 2006. The 2009 JMPR then derived a number of MRLs following consideration of the residue situation in rotational crops. The compound was listed for additional residue assessment by the 2010 JMPR at the Forty-first Session of the CCPR. At the Forty-second Session of the CCPR, the Committee noted the reservation of the EU regarding the proposed maximum residue level for leafy vegetables in light of their higher MRLs for lamb's lettuce (ALINORM 10/33/24, para 79). GAP information and residue data for citrus fruits, lambs lettuce, celery and hops were submitted by the manufacturer.

Results of supervised trials on crops

The 2009 JMPR evaluated the boscalid residue data according the following principles:

- For a maximum residue level recommendation for boscalid in plant commodities, the addition of probable residues arising from direct treatment in combination with root uptake of boscalid applied in previous years must be taken into account.
- Use of crop groupings for plant food and feed, as established in the Codex Classification System, to give recommendations based on the overall anticipated residue levels of boscalid in these commodities rather than for single commodities.
- That the use of statistical methods, for the estimation of maximum residue levels, is not possible in cases where the potential for carryover residues in following crops exist. All maximum residue levels recommended for boscalid are based on the expertise of the Meeting only.
- The residues arising from direct treatment of permanent (perennial) crops were used for estimation of a maximum residue levels as the uptake of boscalid from the soil is not considered a significant factor.

The current Meeting also applied the above mentioned evaluation principles. New data was submitted for citrus fruits and hops (permanent crops) as well as for lamb's lettuce and celery which are plant commodities grown as potential succeeding crops.

The NAFTA calculator was used as a tool in the estimation of the maximum residue levels for the permanent crops citrus and hops 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 using expert judgement. Then, the NAFTA calculator was employed. If the value derived from use of the statistical calculation spreadsheet was different from that recommended by the JMPR, a brief explanation of the deviation was provided. Some common factors that may lead to rejection of the statistical estimate include those situations where the number of data points was less than 15 or where there a large number of values are below the LOQ.

Citrus fruits

The registered use of boscalid in citrus fruits in the USA is as foliar spray treatment of 0.28–0.33 kg ai/ha (a maximum of 4 treatments with an application interval of 10–21 days) and a PHI of 0 days.

In six US trials on grapefruit matching GAP, boscalid residues in whole fruit were: 0.10, 0.12, 0.15, 0.15, 0.27 and 0.85 mg/kg. No data were received for the edible portion.

In five US trials on lemon matching GAP, boscalid residues in whole fruit were: 0.59, 0.68, 0.74, 0.94 and 1.5 mg/kg. No data were received for the edible portion.

In 13 US trials on oranges matching GAP, boscalid residues in whole fruit were: 0.23, 0.26, 0.30, 0.32, 0.33, 0.35, 0.47, 0.56, 0.64, 0.68, 0.71, 1.2 and 1.4 mg/kg. The residues in pulp were < 0.05 (6), 0.05, 0.06, 0.06, 0.09, 0.09, 0.12 and 0.20 mg/kg.

Based on the orange residue data, the Meeting estimated a maximum residue level of 2 mg/kg for citrus fruits. On the basis of the residues in orange pulp, the Meeting estimated an STMR of 0.05 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 1.84 mg/kg, which when rounded up, was in agreement with the Meeting's estimation.

Leafy vegetables

The 2009 JMPR evaluated boscalid residue data on mustard greens, head lettuce and leafy lettuce. The residues found following direct treatment were:

- mustard greens: 0.45, 0.54, 0.92, 2.8, 3.1, 6.04, 12.9 and 14.4 mg/kg
- head and leafy lettuce (US GAP): 0.11, 0.74, 0.98, 1.6, 1.63, 1.77, 1.91, 2.53, 2.68, 2.73, 3.18, 4.87, 5.14, 5.42, 9.36 and 9.55 mg/kg
- lettuce (EU GAP, outdoor): < 0.05, 0.09, 0.15, 0.21, 0.33, 0.36, 0.38, 0.39, 0.43, 0.45, 0.50, 0.64, 0.65, 0.73, 0.76, 0.86, 1.19 and 1.58 mg/kg
- lettuce (EU GAP, indoor): 0.37, 0.71, 1.52, 2.31, 2.5, 5.63, 5.96 and 6.11 mg/kg.

The 2009 JMPR concluded that the application of boscalid to mustard greens results in the highest population in leafy vegetables and used the mustard greens data to recommend a maximum residue level and an STMR of 30 mg/kg and 2.95 mg/kg respectively for the crop group.

At the Forty-second Session of CCPR, the Committee noted the reservation of the EU regarding the proposed MRL for leafy vegetables in light of their higher MRLs for lamb's lettuce. The French GAP allows one boscalid treatment of 0.4 kg ai/ha with a PHI of 14 days.

Eight trials on lamb's lettuce (six indoor and two outdoor) in line with the French GAP were submitted. The boscalid residues in ranked order (median underlined) were: 0.26, 0.85, 2.4, 3.2, 4.1, 4.1, 16 and 29 mg/kg.

The Meeting concluded that the application of boscalid to lamb's lettuce (instead of mustard greens) results in the highest residue population in leafy vegetables and should be used to recommend a maximum residue level and an STMR for the crop group.

For leafy vegetables no data from studies on follow crops are available. In field studies on succeeding crops mean, median and highest residues in brassica vegetables were 0.03 mg/kg, 0.035 mg/kg and 0.05 mg/kg, respectively. The 2009 JMPR concluded that the results obtained for brassica vegetables would also be applicable in estimating possible residues of boscalid in leafy vegetables. In line with the decision of the 2009 JMPR, the Meeting concluded that residues due to an additional uptake of boscalid via roots could be considered insignificant, in comparison to residue levels arising from direct foliar treatment.

The Meeting estimated a maximum residue level and an STMR value for boscalid in leafy vegetables of 40 mg/kg and 3.65 mg/kg, respectively. The previous recommendation of 30 mg/kg as maximum residue level was withdrawn.

Stalk and stem vegetables

The US GAP allows the use of boscalid on celery at an application rate of 2 × 0.22–0.44 kg ai/ha with a 0 day PHI.

Residues from twelve US trials, matching the US GAP, (median underlined) were: of 1.9, 2.0, 2.7, 5.6, 6.7, 8.3, 8.6, 9.8, 13, 13, 18 and 20 mg/kg.

For stalk and stem vegetables no data from studies on following crops were available. In field studies on succeeding crops mean, median and highest residues in brassica vegetables were 0.03 mg/kg, 0.035 mg/kg and 0.05 mg/kg, respectively. The Meeting concluded that the results obtained for brassica vegetables would also be applicable in estimating possible residues of boscalid in stalk and stem vegetables. The Meeting concluded that residues due to root uptake of boscalid would be insignificant in comparison to residue levels arising from direct foliar treatment.

As per the decision made by the 2009 JMPR, the Meeting decided to give a crop group recommendation on the basis of celery residue data.

The Meeting estimated a maximum residue level of 30 mg/kg and an STMR of 8.55 mg/kg for stalk and stem vegetables.

Hops

The registered use of boscalid in hops in the USA is as a foliar spray treatment of 3 × 0.026 kg ai/hL (0.49 kg ai/ha) with a PHI of 14 days. Eight US trials were submitted, six matching the US GAP. The residues found, in rank order (median underlined) were: 11, 12, 15, 28, 29 and 31 mg/kg.

The Meeting estimated a maximum residue level and an STMR for boscalid residues in hops, dry of 60 mg/kg and 21.5 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 58 mg/kg and was in agreement with the Meeting's estimation.

Fate of residues during processing

The Meeting received information on the fate of boscalid residues during the processing of oranges to juice, oil and dried pulp and of hops to beer. The processing factors and the derived STMR-P values are summarized as follows:

RAC	Processed commodity	Calculated processing factors	PF (median or best estimate)	RAC STMR, mg/kg	STMR-P mg/kg
Orange	Dried pulp	2.7, 3.6	3.2	0.47[a]	1.5
	Juice	< 0.23, < 0.23	< 0.23		0.108
	Oil	55, 63	59		27.7
Hops	Beer	< 0.0024, < 0.0025, < 0.0074, < 0.0085	< 0.005	21.5	0.108

[a] RAC STMR and highest residue based on orange, whole fruit

On processing, boscalid was found to concentrate in orange pulp dried and orange oil.

Based on the highest residue of 1.4 mg/kg (whole fruit), an STMR of 0.47 mg/kg (whole fruit) and a processing factor of 3.2, the Meeting estimated a maximum residue level of 6 mg/kg and an STMR-P of 1.5 mg/kg for citrus pulp, dry.

Based on the STMR of 0.47 mg/kg (whole fruit) and a processing factor of 59, the Meeting estimated a maximum residue level of 50 mg/kg and an STMR-P of 27.7 mg/kg for citrus oil.

For orange juice, a STMR-P value of 0.108 mg/kg was estimated.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of boscalid in farm animals on the basis of the diets listed in Appendix X of the FAO Manual (OECD Feedstuffs Derived from Field Crops) for feed commodities evaluated by the JMPR in 2009 and 2010 (citrus pulp, dry, only). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6.

	Livestock dietary burden, boscalid, ppm of dry matter diet							
	US/CAN		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle	6.6	2.3	17.3	7.1	34.9 [a]	12.1 [b]	1.9	0.85
Dairy cattle	18.9	6.5	16.6	6.5	34.5 [c]	12.0 [d]	2.5	0.94
Poultry - broiler	0.23	0.23	1.01	0.54	0.19	0.19	0.08	0.08
Poultry - layer	0.23	0.23	8.7 [e]	3.04 [f]	0.19	0.19	0.15	0.15

[a] Highest maximum beef or dairy cattle burden suitable for MRL 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 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.

Animal commodities, maximum residue levels

The dietary burdens for the estimation of maximum residue levels for boscalid in cattle commodities calculated by the 2009 JMPR are 34.0 ppm and for the estimation of STMR values 12.1 ppm for beef or dairy cattle.

The only additional feed item evaluated by the 2010 JMPR was citrus pulp, dry. The maximum and mean dietary burdens for cattle calculated by the 2010 JMPR did not differ from the values calculated in 2009 (maximum 34.9 ppm, mean 12.1 ppm for beef or dairy cattle).

The Meeting noted that a revision of the maximum residue levels and STMRs for animal products, like meat (from mammals other than marine mammals), milk fats, milks and edible offal (mammalian) was not necessary. The previous recommendations were confirmed.

The dietary burdens for the estimation of maximum residue levels and STMR values for boscalid in poultry commodities calculated by the 2009 JMPR were 8.4 ppm and 2.82 ppm, respectively. The 2009 Meeting estimated maximum residue levels and STMRs of 0.02 mg/kg for poultry meat, fat and edible offal as well as for eggs on the basis of a metabolism study on laying hens with a dose rate of 12.5 ppm.

The maximum and mean dietary burdens for cattle calculated by the 2010 JMPR did not differ from the values calculated in 2009 (maximum 8.7 ppm, mean 3.04 ppm for poultry).

The Meeting noted that a revision of the maximum residue levels and STMRs for animal products, like poultry meat, fat and edible offal as well as for eggs was not necessary. The previous recommendations were confirmed.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of boscalid resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the thirteen Cluster Diets, based on the estimated STMRs were 10–40% of the maximum ADI of 0.04 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of boscalid from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The 2006 JMPR decided that an ARfD was unnecessary. The Meeting therefore concluded that the short-term intake of boscalid residues is unlikely to present a public health concern.

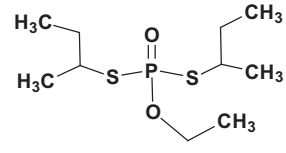
5.4 CADUSAFOS (174)

RESIDUE AND ANALYTICAL ASPECTS

Cadusafos is an organophosphate nematicide. It was evaluated by JMPR 1991(T, R), 1992(R). It was evaluated for toxicological review by JMPR in 2009 as the periodic re-evaluation. The ADI for cadusafos was established as 0–0.0005 mg/kg bw and acute reference dose was 0.001 mg/kg bw

Cadusafos was scheduled at the Forty-first Session of the CCPR (2009) for the periodic re-evaluation of residues by the 2010 JMPR.

Residue studies were submitted by the manufacturer to support the use of cadusafos in or on banana and potatoes.



Animal metabolism

The 2009 JMPR Meeting reviewed studies on the metabolism of ^{14}C-labelled cadusafos in rats. These studies showed that more than 80% of the administered dose was excreted within 24 hours, and more than 90% within 48 hours. Of the recovered radiolabel, 70–80% was found in the urine, 4–14% in the faeces, and 12–18% as CO_2. Cadusafos residues were widely distributed among rat organs, with a peak of 1.2% of the administered dose being found in the body at 7 days after dosing. Highest TRR concentrations were found in the liver, fat, kidney, and lungs. There was no evidence for accumulation of cadusafos residues in the body.

Cadusafos is extensively metabolized in rats. Metabolism proceeds by cleavage of one of the thio-butyl groups to give *sec*-butyl mercaptan and O-ethyl-S-(2-butyl) phosphorothioic acid, which can then be cleaved to S-(2-butyl) phosphorothioic acid or O-ethyl phosphorothioic acid. *Sec*-Butyl mercaptan is biotransformed to methyl *sec*-butyl sulfide, sulfoxide, and sulfone; and then to hydroxysulfones. Alternatively, *sec*-butyl mercaptan can be oxidized to butyl sulfonic acid, then ethyl and methyl sulfonic acid. CO_2 formation may proceed from *sec*-butyl mercaptan or from sulfonic acid. Carbon dioxide is incorporated into urea or other endogenous substances. No significant differences in the metabolic profile of cadusafos in male and female rats were reported.

No livestock metabolism studies were available for consideration since there are no relevant livestock feed items. Based on the results of the rat metabolism studies, cadusafos metabolism in animals consists of an initial hydrolysis reaction followed by a series of oxidation and/or methylation reactions to produce a variety of small, polar compounds.

Plant metabolism

Cadusafos metabolism studies were submitted on the following plants: banana, potato, corn, radish, and tomato. The studies on plant metabolism all involved applications to soil, consistent with intended use patterns. Cadusafos metabolism was relatively consistent in these matrices: hydrolytic cleavage followed by a series of oxidation reactions to give several small, polar compounds. In addition, conjugation with glucose was reported. The primary difference noted between plants was the extent of metabolism observed, with potato demonstrating the most extensive metabolism.

Banana

Two banana plants in the early fruiting stage were treated with [^{14}C]-cadusafos at the rate of 3.0 g ai per tree applied to the soil. Mature fruit and leaves from the plants were harvested and analysed. Initial combustion analysis indicated only low levels of total radioactive residue (TRR) in the fruit, 0.051 mg/kg in ripe pulp and 0.031 mg/kg in unripe pulp. Extraction and partition analysis of radiocarbon residue in ripe banana pulp and peel showed that the majority of the residue consisted of water-soluble polar metabolites with lower levels of organo-soluble metabolites. No parent chemical was detected in the ripe or unripe fruit (i.e., < 1 ppb), whereas 1 ppb of parent chemical was found in the leaf. The predominant residue identified in unripe pulp was methyl 2-butyl sulfone (36% TRR, 0.011 mg/kg). As bananas ripen to yellow, an additional oxidation step occurs resulting in hydroxy 2-butyl methylsulfone being the predominate metabolite observed in ripe pulp (52% TRR, 0.027 mg/kg).

Potato

Radio-labelled cadusafos was applied to soil in pots at a rate equivalent to 6 kg ai/ha. Potatoes were planted into the pots of treated soil and maintained in a greenhouse for 44 days, at which time they were moved to an outdoor screen house until maturity. The potatoes were harvested at normal maturity (160 days after treatment) and analysed. TRR levels of 0.69–0.70 mg/kg were found in potato tubers. Cadusafos undergoes initial hydrolysis to the transient butane-2-thiol, which undergoes a series of oxidations and methylations to yield a major product, hydroxy 2-butyl methylsulfone. This compound is further oxidized to two isomers of 1-carboxyhydroxyisopropylmethylsulfone, which, in conjugated form, represent the major metabolites in potato tubers (32–37% TRR, 0.22–0.25 mg/kg).

Maize

Metabolism of cadusafos was studied in corn (maize) using a 2 kg ai/ha treatment rate. The chemical was applied as a 20% granular formulation in bands to the soil. Corn plants were grown to maturity in the greenhouse. Plant samples were taken at 30 and 60-days post-treatment, at silage, and finally at maturity, i.e., grain and stover. TRR levels ranged from 0.85 mg/kg (cadusafos equivalents) in the 60-day post plant forage, to 2.87 mg/kg in the stover. Grain TRR levels were 0.23 mg/kg cadusafos equivalents found only in the mature (160 day) plant. Cadusafos is not stable in the plant and is degraded to more polar and water soluble metabolites. Specifically, analysis of the 30 day, 60 day, silage, and stover samples showed that cadusafos degrades to 2-butanesulfonic acid, hydroxy-2-butanesulfonic acid, and butanediols. S-2-butyl phosphorothioic acid was a minor metabolite in corn samples, while S,S-di-(2-butyl) phosphorodithioic acid was present only in the 30 and 60 day plant samples at less than 0.01 mg/kg. Further analysis of the organosoluble metabolites showed the presence of methyl 2-butyl sulfone, and hydroxy 2-butyl methylsulfone as minor components. Radiocarbon in the grain was analysed and was found to be primarily due to incorporation into glucose, indicating that the parent chemical undergoes a rapid and facile degradation in the corn plant.

Radish

Cadusafos was applied to soil at a rate of 9 kg ai/ha, and radish seeds were sown in the soil. At 50 days after treatment of [^{14}C]-cadusafos, mature radishes were harvested. The radishes were separated into the roots and the foliage for separate analysis. The recoveries of radioactivity in the root, foliage and soil accounted for 0.3%, 1.0% and 70.9% of the applied radioactivity, respectively. The total radioactive residues (TRRs) in the root, foliage and soil were 1.6 mg/kg, 5.0 mg/kg and 10.7 mg/kg equivalents of cadusafos, respectively.

The radish metabolism study showed that numerous compounds were detected in the extractable fractions from the root. There were no metabolites which were more than 4%TRR (0.07 mg/kg equivalent of cadusafos). The parent compound was detected at 0.8%TRR (0.014 mg/kg)

in the root. Numerous compounds were also detected in the extractable fractions from the foliage. All the metabolites were less than 10%TRR or 0.5 mg/kg except for methyl 2-butyl sulfone (19%TRR, 0.88 mg/kg). The parent compound was detected at 0.4% (0.018 mg/kg) in foliage. Many metabolites in the root and foliage were polar compounds which were found in the water-soluble fraction. In the soil no metabolite comprised more than 2%TRR.

Tomato

Radio-labelled cadusafos was applied by drip irrigation to the soil surface on two separate occasions at a total nominal rate of 6 kg ai/ha. The first application was made prior to transplanting at a rate of 4 kg ai/ha with a second 60 days later at 2 kg ai/ha. In tomato plants, cadusafos is metabolised via butane-2-thiol to butane-2-sulfonic acid and numerous minor metabolites and conjugates. Radioactive residues were mainly taken up via the roots into the shoots, whereas the uptake of residues into fruits was low. The TRR in edible tomato fruit ranged between 0.028 to 0.093 mg/kg. Tomatoes were separated into pomace and juice fractions and analysed. It was observed that the major part of the radioactivity (up to 95%) found in the fruits was present in tomato juice. Analyses of the tomato juice samples showed up to 22 radioactive fractions in addition to the parent compound. All fractions were below 10% TRR, except one fraction, likely consisting of several compounds characterized as conjugates, found in green tomatoes. However, none of the radioactive fractions exceeded 0.010 mg/kg in tomato fruit. The major part of the radioactive residue was shown to be conjugated to sugars.

Environmental fate in soil

The degradation of radio-labelled cadusafos in aerobic conditions was investigated in silt loam and sandy loam soils in the US, and in clay loam and silt loam soils in Germany and Spain. The estimated time to 50% degradation (DT_{50}) ranged from 11–62 days in the reported studies. These studies showed that cadusafos has a relatively short estimated half-life in soil.

To investigate the possible photodegradation of cadusafos in soil, sandy loam soil samples were exposed to natural sunlight (11 hour photo periods per day) following treatment with radio-labelled cadusafos at approximately 1 mg/kg and analysed at standard intervals up to 30 days. After 30 days, only 1% of the applied cadusafos was found to have degraded into three compounds. The slow photochemical degradation is in line with the low UV/visible absorbance of cadusafos. Thus, cadusafos may be considered a photolytically-stable compound.

Buffered aqueous solutions (pH 5, 7 and 9) containing approximately 3 mg/L of radio-labelled cadusafos were analysed for hydrolysis at intervals up to 34 days. Cadusafos was stable at pH 5 and 7 during the 34-day study period. At pH 9, slow hydrolysis was observed. Cadusafos may be considered a hydrolytically-stable compound.

Rotational crops

No rotational crop studies were submitted for review. For rotated crops there would be no expectation of residues remaining in the soil following early season applications as cadusafos has a relatively short estimated half-life in soil.

Methods of analysis

The Meeting received description and validation data for a single-residue analytical method for cadusafos in samples of plant origin. The method is based on extraction with a methanol/water mixture, gravity filtering though glass wool and partitioning with methylene chloride, followed by liquid-liquid extraction using water and dichloromethane and an additional clean-up on an alumina column. The organic phase was filtered through anhydrous sodium sulfate, concentrated and taken up with hexane. Further clean up was achieved using silicagel SEP PAK cartridges and eluting

cadusafos with 25% ethyl acetate in hexane. Quantitative determination of the active substance was performed using gas chromatography and a flame photometric detector operating in phosphorous mode.

The method was validated for banana, potato, melon, green beans, strawberry and peppers with a LOQ of 0.005 mg/kg (0.001 mg/kg for banana). Method recoveries ranged from 80–94% for banana pulp and 87–94% for potatoes, with RSDs < 10%. The method was used in the supervised trials on plant commodities evaluated by this Meeting (banana and potato) with concurrent recoveries within the range of 70–110% and RSD < 10%.

Adequate single-residue methods exist for both gathering data in supervised trials and for monitoring and enforcing cadusafos MRLs in the matrices validated. No information regarding the recovery of cadusafos through multiresidue methods was submitted. However, organophosphate compounds are generally amenable to analysis by multiresidue methods and the Pesticide Data Programme of the United States Department of Agriculture has reported monitoring results for cadusafos residues in banana samples.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of cadusafos in freezer-stored samples of banana, potato, and corn. The results show that cadusafos was stable under freezer-storage conditions during the tested storage interval of 14–15 months, which covers the storage intervals in the supervised trials evaluated by this Meeting.

Definition of the residue

The plant metabolism studies indicate that significant portions of cadusafos are oxidized and then converted to the corresponding conjugates in plant matrices. However, due to the lower toxicity of the polar conjugates formed, the Meeting concluded that the residue definition for plant commodities for purposes of enforcement is cadusafos. The Meeting also concluded that for purposes of dietary intake considerations, the residue definition is cadusafos alone. This determination is consistent with conclusions of the 2009 JMPR, which listed cadusafos as the only toxicologically significant compound in plants, animals, and the environment.

The octanol-water partition coefficient of cadusafos (log K_{OW} = 3.9) implies that cadusafos is likely to be fat soluble. The Meeting determined there was insufficient information available to reach a conclusion regarding the fat solubility of cadusafos in livestock commodities.

Results of supervised trials on crops

The Meeting received results from supervised trials with cadusafos on banana and potato. All results on relevant commodities in trials conducted according to GAP were less than the method LOQ. Consequently, it was not suitable to use the NAFTA calculator to estimate the maximum residue levels. Instead, maximum residue estimation was based on the method LOQ.

Banana

The Meeting received results from supervised trials with cadusafos used on bananas in Australia, Costa Rica (n = 6), Ecuador, Guatemala, Honduras (n = 2), Ivory Coast (n = 2), Martinique, Mexico, and Philippines (n = 2). The GAP in all these countries (except Ecuador: 2 × 2 g ai/plant) specifies two soil applications at a rate of 3 g ai/plant, or three applications at a rate of 2 g ai/plant, for a total rate of 6 g ai/plant per year, with no retreatment interval (RTI) or pre-harvest interval (PHI) given.

The trials reported cadusafos residues in banana peel and pulp samples over a wide range of PHIs and at several treatment rates. The LOQ for all trials was 0.005 mg/kg except for the trial conducted in the Philippines, where the LOQ was 0.02 mg/kg.

All banana pulp samples had residues < 0.005 mg/kg, except for the Philippines trial, where < 0.02 mg/kg was reported. Similarly, all peel samples were < 0.005 mg/kg, except for the Martinique trial which reported detectable cadusafos levels in peel samples harvested at several PHIs, including a maximum level of 0.022 mg/kg at a 0-day PHI following a single application of 6 g ai/plant; and one trial from Costa Rica where a two peel samples had cadusafos residues at 0.005 mg/kg.

Based on the submitted trials reflecting the GAP, the Meeting estimated a maximum residue level for cadusafos in banana of 0.01 mg/kg to confirm the previous recommendation of 0.01 mg/kg, an STMR of 0.005 mg/kg and an HR of 0.005 mg/kg.

The recommendations are supported by monitoring data results from the USDA's Pesticide Data Programme (PDP), which reported no detects in 1393 samples analysed in the years 2001 and 2002, when the LOQ ranged from 0.005 – 0.025 mg/kg, and no detects in 532 samples analysed in the years 2006 and 2007, when the LOQ was 0.005 mg/kg.

Potato

The Meeting received results from supervised trials with cadusafos used on potato in Brazil, Mexico (3), Spain (3), and Greece (2).

The GAP of Brazil for potato specifies 3 kg ai/ha, 1 application, with a 90-day PHI. One trial in Brazil was conducted at the GAP, including a double rate treatment. Cadusafos residues were < 0.02 mg/kg in both cases.

The GAP of Mexico for potatoes specifies 5 kg ai/ha, 1 application, and a 144-day PHI. Two trials in Mexico were conducted at the GAP rate; a third trial conducted in Mexico reported a PHI of 193 days and, therefore, was not according to GAP. There were two trials conducted in Spain at a double rate. A third Spanish trial reported a residue level of 0.03 mg/kg; however, the PHI was only 88 days in this trial. As no GAP was submitted from Spain or Greece, trials conducted in those countries were not considered further for maximum residue level estimations. At the Mexico GAP, cadusafos residues were: < 0.005 and 0.008 mg/kg.

The Meeting determined that insufficient residue data were available to estimate a maximum residue level for potato. The Meeting therefore agreed to withdraw its previous maximum residue level recommendation of 0.02 mg/kg for potato.

Fate of residues during processing

The Meeting received processing studies for potato. The residue definition recommended for plant commodities will suffice for processed plant commodities (parent only).

The processing (or transfer) factors derived from the processing studies are summarized in the table below. The factors are the ratio of the total residue in the processed commodity divided by the total residue in the raw agricultural commodity (RAC).

Processing (Transfer) factors from the processing of raw agricultural commodities (RACs) with field-incurred residues from foliar treatment with cadusafos

RAC	Processed Commodity	Processing Factor [a]
Potato	Peel [b]	0.6, 0.33, 0.5 Mean: 0.48
	Peeled potato [c]	< 0.5,< 0.2,< 0.33, < 0.25 Mean: < 0.2
	Boiled potato [d]	< 0.5,< 0.2,< 0.33, < 0.25 Mean: < 0. 2

[a] Each value represents a separate study. The processing factor is the ratio of the total residue in the processed item divided by the total residue in the RAC.

[b] Peels were from boiled potatoes. In one trial with raw peels, a PF of 7.5 was determined.

[c] Potato with no peel after boiling.

[d] Boiled potato with peel.

No maximum residue level recommendations were appropriate for processed potato commodities.

Estimated maximum and mean dietary burdens of farm animals

There are no cattle or poultry feed items resulting from the RACs for which the 2010 Meeting made maximum residue level recommendations, and hence, no need to calculated dietary burden levels for farm animals.

Animal commodity maximum residue levels

A bovine feeding study was not provided. However, there are no cattle feed items resulting from the RACs for which the 2010 Meeting made maximum residue level recommendations, and hence, no need to recommend maximum residue levels for ruminant commodities.

A poultry feeding study was not provided. However, as there are no poultry feed items resulting from the RACs which the 2010 Meeting evaluated, recommendations for maximum residue levels for poultry commodities were unnecessary.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of cadusafos has resulted in recommendations for MRLs and STMRs for bananas. Bananas were included at the appropriate level in the dietary intake calculations. The International Estimated Daily Intakes (IEDI) for the 13 GEMS/Food regional diets, based on the banana STMR were in the range 0–1% of the maximum ADI of 0.0005 mg/kg bw.

The Meeting concluded that the long-term intake of residues of cadusafos from its use on bananas was unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intake (IESTI) for cadusafos was calculated for bananas. The short term intake of bananas represented 20% of the ARfD of 0.001 mg/kg bw for the general population, and 40% of the ARfD of 0.001 mg/kg bw for children $\leq$ 6 years. Accordingly, the Meeting concluded that the short-term intake of residues of cadusafos from its use on bananas was unlikely to present a public health concern.

5.5 CHLORANTRANILIPROLE (230)

RESIDUE AND ANALYTICAL ASPECTS

Chlorantraniliprole is a novel insecticide belonging to the class of selective ryanodine receptor agonists and was evaluated for the first time by JMPR in 2008 for toxicology and residues. The compound was listed for additional residue assessment by 2010 JMPR at the Forty-first Session of the CCPR.

The Meeting received information on chlorantraniliprole methods of residue analysis, national registered use patterns, supervised residue trials and fate of residues in processing.

The 2008 JMPR established an ADI and ARfD for chlorantraniliprole of 0–2 mg/kg bw/day and "not required" respectively.

Methods of analysis

A range of analytical methods have been reported for the analysis of chlorantraniliprole in plant and animal commodities. The basic approach employs extraction by homogenisation with acetonitrile:water, and column clean-up using solid phase extraction (hydrophilic-lipophilic balanced polymeric (HLB) and strong anion exchange (SAX) in sequence). Residues are determined by gas chromatography with an electron capture detector or liquid chromatography with mass spectrometric detection. The methods for chlorantraniliprole have been extensively validated with numerous recoveries on a wide range of substrates with LOQs of 0.01 mg/kg.

Results of supervised trials on crops

Supervised trials were available for the use of chlorantraniliprole on numerous crops: citrus (oranges, mandarins and tangelos), blackberries, raspberries, strawberries, Brassica vegetables (broccoli, cabbage and cauliflower), legume vegetables, sweet corn, maize, root and tuber vegetables (Japanese radish and turnips), soybeans, sugarcane, alfalfa and mint.

Residue trial data was made available from Brazil, Canada, member states of the European Union, Japan, The Philippines and the USA. Additionally for some crops residue trial data reported by the 2008 JMPR from Australia, New Zealand and member states of the European Union were not evaluated at that time as GAP was not available. These data are re-evaluated here where new GAP information has become available and the data would lead to a revised maximum residue level recommendation.

The NAFTA calculator was used as a tool in the estimation of the maximum residue level 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 using expert judgement. Then, the NAFTA calculator was employed. If the statistical spreadsheet suggested a different value from that recommended by the JMPR, a brief explanation of the deviation was provided. Some common factors that may lead to rejection of the statistical estimate include those situations where the number of data points is less than 15 or where there are too many values below LOQ.

Additionally the Meeting has utilised a new tool that can provide additional useful information for estimating maximum residue levels. The tool is based on a compilation of residues in various crops following a single spray application where the data were normalised to an application rate of 1 kg ai/ha or 1 kg ai/hL (General Consideration Item 2.8). Estimates of high residues can be made for certain pesticides by combining the database of normalised day 0 residues with simple equations for decline. Chlorantraniliprole is a suitable candidate for using the approach to inform expert judgement.

Citrus fruits

Data for citrus with corresponding GAP information were available from supervised trials conducted in Brazil and the Republic of South Africa.

In Brazil chlorantraniliprole is permitted to be used on citrus with a maximum of one soil application at the equivalent of 240 g ai/ha and two foliar sprays at a spray concentration of 3 g ai/hL and a PHI of 5 days. Residues of chlorantraniliprole in citrus from four trials in Brazil approximating GAP were: 0.09, 0.09, 0.13 and 0.15 mg/kg.

In South Africa chlorantraniliprole is permitted to be used on citrus with a maximum of two foliar sprays at a spray concentration of 3.5 g ai/hL and a PHI of 7 days. Eight trials complied with GAP of South Africa with residues in whole fruit of 0.14, 0.15, 0.18, 0.22, 0.22, 0.25, 0.27 and 0.35 mg/kg. Residues in the edible portion (flesh) were 0.05, 0.05, 0.06, 0.07, 0.07, 0.08, 0.09 and 0.11 mg/kg. In peel residues were: 0.44, 0.49, 0.58, 0.62, 0.74, 0.78, 0.81 and 1.1 mg/kg.

The Meeting noted that the use patterns for citrus in Brazil and the Republic of South Africa were different and decided to use the data from South Africa for the purposes of estimating a maximum residue level and STMR and to make a recommendation for citrus fruit.

Residues in whole fruit in ranked order (n = 8) were: 0.14, 0.15, 0.18, 0.22, 0.22, 0.25, 0.27 and 0.35 mg/kg. The median residue in the edible portion was 0.07 mg/kg.

The Meeting estimated a maximum residue level for whole fruit and an STMR for the edible portion for chlorantraniliprole in citrus of 0.5 and 0.07 mg/kg respectively. Use of the NAFTA calculator yielded a value of 0.44 mg/kg while a day 0 decline model[29] yielded 0.35 mg/kg.

Berries and other small fruit

Data were available from supervised trials on raspberries and blackberries (dewberries) in Canada and the USA and strawberries in Japan.

The GAPs of Canada and the USA are similar and the GAP of the USA was used to evaluate trials on raspberries and blackberries from the two countries (USA GAP: 110 g ai/ha, PHI 3 days with a maximum seasonal application of 225 g ai/ha).

Residues of chlorantraniliprole in berries from eight trials in Canada and the USA complying with GAP of the USA were: 0.049, 0.091, 0.095, 0.235, 0.436, 0.481, 0.482 and 0.513 mg/kg.

Residues of chlorantraniliprole in strawberries from two trials in Japan complying with GAP (2.5 g ai/100L and PHI 1 day) were 0.23 and 0.30 mg/kg.

The Meeting noted that there are registrations for chlorantraniliprole in caneberries, cranberries, strawberries and grapes and that as these commodities constitute the majority of members of the commodity group berries and small fruit, it would be preferable to estimate a group maximum residue level. Using 17 trials matching GAP of the USA, the 2008 JMPR estimated a maximum residue level of 1 mg/kg for grapes and an STMR and HR of 0.119 and 0.52 mg/kg respectively. The Meeting agreed to recommend a group maximum residue level for berries and other small fruit of 1 mg/kg based on the trials in grapes and an STMR of 0.336 mg/kg based on trials on raspberries and blackberries. The recommendation for the commodity group berries and other small fruit replaces the previous recommendation of 1 mg/kg for grapes.

[29] Maclachlan DJ, Hamilton D. 2010 A new tool for the evaluation of crop residue trial data (day zero-plus decline). Food Additives & Contaminants: Part A,, 27:347–364

Brassica vegetables

New data were available from supervised trials on brassica vegetables conducted in Europe. Additionally new GAP has become available from Australia allowing residue trials reported by the 2008 JMPR to be evaluated against that countries GAP.

Residues in trials from Australian and New Zealand complying with the GAP of Australia (40 g ai/ha and PHI 7 days) were: broccoli 0.07, 0.12, 0.22 and 0.27 mg/kg; cauliflower 0.23 mg/kg; cabbage < 0.01, 0.08, 0.13, 0.17 and 0.20 mg/kg and Brussels sprouts 0.20 and 0.28 mg/kg.

In trials from Europe on brassica vegetables complying with the GAP of Spain (35 g ai/ha and PHI 1 day) residues were: cabbage < 0.01 (10), 0.095, 0.011, 0.012, 0.012, 0.015, 0.018, 0.04, 0.059 and 0.10 mg/kg.

Residues on broccoli were 0.064, 0.10, 0.10, 0.12, 0.14, 0.19 and 0.37 mg/kg, and on cauliflower residues were < 0.01, < 0.01, 0.012, 0.019, 0.036, 0.047 and 0.082 mg/kg.

Chlorantraniliprole is registered in the Canada for use on Brassica vegetables at 100 g ai/ha, PHI of 3 days and a maximum application per season of 2 g ai/ha. Trials were available from Canada and the USA (reported by the 2008 JMPR) in which crops were treated twice at three day intervals at 112 g ai/ha with harvest 3 days after the last spray. Residues on broccoli (n = 9) complying with the revised Canada GAP were: 0.12, 0.30, 0.32, 0.32, 0.35, 0.38, 0.40, 0.41 and 0.56 mg/kg.

Residues on cabbage (n = 10) complying with Canada GAP were: 0.033, 0.066, 0.10, 0.28, 0.29, 0.48, 0.51, 0.64, 0.75 and 1.1 mg/kg.

The Meeting noted that the registered use of chlorantraniliprole in Canada is for Brassica vegetables and decided to recommend a group MRL. Residues were highest in the cabbages and this dataset was used for the purposes of estimating a maximum residue level for the group. The Meeting estimated a maximum residue level and an STMR value for chlorantraniliprole in Brassica vegetables of 2 and 0.385 mg/kg, respectively. Use of the NAFTA calculator yielded a value of 2.45 mg/kg as an estimate of high residues while use of the day 0 plus decline approach[30] (median DT_{50} of 7 days) yielded 2.0 mg/kg.

Sweet corn

Chlorantraniliprole is registered in the US on sweet corn at 73 g ai/ha with a maximum seasonal rate of 225 g ai/ha and a PHI of 1 day. The minimum retreatment interval is 1 day.

Residues on sweet corn in 14 trials conducted in Canada and the USA at an exaggerated application rate (4 × 112 g ai/ha) were all < 0.01 (14) mg/kg. Although the intervals between the sprays were longer than the minimum specified on the approved USA labels, the Meeting considered the data to adequately reflect the residues in kernels and cobs with husk removed.

Trials were also available from Europe that approximated the GAP of Hungary (30 g ai/ha, last application at BBCH 87 and PHI determined by last application growth stage). Residues in 10 trials approximating GAP of Hungary were < 0.01 (10) mg/kg for kernels and cobs with husks removed.

The Meeting estimated maximum residue levels and STMR values for chlorantraniliprole in sweet corn (corn-on-the-cob) of 0.01* and 0.01 mg/kg respectively.

Legume vegetables

Residues trials conducted on green beans were made available from European countries however, chlorantraniliprole does not have a registered use on green beans in this region and the trials are not evaluated further.

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[30] ibid.

Residues in two trials from Japan on green soya beans (seed + pod) and complying with the GAP of that country (1.25 g ai/100 L and PHI 3 days) were 0.15 and 0.32 mg/kg.

In a single trial from the Philippines on pole beans matching the GAP of that country (37.5 g ai/ha and PHI 1 day) residues were 0.145 mg/kg.

The Meeting decided the number of trials was inadequate to estimate a maximum residue level for the legume vegetables pole beans and immature soya beans.

Soya beans (dry)

Trials on soya beans were reported from Brazil (GAP: 2 × 10 g ai/ha, at 14 day intervals and PHI of 21 days).

Chlorantraniliprole residues in soya bean grain from four trials from Brazil matching GAP in rank order (median underlined) were: 0.10, 0.11, 0.11 and 0.12 mg/kg.

Two trials were available from Japan complying with GAP (3 × 1.25 g ai/hL, at 7 day intervals and PHI of 7 days) from that country had residues in grain of < 0.01 and 0.03 mg/kg.

The Meeting decided that the number of trials available was not adequate to enable a recommendation of a maximum residue level for soya beans (dry).

Root and tuber vegetables

Trials on Japanese radish and turnips were reported from Japan however no GAP was available and the data were not evaluated further.

Maize

Trials on maize were reported from the USA (GAP: 73 g ai/ha, PHI of 14 days and a maximum application per season of 225 g ai/ha).

Chlorantraniliprole residues in twenty one trials from the USA approximating GAP in ranked order were: < 0.01 (20) and 0.013 mg/kg.

The Meeting noted that the residues in maize are adequately covered by the existing recommendation of the 2008 Meeting for cereal grains of 0.02 mg/kg.

Sugar cane

Trials on sugar cane were reported from Brazil (GAP: one soil application at 158 g ai/ha and one foliar application at 21 g ai/ha and PHI of 60 days).

Chlorantraniliprole residues in four trials from Brazil matching GAP in rank order were: 0.09, 0.13, 0.16 and 0.16 mg/kg.

No data were available on processing of cane into sugar products, e.g., molasses, bagasse or refined sugar.

The Meeting estimated a maximum residue level and an STMR value for chlorantraniliprole in sugar cane of 0.5 and 0.145 mg/kg, respectively.

Tree nuts

Trials were available to the 2008 JMPR from the USA on residues of chlorantraniliprole in almonds and pecans but could not be evaluated as no relevant GAP existed at the time of evaluation. GAP has since then become available.

Chlorantraniliprole residues in six trials on almonds from the USA approximating GAP (application at 110 g ai/ha, seasonal maximum 220 g ai/ha, interval 7 days and PHI 10 days) were < 0.01 (6) mg/kg.

Chlorantraniliprole residues in six trials on pecans from the USA approximating GAP (4 × 110 g ai/ha, interval 7 days and PHI 10 days) in rank order were: < 0.01 (4), 0.014 and 0.015 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for chlorantraniliprole in tree nuts of 0.02 and 0.01 mg/kg respectively.

Mint

Chlorantraniliprole field trials on mint were made available to the Meeting from the USA (GAP: 73 g ai/ha, PHI of 3 days and a maximum application per season of 225 g ai/ha).

Chlorantraniliprole residues on mint were 2.2, 4.6, 4.6, 5.3 and 5.7 mg/kg (fresh weight basis). The Meeting estimated maximum residue level and STMR values for chlorantraniliprole in mint tops of 15 and 4.6 mg/kg (fresh weight basis). The NAFTA calculator suggested a high residue of 9.0 mg/kg (mean + 3sd).

Animal feedstuffs

Alfalfa

Chlorantraniliprole field trials on alfalfa were made available to the Meeting from the USA (GAP: 73 g ai/ha, one application/cutting, PHI of 0 days and a maximum application per season of 224 g ai/ha).

Trials were available where alfalfa was treated at 1.5 × the maximum rate. The present Meeting considered the proportionality of residue data with application rates and decided that proportionality could be used in certain circumstances in the estimation of maximum residue levels (General Consideration Item 2.6). Considering the evidence that residues scale with application rate for foliar sprays, the Meeting decided to use alfalfa as an initial example and to make use scaling in estimating maximum residue levels and levels for use in estimation of farm animal dietary burdens. Chlorantraniliprole residues on alfalfa forage treated at 1.5 × the maximum rate were 2.0, 2.1, 3.0, 3.0, 3.2, 3.7, 4.1, 4.6, 4.8, 5.2, 5.3, 5.4, 5.7, 5.7, 5.7, 5.9, 5.9, 6.2, 6.2, 6.3, 6.7, 6.8, 6.9, 6.9, 7.5, 7.6, 7.6, 7.8, 8.3 and 11 mg/kg (fresh weight basis). When corrected for reported moisture contents the residues were 9.5, 9.7, 11, 13, 14, 16, 19, 19, 20, 23, 23, 23, 24, 24, 25, 26, 26, 27, 29, 29, 30, 30, 31, 32, 33, 34, 34, 36, 42 and 43 mg/kg (dry weight basis). The residues scaled to the same application rate as GAP were calculated by dividing by 1.5 and are (n = 30): 6.3, 6.5, 7.3, 8.7, 9.3, 10.7, 12.7, 12.7, 13.3, 15.3, 15.3, 15.3, 16, 16, 16.7, 17.3, 17.3, 18, 19.3, 19.3, 20, 20, 20.7, 21.3, 22, 22.7, 22.7, 24, 28 and 28.7 mg/kg. Using the data scaled for application rate, the Meeting estimated an STMR value for chlorantraniliprole in alfalfa forage of 17 mg/kg (dry weight basis).

Chlorantraniliprole residues on alfalfa hay treated at 1.5 × the maximum rate were: 8.6, 9.9, 11, 11, 12, 15, 15, 15, 15, 18, 18, 18, 19, 19, 20, 20, 22, 22, 23, 23, 23, 25, 27, 27, 28, 29, 29, 32, 39 and 46 mg/kg (fresh weight basis). When corrected for reported moisture contents the residues were 9.6, 13, 13, 13, 17, 19, 22, 22, 23, 23, 24, 25, 25, 26, 26, 26, 27, 27, 27, 28, 31, 32, 32, 35, 38, 39, 40, 49, 56 and 57 mg/kg (dry weight basis). The residues scaled to the same application rate as GAP were calculated by dividing by 1.5 and are (n = 30): 6.4, 8.7, 8.7, 8.7, 11.3, 12.7, 14.7, 14.7, 15.3, 15.3, 16, 16.7, 16.7, 17.3, 17.3, 17.3, 18, 18, 18, 18.7, 20.7, 21.3, 21.3, 23.3, 25.3, 26, 26.7, 32.7, 37.3 and 38 mg/kg.

Using the data scaled for application rate, the Meeting estimated MRL and STMR values for chlorantraniliprole in alfalfa hay of 50 and 17.3 mg/kg (dry weight basis) respectively. Use of the NAFTA calculator yielded a value of 44 mg/kg (95 LnUCL) as an estimate of high residues.

Maize forage and fodder

Chlorantraniliprole field trials on corn forage and fodder were made available to the Meeting from the USA (GAP: 73 g ai/ha, a maximum application per season of 225 g ai/ha, PHI of 14 days for maize and 1 day for sweet corn).

Chlorantraniliprole residues on maize and corn forage (PHI 1 day, including sweet corn) were 0.30, 0.77, 1.0, 1.3, 1.5, 1.9, 2.0, 2.1, 2.4, 2.4, 2.7, 2.8, 2.9, 3.0, 3.7, 5.0, 5.1 and 5.7 mg/kg (fresh weight basis). Chlorantraniliprole residues on maize and corn fodder (PHI 14 days) were 0.26, 0.69, 0.82, 1.7, 2.1, 2.1, 2.2, 2.4, 2.8, 3.1, 3.1, 3.6, 3.7, 3.8, 4.0, 4.5, 5.3, 5.4, 7.1, 7.7 and 12 mg/kg (fresh weight basis).

Residues in trials from the USA were used to recommend STMRs for chlorantraniliprole in maize forage and fodder of 2.4 and 3.1 mg/kg (fresh weight basis) respectively and high residues of 5.7 and 12 mg/kg respectively. The Meeting also estimated a maximum residue level for chlorantraniliprole in maize fodder of 25 mg/kg (dry weight basis and assuming 83% dry matter content). Use of the NAFTA calculator yielded a value of 25.5 mg/kg (99 Ln) as an estimate of high residues.

Almond hulls

Chlorantraniliprole residues in almond hulls from six trials on almonds from the USA GAP (4 × 110 g ai/ha, interval 7 days and PHI 10 days) in rank order were (median underlined): 0.38, 0.52, 0.59, 0.88, 1.1 and 1.6 mg/kg (fresh weight basis). The Meeting estimated an STMR value for chlorantraniliprole in almond hulls of 0.735 mg/kg.

Fate of residues during processing

The fate of chlorantraniliprole residues has been examined in cabbages, oranges and mint processing studies. Estimated processing factors and STMRs are summarised below.

Summary of processing factors for chlorantraniliprole residues

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors	PF (Mean, median or best estimate)	RAC-STMR (mg/kg)	Estimated processed commodity = residue RAC-STMR × PF (mg/kg)
Cabbage	Cooked	< 0.17, < 0.25, < 0.56, < 1	< 0.405	0.35	0.14175
	Sauerkraut	< 0.17, < 0.25, <0.56, <1	< 0.405		0.14175
Orange	Juice	0.08, < 0.11, < 0.11, 0.11, 0.11, 0.11, 0.13, 0.15, 0.15, < 0.17, 0.17, 0.20, 0.22, < 0.25, 0.25, 0.25, 0.29, 0.29, 0.30, 0.38	0.17	0.22	0.037
Mint	Oil	< 0.002, < 0.002	<0.002	4.6	0.0092

Chlorantraniliprole did not concentrate in any of the processed commodities studies. As the estimated residues for the processed commodities in the table above are below the maximum residue levels proposed for the raw agricultural commodities, the Meeting decided it was not necessary to make recommendations for maximum residue levels for these processed commodities. The STMR values listed above may be used for the purposes of dietary risk assessment.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of chlorantraniliprole in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual 2009 (Maximum proportion of agricultural commodities in animal feed). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the animal diets from the USA-Canada (US/CAN), EU and Australia in the Maximum proportion of agricultural commodities in animal feed table (Appendix IX of the FAO Manual 2009).

Animal dietary burden, chlorantraniliprole, ppm of dry matter diet					
		US/CAN	EU	Australia	Japan
Beef cattle	max	8.6	24.4	36.1[a]	3.8
	mean	3.7	13.7	17.2[c]	1.7
Dairy cattle	max	14.2	23.8	28.6[b]	16.6
	mean	6.3	10.5	12.8[d]	7.3
Poultry—broiler	max	0.0117	0.007	0.007	1.4
	mean	0.012	0.007	0.007	0.85
Poultry—layer	max	0.012	1.8[e]	0.007	-
	mean	0.012	0.735[f]	0.007	-

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

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

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

[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 chlorantraniliprole dietary burdens for animal commodity MRL and STMR estimation (residue levels in animal feeds expressed on dry weight) are: beef cattle 36.1 and 17.2 ppm, dairy cattle 28.6 and 12.8 ppm, poultry (broilers) 1.8 and 0.85 ppm and poultry (layers) 1.8 and 0.735 ppm.

Animal commodity maximum residue levels

The maximum dietary burden for beef and dairy cattle is 36.1 and 28.6 ppm respectively, so the levels of residues in tissues can be obtained by interpolation between the high residues obtained in tissues and at the 10 and 50 ppm feeding levels. Maximum residues expected in tissues are: fat 0.114 mg/kg, muscle 0.022 mg/kg, liver 0.0989 mg/kg, kidney 0.065 mg/kg and the mean residue for milk 0.013 mg/kg. At the 50 ppm dose level, average residues of chlorantraniliprole were 0.108 mg/kg in cream and 0.027 mg/kg in whole milk. The 2008 JMPR reported that expected residues in cream are 4 × the residues in whole milk or 4 × 0.013 = 0.052 mg/kg. The fat content of cream is 40–60% and the Meeting estimated the mean residue for milk fat to be 2 × the estimated mean cream residue or 2 × 0.052 = 0.104 mg/kg.

The Meeting estimated maximum residue levels for meat (from mammals other than marine mammals) 0.2 mg/kg (fat); edible offal (mammalian) 0.2 mg/kg, milks 0.05 mg/kg and 0.2 mg/kg for milk fat to replace the previous recommendations of 0.01* (fat), 0.01*, 0.01* and 0.1 mg/kg respectively.

The STMR dietary burdens for beef and dairy cattle are 17.2 and 12.8 ppm respectively. Residues in tissues can be obtained by interpolation between the mean residues obtained in tissues at the 10 and 50 ppm feeding levels. The estimated STMRs are: meat (from mammals other than marine mammals) 0.009 mg/kg, fat (from mammals other than marine mammals) 0.049 mg/kg, kidney of cattle, goats, pigs and sheep 0.030 mg/kg, liver of cattle, goats, pigs and sheep 0.047 mg/kg, milks 0.006 mg/kg and milk fat 0.048 mg/kg.

The highest individual tissue residue from the relevant feeding group was used in conjunction with the highest residue dietary burden to calculate the likely highest animal commodity residue level.

Dietary burden (mg/kg)[a] Feeding level [ppm][b]		Chlorantraniliprole residues, mg/kg [c]								
		Milk	Fat		Muscle		Liver		Kidney	
		Mean	High	mean	High	mean	high	mean	High	mean
MRL beef	(36.1) [50, 10] high		(0.114) 0.156		(0.022) 0.029		(0.099) 0.133		(0.065) 0.081	
MRL dairy	(28.6) [50, 10] high	(0.013) 0.022								
STMR beef	(17.2) [50, 10] av			(0.049) 0.14		(0.009) 0.019		(0.047) 0.13		(0.030) 0.068
STMR dairy	(12.8) [50, 10] av	(0.006) 0.022								

[a] Values in parentheses are the estimated dietary burdens

[b] Values in square brackets are the actual feeding levels in the transfer study

[c] Residue values in parentheses in italics are interpolated from the dietary burden, feeding levels in the transfer study and the residues found in the transfer study. High is the highest individual animal tissue residue in the relevant feeding group.

Mean is mean animal tissue (or milk) residue in the relevant feeding group.

The maximum dietary burden for poultry is 1.8 ppm. Maximum residues expected at 23 hours after last feeding are: muscle, skin/fat, liver and eggs are 0.00014, 0.0017, 0.0035 and 0.056 mg/kg.

The Meeting estimated maximum residue levels for poultry meat 0.01* mg/kg (fat); poultry offal 0.01* and eggs 0.1 mg/kg to replace the previous recommendations of 0.01* (fat), 0.01* and 0.01* mg/kg respectively.

The mean dietary burden for poultry is 0.85 ppm for tissues and 0.735 ppm for eggs. STMRs for poultry meat, skin/fat, edible offal and eggs are 0.00007, 0.0008, 0.0016 and 0.023 mg/kg respectively.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of chlorantraniliprole has resulted in recommendations for MRLs and STMRs for raw and processed commodities. Consumption data were available for 31 food commodities and were used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes for the 13 GEMS/Food regional diets, based on estimated STMRs were 0% (0.1–0.4%) of the maximum ADI of 2 mg/kg bw. The Meeting concluded that the long-term intake of residues of chlorantraniliprole from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The 2008 JMPR decided that an ARfD was unnecessary. The Meeting therefore concluded that the short-term intake of chlorantraniliprole residues is unlikely to present a public health concern.

5.6 CHLOROTHALONIL (081) AND METABOLITES R611965 AND SDS-3701

TOXICOLOGY

R611965 (3-carbamyl-2,4,5-trichlorobenzoic acid, formerly known as SDS-46851) is a chlorothalonil metabolite that is formed in the soil and taken up through the roots by crops. The present Meeting evaluated R611965 for the first time.

Chlorothalonil (Chemical Abstracts Service [CAS] No. 1897-45-6) and SDS-3701, a chlorothalonil metabolite that is found in plants, soil and ruminants, were last evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 2009.

The present Meeting evaluated the newly submitted studies on R611965 at the request of the 2009 JMPR, to address the toxicological relevance of this soil degradation product.

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

Biochemical aspects

Following a single oral dose of R611965 at 10 or 1000 mg/kg body weight (bw) in rats, at least 16–27% is absorbed (based on urinary excretion within 48–96 h). Excretion is rapid, with 90% being excreted within 48–96 h, predominantly in faeces (68–77% of the dose). Biliary excretion was not assessed. Seven days after administration, less than 0.3% of the administered dose was found in tissues and carcass; highest levels were observed in liver. No obvious sex differences in kinetics were observed.

Toxicological data

The acute oral toxicity of R611965 in rats is low (median lethal dose [LD_{50}] > 5000 mg/kg bw). No data on acute dermal or inhalation toxicity, eye or skin irritation or skin sensitization were available.

Repeated-dose toxicity studies showed that R611965 had low oral toxicity in mice, rats and dogs. The overall no-observed-adverse-effect level (NOAEL) in short-term (28 and 90 days) and chronic studies (18 months) in mice was 1022 mg/kg bw per day, the highest dose tested in an 18-month carcinogenicity study. In rats, the overall NOAEL in short-term (14, 30 and 90 days) and chronic studies (2 years) was 200 mg/kg bw per day, based on bilateral retinal atrophy observed at 500 mg/kg bw per day in a 2-year combined chronic toxicity and carcinogenicity study.

In a 90-day study in dogs, the NOAEL was 50 mg/kg bw per day, based on reduced body weight gain and watery stools in both sexes at 500 mg/kg bw per day.

In an 18-month study in mice and a 2-year study in rats, no carcinogenic effects of R611965 were observed. The Meeting concluded that R611965 is not carcinogenic in rodents.

R611965 was tested in an adequate range of studies of genotoxicity in vitro and in vivo. There was no evidence for genotoxicity. The Meeting concluded that R611965 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 R611965 is unlikely to pose a carcinogenic risk to humans.

In one-generation and two-generation studies of reproductive toxicity with R611965 in rats, the overall NOAEL for parental, reproductive and offspring toxicity was 20 000 ppm, equal to 911 mg/kg bw per day, the highest dose tested.

In a study of developmental toxicity in rats, the NOAEL for maternal and developmental toxicity was 2000 mg/kg bw per day, the highest dose tested. In a study of developmental toxicity in rabbits, a NOAEL for maternal toxicity could not be determined. The lowest-observed-adverse-effect

level (LOAEL) for maternal toxicity was 250 mg/kg bw per day, the lowest dose tested, on the basis of abortions, clinical signs (increased incidences of few or no faeces, soft faeces, anorexia and thinness) and slightly reduced body weight gain. The NOAEL for fetal toxicity was 500 mg/kg bw per day, based on a decreased number of live fetuses and decreased fetal weight observed at 1000 mg/kg bw per day.

No neurotoxicity studies with R611965 were available. In acute and repeated-dose oral studies in mice, rats, rabbits and dogs in which R611965 was administered in the diet, by gavage or by capsule, no neurotoxic signs were observed.

No data on R611965 in humans were provided.

The Meeting concluded that the existing database on R611965 was sufficient to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting noted that the soil metabolite R611965 is considerably less toxic than the parent compound chlorothalonil (e.g., NOAELs of 200 versus 1.8 mg/kg bw per day in 2-year rat studies, respectively). R611965 is not acutely toxic by the oral route. The metabolite induced adverse effects in only a few repeated-dose oral toxicity studies in rats and dogs, at levels of 250–500 mg/kg bw per day. In the majority of the repeated-dose studies in rodents, no effects were observed at doses of 911–2000 mg/kg bw per day.

In view of the lower toxicity of the metabolite R611965 in comparison with the parent compound chlorothalonil (acceptable daily intake [ADI] = 0–0.02 mg/kg bw; acute reference dose [ARfD] = 0.6 mg/kg bw), the Meeting considered it unnecessary to derive a separate ADI and ARfD for this metabolite, for risk management purposes.

An addendum to the toxicological monograph was prepared.

Levels relevant for risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of carcinogenicity	Carcinogenicity	1022 mg/kg bw per day[a]	—
Rat	Two-year study of toxicity and carcinogenicity[b]	Toxicity	200 mg/kg bw per day	500 mg/kg bw per day
		Carcinogenicity	1000 mg/kg bw per day[a]	—
	One- and two-generation studies of reproductive toxicity[b]	Parental toxicity	20 000 ppm, equal to 911 mg/kg bw per day[a]	—
		Offspring toxicity	20 000 ppm, equal to 911 mg/kg bw per day[a]	—
		Reproductive toxicity	20 000 ppm, equal to 911 mg/kg bw per day[a]	—
	Developmental toxicity[c]	Maternal toxicity	2000 mg/kg bw per day[a]	—
		Fetotoxicity	2000 mg/kg bw per day[a]	—
Rabbit	Developmental toxicity[c]	Maternal toxicity	—	250 mg/kg bw per day[d]
		Fetotoxicity	500 mg/kg bw per day	1000 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
Dog	Ninety-day study [e]	Toxicity	50 mg/kg bw per day	500 mg/kg bw per day

[a] Highest dose tested.

[b] Dietary administration.

[c] Gavage administration.

[d] Lowest dose tested.

[e] Capsule administration.

Estimate of acceptable daily intake for humans

Unnecessary

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 exposures in humans

Critical end-points for setting guidance values for exposure to chlorothalonil metabolite R611965

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of absorption	Rapid; at least 16–27% at 10 and 1000 mg/kg bw (rat)
Distribution	Highest concentration in liver (rat)
Potential for accumulation	Low (rat)
Rate and extent of excretion	90% excretion within 48–96 h (rat)
Metabolism in animals	No data
Toxicologically significant compounds (in animals, plants and the environment)	R611965
Acute toxicity	
LD_{50}, oral, rat	> 5000 mg/kg bw
LD_{50}, dermal, rat	No data
LC_{50}, inhalation, rat	No data
Dermal irritation	No data
Ocular irritation	No data
Dermal sensitization	No data
Short-term studies of toxicity	
Target/critical effect	Body weight, clinical signs (dog)
Lowest relevant oral NOAEL	50 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Bilateral retinal atrophy (rat)

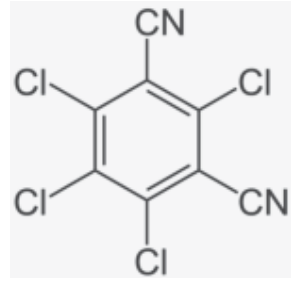
Lowest relevant NOAEL	200 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects (rats)
Lowest relevant reproductive NOAEL	20 000 ppm, equal to 911 mg/kg bw per day, highest dose tested (rats)
Developmental target	Decreased number of live fetuses, decreased fetal weight in the presence of maternal toxicity (rabbits); not teratogenic
Lowest relevant developmental NOAEL	500 mg/kg bw per day (rabbits)
Neurotoxicity/delayed neurotoxicity	
Neurotoxicity	No data; no indication of neurotoxic potential in acute and repeated-dose oral studies
Medical data	
	No data

RESIDUE AND ANALYTICAL ASPECTS

Chlorothalonil is a non-systemic fungicide first evaluated by JMPR in 1974 and a number of times subsequently. It was recently reviewed for toxicology by the 2009 JMPR within the periodic review programme of the CCPR. For the parent substance an ADI of 0–0.02 mg/kg bw and an ARfD of 0.6 mg/kg bw were established. In addition to the parent substance an ADI of 0–0.008 mg/kg bw and an ARfD of 0.03 mg/kg bw were established for the metabolite SDS-3701. In the 2010 JMPR chlorothalonil was scheduled for periodic review for residues. The 2010 JMPR evaluated newly submitted studies on the metabolite R611965 at the request of the 2009 JMPR to address the toxicological relevance of this soil degradation product.

CCPR, at its Forty-first Session in 2009, noted that one manufacturer would submit residue data to JMPR for the consideration by the 2010 JMPR. Additional information on the uses in okra and papaya were submitted by the COLEACP (Comité de Liaison Europe-Afrique-Caraïbes-Pacifique). Information on GAP was also provided by Australia, the Ivory Coast, Japan and the Netherlands.

This evaluation is based on the latest FAO specifications for chlorothalonil, limiting the amount of the impurity hexachlorobenzene (HCB) to a maximum of 0.04 g/kg. There may be implications for HCB in animal commodities, if chlorothalonil were to contain higher levels of this impurity.



The following abbreviations are used for the metabolites discussed below:

chlorothalonil	tetrachloroisophthalonitrile
SDS-3701	2,5,6-trichloro-4-hydroxyisophthalonitrile
R611965	3-carbamyl-2,4,5-trichlorobenzoic acid
R417888	2-carbamyl-3,5,6-trichloro-4-cyanobenzenesulfonic acid
R611966	2,4,5-trichloro-3-cyano benzamide

Animal metabolism

The Meeting received animal metabolism studies with [^{14}C]chlorothalonil and [^{14}C]SDS-3701 in rats, lactating goats and laying hens. In all studies carbon atoms in the ring structure were substituted with ^{14}C. In general the metabolism of chlorothalonil is very limited giving only SDS-3701 as the detectable residue beside the unchanged parent.

In the 2009 Evaluation for toxicology it was reported that "in rats given a single oral dose of chlorothalonil at 1.5–50 mg/kg bw, absorption was about 31%, with 17–21% being excreted in the bile and about 8–12% being excreted in the urine. In rats, the highest tissue concentrations were found in the kidney, probably due to binding to kidney proteins. Chlorothalonil is metabolized via initial glutathione conjugation and subsequent enzymatic processing of the di-and triglutathion substituents via the mercapturic acid and cysteine conjugate β-lyase pathways yielding N-acetyl cysteine, cysteinyl-glycine and S-methyl-derivates."

For lactating goats five animals were dosed with parent [^{14}C]-chlorothalonil at rates of 3 or 30 ppm in the diet over a period of 8 consecutive days. TRR found in muscle and fat were at a comparable level of 0.004 mg/kg for the low dose animals and 0.03–0.038 mg/kg for the high dose animals. In milk TRR levels up to 0.015 mg/kg and 0.19 mg/kg were found for the two dose groups. Highest TRR levels were found in liver and kidney and concentrations equivalent to 0.085 and 0.24 mg/kg, respectively, for the low dose animals and 0.73 to 2.3 mg/kg, respectively, for the high dose animals. The only metabolite identified was SDS-3701 found at 30–58% in milk, 3–6% in liver and 2–3% in kidney of the TRR. Muscle and fat were not further identified. Although no other specific metabolites could be identified, complex mixtures of components were found in the samples with a molecular weight of 46000–54000 Da.

In a comparable study animals were dosed with 0.2 or 2 ppm SDS-3701 for 9 consecutive days. TRR levels found in the various tissues and milk for the low and high does animals were: muscle 0.02/0.13 mg/kg, fat 0.02/0.08 mg/kg, liver 0.07/0.77 mg/kg, kidney 0.26/1.35 mg/kg and milk 0.15/1.0 mg/kg. For all matrices > 90% of the radioactivity could be released and was identified as unchanged SDS-3701.

For laying hens the animals were dosed with [^{14}C]-chlorothalonil at rates of 2, 6 or 20 ppm over 21 consecutive days. In the eggs collected over the length of the study a plateau of the TRR was observed after 13–17 days at a level of 0.035–0.047 mg/kg for the 20 ppm dose group. In all tissues,

except liver, TRR levels were below the LOQ of the LSC method (0.01 mg/kg). In liver TRR levels of 0.098 and 0.05 mg/kg were found for the 6 and 20 ppm dose group, respectively. Further analysis on the composition of radioactivity was not conducted.

A comparable study was conducted using [^{14}C]-SDS-3701 at dose rates of 0.1, 0.3 and 1.0 ppm over 21 consecutive days. In egg white, pectoral muscle, adductor muscle and fat, no TRRs above the LOQ of 0.01 mg/kg were found in any dose group. TRR in cardial muscle were < 0.01 mg/kg for the 0.1 ppm group, 0.55 mg/kg for the 0.3 ppm dose group and 0.15 mg/kg for the 1.0 ppm dose group. TRR in skin gave a single high result for the 1.0 ppm dose group of 37 mg/kg, but no detectable residues for the 0.1 and 0.3 ppm group were found. Egg yolk and liver gave detectable TRRs for all dose groups (0.1, 0.3 and 1.0 ppm) at levels of 0.044, 0.12 and 0.42 mg/kg for egg yolk and 0.056, 0.27 and 0.78 mg/kg for liver, respectively. Further identification of the radioactivity was conducted for egg yolk, revealing that > 80% of the TRR consisted of unchanged SDS-3701.

Plant metabolism

The Meeting received plant metabolism studies with [^{14}C]-chlorothalonil in lettuce, tomatoes, carrots, celery and snap beans. Parent substance labelled in the phenyl-ring was used in all of these studies.

Generally in all matrices, unchanged chlorothalonil was identified as the major residue. The only metabolite identified was SDS-3701, which was present in amounts of < 10% of the TRR in edible parts and up to 12% of the TRR in non-edible parts of the plants. The remaining radioactivity consisted of numerous polar metabolites at individual levels too low for further investigation. Translocation within the plants was very limited.

In a study on lettuce the plants were treated four times at dose rates equivalent to 1.75 kg ai/ha. Lettuce samples were taken after 1, 3, 7, 10, 14 and 21 days. The mean TRRs were 118 mg/kg at PHI 1 day, increasing to 170 mg/kg at PHI 3 days and 158 mg/kg after 21 days. Identification of the radioactivity revealed at least 87% (88–155 mg/kg) of unchanged chlorothalonil in the extract. The only other metabolite identified was SDS-3701, found in amounts of 2% of the TRR (1.5–3.1 mg/kg). Polar water-soluble residue, which did not partition into diethyl ether, accounted for between 4.7 and 7.0% TRR (approximately 5–11 mg/kg).

For tomatoes the metabolism of chlorothalonil was investigated following three applications at rates of 2.3 kg ai/ha each made to plants in growth chambers. Samples of fruit and vines were collected after 1, 7 and 14 days. TRR levels in the fruit declined from 2.6 mg/kg after 1 day to 0.6 mg/kg after 14 days. In vines TRRs stayed relatively stable at levels between 12.7–20.6 mg/kg. Extraction of fruit showed that 56–75% of the total residue was present in the dichloromethane rinse. The major identified component of the total organosoluble fraction was parent chlorothalonil, which accounted for 56–76% and 41–73 % of the total residue in fruit and vines respectively. The metabolite SDS-3701 was identified as a minor component of the organosoluble fractions but represented < 4% of the residue in fruit and a maximum of 8% of the residue in vines.

In a study on carrots, treated three times at rates of 1.6 kg ai/ha each, samples of roots and foliage were collected 1, 7, 14 and 21 days after the final treatment. TRR levels in roots were relatively stable ranging from 0.012 to 0.12 mg/kg. In foliage TRR was measured at 9.7–40.2 mg/kg. In roots collected after 21 days, about 45% of the TRR (0.023 mg/kg) was identified as chlorothalonil. SDS-3701 was found at amounts of 3.9% of the TRR (0.002 mg/kg). In the foliage a large part of the radioactivity remained unextracted (39.1–45.9%). Chlorothalonil levels decreased from 13.7% of the TRR (1.85 mg/kg) down to 4% (0.1 mg/kg). In parallel SDS-3701 residues increased from 3.4% of the TRR (0.49 mg/kg) to 12.1% (0.3 mg/kg) at day 21.

The metabolism of chlorothalonil in celery was investigated using 12 applications of 2.5 kg ai/ha at intervals of 6–8 days. Samples of stalks and foliage were collected 7 and 21 days after the final treatment. Total radioactive residues found in stalks were 0.7 to 4.6 mg/kg. In the foliage much higher TRR levels of 52–263 mg/kg were detected. The only substance identified was unchanged

chlorothalonil at levels of 10–55% of the TRR in the stalks and 42–80% of the TRR in foliage. Unextracted residues were in the range of 21-35% of the TRR for stalks and 8–24% of the TRR for foliage. Further treatment using hydrolytic enzymes and hydrochloric acid released about 30% of the unextracted residues, but further identification was not possible due to a complex mixture of components.

For snap beans, grown outdoor, the metabolism of chlorothalonil was investigated following four, weekly applications, at rates of 2.5 kg ai/ha each. Samples of beans and foliage were collected after 7 and 28 days. The TRRs in the foliage (154 mg/kg at PHI 7 days; 90 mg/kg at PHI 28 days) were higher than those in the edible beans (mean of 1.0 mg/kg at PHI 7 days; 1.8 mg/kg at PHI 28 days). Analysis of the organosoluble fractions by HPLC showed that chlorothalonil was the only significant component in both the bean and foliage samples. Further analyses indicated the probable presence of SDS-3701 and R611965, however levels were too low for definitive identification or quantification (LOQ 0.02 mg/kg and 0.03 mg/kg for SDS-3701 and R611965 respectively).

Environmental fate in soil

The Meeting received information on photolysis on soil, aerobic soil metabolism and residues in rotational crop (confined and field studies).

The photolysis of chlorothalonil and its metabolite SDS-3701 was investigated in two soil types using artificial irradiation. Both substances were stable with more than 97% of the applied radioactivity still being extractable.

Aerobic soil metabolism was investigated in four soils using [^{14}C]-chlorothalonil. The parent compound was found to be degraded quickly with estimated half-life times of less than 1.9 days. Several metabolites could be identified. Primary degradation products were SDS-3701 (6.3–25.3% of the dose), R417888 (5.8–14.1% of the applied dose) and R611965 (2.0–13.2% of the applied dose). Mineralisation after 120 days was relatively low at 6.3–23.8% of the applied dose.

In a confined rotational crop study radio labelled chlorothalonil was applied to soil at a rate equivalent to approx. 12 kg ai/ha. Follow crops (lettuce, carrots and wheat) were planted after 30 or 88 days and grown to the point of commercial harvest. After 30 days TRR levels in lettuce (3.3 mg/kg), carrots (1.0 mg/kg for roots, 2.2 mg/kg for tops) and wheat grain (3.3 mg/kg) were of the same magnitude, while in wheat straw higher TRRs of 51.9 mg/kg were found. After the 88 day plant back interval (PBI) TRRs in lettuce (1.0 mg/kg) and carrot (0.9 mg/kg for roots, 3.2 mg/kg for tops) remained more or less unchanged while in wheat higher radioactive residue levels were found in comparison to the 30 day PBI (21.6 mg/kg in grain, 63.8 mg/kg in straw).

Identification of the radioactivity revealed no unchanged parent substance in the radioactive residue. In the organosoluble fraction 37.3–63.1% of the TRR consisted of R611965, while up to 2.5% of the TRR were identified as SDS-3701. In the aqueous fraction the amounts were up to 16.9% of the TRR being R611965 and up to 11.9% SDS-3701.

Field crop rotation studies using chlorothalonil were conducted in the USA. At three location soil was treated with eight application of 2.5 kg ai/ha each. Follow crops (spinach, snapbeans, carrots and wheat) were planted 14 to 450 days after the final application. All samples collected at the point of commercial harvest were analysed for residues of SDS-3701 and R611965.

Residues of SDS-3701 were found at relatively low levels, ranging from < 0.01 mg/kg in legume vegetables and cereals grains up to 0.19 mg/kg in leafy vegetables. In root and tuber vegetables (tubers and tops) as well as in straw of cereal grains SDS-3701 residues were between 0.03 mg/kg and 0.08 mg/kg.

A second set of studies investigated the residues of chlorothalonil, SDS-3701 and R611965 following treatments of primary crops according to US GAP at 12 locations. Application rates involved 3–12 treatments at rates of 1.2–2.5 kg ai/ha each. As follow crops a large spectrum of crop

groups (root and tuber vegetables, bulb vegetables, fruiting vegetables, legume vegetables, leafy and brassica vegetables, pulses, oilseeds and cereals) were selected.

In the follow crops residues of chlorothalonil and SDS-3701 were not found above the LOQs in most cases. Single results at or slightly above the LOQ of 0.01–0.02 mg/kg were found occasionally. For peanut vines one result of 0.22 mg/kg chlorothalonil was found. At another location pea fodder and bean hay contained chlorothalonil at levels of 0.06 mg/kg and 0.09 mg/kg, respectively and SDS-3701 of 0.07 mg/kg and < 0.02 mg/kg, respectively.

Residues of R611965 above the LOQ of 0.03 mg/kg were detected more frequently. While in most trials R611965 residue levels were below 0.3 mg/kg single high results were found for turnip tops (0.59 mg/kg), oat straw (2.95 mg/kg), spinach (0.8 mg/kg), winter squash (1.05 mg/kg) and potatoes (0.64 mg/kg).

A field dissipation study conducted at locations in Canada and the USA confirmed the results from the aerobic soil metabolism. After 3 to 10 subsequent applications of chlorothalonil, residues in soil declined to less than 50% of the initial residue within the first 30 days, reaching the LOQ of 0.01 mg/kg after approximately 120 days. Residues of SDS-3701 were detectable for the whole study period of up to 540 days, but its levels in soil were relatively low mostly around 0.02–0.05 mg/kg. In the study conducted in the USA higher residues of SDS-3701 were found in the first 30 days after the final treatment, ranging from 0.05 mg/kg up to 0.23 mg/kg.

The Meeting concluded that parent chlorothalonil degrades quickly within the first 100 days after treatment. No significant transfer into follow crops was observed. SDS-3701 was present for a period of more than one year, but at levels between the LOQ and 0.1 mg/kg in soil as well as in follow crops. Following treatment with chlorothalonil higher residues of the soil metabolite R611965 were found, being the major residue in soil as well as in rotational crops.

Methods of analysis

The Meeting received information on analytical methods for the determination of chlorothalonil, SDS-3701 and R613636 in plant matrices and SDS-3701 in bovine tissues, milk and eggs.

Methods for plant matrices involve extraction and homogenisation with acetone:5M sulphuric acid solution (95:5 v/v). After centrifugation and further clean-up (e.g., by SPE extraction) the extracts are analysed either by gas- or liquid-chromatography in combination with electron-capture- or mass-selective detection (MS or MS/MS for R613636 only: m/z 282.91 to 239.75 and 282.91 to 42.1). Using MS-techniques LOQs of 0.01 mg/kg were achieved for all plant matrices. A specific method submitted for the determination of celery using GC-ECD was validated at 0.03 mg/kg. The Meeting concluded that a LOQ of 0.01 mg/kg for chlorothalonil, SDS-3701 and R613636 achievable with the analytical methods available. Analytical recovery data were satisfactory in plant commodities. Residue methods were tested by independent laboratories unfamiliar with the analysis and were found to have satisfactory recoveries and no background interferences.

The Meeting noted that in some matrices (e.g., lettuce, celery and cabbage) careful treatment during the homogenisation may be required for parent chlorothalonil to avoid a loss of extractable residues during the sample preparation due to enzymatic degradation. A study was submitted showing the stability of chlorothalonil residues in fortified samples prior to homogenisation following addition of sulphuric acid (0.1M) at 10% v/w. The 1997 JMPR reported that homogenisation of frozen samples under addition of dry ice or inactivation of the cell structure by microwaving before the sample preparation also improves the extraction rate.

In animal matrices one method for analysis of SDS-3701 was reported also using extraction and homogenisation with acetone:5M sulphuric acid (95:5 v/v) from muscle, liver and kidney, with acetonitrile:5M sulphuric acid (95: 5 v/v) from fat, with acetonitrile from milk and with acetonitrile:water (3:1 v/v) from eggs. SDS-3701 residues are analysed by high performance liquid

chromatography with triple quadrupole mass spectrometric detection (LC-MS/MS, m/z 244.9 to 181.9). The LOQ achieved in the validations was 0.01 mg/kg for all matrices.

Although no data on analytical multi-residue method for plant commodities were submitted to Meeting it is noted that chlorothalonil parent substance is validated within existing QuEChERS-Multimethods.

Stability of residues in stored analytical samples

Information was received on the freezer storage stability of chlorothalonil in plant commodities and SDS-3701 in animal commodities.

In plant commodities two types of data were used. The first data set consisted of incurred residues in different samples from one treated field trial plot, which were analysed up to 7 years after harvest. The variation within the results indicated a sampling uncertainty much higher than possible from degradation during freezer storage. Therefore it was consluded that this information could not be used for further investigation on the freezer storage stability of chlorothalonil.

In fortified samples stored up to 12 months no significant degradation (> 70% remaining) was observed in peach, strawberries, orange, potato, carrot, onion, cabbage, leek, lentil tomato, melon, sugarbeet and barley forage. In peas and barley straw less than 70% of the initial concentration of chlorothalonil was found after 6 months or more.

For animal commodities the freezer storage stability of SDS-3701 was investigated in fortified bovine tissues and milk for up to 12 months. In muscle, fat and milk recoveries were stable (> 70%) for the whole test period. In liver samples analytical recoveries were 63% after 9 months and 67% after 12 months, indicating a possible degradation of the residue when stored longer than 6 months.

Definition of the residue

In animals chlorothalonil is quickly metabolised with SDS-3701 being the only metabolite in all matrices. Separation between skim milk and cream in livestock feeding studies gave comparable residue levels in both compartments. The same result can be found in muscle and fat, giving slightly higher residues in fat at the lowest dose group but comparable residue levels in these tissues at higher dosing.

The Meeting concluded that the residue definition (risk assessment and enforcement) for chlorothalonil in animal matrices is SDS-3701 only. The residue in not considered fat-soluble.

The residue following use of chlorothalonil in crops is predominantly unchanged chlorothalonil. In all metabolism studies the unchanged parent compound was the major residue, mainly located on the surface of the plants. The only other metabolite identified was SDS-3701 in amounts of less than 3% of the TRRs.

In soil, the degradation of chlorothalonil happens relatively quickly with an estimated half-life of less than 2 days. Significant metabolites identified in soil metabolism and in rotational crops were SDS-3701 and R611965. The residue in follow crops mainly consists of R611965 (up to 50% of the TRR), while SDS-3701 remained at levels between 0.01 and 0.05 mg/kg. Unchanged parent substance was found at or below the LOQ in most cases.

The Meeting concluded that parent chlorothalonil is a representative marker in all plant commodities and decided to set the residue definition for enforcement purposes in plant commodities to be parent chlorothalonil only.

For dietary intake purposes the metabolite SDS-3701 was identified to be of higher acute and chronic toxicity than the parent substance (maximum ADI value of 0.008 mg/kg bw, ARfD of 0.03 mg/kg bw), but follows a different toxicological endpoint. Although found at low levels

following direct treatment, in follow crops or after processing, the low toxicological reference values require an independent additional dietary intake assessment. Therefore the Meeting decided to consider SDS-3701 separately in the residue definition for the estimation of the dietary intake.

The soil metabolite R611965 was identified to be the major residue in follow crops found in a broad variety of commodities. The 2010 Meeting of the JMPR concluded that R611965 is considerably less toxic (e.g., NOAEL = 200 mg/kg bw per day; 2-year-rat study) than the parent compound chlorothalonil (e.g., NOAEL 1.8 mg/kg bw per day; 2-year-rat study). R611965 is not acutely toxic by the oral route. The Meeting decided that the contribution of R611965 to the overall dietary intake of plant and animal commodities arising from residues in follow crops is insignificant in comparison to chlorothalonil and that its inclusion in the residue definition for risk assessment purposes was not required.

Definition of the residue (for compliance with MRL) for plant commodities: *chlorothalonil*

Definitions of the residue (for estimation of dietary intake) for plant commodities:

- *chlorothalonil*
- *SDS-3701 (2,5,6-trichloro-4-hydroxyisophthalonitrile), all considered separately*

Definition of the residue (for compliance with MRL and for estimation of dietary intake) for animal commodities: *SDS-3701 (2,5,6-trichloro-4-hydroxyisophthalonitrile)*

The residue is not fat-soluble.

Results of supervised trials on crops

The Meeting received supervised residue trials data for chlorothalonil on peaches, plums, blueberries, cranberries, currants, grapes, strawberries, bananas, mangoes, papaya, bulb onions, spring onions, leek, cauliflower, Brussels sprouts, head cabbage, courgettes, cucumbers, melons, winter squash, okra, peppers, tomatoes, sweet corn, carrots, potatoes, asparagus, celery, green beans, pulses, soya beans, maize, almonds, pistachios and peanuts.

In trials where duplicate field samples from replicated or unreplicated plots were taken at each sampling time and analysed separately, the higher residue was taken as the best estimate of the residue from the plot. Supervised field trials conducted with different formulations on identical varieties, locations and dates were not considered as independent. The highest result according to the corresponding GAP was selected in these cases.

Labels (or translation of labels) were available from Australia, Brazil, Costa Rica, Cyrpus, Ireland, Ivory Coast, Japan, Moldavia, Slovenia, Spain, the Netherlands, the United Kingdom and the United States of America describing the registered uses of chlorothalonil.

The NAFTA calculator was used as a tool in the estimation of the maximum residue level 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 using expert judgement. 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.

The Meeting noted that in several commodities (e.g., lettuce, celery, cabbage) careful treatment for chlorothalonil during sample preparation may be required to ensure a deactivation of enzymes at or before the homogenisation process, otherwise possibly resulting in a reduced rate of extraction. It was concluded that trials not following this procedure can not be considered valid for a recommendation by the JMPR, but the results may be taken into account as additional information for the evaluation.

In this section the assessment of residues resulting from uses of chlorothalonil on plants for the purpose of estimating maximum residue levels, STMR and HR values are reported. The estimation of STMR and HR values for SDS-3701 in crops being subject to crop rotation is described in the section for residues in follow crops.

Stone fruits

The use of chlorothalonil on peaches, nectarines and plums is registered in Cyprus with up to 4 applications at rates of 1.5 kg ai/ha (0.15 kg ai/hL) with a PHI of 15 days.

Three supervised field trials conducted in Southern Europe according to this GAP was submitted, but these trials did not involve appropriate treatment of the samples during homogenisation so as to avoid a loss of extractable residues.

The Meeting decided that the data submitted for the use of chlorothalonil on stone fruits was not sufficient for the estimation of maximum residue levels and HR or STMR values.

The Meeting withdraws its previous recommendation for chlorothalonil in cherries of 0.5 mg/kg and in peaches of 0.2 mg/kg.

Blueberries

Chlorothalonil is registered on blueberries in the USA with application rates of 3.4 kg ai/ha with a PHI of 42 days. Supervised field trials conducted in the USA according to this GAP were submitted.

The corresponding chlorothalonil residues in fruits were (n = 2): 0.1 and 0.32 mg/kg. Residues of SDS-3701 were: < 0.01 and < 0.01 mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 0.55 and 0.65 mg/kg. Residues of SDS-3701 were: < 0.01 and 0.042 mg/kg.

The Meeting concluded that the available information on chlorothalonil in blueberries was not sufficient for a recommendation.

Cranberries

The use of chlorothalonil on cranberries is registered in the USA with application rates of 5.5 kg ai/ha with a PHI of 50 days and a maximum annual rate of 17 kg ai/ha. Supervised field trials conducted in the USA according to this GAP were submitted.

The corresponding chlorothalonil residues in fruits were: 0.79 and 3.7 mg/kg. Residues of SDS-3701 were: < 0.01 and 0.06 mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 0.75, 1.4, 2.9 and 4.3 mg/kg. Residues of SDS-3701 were: < 0.01(4) mg/kg.

The Meeting concluded that the overall information on chlorothalonil in cranberries are not sufficient for a recommendation and withdraws its previous recommendation for chlorothalonil in cranberries of 5 mg/kg,

Currants and gooseberries

For currants chlorothalonil is registered in the United Kingdom with up to 4 application of 2.5 kg ai/ha each with a PHI of 28 days. Supervised field trials conducted in the United Kingdom according to this GAP were submitted.

The corresponding chlorothalonil residues in fruits were: 0.99, 1.9, 3.5 and 5.0 mg/kg. Residues of SDS-3701 were not analysed.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 5.6 and 10 mg/kg. Residues of SDS-3701 were not analysed.

The Meeting recognized that additional information from two supervised residue trials in currants homogenised without measures to inhibit enzymic activity are available, resulting in higher residues than the field trial data considered as valid. Since the valid dataset available is sufficient for a recommendation of a maximum residue level for currants on its own, the Meeting decided to take the additional informative data into account for its recommendation also, including the probability of higher residues in its estimate.

The Meeting recommends a maximum residue level for chlorothalonil in currants (black, red, white) of 20 mg/kg and concluded to extrapolate the data from currants to gooseberries also. To accommodate for the uncertainty involved with the additional data, the Meeting decided to base the dietary risk assessment (chronic and acute) on the maximum residue level also.

The value derived from use of the NAFTA Calculator was 12.5 mg/kg. The Meeting considered a value of 20 mg/kg as more appropriate in view of the additional information based on currant samples with possible extraction loss.

The Meeting withdraws its previous recommendations for chlorothalonil currants (black, red, white) of 5 mg/kg.

Strawberry

Chlorothalonil is registered on strawberries grown indoor or outdoor in Cyprus and Slovenia with application rates of 1.5 kg ai/ha with a PHI of 7 days. Supervised field trials conducted in Southern Europe according to these GAPs were submitted.

For strawberries grown in the field (outdoor) the corresponding chlorothalonil residues were (n = 8): 1.9, 1.9, 2.0, 2.1, 2.2, 2.4, 2.5 and 3.0 mg/kg.

Residues of SDS-3701 were not analysed.

On protected strawberries the corresponding chlorothalonil residues in fruits were (n = 8): 0.64, 0.68, 1.0, 1.1, 1.3, 1.4, 2.3 and 2.4 mg/kg.

Residues of SDS-3701 were not analysed.

Based on the use of chlorothalonil in field the Meeting estimated a maximum residue level, an STMR and an HR value for strawberries of 5, 2.05 and 3 mg/kg, respectively.

The value derived from use of the NAFTA Calculator was 3.2 mg/kg. The Meeting considered a higher value of 5 mg/kg for its recommendation taking into account that the small variation within the data probably results in an underestimation of the MRL by statistical methods.

Grapes

In Moldavia the use of chlorothalonil on grapes is registered with four applications of 1 kg ai/ha and a PHI of 21 days. Corresponding supervised field trials conducted in Europe were submitted.

Residues of chlorothalonil in grapes were (n = 8): 0.34, 0.48, 0.71, 0.92, 0.99, 1.1, 1.4 and 1.6 mg/kg.

Residues of SDS-3701in grapes were not analysed.

The Meeting decided to recommend a maximum residue level for grapes of 3 mg/kg, and estimated an STMR and an HR value of 0.955 mg/kg and 1.6 mg/kg, respectively, for chlorothalonil, based on the use of chlorothalonil on grapes in Moldavia.

The value derived from use of the NAFTA Calculator was 2.9 mg/kg, providing good correlation with the Meetings recommendation.

The Meeting withdraws its previous recommendation for chlorothalonil in grapes of 0.5 mg/kg.

For SDS-3701 in grapes supervised field trials data from Europe are available which were conducted according to GAP reported for Moldavia. Residues were < 0.01, < 0.01 and 0.15 mg/kg. Although these trails were not considered valid for the evaluation of chlorothalonil residue due to a possible loss of residue during the extraction, enzymic degradation is not reported for SDS-3701. The Meeting therefore decided that the data may be used for the estimation of an STMR of 0.01 mg/kg and an HR of 0.15 mg/kg for SDS-3701 in grapes.

Bananas

For bananas chlorothalonil is registered in Brazil with application rates of 1 kg ai/ha with a PHI of 0 days. Supervised field trials conducted in the Middle America involved treatment of bagged bananas at application rates of at least 1.7 kg ai/ha.

The Meeting concluded that the data on bananas are not corresponding to the GAP and therefore a recommendation on a maximum residue levels is not possible.

The Meeting withdraws its previous recommendation of a maximum residue level of 0.01* mg/kg (including a footnote: “Based on trials with bagged bananas”).

Mangoes

The use of chlorothalonil on mangoes is registered in the USA with application rates of 2.9 kg ai/ha with a PHI of 21 days. One supervised field trial conducted in the USA according to this GAP was submitted, but no appropriate treatment of the samples during homogenisation to avoid a loss of extractable residues was applied.

The Meeting decided that the data submitted for the use of chlorothalonil on mangoes are not sufficient for the estimation of maximum residue levels, HR or STMR values.

Papaya

For papaya chlorothalonil is registered in the Ivory Coast with 6 applications of 1.4 kg ai/ha with a PHI of 3 days. Supervised field trials conducted in the Ivory Coast according to this GAP were submitted.

The corresponding chlorothalonil residues in fruits were (n = 2): 1.2 and 3.6 mg/kg.

In Brazil chlorothalonil is registered for the use on papaya with up to 7 treatments at spray concentrations of 0.21 kg ai/hl each with a PHI of 7 days. Supervised field trials conducted in Brazil according to this GAP were submitted.

The corresponding chlorothalonil residues in whole fruits were (n = 10): 0.74, 1.3, 1.6, 1.9, 4.5, 4.9, 5.1, 9.4, 10 and 13 mg/kg. In the pulp residues were (n = 2): 0.49 and 0.64 mg/kg. The ratio of the residue levels between whole fruit and pulp in two trials was 0.49 and 0.09.

Residues of SDS-3701 in whole papaya fruits were (n = 4): < 0.01(3) and 0.01 mg/kg. In the pulp residues were (n = 2): < 0.01 and < 0.01 mg/kg.

Based on the data for whole fruits treated according to Brazilian GAP the Meeting estimated a maximum residue level of 20 mg/kg for chlorothalonil in papayas. The NAFTA procedure suggested a maximum residue level of 30 mg/kg, based on the UCL 95 Median. For the estimation the Meeting also considered additional information on the decline of residues starting from day 0, which indicate a stable level of overall residues in papaya fruits independent of the PHI with residues all below the estimated maximum residue level by the Meeting of 20 mg/kg.

Since supervised field trial data are very limited on chlorothalonil residues in papaya pulp, the Meeting decided to apply the higher ratio of 0.49 for residue concentrations between whole fruit

and pulp to the median and highest residue found for the whole fruit. Under consideration of metabolism data suggesting that the application of chlorothalonil results in surface residues, the ratio of 0.49 is considered as an overestimation of the likely residue in papaya pulp. Based on this approach the Meeting estimated an STMR value of 2.3 mg/kg (0.49 × 4.7 mg/kg) and an HR value of 6.4 mg/kg (0.49 × 13 mg/kg) for chlorothalonil in papaya pulp.

Based on the data following direct treatment of papayas the Meeting estimated an STMR and an HR value of 0.01 mg/kg for SDS-3701.

Bulb onions

For bulb onions chlorothalonil is registered in the United Kingdom with 2 application of 1 kg ai/ha each with a PHI of 14 days. Supervised field trials conducted according to this GAP were submitted, but these trials did not involve appropriate treatment of the samples during homogenisation to avoid a loss of extractable residues.

The Meeting concluded that the data submitted for the use of chlorothalonil on bulb onions are not sufficient for a recommendation and withdraws its previous recommendation for chlorthalonil of 0.5 mg/kg.

Leek

For leek chlorothalonil is registered in the Netherlands with 5 application of 1.5 kg ai/ha each with a PHI of 14 days. Supervised field trials from Northern France and the United Kingdom, conducted according to GAP were submitted.

The corresponding chlorothalonil residues in whole plants (bulb and leaves) were (n = 6): 8.2, 11, 15, 18, 21 and 22 mg/kg.

Residues of SDS-3701 were not analysed.

An additional GAPs for the use of chlorothalonil on leek was reported from Spain involving up to 4 applications with 1.5 kg ai/ha each and a PHI of 10 days. Supervised field trials conducted in Italy according to this GAP were submitted.

The corresponding chlorothalonil residues in whole plants (bulb and leaves) were (n = 2): 4.7 and 7 mg/kg.

Residues of SDS-3701 were not analysed.

Based on the dataset for the use of chlorothalonil on leek in Northern Europe the Meeting considered a value of 40 mg/kg appropriate as a maximum residue level for leek. The value derived from the NAFTA calculator agreed with the estimate of 40 mg/kg made by the present Meeting (after rounding (NAFTA = 37 mg/kg)).

The Meeting estimated a maximum residue level, and STMR and an HR value of 40 mg/kg, 17.5 mg/kg and 22 mg/kg, respectively.

Spring onions

The use of chlorothalonil on spring onions is registered in United Kingdom with 2 application of 1 kg ai/ha each with a PHI of 14 days. Supervised field trials conducted in United Kingdom according to this GAP were submitted.

The corresponding chlorothalonil residues in spring onions were (n = 4): 0.17, 0.77, 0.9 and 7.5 mg/kg.

Residues of SDS-3701 were (n = 4): < 0.01, < 0.01, 0.01 and 0.05 mg/kg.

Additional supervised field trials on spring onions conducted in Italy were submitted, but no corresponding GAP was reported for chlorothalonil.

For spring onions the value derived from the NAFTA calculator was 8.75 mg/kg, based on the UCL95 Median. The Meeting estimated a maximum residue level, and STMR and an HR value of 10 mg/kg, 0.835 mg/kg and 7.5 mg/kg for spring onions, respectively, and decided to extrapolate this recommendation to Chinese onions and Welsh onions also.

Brussels sprouts

The use of chlorothalonil on Brussels sprouts is registered in the United Kingdom with 2 applications at rates of 1.5 kg ai/ha each with a PHI of 7 days. Supervised field trials conducted with several formulations in Northern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues were: 0.22, 0.44, 0.65, 1.2, 1.5(3), 1.6 and 2.8 mg/kg.

Residues of SDS-3701 were (n = 7): < 0.01(5), 0.01 and 0.01 mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 0.18, 0.28, 0.45, 0.47, 0.53, 0.92 and 1.1 mg/kg. Residues of SDS-3701 were not analysed.

For Cyprus chlorothalonil is registered for Brussels sprouts with 4 applications of 1.5 kg ai/ha each with a PHI of 7 days. Supervised field trials conducted in the Southern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues in Brussels sprouts were (n = 4): 0.73, 0.81, 0.95 and 1.3 mg/kg.

Residues of SDS-3701 were (n = 4): < 0.01(3) and 0.02 mg/kg.

Based on the dataset for the use of chlorothalonil on Brussels sprouts in United Kingdom the Meeting considered a value of 6 mg/kg appropriate as a maximum residue. The value derived from the NAFTA calculator was 6.3 mg/kg.

The Meeting estimated a maximum residue level, and STMR and an HR value of 6 mg/kg, 1.5 mg/kg and 2.8 mg/kg, respectively.

The Meeting withdraws its previous recommendation for chlorothalonil in Brussels sprouts of 5 mg/kg.

Cabbages, Head

No trials matching GAP for chlorothalonil residues in head cabbage were submitted to the Meeting.

The Meeting withdraws its previous recommendation for chlorothalonil in head cabbage of 1 mg/kg.

Flowerhead brassica

For cauliflower chlorothalonil is registered in the United Kingdom with 2 application of 1.5 kg ai/ha each with a PHI of 7 days. Supervised field trials conducted in the United Kingdom according to this GAP were submitted.

The corresponding chlorothalonil residues in cauliflowers were: 0.07, 0.09, 0.11, 0.2, 0.5 and 0.84 mg/kg.

Residues of SDS-3701 were (n = 4): < 0.01(4) mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 0.45, 0.47, 0.8, 2.1 and 2.3 mg/kg. Residues of SDS-3701 were not analysed.

In Cyprus the use of chlorothalonil on cauliflower is registered with up to 4 application with 1.5 kg ai/ha each with a PHI of 7 days. Supervised field trials conducted in the Southern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues in cauliflowers were (n = 4): 0.09, 0.19, 0.39 and 0.52 mg/kg.

Residues of SDS-3701 were (n = 4): < 0.01(4) mg/kg.

The Meeting recognized that additional information from supervised residue trials in cauliflowers homogenised without measures to inhibit enzymic activity are available, resulting in higher residues than the field trial data considered as valid. Since the valid dataset available is sufficient for a recommendation of a maximum residue level for cauliflower on its own, the Meeting decided to take the additional informative data into account for its recommendation also, including the probability of higher residues in its estimate.

The Meeting recommends a maximum residue level for chlorothalonil in flowerhead brassica of 5 mg/kg. To accommodate for the uncertainty involved with the additional data, the Meeting decided to base the dietary risk assessment (chronic and acute) on the maximum residue level also.

The Meeting withdraws its previous recommendation for chlorothalonil in cauliflower of 1 mg/kg.

Cucumber, gherkins and summer squash

The use of chlorothalonil on cucumbers (outdoor) is registered in Spain with 3 application of 2.25 kg ai/ha each with a PHI of 3 days. Supervised field trials conducted in Italy did not match the PHI registered.

In the USA the use of chlorothalonil on cucumbers (outdoor) is registered with application rates of 2.5 kg ai/ha with a PHI of 0 days. Supervised field trials conducted in the USA according to this GAP were submitted.

The corresponding chlorothalonil residues in cucumbers were (n = 5): 0.14, 0.25, 0.41, 0.79 and 1.3 mg/kg.

For chlorothalonil on protected cucumbers a registered use from the Netherlands was reported involving 3 application with 2.25 kg ai/ha with a PHI of 3 days. One supervised field trials conducted in Germany according to this GAP was submitted.

The corresponding chlorothalonil residue in cucumbers was: 0.36 mg/kg.

Based on the dataset for cucumbers from the US the Meeting estimated a maximum residue level, an STMR and an HR for chlorothalonil in cucumbers of 3 mg/kg, 0.41 mg/kg and 1.3 mg/kg, respectively. The result from the NAFTA-calculator was 3.4 mg/kg, providing good compliance with the Meetings estimation. The Meeting also decided to extrapolate its recommendations for cucumbers to gerkins and summer squash.

The Meeting withdraws its previous recommendation for chlorothalonil in cucumbers and summer squash of 5 mg/kg.

Melons, except Watermelon

The use of chlorothalonil on melons (outdoor) is registered in Cyprus with 4 application of 1.5 kg ai/ha each with a PHI of 3 days. Supervised field trials conducted in Southern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues in melons (whole fruits) were: 0.31, 0.57, 0.6, 0.6 and 1.0 mg/kg.

Residues of chlorothalonil in melon pulp were (n = 5): < 0.01, < 0.01, 0.04, 0.2 and 0.21 mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 0.018, 0.03, 0.039, 0.043, 0.1, 0.12, 0.18, 0.19, 0.31, 0.32, 0.39 and 0.87 mg/kg in the whole fruit. Residues of SDS-3701 were not analysed.

For chlorothalonil on protected melon a registered use from Cyprus with 4 application of 1.5 kg ai/ha each and a PHI of 3 days was reported. Supervised field trials conducted in Southern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues in melons (whole fruits) were: 0.13, 0.21, 0.27, 0.31, 0.52 and 0.58 mg/kg.

Residues of chlorothalonil in melon pulp were (n = 5): < 0.01, < 0.01, 0.04 and 0.05 mg/kg.

Based on the data for field melon from Southern Europe the Meeting confirms the maximum residue level of 2 mg/kg for melons, except watermelons and estimated an STMR and an HR value 0.04 mg/kg and 0.21 mg/kg in the pulp, respectively.

The MRL derived from use of the NAFTA Calculator was 1.5 mg/kg. Due to the low number of results the Meeting concluded that the results of the NAFTA-calculator are not reliable and should not be used for a recommendation.

Winter squash

For chlorothalonil on winter squash a registered use from the USA involving applications with 2.5 kg ai/ha and a PHI of 0 days was reported. One supervised field trial conducted according to this GAP was submitted, but it did not involve appropriate treatment of the samples during homogenisation to avoid a loss of extractable residues.

The Meeting concluded that the data submitted for the use of chlorothalonil on winter squash is not sufficient for a recommendation and withdraws its previous recommendation for chlorthalonil of 5 mg/kg.

Okra

For okra chlorothalonil is registered in the Ivory Coast with 2 application of 1.0 kg ai/ha each with a PHI of 2 days. Supervised field trials conducted in the Ivory Coast according to this GAP were submitted, but did not involve appropriate treatment of the samples during homogenisation to avoid a loss of extractable residues. The corresponding chlorothalonil residues in okras were (n = 4): 0.06, 0.15, 0.82 and 1.0 mg/kg.

The Meeting concluded that the data submitted for the use of chlorothalonil on okra is not sufficient for a recommendation.

Peppers

For peppers supervised field trials involving chlorothalonil from Brazil were submitted matching the GAP of 0.2 kg ai/hL with a PHI of 7 days.

Corresponding residues in bell peppers were (n = 4): 1.1, 1.5, 1.7 and 4.4 mg/kg.

The Meeting decided that the data submitted are not sufficient for a recommendation on maximum residue levels or for the estimation of STMR and HR values for chlorothalonil in peppers.

The Meeting withdraws it previous recommendation for peppers, sweet of 7 mg/kg and peppers, chili (dry) of 70 mg/kg.

Tomatoes

For tomatoes chlorothalonil is registered in the United States with applications of 2.4 kg ai/ha each with a PHI of 0 days. Supervised field trials conducted in the US according to this GAP were submitted, but they either did not involve appropriate treatment of the samples during homogenisation to avoid a loss of extractable residues or were not collected according to the recommended FAO sampling procedure. The corresponding chlorothalonil residues in tomato fruits were: 0.94, 1.0, 1.3, 1.3, 1.4, 1.4, 1.8, 1.9, 2.2, 2.7, 2.7, 5.3, 6.0 and 6.4 mg/kg, the corresponding SDS-3701 residues in tomato fruits were: < 0.03, < 0.03, 0.06 mg/kg.

The Meeting concluded that the data submitted for the use of chlorothalonil on tomatoes is not sufficient for an recommendation and withdraws its previous recommendation for chlorthalonil of 5 mg/kg.

Sweet corn

The use of chlorothalonil on sweet corn is registered in the United States with applications of 1.7 kg ai/ha each with a PHI of 14 days. Supervised field trials conducted in the US according to this GAP were submitted, but did not involve appropriate treatment of the samples during homogenisation to avoid a loss of extractable residues. The corresponding chlorothalonil residues in ears were: < 0.01(3) mg/kg, the corresponding SDS-3701 residues in ears were: < 0.01, < 0.01 and 0.01 mg/kg.

The Meeting concluded that the data submitted for sweet corn is not sufficient for a recommendation and withdraws its previous recommendation for chlorothalonil in sweet corn of 0.01* mg/kg.

Beans, shelled (legume vegetables)

For the use of chlorothalonil on legume vegetables supervised field trials in the United Kingdom on green beans without pods were submitted, but no corresponding GAP was reported.

The Meeting withdraws its previous recommendation for chlorothalonil in common beans (pods and/or immature seeds) of 5 mg/kg.

Pulses

For beans (pulses) chlorothalonil is registered in Spain with 2 application of 1.5 kg ai/ha each with a PHI of 15 days. Supervised field trials conducted in Southern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues in dry seeds were (n = 7): 0.05, 0.05, 0.11, 0.19, 0.32, 0.52 and 0.68 mg/kg.

The corresponding SDS-3701 residues in dry seeds were (n = 7): < 0.01, < 0.01, 0.02(3), 0.04 and 0.04 mg/kg.

For chick peas (pulses) chlorothalonil is registered in Spain with 2 application of 1.5 kg ai/ha each with a PHI of 15 days. Supervised field trials were conducted in Southern Europe according to this GAP.

The corresponding chlorothalonil residues in dry seeds were: 0.1, 0.28, 0.34 and 0.62 mg/kg.

The corresponding SDS-3701 residues in dry seeds were (n = 4): < 0.01(3), 0.02 mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 0.11, 0.11, 0.17, 0.29, 0.31, 0.39 and 0.44 mg/kg. Residues of SDS-3701 were not analysed.

The use of chlorothalonil on soya beans (pulses) is registered in the United States with applications of 1.9 kg ai/ha each with a PHI of 42 days. Supervised field trials conducted in the US according to this GAP were submitted.

The corresponding chlorothalonil residues in dry seeds were: < 0.01(3) and 0.019 mg/kg.

The Meeting decided to make a recommendation for the whole group of pulses based on the data on beans treated according to the submitted GAP from Spain and estimated a maximum residue level and an STMR value for pulses of 1 and 0.19 mg/kg, respectively.

The value derived from use of the NAFTA Calculator was 1.4 mg/kg, providing good compliance with the value estimated by the Meeting.

The Meeting withdraws its previous recommendation for chlorothalonil in beans (dry) of 0.2 mg/kg.

Root and tuber vegetables

For carrots chlorothalonil is registered in Spain with 3 application of 1.5 kg ai/ha each with a PHI of 15 days. Supervised field trials conducted in Southern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues in carrots were (n = 6): < 0.01, 0.01, 0.02, 0.02, 0.05 and 0.06 mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 0.08 and 0.19 mg/kg. Residues of SDS-3701 were not analysed.

The use of chlorothalonil on potatoes is registered in the United Kingdom with 5 applications of 1.5 kg ai/ha each with a PHI of 7 days. Supervised field trials conducted in Northern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues in potato tubers were: < 0.01(7) and 0.01 mg/kg.

In Cyprus chlorothalonil is registered on potatoes with 3 applications of 1.5 kg ai/ha each with a PHI of 10 days. Supervised field trials conducted in Southern Europe according to this GAP were submitted.

The corresponding chlorothalonil residues in potato tubers were: < 0.01(4) mg/kg.

The Meeting recognized that additional information from supervised residue trials in carrots homogenised without measures to inhibit enzymic activity are available, resulting in higher residues than the field trial data considered as valid. Since the valid dataset available is sufficient for a recommendation of a maximum residue level for root and tuber vegetables on its own, the Meeting decided to take the additional informative data into account for its recommendation also, including the probability of higher residues in its estimate.

The Meeting recommends a maximum residue level for chlorothalonil in root and tuber vegetables of 0.3 mg/kg. To accommodate for the uncertainty involved with the additional data, the Meeting decided to base the dietary risk assessment (chronic and acute) on the maximum residue level also.

The Meeting withdraws its previous recommendations for chlorothalonil in carrots of 1 mg/kg and in potatoes of 0.2 mg/kg.

Asparagus

For asparagus chlorothalonil is registered in the United States with application of 3.4 kg ai/ha each with a PHI of 190 days. Supervised field trials conducted in the US according to this GAP were submitted, but did not involve appropriate treatment of the samples during homogenisation to avoid a

loss of extractable residues. The corresponding chlorothalonil residues in asparagus spears were (n = 6): < 0.01(5), 0.033 mg/kg, the corresponding SDS-3701 residues were (n = 6): < 0.01(6) mg/kg.

The Meeting concluded that the data submitted for asparagus is not sufficient for a recommendation for chlorothalonil.

Celery

The use of chlorothalonil on celery is registered in the United States with applications of 2.5 kg ai/ha each with a PHI of 7 days. Supervised field trials conducted in the US according to this GAP were submitted.

The corresponding chlorothalonil residues in celery stalks were: 0.06, 2.0, 3.3 and 7.5 mg/kg.

The corresponding SDS-3701 residues in celery stalks were: 0.02 mg/kg.

The Meeting estimated a maximum residue level, an STMR and an HR value for celery of 20, 2.65 and 7.5 mg/kg, respectively.

The value derived from use of the NAFTA Calculator was 28 mg/kg. Under consideration of additional trial data conducted at higher application rates the Meeting concluded that the value derived by the calculator was probably an overestimation of the maximum residue level due to a small dataset matching GAP.

The Meeting withdraws its previous recommendations for chlorothalonil in celery of 10 mg/kg and in celery leaves of 3 mg/kg.

Barley

No information on chlorothalonil residues in barley were submitted to the Meeting.

The Meeting withdraws its previous recommendation for chlorothalonil in barley of 0.1 mg/kg.

Maize

The use of chlorothalonil on maize is registered in the United States with applications of 1.7 kg ai/ha each with a PHI of 14 days. No supervised field trials matching this GAP were submitted.

Wheat

No information on chlorothalonil residues in wheat were submitted to the Meeting.

The Meeting withdraws its previous recommendation for chlorothalonil in wheat of 0.1 mg/kg.

Almonds

The use of chlorothalonil on almonds is registered in the United States with applications of 3.4 kg ai/ha each with a PHI of 150 days. Supervised field trials conducted in the US according to this GAP were submitted.

The corresponding chlorothalonil residues in nutmeat were: < 0.03 and < 0.03mg/kg.

The corresponding SDS-3701 residues in nutmeat were: < 0.03 and < 0.03 mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of < 0.01(3), 0.01 and 0.01 mg/kg. Residues of SDS-3701 were < 0.01(6).

The Meeting concluded that the data submitted for almonds is not sufficient for a recommendation for chlorothalonil.

Pistachio nut

The use of chlorothalonil on pistachios is registered in the United States with applications of 2.5 kg ai/ha each with a PHI of 14 days. Supervised field trials were conducted in the US with application rates of 5 kg ai/ha and a PHI of 14 days.

The Meeting concluded that the data on pistachios are not corresponding to the GAP reported and therefore recommendations on a maximum residue levels are not possible.

Peanuts

The use of chlorothalonil on peanuts is registered in the United States with applications of 1.3 kg ai/ha each with a PHI of 14 days. Supervised field trials conducted in the US according to this GAP were submitted.

The corresponding chlorothalonil residues in nutmeat were (n = 12): < 0.01(9), 0.01, 0.02, 0.05 mg/kg.

The corresponding SDS-3701 residues in nutmeat were (n = 10): < 0.01(10) mg/kg.

The corresponding R611965 residues in nutmeat, taken up from the soil within the vegetation period, were (n = 10): < 0.03(4), 0.03, 0.03, 0.04, 0.05, 0.05, 0.06 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for peanuts of 0.1 and 0.01 mg/kg, respectively.

Due to the high percentage of residue values below the LOQ the Meeting concluded that the NAFTA procedure is no applicable for the estimation of maximum residue levels in peanuts.

The Meeting withdraws its previous recommendation for chlorothalonil in peanuts of 0.05 mg/kg.

Sweet corn forage

Supervised field trials on sweet corn forage conducted in the United States were submitted, but the US GAP states that sweet corn may not be utilized as forage or silage.

Barley, straw and fodder

No information on chlorothalonil residues in barley were submitted to the Meeting.

The Meeting withdraws its previous recommendation for chlorothalonil in barley, straw and fodder, dry of 20 mg/kg.

Maize stover

Supervised field trials on maize stover conducted in the United States were submitted, but the US GAP states that sweet corn may not be utilized as forage or silage.

Wheat, straw and fodder

No information on chlorothalonil residues in wheat were submitted to the Meeting.

The Meeting withdraws its previous recommendation for chlorothalonil in wheat, straw and fodder, dry of 20 mg/kg.

Almond hulls

The use of chlorothalonil on almond is registered in the United States with applications of 3.4 kg ai/ha each with a PHI of 150 days. Supervised field trials conducted in the US according to this GAP were submitted.

The corresponding chlorothalonil residues in almond hulls were: < 0.03, < 0.03 mg/kg.

The corresponding SDS-3701 residues in almond hulls were: < 0.03 and < 0.03 mg/kg.

Additional information from supervised field trials conducted according to GAP, but not using homogenisation that involves enzyme deactivation, are available, giving residues of 0.03, 0.03, 0.09, 0.63, 0.91 and 1.1 mg/kg. Residues of SDS-3701 were < 0.01(6).

The Meeting concluded that the data submitted for almond hulls is not sufficient for a recommendation for chlorothalonil.

Residues following treatment with chlorothalonil in follow crops

Although residues of chlorothalonil are quickly degraded in soil, the toxicological relevant metabolite SDS-3701 may be taken up by succeeding crops. Information on the DT50 value is not available, but in field dissipation studies residues were found up to 540 days after treatment. It is likely that soil residues would require several years to reach plateau levels and residues in succeeding crops could be higher than those observed in the rotational crop following a single season of applications.

For the estimation of residues in follow crops all residues in field rotational crop studies were compared to the highest annual application rate of 20 kg ai/ha reported for celery from the United States. In the following table residues found in the different commodities were directly scaled based on the individual ratio of active substance applied in the respective trial to a theoretical annual rate of 20 kg ai/ha.

Since residues of parent chlorothalonil were very low giving results at or below the LOQ of the analytical method used, the Meeting concluded that no significant transfer of chlorothalonil into follow crops has to be expected. For dietary intake purposes only residues of SDS-3701 are considered.

The estimation of STMR and HR values was based on the data from follow crops or direct treatment resulting in the highest residue level in the respective crop group. For all permanent crops no significant transfer of SDS-3701 into commodities is expected.

Summary of SDS-3701 residues found in field rotational crop studies scaled to the highest annual rate of 20 kg ai/ha.

Group	No. of trials	Highest results per trial (mg/kg)	Mean in mg/kg	Median in mg/kg	Highest residue in mg/kg
SDS-3701					
Bulb vegetables	3	< 0.01(3)	< 0.01	< 0.01	< 0.01
Brassica vegetables	5	< 0.01, < 0.01, < 0.02(3)	< 0.02	< 0.02	< 0.02
Fruiting vegetables	6	< 0.01(5), < 0.02	< 0.01	< 0.01	< 0.02
Leafy vegetables	9	< 0.01(4), < 0.02, 0.04, 0.04, 0.05, 0.19	0.076	0.02	0.19
Legume vegetables	4	< 0.01(3), < 0.02	< 0.01	< 0.01	< 0.02
Pulses	5	< 0.01, < 0.01, < 0.02(3)	< 0.02	< 0.02	< 0.02
Root and tuber vegetables	12	< 0.01(3), < 0.02(5), 0.02, 0.03(3)	0.02	0.02	0.03
Stem vegetables	1	< 0.02	< 0.02	< 0.02	< 0.02

Group	No. of trials	Highest results per trial (mg/kg)	Mean in mg/kg	Median in mg/kg	Highest residue in mg/kg
Cereal grains	15	< 0.01(7), < 0.02(6), < 0.05, < 0.05	< 0.02	< 0.02	< 0.05
Oilseeds	5	< 0.01, < 0.02(3), < 0.05	0.02	0.02	0.05
Legumes hay and fodder	2	< 0.02, 0.14	0.08	0.08	0.14
Forage of cereal grains	2	< 0.02, 0.04	0.03	0.03	0.04
Straw and fodder of cereal grains	10	< 0.02, 0.02, < 0.03(4), < 0.04, 0.04, 0.04, 0.08	0.036	0.03	0.08
Root leaves and tops	8	< 0.01, 0.01, < 0.02, < 0.02, 0.02, 0.03, 0.04, 0.04	0.024	0.02	0.04

For dietary intake purposes of SDS-3701 in the group of berries and other small fruits, except grapes, residue data on blue- and cranberries are available giving residues of < 0.01(3) and 0.06 mg/kg. Crops within this group are normally not subject to crop rotation. Under consideration of plant metabolism data indicating an overall very low level of SDS-3701 in all plants following direct treatment, the Meeting concluded that the data on blue- and cranberries are also representative for other berries and small fruits, except grapes, and estimated an STMR value of 0.01 mg/kg and an HR value of 0.06 mg/kg for SDS-3701.

Residues in bulb vegetables grown as a rotational crop were < 0.01(3) mg/kg for SDS-3701. For spring onion supervised field trial data are available with SDS-3701 residues of < 0.01, < 0.01, 0.01 and 0.04 mg/kg.

Under consideration of higher residue data from supervised field trials the Meeting estimated an STMR and an HR value of 0.01 mg/kg and 0.04 mg/kg for SDS-3701 in bulb vegetables, respectively.

For brassica vegetables residues of SDS-3701 found in field rotational crop studies were < 0.01, < 0.01 and < 0.02(3) mg/kg. Additional supervised field trial data are available for Brussels sprouts (< 0.01(9), 0.01 and 0.02 mg/kg) and cauliflower (< 0.01(8) mg/kg). Under consideration of all data available the Meeting estimated an STMR and an HR value for SDS-3701 in brassica vegetables of 0.01 mg/kg and 0.02 mg/kg, respectively.

Residues in SDS-3701 in fruiting vegetables grown as a rotational crop were found in field crop rotation studies at levels of < 0.01(5) and < 0.02 mg/kg. In supervised field trials residues of SDS-3701 were investigated in winter squash (0.02 mg/kg) and tomatoes (< 0.03, < 0.03 and 0.06 mg/kg). Under consideration of all residue data available (< 0.01(5), < 0.02, 0.02, < 0.03, < 0.03 and 0.06 mg/kg) the Meeting estimated an STMR and an HR value of 0.015 mg/kg and 0.06 mg/kg, respectively, for fruiting vegetables (cucurbits and other than cucurbits).

In leafy vegetables SDS-3701 residues found in field rotational crops studies were < 0.01(4), < 0.02, 0.04, 0.04, 0.05 and 0.19 mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR and an HR value of 0.02 mg/kg and 0.19 mg/kg, respectively, for SDS-3701 residues in leafy vegetables.

The Meeting decided to extrapolate the estimations for SDS-3701 from leafy vegetables to herbs.

For legume vegetables residues of SDS-3701 found in field rotational crop studies were < 0.01(3), < 0.02 mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR and an HR value of 0.01 mg/kg and 0.02 mg/kg, respectively, for SDS-3701 residues in legume vegetables.

Residues in SDS-3701 in pulses grown as a rotational crop were found in field crop rotation studies at levels of < 0.01, < 0.01 and < 0.02(3) mg/kg. In supervised field trials residues of SDS-

3701 were investigated in beans (< 0.01, < 0.01, 0.02(3), 0.04 and 0.04 mg/kg) and chick peas (< 0.01(3), 0.02 mg/kg). Under consideration of all residue data available (< 0.01(7), < 0.02(3), 0.02(4), 0.04 and 0.04 mg/kg) the Meeting estimated an STMR value of 0.02 mg/kg.

In root and tuber vegetables SDS-3701 residues found in field rotational crops studies were < 0.01(3), < 0.02(5), 0.02 and 0.03(3) mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR and a HR value of 0.02 mg/kg and 0.03 mg/kg, respectively, for SDS-3701 residues in root and tuber vegetables.

Residues in SDS-3701 in stalk and stem vegetables grown as rotational crops were found in field crop rotation studies at levels of < 0.02 mg/kg. In supervised field trials residues of SDS-3701 were investigated in asparagus (< 0.01(6) mg/kg) and celery (0.02 mg/kg). Under consideration of all available residue data (< 0.01(6), < 0.02 and 0.02 mg/kg) the Meeting estimated an STMR value and a HR value of 0.01 mg/kg and 0.02 mg/kg, respectively.

For cereal grains residues of SDS-3701 found in field rotational crop studies were < 0.01(7), < 0.02(6), < 0.05, < 0.05 mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR value of 0.02 mg/kg for SDS-3701 residues in cereal grains.

In oilseeds SDS-3701 residues found in field rotational crops studies were < 0.01, < 0.02(3), and < 0.05 mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR value of 0.02 mg/kg for SDS-3701 residues in oilseeds.

Residues in SDS-3701 in legume hay and fodder grown as a rotational crop were found in field crop rotation studies at levels of < 0.02 and 0.04 mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR and a highest residue value of 0.03 mg/kg and 0.04 mg/kg, respectively, for SDS-3701 residues in legume hay and fodder.

For forage of cereal grains residues of SDS-3701 found in field rotational crop studies were < 0.02 and 0.04 mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR value of 0.03 mg/kg and a highest residue value of 0.04 mg/kg for SDS-3701 residues in forage of cereal grains.

For straw and fodder of cereal grains residues of SDS-3701 found in field rotational crop studies were < 0.02, 0.02, < 0.03(4), < 0.04, 0.04, 0.04, 0.08 mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR value of 0.03 mg/kg and a highest residue of 0.08 mg/kg for SDS-3701 residues in straw and fodder of cereal grains.

In tops and leaves of root crops SDS-3701 residues found in field rotational crops studies were < 0.01, 0.01, < 0.02, < 0.02, 0.02, 0.03, 0.04 and 0.04 mg/kg. No information on SDS-3701 residues from supervised field trials was available. The Meeting estimated an STMR and a highest residue value of 0.02 mg/kg and 0.04 mg/kg, respectively, for SDS-3701 residues in tops and leaves of root crops.

Fate of residues during processing

The Meeting received information on the fate of incurred residues of chlorothalonil during the processing of grapes, strawberries, tomatoes, courgettes, cucumbers, winter squash, head cabbage, leek and French beans. Also information was provided on hydrolysis studies of chlorothalonil to assist with identification of the nature of the residue during processing.

The degradation of chlorothalonil was investigated under conditions representative of pasteurisation (pH 4, 90 °C for 20 minutes), baking, brewing and boiling (pH 5, 100 °C for 60 minutes) and sterilisation (pH 6, 120 °C for 20 minutes). Additional experiments were also performed at pH 4 at 120 °C and pH 6 at 90 °C for 20 minutes to investigate which of pH or temperature was the key variable in hydrolytic degradation of chlorothalonil.

At pH 4 chlorothalonil residues were relatively stable with > 90% remaining at 90 °C and 73% remaining at 120 °C.

For pH 5 at 100 °C a moderate degradation was observed in all samples leaving approx. 80% of the initial chlorothalonil. The major degradation product was identified as SDS-3701 at 19% of the initial residue.

For pH6 at 120 °C chlorothalonil is quickly degraded. Under addition of a sodium acetate buffer less than 4% of the chlorothalonil remained. Main degradation products were SDS-3701 (48%) and an artefact (28%, identified as 4-amino-2,5,6-trichloroisophthalonitrile). In sterile water without buffer approx. 26% of the chlorothalonil remained. SDS-3701 constituted 59% of the residue while no formation of the artefact was found.

In contrast to the results obtained from sterile buffer solutions processing studies involving background matrices gave much lower levels of SDS-3701 after the processing. The Meeting decided that besides the normal processing factors for chlorothalonil yield factors for the conversion of parent substance into SDS-3701 should be taken into account for the estimation of the dietary intake. Depending on the outcome the higher STMR-P or HR-P of SDS-3701 → SDS-3701 or chlorothalonil → SDS-3701 is used for the overall estimation of STMR-P and HR-P for SDS-3701 in the processed product. The resulting processing factors relevant for dietary intake of the estimation of maximum residue levels are summarized below:

Processing factors for chlorothalonil

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors	Median or best estimate	STMR (mg/kg)	STMR-P (mg/kg)	HR (mg/kg)	HR-P (mg/kg)
Grapes	Wine, red	Chlorothalonil: < 0.01(6), < 0.02, < 0.02	Chlorothalonil: < 0.01	0955	0.0096		
	Raisins	Chlorothalonil: 0.01, 0.51	Chlorothalonil: 0.26	0.955	0.248	1.6	0.416
	Juice, unpasteurized	Chlorothalonil: 0.02, 0.26	Chlorothalonil: 0.14	0.955	0.134		
	Pomace, wet	Chlorothalonil: 0.61, 1.9	Chlorothalonil: 1.3	0.955	1.24	1.6	2.08
	Pomace, dry	Chlorothalonil: 0.33, 1.5	Chlorothalonil: 0.78	0.955	0.745	1.6	1.25

Yield factors for SDS-3701 → SDS-3701

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors	Median or best estimate	STMR (mg/kg)	STMR-P (mg/kg)	HR (mg/kg)	HR-P (mg/kg)
Grapes	Wine, red	SDS-3701: < 0.11, < 1, < 1	SDS-3701: < 0.11	0.01	0.009		
	Raisins	SDS-3701: 0.57, 1	SDS-3701: 0.79	0.01	0.0079	0.15	0.1185
	Juice, unpasteurized	SDS-3701: < 0.25, < 0.29	SDS-3701: < 0.27	0.01	0.0027		
	Pomace, wet	SDS-3701: 0.86, 1.5	SDS-3701: 1.2	0.01	0.012	0.15	0.18
	Pomace, dry	SDS-3701: 2.8, 3.4	SDS-3701: 3.1	0.01	0.031	0.15	0.465

Yield factors of chlorothalonil → SDS-3701 during processing

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors chlorothalonil → SDS-3701	Median or best estimate	STMR chlorothalonil (mg/kg)	STMR-P SDS-3701 (mg/kg)
Grapes	Wine, red	< 0.004, < 0.02, < 0.26	< 0.02	0.955	0.0191
	Raisins	0.002, 0.004	0.003	0.955	0.00287
	Juice, unpasteurized	< 0.001, < 0.001	< 0.001	0.955	0.00096
	Pomace, wet	0.004, 0.006	0.005	0.955	0.00478
	Pomace, dry	0.01, 0.014	0.012	0.955	0.0115

Chlorothalonil

For processed grapes the Meeting estimated STMR-P values for chlorothalonil of 0.0096 mg/kg in wine, 0.134 mg/kg in juice and 1.24 mg/kg and 0.745 mg/kg in wet and dry grape pomace, respectively (chlorothalonil → chlorothalonil).

For raisins an STMR-P of 0.248mg/kg and an HR-P of 0.416 mg/kg were estimated (chlorothalonil → chlorothalonil). Since the processing of grapes into raisins is covered by the recommendation for a maximum residue level for the raw commodity, a separate recommendation for dried grapes is not necessary.

SDS-3701

For the effect of processing the Meeting selected the higher STMR-P or HR-P value for each commodity following either SDS-3701 → SDS-3701 or chlorothalonil → SDS-3701.

For processed grapes the Meeting estimated STMR-P values for SDS-3701 of 0.019 mg/kg in wine (chlorothalonil→ SDS -3701), 0.0079 mg/kg for raisins (SDS-3701→ SDS-3701), 0.0027 mg/kg in juice (SDS-3701→ SDS-3701) and 0.012 mg/kg and 0.031 mg/kg in wet and dry grape pomace (SDS-3701→ SDS-3701), respectively.

For raisins the Meeting estimated a HR-P of 0.12 mg/kg for SDS-3701 (SDS3701 → SDS -3701).

Residues in animal commodities

Livestock dietary burden

The Meeting received a lactating dairy cow feeding study which provided information on likely SDS-3701 residues resulting in animal commodities and milk from chlorothalonil residues in the animal diet.

In this study lactating cows (4 per dose group) were administered daily doses of chlorothalonil and SDS-3701 via gelatine capsule. The dose levels of the animals were 1.5 ppm chlorothalonil/0.1 ppm SDS-3701 (0.5×), 3 ppm chlorothalonil/0.2 ppm SDS-3701 (1×), 9 ppm chlorothalonil/0.6 ppm SDS-3701 (3×) and 30 ppm chlorothalonil/2.0 ppm SDS-3701 (10×) over 28 consecutive days. Milk was collected over whole study period.. Samples of fat, muscle, kidney and liver were taken for analysis.

In milk SDS-3701 residues reached a plateau after approximately 7–10 days of dosing. Plateau levels found for the different dose groups were 0.03 mg/kg (0.5×), 0.07 mg/kg (1×), 0.21 mg/kg (3×) and 0.49 mg/kg (10×). Separation of skim milk and cream revealed comparable residue levels in the two fractions.

In tissues highest residues of SDS-3701 were found in kidney and liver. Residues in kidney were always higher than liver with 0.14 mg/kg (0.5×), 0.2 mg/kg (1×), 0.49 mg/kg (3×) and 0.95 mg/kg (10×) in comparison to 0.02 mg/kg (0.5×), 0.03 mg/kg (1×), 0.16 mg/kg (3×) and 0.45 mg/kg (10×). Residues in fat were at a comparable level to residues in liver, giving 0.02 mg/kg (0.5×), 0.04 mg/kg (1×), 0.06 mg/kg (3×) and 0.67 mg/kg (10×) in perirenal fat. In muscle SDS-3701 was found at low levels only: < 0.01 mg/kg (0.5×), 0.01 mg/kg (1×), 0.05 mg/kg (3×) and 0.15 mg/kg (10×).

For poultry matrices no feeding studies are available. In radio-labelled metabolism studies using [^{14}C]-chlorothalonil no TRR above the LOQ of 0.01 mg/kg were found in any dose group (2, 6 and 20 ppm) for muscle and fat. Eggs contained TRR levels between 0.035–0.047 mg/kg for the 20 ppm group. In liver TRR levels were < 0.01 mg/kg for the 2 ppm group, 0.098 mg/kg for the 6 ppm group and 0.05 mg/kg for the 20 ppm group.

Poultry metabolism studies using ^{14}C-SDS-3701 were conducted at dose levels of 0.1, 0.3 and 1 ppm. For the 0.1 ppm dose group, which corresponds to the highest estimated dietary burden for poultry of 0.094 ppm (poultry layer – EU), no TRR above the LOQ of 0.01 mg/kg was found for egg whites, muscle, fat and skin. In liver TRR were 0.056 mg/kg while in egg yolk a TRR of 0.044 mg/kg was found. At higher dose rates residues in eggs yolk and liver correlated to the dose increasement. In cardial muscle single high residue of 0.55 mg/kg for the 0.3 ppm group and 0.154 mg/kg for the 1.0 ppm group were found. In the pectoral and adductor muscles no residues above the LOQ were found for any dose group.

For both studies the hens were sacrificed after 6 hours after the final dosing.

Estimated maximum and mean dietary burdens of livestock

Dietary burden calculations based on chlorothalonil and SDS-3701 for beef cattle, dairy cattle, broilers and laying poultry are presented in Annex 6. The calculations were made according to the livestock diets from US/CAN, EU, Australia and Japan in the OECD Table (Annex 6 of the 2006 JMPR Report).

In the following table the estimated livestock dietary burden is presented for chlorothalonil and SDS-3701 simultaneously, since both substances were administered in combined doses to the test animals.

	Livestock dietary burden, chlorothalonil and SDS-3701, ppm of dry matter diet (chlorothalonil / SDS-3701)							
	US/CAN		EU		Australia		Japan	
	max.	mean	max.	mean	max.	mean	max.	mean
Beef cattle	0.46 / 0.112	0.46 / 0.09	1.24 / 0.25	1.24 / 0.17	2.06 / 0.31[a]	2.06 / 0.27 [b]	0.03 / 0.04	0.03 / 0.03
Dairy cattle	0.27 / 0.15	0.27 / 0.12	0.79 / 0.22	0.79 / 0.15	2.0 / 0.3	2.0 / 0.28	0.02 / 0.09	0.02 / 0.05
Poultry - broiler	0.04 / 0.02	0.04 / 0.02	0.42 / 0.069[c]	0.42 / 0.05[d]	0.15 / 0.02	0.15 / 0.02	0 / 0.02	0 / 0.01
Poultry - layer	0.04 / 0.02	0.04 / 0.02	0.38 / 0.09[e]	0.38 / 0.07[d,f]	0.15 / 0.02	0.15 / 0.02	0 / 0.01	0 / 0.01

[a] Highest maximum beef or dairy cattle burden suitable for MRL estimates for mammalian meat and milk

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

[c] Highest maximum poultry burden suitable for MRL estimated for poultry meat

[d] Highest mean poultry burden suitable for STMR estimates in poultry meat

[e] Highest maximum poultry burden suitable for MRL estimated for eggs

[f] Highest mean poultry burden suitable for STMR estimates in eggs

Animal commodities, MRL estimation

In the table below, dietary burdens for chlorothalonil and SDS-3701 are shown in round brackets (), feeding levels and residue concentrations from the feeding studies are shown in square brackets [] and estimated concentrations related to the dietary burden are shown without brackets. Since the corresponding dairy cattle feeding study chlorothalonil and SDS-3701 were administered simultaneously, both levels are listed for comparison. In view of SDS-3701 being the only residue of concern in livestock animals after administration of both chlorothalonil and SDS-3701, the combined dose was considered relevant for the estimation of residues in tissues and milk.

Dietary burden (ppm) Feeding level [ppm]	Milk	Muscle	Liver	Kidney	Fat
MRL	mean	highest	highest	highest	highest
MRL beef or dairy cattle (2.06 / 0.31) [1.5 chlorothalonil + 0.1 SDS-3701, 3 chlorothalonil + 0.2 SDS-3701]	0.05 [0.04, 0.07]	0.013 [< 0.01, 0.02]	0.033 [0.03, 0.04]	0.18 [0.14, 0.28]	0.05 [0.03, 0.07]
STMR	mean	mean	mean	mean	mean
STMR beef or dairy cattle (2.06 / 0.27) [1.5 chlorothalonil + 0.1 SDS-3701, 3 chlorothalonil + 0.2 SDS-3701]	0.05 [0.04, 0.07]	0.01 [< 0.01, 0.01]	0.03 [0.03, 0.03]	0.16 [0.14, 0.2]	0.025 [0.02, 0.04]

In lactating cows residues above the LOQ of the analytical method of 0.01 mg/kg are expected for all commodities. The Meeting estimated maximum residue levels for mammalian meat of 0.02 mg/kg, for mammalian fat of 0.07 mg/kg, for milk of 0.07 and for edible offal (mammalian), based on kidney, of 0.2 mg/kg.

The Meeting estimated an STMR value for SDS-3701 in whole milk of 0.05 mg/kg.

For mammalian meat an STMR and an HR value of 0.01 mg/kg and 0.013 mg/kg were estimated by the Meeting. In mammalian fat the STMR and HR values were estimated at levels of 0.025 mg/kg and 0.05 mg/kg, respectively. For edible offal (mammalian) the Meeting estimated STMR and HR values of 0.16 mg/kg and 0.18 mg/kg, respectively, based on kidney.

For poultry a maximum dietary burden of 0.42 ppm was calculated for chlorothalonil. In absence of appropriate feeding studies the Meeting considered the available metabolism study with [^{14}C]-chlorothalonil dosed to laying hens for the estimation of SDS-3701 residues in poultry. In the lowest dose group of 2 ppm no detectable residues above the LOQ of 0.01 mg/kg were found in tissues or eggs, indicating an insignificant contribution to the overall residues of SDS-3701 in poultry matrices and eggs.

For the transfer of SDS-3701 into poultry matrices or eggs also no data from unlabelled feeding studies are available. Therefore the Meeting decided to estimating residues in poultry tissues and eggs based on the metabolism study on poultry, dose with [^{14}C]-SDS-3701 for a period of 21 days.

In this study for all matrices except egg yolk only TRR levels were reported. Under consideration of the results for egg yolk, revealing > 80% of the TRR being unchanged SDS-3701, the Meeting decided to directly use the TRR levels for the estimation of residues in poultry tissues and eggs.

Dietary burden (ppm) Feeding level [ppm]	Eggs [a]	Muscle	Liver	Fat
MRL				
	mean	highest	highest	highest
MRL boiler or layer poultry (0.09 SDS-3701) [0.1 SDS-3701]	0.04 [0.044]	< 0.01 [< 0.01]	0.05 [0.056]	< 0.01 [< 0.01]
STMR				
	mean	mean	mean	mean
STMR boiler or layer poultry (0.07) [0.1 SDS-3701]	0.031 [0.044]	< 0.01 [< 0.01]	0.039 [0.056]	< 0.01 [< 0.01]

[a] In the metabolism study pooled whites and yolk were analysed, without reporting of separate weights. The Meeting concluded to based it estimations for whole eggs on the critical values reported for yolk only

Under consideration of the results of the 0.1 ppm dose group the Meeting estimated maximum residue levels for SDS-3701 in poultry muscle, skin and fat of 0.01 mg/kg, 0.05 mg/kg for eggs and 0.07 mg/kg for poultry, edible offal of, based on liver.

For the estimation of the dietary intake the Meeting estimated STMR and HR values of 0.031 and 0.04 mg/kg for eggs, 0.039 and 0.05 mg/kg for poultry, edible offal of and 0.01 and 0.01 mg/kg for poultry muscle, skin and for fat.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of chlorothalonil and SDS-3701 resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs for chlorothalonil in the thirteen Cluster Diets, based on the estimated STMRs were 9-40% of the maximum ADI (0.02 mg/kg bw). The Meeting concluded that the long-term intake of residues of chlorothalonil from uses that have been considered by the JMPR is unlikely to present a public health concern.

The IEDIs for SDS-3701 in the thirteen Cluster Diets, based on the estimated STMRs were 5-10% of the maximum ADI (0.008 mg/kg bw). The Meeting concluded that the long-term intake of residues of SDS-3701 from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The IESTI for chlorothalonil calculated on the basis of the recommendations made by the JMPR represented 0-100% of the ARfD (0.6 mg/kg bw) for children and 0–20% for the general population.

The Meeting points out that the IESTI of 100 % of the ARfD for children results from to the conservative assumption of residues in currants at the maximum residue level.

The IESTI for SDS-3701 calculated on the basis of the recommendations made by the JMPR represented 0–50% of the ARfD (0.03 mg/kg bw) for children and 0–20% for the general population.

The Meeting concluded that the short-term intake of residues of chlorothalonil or SDS-3701 resulting from uses that have been considered by the JMPR are unlikely to present a public health concern.

5.7 CLOTHIANIDIN (238)

TOXICOLOGY

Clothianidin is the International Organization for Standardization (ISO)–approved name for (*E*)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine (International Union of Pure and Applied Chemistry [IUPAC]) (Chemical Abstracts Service [CAS] No. 210880-92-5). Clothianidin is a neonicotinoid insecticide that controls insects by acting as an agonist at the nicotinic acetylcholine receptor, affecting the synapses in the insect central nervous system.

Clothianidin has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed at the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR).

All pivotal studies with clothianidin were certified to be compliant with good laboratory practice (GLP) and met the basic requirements of the relevant Organisation for Economic Co-operation and Development (OECD) or national test guideline.

Biochemical aspects

Clothianidin was almost completely (90%) absorbed from the gastrointestinal tract within 24 h following oral dosing of rats. The rate and extent of absorption were essentially independent of sex, dose or dose rate.

The compound was widely and homogeneously distributed throughout the tissues (time to maximum concentration = 1.5 h), with a rapid decrease of residues to levels at or near the limit of quantification. There was no evidence of accumulation, although higher levels were detected in kidney and liver up to 4 h post-dosing.

Within 24 h, about 94–96% of the compound was excreted. Urinary excretion was the major elimination route, accounting for about 89–95%, with faecal elimination accounting for about 3–6%. The excretion profile over 72 h after high-dose administration (elimination half-life = 1.9 h) was almost identical to that after low-dose administration (elimination half-life = 1.2 h), although the plasma concentration exhibited biphasic kinetics, suggesting moderate enterohepatic cycling.

Clothianidin metabolism was incomplete, with 56–74% of the dose being excreted unchanged over 72 h. The main metabolic pathways were 1) oxidative demethylation and 2) cleavage of the nitrogen–carbon bond between the thiazolyl-methyl position and the nitroimino moiety. The main urinary metabolites recovered after low-dose testing were thiazolylnitroguanidine (TZNG) (7–11%), *N*-methyl-*N*′-nitroguanidine (MNG) (8–13%) and nitroguanidine (NTG) (1–4%). In the faeces, 2-methylthiothiazole-5-carboxylic acid (MTCA) (9%) and thiazolmethylguanidine (TMG) (2%) were found. Other characterized metabolites were present at less than 2% of the dose.

Based upon the intended uses of clothianidin, representative metabolism studies in farm animals (goat, hen) were evaluated. It was demonstrated that the degradation pathways in farm animals were roughly comparable to those found in the rat (although absorption was probably somewhat lower) and that plant metabolism was less extensive. The major farm animal and plant metabolites (> 5% of the total radioactive residue) were also found in the rat, were structurally related to rat metabolites and/or were of lower toxicity. A notable exception was the plant metabolite methylguanidine (MG), which is similar in toxicity to the parent compound, but which was observed only at low residue levels (maximally 0.25 ppm in sugar beet leaves at harvest).

Toxicological data

Clothianidin is of moderate acute oral toxicity, with a median lethal dose (LD_{50}) between 523 and 1216 mg/kg bw in rats and of 389 mg/kg bw in male mice. The dermal LD_{50} is greater than 2000 mg/kg bw, and the inhalation median lethal concentration (LC_{50}) is greater than 6.14 mg/L (5.54 mg/L by gravimetry). Clothianidin is not irritating to the skin, is practically non-irritating to eyes and is not sensitizing to guinea-pig skin (maximization test).

In repeated-dose studies in mice, rats and dogs, no consistent toxicological profile was evident in any of the species at any of the dose ranges or study durations tested. Effects included lower body weights and body weight gains, decreased food consumption and changes in some clinical chemistry parameters. In the rat, mild induction of hepatic cytochrome P450 enzymes was observed in the 90-day feeding study. Hepatic induction was not assessed in either mouse or dog, although liver effects were also detected in dogs at a high dose.

In a 28-day feeding study in the mouse, atrophic changes in ovaries and uterus were reported at 2000 ppm (equal to 491 mg/kg bw per day). These changes in the reproductive system are considered to reflect the markedly reduced body weight gain.

Reports of increased ovary and uterus weights in a 90-day feeding study in rats at 1250 ppm (equal to 119 mg/kg bw per day for females) and above, accompanied by gross pathological and histopathological findings (uterus fluid distension/uterus luminal dilatation), could not be confirmed in a second study. In the dog, the targets were the haematopoietic system and lymphoid organs (anaemia and leukopenia). The findings in the 30-day study were consistent with those found in the 90-day and 1-year study, with a peak effect around 5 weeks and a time-related adaptation at later times. The overall no-observed-adverse-effect level (NOAEL) for these effects was 1500 ppm (equal to 36.3 mg/kg bw per day).

The lowest relevant NOAEL for short-term studies was 500 ppm (equal to 27.9 mg/kg bw per day) from a 90-day study in the rat, on the basis of reduced body weight and body weight gain at 3000 ppm (equal to 202 mg/kg bw per day). A 90-day study in the mouse was considered unreliable due to deficiencies in the study conduct.

In an 18-month carcinogenicity study in mice with dietary concentrations of up to 2000 ppm, the onset of mortality in females occurred early in the study, and the overall mortality in females was increased. This was most likely due to exceedance of the maximum tolerated dose (MTD) for a few months while the dose was adjusted. Body weight and body weight gain were reduced at 1250 ppm, and there was increased vocalization at this and the highest dose. There was an increase in hepatocellular hypertrophy at 1250 ppm and above. Fibromuscular hyperplasia of the cervix at 1250 ppm and above was observed, although such lesions are common in nulliparous ageing females. In males at 1250 ppm, there was increased incidence of myocardial degeneration. There was no statistically significant increase in the incidence of tumours of any site. The NOAEL was 350 ppm (equal to 47.2 mg/kg bw per day), based on body weight effects, clinical signs, and heart and cervical lesions at 1250 ppm.

Clothianidin was not carcinogenic in mice.

In a 24-month feeding study in rats with dietary concentrations up to 3000 ppm, feed consumption was reduced at 1500 ppm in males and at 500 ppm in females. Body weight and body weight gain were reduced in both sexes at 1500 ppm and above, mainly during the first year. Food efficiency was unaffected. At the highest dose, there was clear histological evidence of local effects in the glandular stomach. The NOAEL for non-neoplastic effects in this study was 150 ppm (equal to 9.7 mg/kg bw per day), based on changes in terminal body weight and feed consumption at 500 ppm.

The incidence of hepatocellular carcinoma in male rats was slightly increased at 500 ppm (one at termination, two in unscheduled deaths) and at 3000 ppm (four in unscheduled deaths). As there was no relationship with dose or duration of treatment and as such tumours occur occasionally in untreated rats, it was concluded that these tumours were not compound related. Increases in the

incidence of thyroid T-cell adenomas in the mid- and high-dose groups were not considered to be compound related, as there was no dose–response relationship in the incidence of adenomas plus carcinomas, and the combined incidence was not significantly increased in the top dose group.

The Meeting concluded that clothianidin was not carcinogenic in rats.

The potential genotoxicity of clothianidin was tested in an adequate range of in vitro and in vivo studies. In general, clothianidin showed no evidence of mutagenicity. There was some evidence of clastogenicity in tests with mammalian cells in vitro at cytotoxic doses. Clothianidin was consistently negative in tests for genotoxicity in vivo.

The Meeting concluded that clothianidin was unlikely to be genotoxic in vivo.

On the basis of the absence of genotoxicity in vivo and the absence of carcinogenicity in the rat and the mouse, the Meeting concluded that clothianidin is unlikely to be carcinogenic in humans.

In a two-generation study of reproductive toxicity in rats at dietary concentrations up to 2500 ppm, both maternal and offspring toxicity were observed at 500 ppm and above, with decreased body weight (F_1, F_2) leading to lower body weight gains (F_1). Offspring toxicity was observed at the top dose and included delayed preputial separation and vaginal patency at clearly maternally toxic doses. The NOAEL for both parental and offspring toxicity was 150 ppm (equal to 10.2 mg/kg bw per day), based on decreased body weight at 500 ppm (equal to 32.7 mg/kg bw per day) for parental animals and on decreased body weight and subsequent effects on preputial separation at 500 ppm (equal to 32.7 mg/kg bw per day) for offspring. The NOAEL for reproductive toxicity was 2500 ppm (equal to 179.6 mg/kg bw per day), the highest dose tested.

In rat developmental studies, the maternal NOAEL was 10 mg/kg bw per day, based on reductions in body weight gain and food consumption. The NOAEL for developmental toxicity was 125 mg/kg bw per day, the highest dose tested.

In the rabbit, fetal and developmental toxicity occurred only at maternally toxic doses. The maternal NOAEL was 10 mg/kg bw per day, based on clinical signs (starting at gestation day 13) at 25 mg/kg bw per day, and the developmental NOAEL was 75 mg/kg bw per day, based on increased post-implantation loss, reduced fetal body weight and retarded sternal ossification at 100 mg/kg bw per day.

The Meeting concluded that clothianidin induced developmental toxicity only in the presence of maternal toxicity and that it was not teratogenic.

The acute neurotoxicity of clothianidin was investigated in three gavage studies in rats at doses up to 400 mg/kg bw. Clinical signs, including behavioural effects, were observed at the top dose on the day of treatment. Dose-dependent effects on arousal were observed at 100 mg/kg bw and above in males and at 200 mg/kg bw and above in females. There were no compound-related histopathological effects on neuronal tissue. The NOAEL for acute neurotoxicity was 60 mg/kg bw, on the basis of reduced locomotor activity in males at 100 mg/kg bw.

In a 13-week rat feeding study of neurotoxicity with dietary concentrations up to 3000 ppm, animals were assessed on weeks 4, 8 and 13 of clothianidin intake. No effects were observed on motor activity, learning or memory capacity. There were no histopathological changes in neuronal tissue. Thus, the NOAEL for neurotoxicity was 177 mg/kg bw per day, the highest dose tested.

A developmental neurotoxicity study was undertaken with clothianidin administered in the diet to rats at concentrations up to 1750 ppm (equal to 142 mg/kg bw per day during gestation and 299 mg/kg bw per day during lactation). The NOAEL for fetal and maternal toxicity was 42.9 mg/kg bw per day, based on changes in body weight at higher doses. At the top dose, subtle modification of acoustic startle habituation and motor activity observed in the pups immediately after weaning were considered secondary to nonspecific toxicity. No biologically significant effects on the central nervous system were observed histomorphometrically or histologically.

The Meeting concluded that clothianidin is not a developmental neurotoxicant. At relatively high doses, it can cause transient, acute neurobehavioural effects.

In a 28-day feeding study of the immunotoxicity of clothianidin in rats at doses up to 3000 ppm, body weights and food consumption were significantly reduced in the high dose group. Based on these changes, the NOAEL for systemic toxicity was 500 ppm (equal to 45.8 mg/kg bw per day). Clothianidin had no effect on the immunoglobulin M antibody-forming cell response to the T cell–dependent antigen (sheep erythrocytes). The NOAEL for immunotoxicity was 3000 ppm (equal to 252.8 mg/kg bw per day), the highest dose tested.

In a developmental immunotoxicity study in rats, pregnant animals were offered diets containing up to 2000 ppm clothianidin from day 6 of gestation. The maternal NOAEL for systemic toxicity was 500 ppm (equal to 35 mg/kg bw per day during gestation and 68.3 mg/kg bw per day during lactation), based on reductions in body weight and food consumption and an increased incidence of ptosis at 3000 ppm. In the F_1 generation, the NOAEL for systemic toxicity was 150 ppm (equal to 26.4 mg/kg bw per day), based on reductions in body weight in females at weaning at 500 ppm. There were no immunologically relevant adverse effects on humoral immunity or cell-mediated immunity in male and female F_1 generation rats following exposure to clothianidin in the uterus during gestation, via maternal milk and maternal feed during the postpartum period or via the diet during the post-weaning period.

The Meeting concluded that clothianidin is not immunotoxic to adults or during development.

Some major (TZNG, > 5% of dose) and minor (thiazolylmethylurea [TZMU], TMG, MG, < 5% of dose) metabolites of clothianidin in the rat are also detected in the hen, goat, plants and environment. They all have oral LD_{50} values less than 2000 mg/kg bw and should thus be considered intrinsically harmful by ingestion.

Other compounds, such as NTG (rat metabolite, 1–4% of the administered dose), *N*′-[amino(2-chlorothiazol-5-ylmethylamino)methylene] acetohydrazide (ATG-Ac) (hen metabolite) and *N*′-[(2-chlorothiazol-5-ylmethylamino)(methylamino)methylene]-2-oxopropanohydrazide (ATMG-Pyr) (goat metabolite) were less toxic, with LD_{50}s above 2000 mg/kg bw.

Metabolite MG may be considered a potential plant residue of concern (known neurotoxicant, like most guanidino compounds), but it is a rat metabolite and it occurred at very low residue levels in plant commodities used for animal feeding only. Thus, further testing on MG is not necessary.

Metabolite MNG was not tested for acute oral toxicity. However, as it was a rat metabolite accounting for about 13% of the dose, it was considered to be covered by the toxicological assessment of clothianidin.

Metabolites TZNG, TZMU, TMG, MG, MNG, ATG-Ac, ATGM-Pyr and 3-methylamino-1H-imidazo[1,5-c]imidazole (MAI) were tested in the *Salmonella typhimurium* reverse gene mutation assay, and all were negative.

In conclusion, metabolic activity in mammals and plants and hydrolytic activity in the environment result in the transformation of clothianidin to breakdown products, which are relatively more toxic than or of the same order of toxicity as the parent compound. As many of these products are also rat metabolites, occur at very low residue levels and are not genotoxic, further testing is not warranted.

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

Toxicological evaluation

An acceptable daily intake (ADI) of 0–0.1 mg/kg bw was established on the basis of the NOAEL in the chronic study in the rat of 9.7 mg/kg bw per day for decreased body weight and food consumption. A safety factor of 100 was applied.

An acute reference dose (ARfD) of 0.6 mg/kg bw was established on the basis of the NOAEL of 60 mg/kg bw in the acute neurotoxicity study in the rat, based on reduced locomotor activity at 100 mg/kg bw. A safety factor of 100 was applied.

The Meeting considered that the effects seen in mice at 50 mg/kg bw per day in pharmacological studies were marginal and transient (less than 0.5–1 h) at this dose level, whereas at the next dose level, 100 mg/kg bw per day, several effects were evident simultaneously in the same animals for longer times (3 h).

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	350 ppm, equal to 47.2 mg/kg bw per day	1250 ppm, equal to 171.4 mg/kg bw per day
		Carcinogenicity	2000 ppm, equal to 251.9 mg/kg bw per day[b]	—
Rat	Ninety-day studies of toxicity[a]	Toxicity	500 ppm, equal to 27.9 mg/kg bw per day	1250 ppm, equal to 96 mg/kg bw per day
	Two-year studies of toxicity and carcinogenicity[a]	Toxicity	150 ppm, equal to 9.7 mg/kg bw per day	500 ppm, equal to 32.5 mg/kg bw per day
		Carcinogenicity	3000 ppm, equal to 157 mg/kg bw per day[b]	—
	Two-generation study of reproductive toxicity[a]	Parental toxicity	150 ppm, equal to 10.2 mg/kg bw per day	500 ppm, equal to 32.7 mg/kg bw per day
		Offspring toxicity	150 ppm, equal to 10.2 mg/kg bw per day	500 ppm, equal to 32.7 mg/kg bw per day
		Reproductive toxicity	2500 ppm, equal to 179.6 mg/kg bw per day[b]	—
	Developmental toxicity study[c]	Maternal toxicity	10 mg/kg bw per day	40 mg/kg bw per day
		Embryo and fetal toxicity	125 mg/kg bw per day[b]	—
	Acute neurotoxicity study [c]	Neurotoxicity	60 mg/kg bw	100 mg/kg bw
	Developmental neurotoxicity study[a]	Maternal toxicity	500 ppm, equal to 42.9 mg/kg bw per day	1750 ppm, equal to 142 mg/kg bw per day
		Offspring toxicity	500 ppm, equal to 42.9 mg/kg bw per day	1750 ppm, equal to 142 mg/kg bw per day
		Developmental neurotoxicity	1750 ppm, equal to 142 mg/kg bw per day[b]	—

Species	Study	Effect	NOAEL	LOAEL
	Immunotoxicity study[a]	General toxicity	500 ppm, equal to 45.8 mg/kg bw per day	3000 ppm, equal to 252.8 mg/kg bw per day
		Immunotoxicity	3000 ppm, equal to 252.8 mg/kg bw per day[b]	—
	Developmental immunotoxicity study[a]	Maternal toxicity	500 ppm, equal to 35–68.3 mg/kg bw per day	2000 ppm, equal to 120.6–249.7 mg/kg bw per day
		Offspring toxicity	150 ppm, equal to 26.4 mg/kg bw per day	500 ppm, equal to 88.9 mg/kg bw per day
		Developmental immunotoxicity	2000 ppm, equal to 337.7 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity study[c]	Maternal toxicity	10 mg/kg bw per day	25 mg/kg bw per day
		Embryo and fetal toxicity	75 mg/kg bw per day	100 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity[a,d]	Toxicity	1500 ppm, equal to 36.3 mg/kg bw per day	2000 ppm, equal to 46.4 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.1 mg/kg bw

Estimate of acute reference dose

0.6 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid; 90% within 24 h
Distribution	Wide; highest concentrations in kidney and liver
Potential for accumulation	None
Rate and extent of excretion	Largely complete within 72 h
Metabolism in animals	Moderately metabolized; excreted unchanged at 56–74% at 72 h; main pathway was oxidative demethylation and cleavage of the nitrogen–carbon bond between the thiazolyl-methyl position and the nitroimino moiety

Toxicologically significant compounds in animals, plants and the environment	Parent compound and animal metabolites TZNG, MNG, NTG, MTCA and TMG; main plant metabolite is MG
Acute toxicity	
Rat, LD_{50}, oral	523–1216 mg/kg bw
Mouse, LD_{50}, oral	389 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.54 mg/L (4.5 h, nose-only exposure)
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Practically non-irritating
Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman test)
Short-term studies of toxicity	
Target/critical effect	Decreased body weights and body weight gain, decreased kidney weights, decreased food consumption, clinical chemistry changes
Lowest relevant oral NOAEL	27.9 mg/kg bw per day (90-day study in rats)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (28-day study in rats)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Decreased food consumption and body weights
Lowest relevant NOAEL	9.7 mg/kg bw per day (rat carcinogenicity study)
Carcinogenicity	Not carcinogenic
Genotoxicity	
	Clothianidin unlikely to be genotoxic in vivo; metabolites not genotoxic (Ames test)
Reproductive toxicity	
Reproduction target/critical effect	None
Lowest relevant reproductive NOAEL	179.6 mg/kg bw per day (highest dose tested)
Developmental target/critical effect	Decreased fetal weight, increased post-implantation loss, decreased sternal ossification centres
Lowest relevant developmental NOAEL	75 mg/kg bw per day (rabbit)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity target/critical effect	Decreased locomotor activity
Lowest relevant acute neurotoxic NOAEL	60 mg/kg bw per day
Short-term neurotoxicity target/critical effect	Decreased body weight and feed consumption
Lowest relevant subchronic neurotoxic NOAEL	60 mg/kg bw per day
Developmental neurotoxicity target/critical effect	No biologically significant effects
Lowest relevant developmental neurotoxic NOAEL	142 mg/kg bw per day (highest dose tested)
Other toxicological studies	
Twenty-eight-day immunotoxicity	No effects on the immune system

Developmental immunotoxicity	No effects on the immune system
Medical data	
	No data

Summary

	Value	Study	Safety factor
ADI	0–0.1 mg/kg bw	Rat, 2-year study	100
ARfD	0.6 mg/kg bw	Rat, acute neurotoxicity study	100

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of clothianidin were considered for the first time by the present Meeting. The residue evaluation was scheduled for the 2010 JMPR by the Forty-first Session of the CCPR (ALINORM 09/32/24).

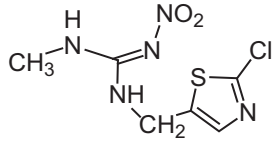
Clothianidin is an insecticide that can be used for soil, foliar and seed treatment belonging to the chemical class of nitromethylenes or neonicotinoids and acts as an agonist of the nicotinic acetylcholine receptor, affecting the synapses in the insect central nervous system of sucking and chewing insects. It has registered uses in many countries on soya beans, cereals, sugar cane, oilseeds, tea and a range of fruits and vegetables.

The Meeting received information from the manufacturer on identity, metabolism, storage stability, residue analysis, use pattern, residues resulting from supervised trials on pome fruit, stone fruit, cranberries, grapes, persimmon, bananas, Brassica vegetables, fruiting vegetables, lettuce, dry soya beans, root and tuber vegetables, cereal grains, sugar cane, oilseeds, animal feeds and teas, fate of residue during processing, and livestock feeding studies. In addition, the Meeting received information from the Netherlands and Japan on use pattern.

Chemical name

Clothianidin or (E)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine

Structural formula:



Clothianidin exists predominantly in the E-form. This has been confirmed by NMR analysis. Quantum chemical calculations revealed that in water the E-isomer is more stable than the Z-isomer. At room temperature the theoretical ratio between E/Z isomers is estimated as 65:1.

The compound clothianidin is equivalent to the E form of CGA 322704, a metabolite arising from thiamethoxam use. Thiamethoxam is described as an E/Z mixture and the situation is similar for metabolite CGA 322704. No information is given on the actual ratio between E and Z isomers, nor which of these isomers is the active one. Information on the activation energy to convert Z-isomers to E-isomers is not available. If the activation energy for conversion is high, it is likely that the CGA 322704 appears as E/Z mixture in crops, soil, water and animal commodities. HPLC chromatograms of CGA 322704 from supervised trials show a single peak, so it is not clear whether E/Z mixtures cannot be separated by HPLC or whether there is only one isomer present in plant and animal commodities. As a consequence both isomers need to be considered.

Metabolites referred to in the appraisal by codes:

ACT	2-chlorothiazolyl-5-ylmethylamine
ATG	N'-[amino(2-chlorothiazol-5-ylmethyl)guanidine
ATMG	N'-[amino(2-chlorothiazol-5-ylmethyl)-N"-methylguanidine
ATMT	3-amino-4-(2-chlorothiazolyl-5-yl)methyl-5-methyl-4H-1,2,4-triazole
MG	methylguanidine
MNG	methylnitroguanidine
MU	methylurea
TMG	thiazolylmethylguanidine
TMT	3-(2-chlorothiazolyl-5-yl)methylamino-5-methyl-1H-1,2,4-triazole
TZG	thiazolylguanidine
TZMU	thiazolylmethylurea
TZNG	thiazolylnitroguanidine
TZU	thiazolylurea

Animal metabolism

The Meeting received results of animal metabolism studies in a lactating goat and in laying hens. Experiments were carried out using clothianidin ^{14}C labelled at the nitroimino position.

Metabolism in laboratory animals was summarized and evaluated by the WHO panel of the JMPR in 2010.

A lactating goat, orally treated once daily for three consecutive days with nitroimino-[^{14}C]clothianidin at an actual dose rate of 201 ppm in the dry weight feed (equivalent to 9.8 mg ai/kg bw/d), was sacrificed 5 hours after the last dose. Of the administered dose 70.4% was recovered: 13.5% in faeces, 48.8% in urine, 6.6% in tissues and 6.6% in milk. The radioactivity in the gastrointestinal tract or in breathed air was not measured. The radioactivity in the tissues ranged from 16 mg/kg in liver and 9.3 mg/kg in kidney to 4.3 mg/kg in muscle and 2.1 mg/kg clothianidin equivalents in fat. Maximum residue levels in milk were found within 24 hours: 6.0–6.6 mg/kg was found at 8 hours after the 1st, 2nd and 3rd doses and decreased to 0.92–0.97 mg/kg clothianidin equivalents at 24 hours after the 1st and 2nd doses.

Radioactivity was characterized in all tissues and milk. A total of 51%, 67%, 81%, 89% and 94% of the total radioactivity could be identified in liver, kidney, muscle, fat and milk, respectively. Parent was the major compound found at 51%, 25% and 37% of the total radioactivity in milk, muscle and fat, respectively. The major metabolites were TZNG at 14% in milk, TZMU at 13% in fat, and TZU at 11% in milk, 13% in muscle and 12% in fat. In liver and kidney, the parent compound was not found. The major metabolite in liver was TMG and conjugates at 13%. The major metabolites in kidney were TZU at 15%, TZG at 12%, TZMU at 11% and an ATMG-pyruvate at 10%. Other minor metabolites identified were below 8% of the total radioactivity. Part of the extractable residue in tissues and milk remained unidentified (7.3%–42% of the total radioactivity). The non-identified part of the radioactivity consisted mainly of polar compounds. Up to 14% of the total radioactivity remained unextracted.

Six laying hens, orally treated once daily for three consecutive days with nitroimino-[^{14}C]clothianidin at an actual dose rate of 134 ppm in the dry weight feed (equivalent to 10.4 mg ai/kg bw/d), were sacrificed 5 hours after the last dose. Of the administered doses 98% was recovered: 95% in excreta, 3.1% in tissues and 0.15% in eggs. The radioactivity in the tissues ranged from 7.9 mg/kg in kidney and 5.1 mg/kg in liver to 1.4–1.7 mg/kg in muscle, 1.1 mg/kg in skin and 0.19 mg/kg clothianidin equivalents in fat. Residue levels in eggs increased from 0.38–0.94 mg/kg clothianidin equivalents at 24 to 53 hours after the 1st dose.

Radioactivity was characterized in liver, muscle, fat and eggs. At least 65% of the total radioactivity could be identified. Parent was only a minor compound and was found at levels of up to 5.3% of the total radioactivity in tissues and at 21% in eggs. Major metabolites were TZNG at 88% in eggs, 46% in liver and 24% in fat, TZG at 22% in liver and ATG conjugates at 35% in muscle and 38% in fat. Other minor metabolites identified were below 4% of the total radioactivity. Part of the extractable residue in tissues and eggs remained unidentified (0.7%–31% of the total radioactivity). Up to 11% of the total radioactivity remained unextracted.

Clothianidin is efficiently degraded in goats and hens into a large number of metabolites reflecting the existence of numerous degradation pathways such as denitrification, hydrolysis, oxidative methylation and C-N bond cleavage to form TMG, TZMU, TZNG, or MNG, respectively, followed by further transformation to form ATMG conjugates, TZU, TZG and ATG conjugates.

The metabolic pathway proposed for ruminants and poultry is consistent with that for rats. Some poultry specific metabolites such as the ATG conjugates (35–38% in muscle and fat), TMT (2.4% in muscle) and ATMT (3.0% in muscle) and some ruminant specific metabolites like THMG (1.6% in milk) and ATMG-pyruvate (2.5–10.4% in liver, kidney, muscle, fat) were not present in rat metabolism.

Plant metabolism

The Meeting received plant metabolism studies for clothianidin seed treatments on sugar beets or maize, foliar spray treatment of apple trees or tomatoes and granular soil treatment of tomatoes. Experiments were carried out using clothianidin ^{14}C labelled at the nitroimino or the thiazolyl moiety.

Sugar beet seeds were treated with nitroimino-[^{14}C]clothianidin at a rate of 190 g ai/ha. Sugar beets were grown outdoors. Total radioactive residues in the roots harvested 48, 55 and 144 days following last application were 0.86, 0.20, and 0.034 mg/kg clothianidin equivalents. Total radioactive residues in the leaves harvested 48, 55 and 144 days following last application were 1.8, 0.52 and 0.89 mg/kg clothianidin equivalents. At harvest (144 days) a total of 46% and 75% of the total radioactivity could be identified in respectively roots and leaves. At harvest, sugar beet roots contained predominantly the parent compound at 24% of the total radioactivity, whereas the leaves showed a predominant amount of TMG and MG metabolites at 27–29% of the radioactivity and only a low level of parent (4.3%). Other minor metabolites identified were below 10% of the total radioactivity. Part of the extractable residue in roots and leaves at harvest remained unidentified (19–41% of the total radioactivity). Up to 13% of the total radioactivity remained unextracted. At earlier harvest times (48 and 55 days) parent was the major compound in both roots and leaves (49–68%).

Maize seeds were treated with nitroimino-[^{14}C]clothianidin at a rate of 1.06 mg ai/seed. Maize was grown outdoors. Total radioactive residues in the forage harvested 60 days following last application was 0.130 mg/kg clothianidin equivalents. Total radioactive residues in the stover and kernels harvested 145 days following last application were 0.170 and 0.006 mg/kg clothianidin equivalents. A total of 70%, 56% and 53% of the total radioactivity could be identified in forage, stover and kernels, respectively. The parent was the major compound recovered in forage, stover and kernels and accounted for 43%, 20% and 14% of the total radioactivity, respectively. A major metabolite found in stover and kernels was MG at 15% and 22% of the total radioactivity. Other minor metabolites identified were below 10% of the total radioactivity. Part of the extractable residue in forage, stover and kernels remained unidentified (27–36% of the total radioactivity). Up to 12% of the total radioactivity remained unextracted.

Maize seeds were treated with thiazolyl-2-[^{14}C]clothianidin at a rate of 2.52 mg ai/seed. Maize was grown indoors. Total radioactive residues in the forage harvested 63 days following last application was 0.89 mg/kg clothianidin equivalents. Total radioactive residues in the stover and kernels harvested 160 days following last application were 3.1 and 0.063 mg/kg clothianidin equivalents. A total of 80%, 65%, and 62% of the total radioactivity could be identified in respectively forage, stover and kernels. The parent was the major compound recovered in forage,

stover and kernels and accounted for 64%, 40% and 58% of the total radioactivity, respectively. Minor metabolites identified were below 10% of the total radioactivity. Part of the extractable residue in forage, stover and kernels remained unidentified (14–33% of the total radioactivity). Up to 8.5% of the total radioactivity remained unextracted.

Outdoors grown apple trees were sprayed two times with nitroimino-[^{14}C]clothianidin at a dose rate of 150 g ai/ha each and an interval of 85 days. Total radioactive residues in the apple fruits and leaves harvested 14 days following last application were 0.076 and 6.45 mg/kg clothianidin equivalents. The radioactivity was distributed within the fruit and leaves: 33% and 70% of the total radioactivity could be removed from fruits and leaves by a methanolic surface wash respectively, while 63% and 24% could be extracted from fruits and leaves, respectively. A total of 80% and 84% of the total radioactivity could be identified in fruits and leaves, respectively. Parent was the major compound both in the surface washed phase and in the solvent extract accounting for 61% and 54% and of the total radioactivity in fruits and leaves, respectively. The major metabolite found in fruits was TZMU at 11% of the total radioactivity. Minor metabolites identified in fruits and leaves were below 10% of the total radioactivity. Part of the extractable residue remained unidentified (10–16% of the total radioactivity). Up to 5.6% of the total radioactivity remained unextracted.

Indoors grown tomato plants were sprayed two times with nitroimino-[^{14}C]clothianidin at a dose rate of 158 g ai/ha each and an interval of 14 days. Total radioactive residues in the tomato fruits harvested 3 days following last application were 0.57 mg/kg clothianidin equivalents. The major part of the radioactivity was located on the surface: 97% of the radioactivity could be removed by a methanolic surface wash. A total of 97% of the total radioactivity could be identified, which was allocated solely to the parent compound. Only a small part of the extractable residue remained unidentified (3.3% of the total radioactivity), while only 0.1% of the total radioactivity remained unextracted.

Planting holes were treated with nitroimino-[^{14}C]clothianidin at a dose rate of 15 mg ai/hole and 33 day old tomato plants were transplanted in the holes. Tomato plants were grown indoors. Total radioactive residues in the tomato fruits harvested 97 days following the application were 0.014 mg/kg clothianidin equivalents. A total of 92% of the total radioactivity could be identified. Parent was the predominant residue at 66% of the total radioactivity. The major metabolite found was MNG at 18% TRR. Other minor metabolites were below 10% of the radioactivity. Only a small part of the extractable residue remained unidentified (6.0% of the total radioactivity), while only 1.9% of the total radioactivity remained unextracted.

In each commodity tested, except sugar beet leaves at harvest, clothianidin was found to be the major residue (14–97% of the total radioactivity). Major metabolites found were TMG (27% in mature sugar beet leaves), MG (29% in mature sugar beet leaves, 15% in maize stover, 22% in maize kernels), TZMU (11% in apple fruit), and MNG (18% in tomato fruit).

In crops, clothianidin is degraded into a large number of metabolites reflecting the existence of numerous degradation pathways. The major pathways are denitrification, hydrolysis, and C-N bond cleavage to form TMG, TZMU, and MNG, followed by further transformation to MG. Degradation occurred at a relatively low to medium level, leaving the parent compound as the predominant component.

All plant metabolites identified were also found in rats.

Environmental fate in soil

The Meeting received information on the fate of clothianidin after aerobic degradation in soil and after photolysis on the soil surface. In addition, the Meeting received information on the uptake of clothianidin soil residues by rotational crops. Experiments were carried out using clothianidin ^{14}C labelled at the nitroimino or the thiazolyl moiety.

An aerobic soil degradation study was conducted with three different soils. Soils were mixed with nitroimino-[^{14}C]clothianidin at 0.133 mg ai/kg, equivalent to 300 g ai/ha. Soils were incubated for 120 days in the dark at 20 °C at 40% of maximum water holding capacity (silt loam and silt), or for 365 days at 75% of 333 mbar moisture (sandy loam). Calculated half lives (DT_{50}) were 143, 227, and 490 days for silt, silt loam, and loamy sand, respectively. Parent was the predominant residue at the end of the study (54–69% of the total applied radioactivity). The major metabolites were TZNG at 9.1% and MNG at 11% of the total applied radioactivity.

A second aerobic soil degradation study was conducted with two silt loam soils. Soils were mixed with thiazolyl-2-[^{14}C]clothianidin at 0.133 mg ai/kg, equivalent to 300 g ai/ha. Soils were incubated for 181 or 379 days in the dark at 20 ºC at 75% of 333 mbar moisture. Calculated half lives (DT_{50}) for the silt loam soils were 541 and 808 days. Parent was the predominant residue at the end of the study (60–78% of the total applied radioactivity). Only minor metabolites were found (less than 2% of total applied radioactivity).

A photolysis study was conducted on a soil surface. Nitroimino-[^{14}C]clothianidin was applied uniformly on a sandy loam soil surface, equivalent to a rate of 300 g ai/ha. Samples were exposed to artificial sunlight for 17 days, equivalent to 42 days of natural sunlight. The half live was calculated as 8.2 days. Parent was the predominant residue at the end of the study (22% of the total applied radioactivity). Only minor metabolites were found (less than 5% of the applied radioactivity).

In a confined rotational crop study, nitroimino-[^{14}C]clothianidin was sprayed on a sandy loam soil at a rate of 328 g ai/ha under greenhouse conditions. Rotational crops were sown 29, 153 and 314 days after the application, representing first, second and third rotations. Wheat forage was harvested at 41–50 days after sowing, wheat hay 77–106 days after sowing and wheat straw/grain, Swiss chard and turnip leaves/roots at 123–161 and 41–61, 75–84 days after sowing, i.e., at maturity. Total radioactivity was 0.016, 0.011 and 0.007 mg/kg clothianidin equivalents in turnip roots after the first, second and third rotations respectively, 0.11, 0.052 and 0.044 mg/kg in the wheat grain, 0.15, 0.25 and 0.12 mg/kg in the Swiss chard, 0.36, 0.22 and 0.11 mg/kg in the turnip leaves, 0.30, 0.39 and 0.34 mg/kg in wheat forage, 0.53, 0.36 and 0.37 mg/kg in wheat hay and 2.6, 1.2 and 1.2 mg/kg in wheat straw. Parent was the major compound in turnip roots at 27–40% of total radioactivity. The metabolite TZNG was the major compound in wheat grain at 10–23% of total radioactivity. Parent, TZNG and MNG were the major compounds at 12–46%, 3.9–16% and 11–37% of total radioactivity in green crop parts including wheat hay. Parent, TZNG, MG and MNG were the major compounds in wheat straw at 7.2–12%, 7.3–11%, 9.3–18% and 9.1–13% of total radioactivity, respectively.

In a field rotational crop study, maize seeds were treated at a rate of 2 mg ai/seed and sown in the field, corresponding to a rate of 162–192 g ai/ha. Maize plants were tilled into the soil and rotational crops were sown 1, 4, 8 and 12 months after sowing the maize seeds. Turnips (roots, tops), wheat (forage, hay, straw, grain) and mustard greens were harvested at earliest crop maturity. Clothianidin levels in green crop parts including wheat hay ranged from < 0.01–0.025 mg/kg, < 0.01–0.017 mg/kg, and < 0.01–0.023 mg/kg at the 1, 4 and 8 month plant back intervals, respectively. Clothianidin was not found at the 12 month plant back intervals (< 0.01 mg/kg). Clothianidin was not found in turnip roots, wheat grain and wheat straw at any of the plant back intervals (< 0.01 mg/kg). TZNG was only quantified at the 1 month plant back interval and was not found in any of the commodities (< 0.01 mg/kg).

The proposed degradation pathway in soil proceeds via two main routes with clothianidin being transformed in TZNG by oxidative methylation and to MNG by C-N bond cleavage. These soil metabolites could then be taken up by plants and further metabolised.

Environmental fate in water-sediment systems

The Meeting received information on the hydrolysis and photolysis of clothianidin in sterile water. Experiments were carried out using clothianidin ^{14}C labelled at the nitroimino or the thiazolyl moiety.

Clothianidin is regarded as hydrolytically stable at pH 4 and 7 at 50 °C, but is unstable at pH 9 at this high temperature. At ambient temperature, clothianidin is stable at pH 4, 7 and 9. The experimental half-life for clothianidin at pH 9 was 14.4 days at 50 °C, 3.7 days at 62 °C and 0.68 days at 74 °C. After 33 days there is a clothianidin decrease of 6% at 25 °C. Clothianidin is degraded to a low extent by hydrolysis to form mainly TZMU and ACT.

A photolysis study was conducted in sterile water with artificial sunlight for 18 days, equivalent to 22.5 days of natural sunlight. The half-life for clothianidin was 3.3 hours for artificial sunlight, equivalent to 4.1 hours in natural sunlight. When the study was repeated with non-sterile water, a half-life for clothianidin of 35–37 minutes was found. Photo-degradation therefore contributes significantly to the elimination of clothianidin in aquatic systems. Clothianidin is degraded by hydrolysis, denitrification and complex cyclisation reactions to form mainly TZMU, MU and MG.

Methods of analysis

The Meeting received description and validation data for analytical methods for clothianidin, TZNG, TMG, TZMU and MNG in plant commodities or for clothianidin, TZG, TZU and the pyruvate conjugate of ATMG in animal commodities.

Three single residue analytical methods were proposed to the Meeting as post-registration monitoring and enforcement method for parent clothianidin in plant and animal commodities. Compatibility of clothianidin in an existing multi-residue HPLC-MS method (e.g., DFG S19) was not tested.

The Meeting considers the HPLC-MS-MS single residue method 00552 and modifications thereof and the HPLC-UV single residue method 00657 and modifications thereof sufficiently validated for the determination of parent clothianidin in plant commodities with high water content, plant commodities with high acid content, plant commodities with high fat content, and dry plant commodities. The use of deuterated standards in HPLC-MS-MS method 00552 makes the method very expensive and therefore less suitable as enforcement-monitoring method for world-wide use. The Meeting considers the HPLC-UV single-residue method 00656 and modifications thereof sufficiently validated for the determination of parent clothianidin in animal tissues, milk and eggs. The LOQs for these three methods were in the range of 0.01–0.02 mg/kg, depending on the matrix.

The methods reported to the Meeting and used in the supervised residue trials, processing studies, storage stability studies and feeding studies determined parent clothianidin and in some cases also the metabolites TZNG, TMG, TZMU and MNG (in plant commodities) or TZG, TZU and the pyruvate conjugate of ATMG (in animal commodities). Macerated samples were generally extracted with acetonitrile/water. The extract was cleaned up by solvent partition and/or column chromatography and/or solid phase extraction, if necessary. The final residue could then be determined by HPLC-UV or HPLC-MS-MS. The Meeting considers validation sufficient for all commodities and all analytes analysed in the supervised residue trials and feeding studies. LOQs were in the 0.01–0.05 mg/kg range for clothianidin and its metabolites in plant and animal commodities. LOQs for milk were in the 0.002–0.01 mg/kg range for clothianidin.

Extraction efficiencies for acetonitrile/water (2:1) including clean-up steps as used in HPLC-MS-MS method 00552 for plant commodities were verified using samples with incurred radioactive residues from metabolism studies on apple (14 day surface washed fruit sample) and maize (63 day forage, 160 day stover and 160 day kernel sample). Extraction efficiency for acetonitrile/water (2:1) for clothianidin was 85%, 81%, 74%, 61% respectively in surface washed apple fruit, maize forage, maize stover and maize kernels. The Meeting considers the extraction efficiencies for the extraction and clean-up steps as used in the analytical methods generally sufficient for plant commodities. However the study is not conclusive on grains, since the recovery of 61% might be within analytical errors at such low residue levels.

Extraction efficiencies for acetonitrile/water (2:1) including clean-up steps as used in HPLC-MS-MS method 00624 for animal commodities were verified using samples with incurred radioactive residues from metabolism studies on goat (milk, muscle, fat and liver). Extraction efficiency was 100%, 75%, 73% in milk, muscle and fat for clothianidin, 72%, 46%, 106% in muscle, fat and liver for the pyruvate conjugate of ATMG, 62%, 69%, 67% in muscle, fat and liver for TZG, and 87%, 73%, 94% and 68% for milk, muscle, fat and liver for TZU. The Meeting considers the extraction efficiencies for the extraction and clean-up steps as used in the analytical methods for clothianidin sufficient for animal commodities. However, extractions efficiencies for metabolites TZG, the pyruvate conjugate of ATMG and TZU are considered insufficient (less than 70% for some or all commodities).

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of clothianidin and TMG in plant commodities stored frozen. No storage stability studies were provided for animal commodities. Since the samples from the animal feeding study were analysed within 30 days after slaughter, there is no need to have storage stability studies on animal commodities.

Parent clothianidin was stable when stored at –10 °C or lower for at least 24 months in crops with high water content (apple, Japanese pear, apricot, peach, cauliflower, head cabbage, cucumber, tomato, lettuce, maize and forage), for at least 18 months in crops with high acid content (cranberries and grapes), for at least 24 months in crops with high oil content (dry soya beans, cottonseed, rape and seed), for at least 24 months in crops with high starch content (maize grain, rice grain, sugar beet roots and potatoes), for at least 10 months in dry tea leaves, for at least 24 months in maize straw, for at least 2 months in tomato paste, for at least 4 months in cotton meal, and for at least 4 months in cotton oil.

Metabolite TMG was stable when stored at –10 °C or lower for at least 25 months in crops with high water content (cauliflower, lettuce and sugar beet leaves), at least 162 days in crops with high acid content (grapes), at least 25 months in crops with high starch content (potatoes) and at least 25 months in processed potato commodities (flakes and chips).

All crop commodities from supervised residue trials were analysed within this period, although storage temperatures varied. Since clothianidin is shown to be stable for a long period of time, trials where samples were stored for a few days at + 5 °C before being frozen and trials where temperatures of frozen samples increased to –1 °C were not rejected.

Definition of the residue

The composition of the residue was investigated for livestock, plant commodities, soil and water.

Based on the available livestock studies, parent clothianidin was the major component in ruminant muscle, ruminant fat and milk (21–51% of the total radioactivity TRR), but was metabolised further in ruminant liver, ruminant kidney, poultry tissues and eggs. The major residue in ruminant liver consists of TMG including conjugates (13%); the major residue in ruminant kidney consists of TZU (15%), TZG (12%), TZMU (11%) and ATMG-pyruvate (10%) and parent was not found in liver and kidney. Because the lactating goat was sacrificed only 5 hours after dosing, parent levels might decrease further, while metabolite levels might rise in time. However the metabolite study on goats shows that maximum levels in milk are reached within 24 hours, showing that the residue disappears very quickly. The major residue in poultry consists of ATG conjugates (35%) in muscle; TZNG (24%) and ATG conjugates (38%) in fat; and TZNG (46%) and TZG (22%) in liver. Parent was only found at low levels (up to 5.2%). The major residue in poultry eggs consists of TZNG (88%), parent was found at 21% of the total radioactivity. Of these metabolites, ATMG (conjugates) and ATG (conjugates) were not found in rats. Additional toxicity studies with ATMG-pyruvate and ATG-acetate indicated no toxicological concern, (LD_{50} > 2000 mg/kg, negative mutagenicity test). Because of this and because the conjugates of ATMG and ATG are expected to be

excreted readily, these metabolites are not included in the residue definition. Since TZNG forms a major part of the residue in poultry fat (24%), poultry liver (46%) and poultry eggs (88%), and TZNG may be significant in ruminants, TZNG is considered for inclusion in the residue definition.

No poultry feeding study has been conducted, therefore actual residue levels in poultry tissues and eggs are not available. Since poultry dietary burden is very low compared to dose levels in the metabolism study (0.25 ppm versus 134 ppm), no residues are anticipated in poultry tissues and eggs. A feeding study on dairy cows was conducted at a maximum level of 2.6 ppm dry feed which is in the same order of magnitude as the dietary burden (0.75 ppm). At this level, the parent compound was only found in milk at levels of up to 0.012 mg/kg. TZNG was not tested. Metabolites TZG, TZU and ATMG-pyruvate were not found in tissues or in milk (< 0.01 mg/kg). Based on these results it is not expected that metabolites will be found in ruminant tissues and milk, nor in poultry tissues and eggs. Therefore the Meeting concluded that the residue definition should only include the parent compound.

Fat solubility of clothianidin in milk has not been investigated in metabolism studies or in feeding studies. The log K_{ow} for clothianidin of approximately 0.7–0.9 does not suggest fat solubility. Fat solubility of TZNG has not been investigated, but based on its molecular structure it is expected to be in the same order of magnitude as the parent compound. The Meeting considers the residue in animal commodities (clothianidin and TZNG) not to be fat-soluble.

Based on the available comparative plant metabolism studies, parent clothianidin is the major component (14–97% of the total radioactivity TRR) of the crops tested, except in mature sugar beet leaves (27% TMG, 29% MG). TMG, MNG, TZMU and TZNG have been analysed in some supervised field trials. TMG was not found in grapes, persimmons, potatoes, sugar beet roots (< 0.01 or < 0.01 mg/kg), but was found in leafy crops like head cabbage (< 0.01–0.013 mg/kg), head lettuce (< 0.01–0.078 mg/kg), cotton gin trash (0.048–0.14 mg/kg), sugar beet tops (< 0.01–0.026 mg/kg). MNG was not found in persimmons (< 0.01 mg/kg). TZMU and TZNG were found in persimmon at 0.02–0.03 mg/kg. In rotational crops, clothianidin was metabolised further and metabolites TZNG, MNG, and MG were found at quantifiable levels. TZNG is found as a minor metabolite in primary crops (< 10% TRR) and as a major metabolite in rotational crops (10–23% in grain, 3.9–16% in green crop parts and 7.3–11% in wheat straw). However in a field rotational crop study, TZNG could not be found (< 0.01 mg/kg) at the earliest 1 month plant back interval. All plant metabolites identified were also found in rats. Therefore, metabolites are not included in the residue definition.

Clothianidin exists predominantly in the E-form. The compound clothianidin is equivalent to the E form of CGA 322704, a metabolite arising from thiamethoxam use. No information is given on the actual ratio between E and Z isomers, nor which of these isomers is the active one. Information on the activation energy to convert Z-isomers to E-isomers is not available. If the activation energy for conversion is high, it is likely that the CGA 322704 appears as E/Z mixture in crops, soil, water and animal commodities. HPLC chromatograms of CGA 322704 from supervised trials show a single peak, so it is not clear whether E/Z mixtures cannot be separated by HPLC or whether there is only one isomer present in plant and animal commodities. Therefore, both isomers should be included in the residue definition. Clothianidin and the CGA 322704 metabolite of thiamethoxam will appear the same as clothianidin in the analytical methods. The Z-isomer may result from use of thiamethoxam.

The Meeting recommended the following as residue definitions for clothianidin:

Definition of the residue for compliance with the MRL or for estimation of the dietary intake for plant commodities: *sum of clothianidin and its Z-isomers*

Definition of the residue for compliance with the MRL or for estimation of the dietary intake for animal commodities: *sum of clothianidin and its Z-isomers.*

The Meeting considers the residue in animal commodities not fat soluble.

Results of supervised trials on crops

The Meeting received supervised trials data for clothianidin on apples, pears, apricots, cherries, nectarines, peaches, plums, cranberries, grapes, persimmons, bananas, head cabbages, broccoli, cucumber, summer squash, egg plants, sweet corn, tomatoes, head lettuce, leaf lettuce, dry soya beans, carrots, chicory roots, potatoes, sugar beet roots, barley, maize, popcorn, rice, sorghum, wheat, sugarcane, cotton seed, rape seed, sunflower seed and tea.

The Meeting noted that clothianidin residues may arise from use of clothianidin as well as from use of thiamethoxam. The compound clothianidin is equivalent to the E form of CGA 322704, a metabolite arising from thiamethoxam use. Residues of CGA 322704 occurring in food are included in the clothianidin MRLs. In the present appraisal first the maximum residue levels, STMRs and HRs for clothianidin use are evaluated. The same is done for the CGA 322704 metabolite in the thiamethoxam appraisal. In the present appraisal an overview table is given, where a recommendation is given for both uses.

Pome fruits

Field trials involving apples were performed in Australia, Germany, Hungary, the UK, France, Italy, Spain, Japan and the USA.

GAP for apples and pears in Australia is for two foliar spray applications (interval 14 days) at 20 g ai/hL with a PHI of 21 days, either with or without adjuvant. In trials from Australia matching this GAP (2 × 20 g ai/hL, interval 15 days and PHI 21 days, with adjuvant) clothianidin residues in apple whole fruit were 0.24 mg/kg (n = 1).

GAP for apples in Australia is for one soil drench application at 2.5 g ai/tree with a PHI of 21 days. Field trials performed in Australia did not match this GAP.

GAP for pome fruit in Hungary is for one foliar spray application at 75 g ai/ha with a PHI of 28 days. Field trials performed in Germany, the UK and France did not match this GAP. In trials in Hungary matching this GAP (1 × 72 g ai/ha and PHI 28 days) clothianidin residues in apple whole fruit were < 0.02 mg/kg (n = 1).

GAP for apples and pears in Italy is for one foliar spray application at 7.5 g ai/hL with a PHI of 14 days). Field trials performed in Italy, France and Spain did not match this GAP. However trials performed with two applications can be taken into account, since results from samples taken prior to the 2nd application showed residues to be < 0.01–0.011 mg/kg. In trials in France and Italy with two applications (2 × 7.5–7.6 g ai/hL, interval 7 days and PHI 14 days) clothianidin residues in apple whole fruit were < 0.01 (3) and 0.014 mg/kg (n = 4).

GAP for apples in Romania is for an unstated number of foliar spray applications at 10 g ai/hL, unstated interval and unstated PHI. In trials in France, Italy and Spain matching this GAP (1–2 × 7.5–13 g ai/hL, interval 7 days, PHI of 0–21 days) clothianidin residues in apple whole fruit were < 0.01, < 0.01, 0.013, 0.014, 0.049, 0.058 0.067 and 0.12 mg/kg (n = 8) without adjuvant and 0.012 and 0.085 mg/kg (n = 2) with adjuvant on the same location. Since an adjuvant is not indicated in the label only the dataset without adjuvant is taken into account.

GAP for apples in Japan is for three spray applications at 8.0 g ai/hL, unstated interval and PHI 1 day. In trials from Japan matching this GAP (3 × 8.0 g ai/hL, interval 7 days and PHI 1 day) clothianidin residues in apple whole fruit were 0.06 and 0.15 mg/kg (n = 2). The Meeting noted that trial plots consisted of only three trees with a height of 3 m. As the trial design complied with official Japanese guidelines with sampling done randomly and of sufficient size, the Meeting decided to accept the residue results.

GAP for Pome fruit in the USA is for one foliar spray application at 224 g ai/ha (maximum of 224 g ai/ha per season, interval 10 days and a PHI of 7 days. In trials from the USA matching this

GAP (1 × 219–225 g ai/ha and PHI 6–7 days) clothianidin residues in apple whole fruit were < 0.01, 0.010, 0.019, 0.025, 0.052, 0.087, 0.094, 0.10, 0.10, 0.12, 0.15, 0.16 and 0.20 mg/kg (n = 13).

The datasets corresponding to the GAPs for Australia, Hungary, Italy and Japan were considered insufficient to support a recommendation. The Meeting noted that the GAP for Romania resulted in a similar dataset when compared to the GAP for USA (Mann-Whitney U test). However, as the GAPs are different the data cannot be combined. Since the highest residue is found in the USA dataset, the Meeting decided to use only the apple data corresponding to the GAP of the USA.

Field trials involving pears were performed in Australia, Germany, France, Italy, Spain, Japan and the USA.

GAP for apples and pears in Australia is for two foliar spray applications at 20 g ai/hL (interval 14 days) and PHI 21 days, either with or without adjuvant. In trials from Australia matching this GAP (2 × 20 g ai/hL, interval 15 days and PHI 21 days, with adjuvant) clothianidin residues in pear whole fruit were 0.13 mg/kg (n = 1).

GAP for Pome fruit in Hungary is for one foliar spray application at 75 g ai/ha and PHI 28 days. Field trials performed in Germany and France did not match this GAP.

GAP for apples and pears in Italy is for one foliar spray application at 7.5 g ai/hL (PHI 14 days). Field trials performed in Italy, France and Spain did not match this GAP.

GAP for pears in Japan is for three spray applications at 8.0 g ai/hL, unstated interval and PHI 1 day. In trials from Japan matching this GAP (3 × 8.0 g ai/hL; interval 7 days and PHI 1 day) clothianidin residues in pear minus stylar scar, core and peduncle base were 0.18 and 0.39 mg/kg (n = 2). The Meeting noted that there was only one tree/plot with tree height 2 m. Since the trial design complied with Japanese guidelines and sampling was random with sufficient size, the Meeting decided to accept the residue results

GAP for Pome fruit in the USA is for one foliar spray application at 224 g ai/ha (max 224 g ai/ha per season, interval 10 days and PHI 7 days. In trials from the USA matching this GAP (1 × 221–224 g ai/ha and PHI 6–7 days) clothianidin residues in pear whole fruit were 0.042, 0.071, 0.10, 0.14, 0.15, 0.15 and 0.18 mg/kg (n = 7).

The datasets corresponding to the GAPs for Australia, Hungary, Italy and Japan were considered insufficient to support a recommendation. The Meeting decided to use only the pear data corresponding to the GAP of the USA.

The Meeting noted that the USA datasets for apples and pears were from similar populations (Mann-Whitney U test). Since residue behaviour within the pome fruit group is expected to be similar, the Meeting agreed that they could be combined. Clothianidin residues in pome fruit (whole fruit) were:< 0.01, 0.010, 0.019, 0.025, 0.042, 0.052, 0.071, 0.087, 0.094, 0.10, 0.10, 0.10, 0.12, 0.14, 0.15, 0.15, 0.15, 0.16, 0.18 and 0.20 mg/kg (n = 20).

The Meeting agreed that the USA data for apples and pears could be used to support a pome fruit commodity maximum residue level recommendation and estimated a maximum residue level of 0.4 mg/kg for clothianidin on pome fruit and estimated an STMR of 0.10 mg/kg and an HR of 0.20 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator (mean + 3 SD) was 0.27 mg/kg, which differed from the estimate made by the Meeting. The chosen level was higher in recognition of the ratio between the median and the highest residue.

Stone fruits

Field trials involving apricots were performed in Japan.

GAP for Ume (Japanese apricot) in Japan is for three spray applications at 8.0 g ai/hL at unstated interval and PHI 3 days. In field trials on apricots and Japanese apricots from Japan

matching this GAP (3 × 8.0 ai g/hL; interval 6–7 days, PHI 3 days) clothianidin residues in Japanese apricot pitted fruit were 0.50 and 1.1 mg/kg (n = 2). The Meeting noted that there were only 1–2 trees/plot with tree heights of 5 m. Since the trial design complied with Japanese guidelines and sampling was random with sufficient size, the Meeting decided to accept the residue results.

Field trials involving cherries were performed in Japan.

GAP for cherries in Japan is for two spray applications at 8.0 g ai/hL, unstated interval with a PHI 1 day. In indoor trials from Japan matching this GAP (2 × 8.0 g/hL, interval 7 days and PHI 1 day) clothianidin residues in cherry pitted fruit were 1.1 and 2.0 mg/kg (n = 2). The Meeting noted that there was only one tree/plot with tree height of 4 m. Since the trial design complied with Japanese guidelines and sampling was random with sufficient size, the Meeting decided to accept the residue results.

Field trials involving nectarines were performed in Australia and Japan.

GAP for peaches and nectarines in Australia is for two foliar spray applications at 20 g ai/hL, 14 day interval, and PHI 21 days. Field trials performed in Australia did not match this GAP.

GAP for nectarines in Japan is for three spray applications at 8.0 g ai/hL, unstated interval and PHI 3 days. In trials from Japan matching this GAP (3 × 8.0 g ai/hL, interval 7 days and PHI 3 days) clothianidin residues in nectarine pitted fruit were 0.58 and 0.64 mg/kg (n = 2). The Meeting noted that there were only 1–2 trees/plot with tree height of 2 m. Since the trial design complied with Japanese guidelines and sampling was random with sufficient size, the Meeting decided to accept the residue results.

Field trials involving peaches were performed in Australia, Hungary, Japan, USA and Canada.

GAP for peaches and nectarines in Australia is for two foliar spray applications at 20 g ai/hL, 14 day interval and PHI 21 days. Field trials performed in Australia did not match this GAP.

GAP for peaches in Hungary is for one foliar spray application at 8.8 g ai/hL and PHI 14 days. In field trials performed in Hungary matching this GAP (1 × 10 g ai/hL and PHI 14 days) clothianidin residues in peach whole fruit were < 0.02 mg/kg (n = 1).

GAP for peaches in Japan is for three spray applications at 8.0 g ai/hL, unstated interval and PHI 7 days. In field trials performed in Japan matching this GAP (3 × 8.0 g ai/hL, interval 7–8 days and PHI 7 days) clothianidin residues in peach pitted fruit were 0.25 mg/kg (n = 1). In indoor trials performed in Japan matching this GAP (3 × 8.0 g ai/hL, interval 6–8 days and PHI 7days) clothianidin residues in peach pitted fruit were 0.33 mg/kg (n = 1). The Meeting noted that there were only 1–3 trees/plot with tree height of 2 m. Since the trial design complied with Japanese guidelines and sampling was random with sufficient size, the Meeting decided to accept the residue results.

GAP for peaches in the USA is for two foliar spray applications at 112 g ai/ha (max 224 g ai/ha per season), 10 day interval and PHI 7 days. Field trials performed in the USA and Canada did not match this GAP.

Field trials involving plums were performed in Japan.

GAP in Japan for Japanese plums is for three spray applications at 8.0 g ai/hL, unstated interval and PHI 3 days. In field trials performed in Japan matching this GAP (3 × 8.0 g ai/hL, interval 7 days and PHI 3 days) clothianidin residues in plums pitted fruit were 0.03 and 0.06 mg/kg (n = 2). The Meeting noted that there was only 1 tree/plot with tree height of 3 m. Since the trial design complied with Japanese guidelines and sampling was random and of sufficient size, the Meeting decided to accept the residue results.

The datasets for apricots, cherries, nectarines, peaches and plums were considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for each of these commodities individually or for a stone fruit group.

Berries and other small fruits

Field trials involving cranberries were performed in the USA. GAP for cranberries in the USA is for three foliar spray applications at 75 g ai/ha (max 224 g ai/ha per season), interval 7 days and PHI 21 days. In field trials performed in the USA matching this GAP (3 × 73–80 g ai/ha, interval 6–8 days and PHI 21–22 days) clothianidin residues in cranberry whole fruit (berries) were < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 5).

GAP for cranberries in the USA is for one soil treatment at 224 g ai/ha (max 224 g ai/ha per season) and PHI 21 days. In field trials performed in the USA matching this GAP (233–243 g ai/ha and PHI 21–22 days) clothianidin residues in cranberry whole fruit (berries) were < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 5).

The Meeting noted that the foliar spray treatment and the soil treatment according to the USA GAP both showed no residues (< 0.01 mg/kg). The Meeting estimated a maximum residue level of 0.01* mg/kg for clothianidin on cranberries and estimated an STMR of 0.01 mg/kg and an HR of 0.01 mg/kg.

Statistical calculations using the NAFTA calculator were not possible, since all levels are below LOQ.

Field trials involving grapes were performed in Australia, Japan and the USA.

GAP for grapes (table) in Australia is for two foliar spray applications at 20 g ai/hL, interval 21 days and with a PHI 42 days, with or without adjuvant. In field trials performed in Australia matching this GAP (2 × 20–25 g ai/hL, interval 13–22 days and PHI 41–44 days) clothianidin residues in grapes (whole fruit without stems) were $0.28^{SC,\$}$, 0.82^{WG}, $1.6^{SC,\$}$ mg/kg (n = 3) without adjuvant and 0.06^{WG}, 0.17^{WG} and 1.9^{WG} mg/kg (n = 3) with adjuvant. SC and WG mark the use of SC and WG formulations. In those cases where residues at higher PHI were higher, these residues were selected instead. However, figures marked with $ cannot be used for a recommendation, because of sampling deficiencies and poor condition of the fruit. In a single bridging study with a WG formulation with and without adjuvant, residue levels with adjuvant were higher (1.9 mg/kg with versus 0.82 mg/kg without). Therefore only the dataset with adjuvant will be used in the estimation.

GAP for grapes (table and wine) in Australia is for one soil treatment at 300 g ai/ha. In field trials performed in Australia matching this GAP (300 g ai/ha and PHI 96–132 days) clothianidin residues in grapes whole fruit without stems were $< 0.02^{SC,\$}$, $< 0.02^{SC}$ and $< 0.02^{WG}$ mg/kg (n = 3). SC and WG mark the use of SC and WG formulations. However, the figure marked with $ could not be used for a recommendation, due to sampling deficiencies and the poor condition of the fruit.

GAP for grapes in Japan is for three spray applications at 8.0 g ai/hL, unstated interval and PHI 1 day. Indoor trials performed in Japan matching this GAP (2 × 8.0 g ai/hL and interval 7–8 days, in grapes (whole fruit without stems) were $0.66^{\$}$ and $1.0^{\$}$ mg/kg (n = 2). In those cases where residues at higher PHI were higher, these residues were selected instead. However, values marked with $ cannot be used for a recommendation because of sampling deficiencies.

GAP for grapes in the USA is for two foliar spray applications at 112 g ai/ha (maximum of 224 g ai/ha per season), interval 14 days and PHI 0 days. In field trials performed in the USA matching this GAP (2 × 110–116 g ai/ha, interval 13–14 days and PHI 0 days) clothianidin residues in grapes whole fruit with stems were 0.042, 0.053, 0.074, 0.090, 0.098, 0.11, 0.13, 0.13, 0.14, 0.28, 0.33 and 0.41 mg/kg (n = 12).

A second GAP for grapes in the USA is for one soil treatment at 224 g ai/ha (max 224 g ai/ha per season) and a PHI of 30 days. In field trials performed in the USA matching this GAP (1 × 221–223 g ai/ha total and PHI 30 days) clothianidin residues in grapes (whole fruit with stems) were < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02 and < 0.02 mg/kg (n = 10).

The datasets corresponding to the GAPs for Australia and Japan were considered insufficient to support a recommendation. The Meeting noted that the GAP for foliar treatment in the USA

resulted in higher residues when compared to the GAP for soil treatment in the USA. Therefore, the Meeting decided to use only the grape data corresponding to the GAP of the USA for foliar treatment: 0.042, 0.053, 0.074, 0.090, 0.098, 0.11, 0.13, 0.13, 0.14, 0.28, 0.33 and 0.41 mg/kg (n = 12).

The Meeting estimated a maximum residue level of 0.7 mg/kg for clothianidin on grapes and estimated an STMR of 0.12 mg/kg and an HR of 0.41 mg/kg.

The maximum residue level estimate derived from use of the NAFTA calculator (95/99 99th percentile) was 0.64 mg/kg, which was in agreement with the Meetings estimate (after rounding up to one figure).

Assorted tropical and sub-tropical fruits, edible peel

Field trials involving persimmon were performed in Japan and Korea.

GAP for Japanese persimmon in Japan is for three spray applications at 8.0 g ai/hL, unstated interval and PHI 7 days. In field trials performed in Japan matching this GAP (3 × 8.0 g ai/hL, interval 5–9 days and PHI 7 days) clothianidin residues in persimmon whole fruit were 0.11 and 0.14 mg/kg (n = 2). The Meeting noted that there were only 1–2 trees/plot with tree height of 3 m. Since the trial design complied with Japanese guidelines and sampling was random with sufficient size, the Meeting decided to accept the residue results.

GAP for persimmon in Korea is for three foliar applications at 8.0 g ai/hL, interval 7–10 days and PHI 10 days. In field trials performed in Korea matching this GAP (3 × 8.0 g ai/hL, interval 10 days and PHI 10 days) clothianidin residues in persimmon whole fruit were 0.047$ mg/kg (n = 1). However, the values marked with $ cannot be used for a recommendation because of sampling deficiencies.

The datasets for persimmon were considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for persimmon.

Assorted tropical and sub-tropical fruits, inedible peel

Field trials involving bananas were performed in Australia.

GAP for bananas in Australia is for one stem spray application at 0.9 g ai/stem. In field trials performed in Australia matching this GAP (0.9 g ai/stem and PHI 256–553 days) clothianidin residues in banana whole fruit (including peel) were < 0.02, < 0.02, < 0.02, < 0.02, < 0.02 and < 0.02 mg/kg (n = 6).

GAP for bananas in Australia is for one stem injection application at 0.6 g ai/stem. In field trials performed in Australia matching this GAP (0.6 g ai/stem and PHI 256–553 days) clothianidin residues in banana whole fruit (including peel) were < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02 and 0.02 mg/kg (n = 8).

The Meeting noted that the stem injection application according to the Australian GAP showed residues below or at LOQ (< 0.02–0.02 mg/kg). The Meeting estimated a maximum residue level of 0.02 mg/kg for clothianidin on banana whole fruit and estimated an STMR of 0.02 mg/kg and an HR of 0.02 mg/kg.

Statistical calculations using the NAFTA calculator were not possible, as all levels were at or below the LOQ.

Brassica vegetables

Field trials involving head cabbage were performed in Belgium, Germany, the UK, France, Italy, Spain, Japan and the USA.

GAPs for seed treatments in Belgium, Germany, the UK, France, Italy and Spain are not available. GAP for New Zealand cannot be matched to European trials because the New Zealand GAP is only for forage Brassicas, not meant for human consumption.

GAP for head cabbage in Japan is for one application, soil incorporated, at 10 mg ai/plant (at seeding up to transplanting) combined with two foliar applications at 8.0 g ai/hL, unstated interval and PHI 3 days. In field trials performed in Japan matching this GAP (1 × 10 mg ai/plant plus two foliar applications at 8.0 g ai/hL, interval 6–8 days and PHI 3 days) clothianidin residues in cabbage (head only without core) were $0.16^{\$}$ and $0.18^{\$}$ mg/kg (n = 2). However, values marked with $ cannot be used for a recommendation because of sampling deficiencies.

GAP for Brassica (cole) leafy vegetables in the USA is for three foliar spray applications at 74 g ai/ha (max 224 g ai/ha per season), interval 10 days and PHI 7 days. Field trials performed in the USA did not match this GAP.

GAP for Brassica (cole) leafy vegetables in the USA is for one soil treatment at 224 g ai/ha (max 224 g ai/ha per season) at planting. In trials performed in the USA matching this GAP (1 × 224 g ai/ha and PHI 77 days) clothianidin residue levels were 0.015 mg/kg (n = 1).

The datasets for head cabbages were considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for head cabbages.

Field trials involving broccoli were performed in Japan.

GAP for broccoli in Japan is for one soil incorporated treatment at 10 mg ai/plant (at seeding up to transplanting) combined with three foliar applications at 8.0 g ai/hL, unstated interval and PHI 3 days. In field trials performed in Japan matching this GAP (1 × 10 mg ai/plant plus three foliar applications at 8.0 g ai/hL, interval 6–7 days and PHI 3 days) clothianidin residues in broccoli (buds without leaves) were $0.07^{\$}$ and $0.33^{\$}$ mg/kg (n = 2). However, values marked with $ cannot be used for a recommendation because of sampling deficiencies.

GAP for broccoli in Japan is for one soil incorporation at 10 mg ai/plant (at seeding up to transplanting). In field trials performed in Japan matching this GAP (1 × 10 mg ai/plant and PHI 71–151 days), clothianidin residues in broccoli (buds without leaves) were $< 0.01^{\$}$ and $0.04^{\$}$ mg/kg (n = 2). However, values marked with $ cannot be used for a recommendation because of sampling deficiencies.

The datasets for broccoli were considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for broccoli.

Fruiting vegetables, Cucurbits

Field trials involving cucumbers were performed in Brazil, Japan and the USA.

GAP for cucumber in Brazil is for four foliar treatments at 10 g ai/hL, unstated interval and PHI 1 day. Field trials performed in Brazil did not match this GAP.

GAP for cucumber in Japan is for one soil incorporation at 10 mg ai/plant (at transplanting) combined with three foliar sprays at 8.0 g ai/hL, unstated interval and PHI 1 day. In indoor trials performed in Japan matching this GAP (1 × 10 mg ai/plant at planting + 3 × foliar spray at 8.0 g ai/hL, interval 7 days and PHI 1 day) clothianidin residues in cucumber were: 0.2 and, 0.70 mg/kg (n = 2).

GAP for cucurbit vegetables in the USA is for three foliar spray applications at 74 g ai/ha (max 224 g ai/ha per season), interval 10 days and PHI 7 days. Field trials performed in the USA did not match this GAP.

GAP for cucurbit vegetables in the USA is for one soil treatment at 224 g ai/ha (max 224 g ai/ha per season) at planting. In field trials performed in the USA matching this GAP (1 ×

232 g ai/ha and PHI 21 days) clothianidin residue levels in cucumber whole fruit were 0.014 mg/kg (n = 1).

Field trials involving summer squash were performed in the USA.

GAP for cucurbit vegetables in the USA is for three foliar spray applications at 74 g ai/ha (max 224 g ai/ha per season), interval 10 days and PHI 7 days. Field trials performed in the USA did not match this GAP.

GAP for cucurbit vegetables in the USA is for one soil treatment at 224 g ai/ha (max 224 g ai/ha per season) at planting. In field trials performed in the USA matching this GAP (1 × 231 g ai/ha and PHI 73 days) clothianidin residue levels in summer squash whole fruit were < 0.01 mg/kg (n = 1).

The datasets for cucumbers and summer squash were considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for each of these commodities individually or for a cucurbit fruiting vegetable group.

Fruiting vegetables, other than Cucurbits

Field trials involving egg plants were performed in Japan.

GAP for egg plants in Japan is for one soil incorporation at 5 mg ai/plant (at transplanting) combined with three foliar sprays at 8.0 g ai/hL, unstated interval and PHI 1 day. In indoor trials performed in Japan matching this GAP (1 × 10 mg ai/plant at planting + 3 × foliar spray at 8.0 g ai/hL, interval 7 days and PHI 1 day) clothianidin residues in egg plants were: 0.29 and 0.38 mg/kg (n = 2). Where residue levels at higher PHIs were higher, these were selected instead.

The dataset for egg plant was considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for egg plant.

Field trials involving sweet corn were performed in the USA and Canada.

GAP for maize (field corn, popcorn and sweet corn) in the USA and Canada is for one seed treatment at 1.25 mg ai/seed. Seed treatment with subsequent field trials performed in the USA and Canada did not match this GAP. However, seed treatments performed at an exaggerated rate of 2.0 mg ai/seed and subsequent field trials performed in the USA and Canada (PHI 72–113) showed no residues in sweet corn (kernels plus cobs with husks removed): < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 17).

The Meeting decided that the trials performed at an exaggerated rate could be used for a recommendation. The Meeting estimated a maximum residue level of 0.01* mg/kg for clothianidin on sweet corn and estimated an STMR of 0.01 mg/kg and an HR of 0.01 mg/kg.

Statistical calculations using the NAFTA calculator were not possible, as all residue levels were below the LOQ.

Field trials involving tomatoes were performed in Japan and the USA.

GAP for tomatoes in Japan is for one soil incorporation at 10 mg ai/plant (at transplanting) combined with three foliar sprays at 8.0 g ai/hL, unstated interval and PHI 1 day. In indoor trials performed in Japan matching this GAP (1 × 10 mg ai/plant at planting + 3 × foliar spray at 8.0 g ai/hL, interval 7 days and PHI 1 day) clothianidin residues in tomatoes were: 0.66 and 0.90 mg/kg (n = 2) in grape tomatoes and 0.12 and 0.23 mg/kg (n = 2) in regular size tomatoes. Where residue levels at higher PHIs were higher, these were selected instead.

GAP for tomatoes in Japan is for one soil incorporation at 10 mg ai/plant (at transplanting) In indoor trials performed in Japan matching this GAP (1 × 10 mg ai/plant and PHI 77–98 days)

clothianidin residues were < 0.01 and < 0.01 mg/kg (n = 2). The laboratory results with the higher LOQ value of 0.05 mg/kg were not taken into account.

GAP for fruiting vegetables in the USA is for three foliar spray applications at 74 g ai/ha (max 224 g ai/ha per season), interval 7 days and PHI 7 days. Field trials performed in the USA did not match this GAP.

GAP for fruiting vegetables in the USA is for one soil treatment at 224 g ai/ha (max 224 g ai/ha per season) at planting. In field trials performed in the USA matching this GAP (1 × 222–226 g ai/ha and PHI 21–82 days) clothianidin residue levels in tomato whole fruit were < 0.01 and 0.028 mg/kg (n = 2).

The datasets for tomato were considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for tomato.

Leafy vegetables

Field trials involving head lettuce were performed in the USA.

GAP for leafy vegetables in the USA is for three foliar spray applications at 74 g ai/ha (max 224 g ai/ha per season), interval 10 days and PHI 7 days. Field trials performed in the USA did not match this GAP.

GAP for leafy vegetables in the USA is for one soil treatment at 224 g ai/ha (max 224 g ai/ha per season) at planting. In field trials performed in the USA matching this GAP (1 × 224 g ai/ha and PHI 32 days) clothianidin residues in head lettuce were 0.044$ mg/kg (n = 1). However, the value marked with $ could not be used for a recommendation because the heads didn't form properly.

Field trials involving leaf lettuce were performed in the USA.

GAP for leafy vegetables in the USA is for three foliar spray applications at 74 g ai/ha (max 224 g ai/ha per season), interval 10 days and PHI 7 days. Field trials performed in the USA did not match this GAP.

GAP for leafy vegetables in the USA is for one soil treatment at 224 g ai/ha (max 224 g ai/ha per season) at planting. In field trials performed in the USA matching this GAP (1 × 227 g ai/ha and PHI 22 days) clothianidin residues in leaf lettuce were 0.046 mg/kg (n = 1).

The datasets for head lettuce and leaf lettuce were considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for each of these commodities individually or for a leafy vegetable group.

Pulses

Field trials involving soya bean (dry) were performed in Japan and the USA.

GAP for soya beans in Japan is either for three high volume spray applications at 8.0 g ai/hL or for three aerial spray applications at 833 g ai/hL or for three dusting applications at 200 g ai/ha, unstated interval and PHI 7 days. Trials performed in Japan did not match this GAP.

GAP for soya beans in the USA is for three foliar spray applications at 75 g ai/ha (maximum 224 g ai/ha per season), interval 7 days and PHI 21 days. Field trials performed in the USA did not match this GAP.

Since the datasets for dry soya beans did not match GAP, the Meeting could not estimate a maximum residue level for soya beans.

Root and tuber vegetables

Field trials involving carrots were performed in Belgium, Germany, Netherlands, the UK, France, Italy, Portugal and Spain.

GAPs for seed treatments in Belgium, Germany, Netherlands, the UK, France, Italy and Spain were not available.

Since there was no GAP available, the Meeting could not estimate a maximum residue level for carrots.

Field trials involving chicory roots were performed in Belgium.

GAP for chicory roots in Belgium is for one seed treatment at 0.3 mg ai/seed. In field trials performed in Belgium matching this GAP (1 × 0.265 mg ai/seed and PHI 161 days) clothianidin residue levels in chicory roots were < 0.01 mg/kg (n = 1).

The dataset for chicory roots was considered insufficient to support a recommendation. The Meeting could not estimate a maximum residue level for chicory roots.

Field trials involving potatoes were performed in the USA and Canada.

GAP for tuberous and corm vegetables in the USA is for four foliar spray treatments at 56 g ai/ha (maximum of 224 g ai/ha per season), interval 7 days with a PHI of 14 days. Field trials performed in the USA and Canada did not match this GAP. However, treatments performed in the USA and Canada at an exaggerated rate (3 × 73–77 g ai/ha, interval 5–8 days and PHI 13–14 days) showed no residues: < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02 and < 0.02 mg/kg (n = 17) in potato tubers with peel.

GAP for tuberous and corm vegetables in the USA is for one soil treatment at 224 g ai/ha (maximum of 224 g ai/ha per season) at planting. In field trials performed in the USA and Canada matching this GAP (1 × 217–226 g ai/ha and a PHI of 48–145 days) clothianidin residue levels in potato tubers with peel were: < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, 0.020, 0.020, 0.029 and 0.033 mg/kg (n = 17) using an SG formulation at planting and < 0.02 and < 0.02 mg/kg (n = 2) using a WG formulation at planting (at the same locations). Since only one value is selected per location, only the results for the SG formulation were considered.

The Meeting noted that the GAP for soil treatment in the USA resulted in higher residues when compared to the GAP for foliar treatment in the USA. Therefore, the Meeting decided to use only the potato data corresponding to the GAP of the USA for soil treatment: < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, 0.020, 0.020, 0.029 and 0.033 mg/kg (n = 17).

The Meeting estimated a maximum residue level of 0.05 mg/kg for clothianidin on potatoes with peel and estimated an STMR of 0.02 mg/kg and an HR of 0.033 mg/kg (considering potatoes with peel as edible portion).

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.03 mg/kg (mean + 3 SD, no MLE used) differed from the estimate made by the Meeting. The higher level was chosen in recognition of the number of majority of values below LOQ and the small number above.

Field trials involving sugar beet roots were performed in Belgium, Germany, the UK, France, Italy, Spain and the USA.

GAP for sugar beets in Belgium, Denmark, Finland, Germany, Netherlands, Slovakia and the UK is for one seed treatment at 0.6 mg ai/seed. For seed treatments and subsequent field trials performed in the UK, France and Germany matching this GAP (1 × 0.6 mg ai/seed and PHI 92–148 days) clothianidin residues in sugar beet roots were < 0.01, < 0.01 and 0.012 mg/kg (n = 3).

GAP for sugar beets in Italy, Slovenia, and Spain is for one seed treatment at 0.6 mg ai/seed. Trials performed in Spain and Italy did not match this GAP.

GAP for sugar beets in the USA is for one seed treatment at 0.6 mg ai/seed (FS formulation). For seed treatments and subsequent field trials performed in the USA matching this GAP (1 × 0.6 mg ai/seed and PHI 109–179 days SE formulation) clothianidin residues in sugar beet roots were < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, 0.015 and 0.019 mg/kg, n = 12.

The Meeting noted that the GAP for Northern Europe resulted in a similar dataset when compared to the GAP for USA (Mann-Whitney U test). Because the GAPs are identical the data can be combined. The Meeting decided to use the combined dataset for sugar beet roots corresponding to the GAP of Northern Europe and the USA: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, 0.012, 0.015 and 0.019 (n = 15).

The Meeting estimated a maximum residue level of 0.03 mg/kg for clothianidin on sugar beet roots and estimated an STMR of 0.01 mg/kg and an HR of 0.019 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.02 mg/kg (mean + 3 SD, no MLE used), which differed from the estimate made by the Meeting. The NAFTA calculator value was not considered as it does not give reliable results with large numbers of censored data.

Cereal grains

Field trials involving maize (corn) were performed in the USA and Canada.

GAP for maize (field corn, popcorn and sweet corn) in the USA and Canada is for one seed treatment at 1.25 mg ai/seed. Seed treatment with subsequent field trials performed in the USA and Canada did not match this GAP. However, seed treatments performed at an exaggerated rate of 2.0 mg ai/seed and subsequent field trials performed in the USA and Canada (PHI 119–170 days) showed no residues in maize seed: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 26).

Field trials involving popcorn were performed in the USA and Canada.

GAP for maize (field corn, popcorn and sweet corn) in the USA and Canada is for one seed treatment at 1.25 mg ai/seed. Seed treatment with subsequent field trials performed in the USA and Canada did not match this GAP. However, seed treatments performed at an exaggerated rate of 2.0 mg ai/seed and subsequent field trials performed in the USA and Canada (PHI 119–170 days) showed no residues: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 < 0.01, < 0.01, < 0.01, < 0.01, < 0.01and < 0.01 mg/kg (n = 26).

Field trials involving rice were performed in Japan.

GAP for rice in Japan is for one application in a seedling box at 0.75 g ai/box and three GR spreading applications at 200 g ai/ha, unstated interval and a 7 day PHI. Since the application in a seedling box is not expected to contribute to the final residue, trials where the spreading applications are according to GAP are considered acceptable. For field trials performed in Japan matching this GAP (seedling treatment at 1.25–1.65 g ai/box + three spreading (GR) applications at 200 g ai/ha, interval 6–29 days and PHI 7 days) clothianidin residues in rice grains were < 0.01, 0.01, 0.02 and 0.04 mg/kg, n = 4. When higher residues were found at later PHIs these residues were selected instead. After harvest, rice was dried and protected from rain for 9–22 days. Residue values are for husked rice grain (brown rice).

GAP for rice in Japan is for one application in a seedling box at 0.75 g ai/box and three DP dust applications at 200 g ai/ha, unstated interval and a 7 day PHI. Since the application in a seedling

box is not expected to contribute to the final residue, trials where dusting applications were according to GAP were considered acceptable. For field trials performed in Japan matching this GAP (seedling treatment at 1.65 g ai/box + three dusting (DP) applications at 200 g ai/ha, interval 7–22 days and a 7 day PHI) clothianidin residues in rice grains were 0.07 and 0.11 mg/kg, n = 2. When higher residues were found at later PHIs these residues were selected instead. After harvest, rice was dried and protected from rain for 9–14 days. Residue values were for husked rice grain.

GAP for rice in Japan is for one application in a seedling box at 0.75 g ai/box and three high volume spray applications at 4 g ai/hL, unstated interval, and PHI 7 days. Since the application in a seedling box is not expected to contribute to the final residue, trials where the spray applications are according to GAP are considered acceptable. For field trials performed in Japan matching the GAP (seedling treatment at 1.65 g ai/box + three high volume spray applications at 4.0 g ai/hL with SC or SP formulations, interval 7–22 days and a 7 day PHI) clothianidin residues in rice grains were 0.12 and 0.14 mg/kg, n = 2 for an SP formulation and 0.12 and 0.16 mg/kg, n = 2 for an SC formulation on the same locations. When higher residues were found at later PHIs these residues were selected instead. After harvest, rice was dried and protected from rain for 9–14 days. Residue values were for husked rice grain.

GAP for rice in Japan is for one application in a seedling box at 0.75 g ai/box and three low volume spray applications at 16 g ai/hL, unstated interval, and PHI 7 days. Since the application in a seedling box is not expected to contribute to the final residue, trials where the spray applications are according to GAP are considered acceptable. For field trials performed in Japan matching the GAP (seedling treatment at 1.25–1.65 g ai/box + three high volume spray applications at 16 g ai/hL with SC or SP formulations, interval 3–21 days and a 7 day PHI) clothianidin residues in rice grains were 0.07 and 0.10 mg/kg, n = 2 for an SP formulation and 0.15 and 0.21 mg/kg, n = 2 for an SC formulation (on different locations). When higher residues were found at later PHIs these residues were selected instead. After harvest, rice was dried and protected from rain for 9–27 days. Residue values were for husked rice grain.

GAP for rice in Japan is for one application in a seedling box at 0.75 g ai/box and three aerial spray applications at 833 g ai/hL, unstated interval and PHI 14 days. Since the application in a seedling box is not expected to contribute to the final residue, trials where the spray applications are according to GAP are considered acceptable. For field trials performed in Japan matching the GAP (seedling treatment at 1.65 g ai/box + three aerial spray applications at 833 g ai/hL with SC formulations, interval 6–21 days and PHI 7 days) clothianidin residues in rice grains were 0.04 and 0.16 mg/kg, n = 2. When higher residues were found at later PHIs these residues were selected instead. After harvest, rice was dried protected from rain for 16–35 days. Residue values were for husked rice.

In all Japanese rice trials, the rice was left to dry after harvest. The Meeting considered this acceptable, since it is normal practice in Japan. Trials conducted at different GAPs generally cannot be combined. However, The Meeting decided that the trials from the three different foliar spray treatments could be combined, since the trials resulted in similar residues. For trials conducted at the same location on the same day, only the maximum value for that location was selected. This resulted in the following dataset: 0.04, 0.07, 0.10, 0.14, 0.15, 0.16, 0.16 and 0.21 mg/kg (n = 8).

The Meeting estimated a maximum residue level of 0.5 mg/kg for clothianidin in husked rice and an STMR of 0.145 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.41 mg/kg (95/99 rule), which was in agreement with the estimate made by the Meeting (after rounding up to one figure).

Field trials involving sorghum were performed in the USA.

The GAP for sorghum in the USA is for one seed treatment at 2.5 kg ai/T seeds. In field trials performed in the USA matching this GAP (1 × 2.5 kg ai/T seeds and PHI 97–167 days) clothianidin

residues in sorghum grain were: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 12).

Field trials involving barley were performed in Germany, the UK, France and Italy.

GAP for winter barley in the UK and Ireland is for one seed treatment at 0.50 kg ai/T seeds. For seed treatments and subsequent trials performed in Germany, the UK and France matching this GAP (1 × 0.44–0.47 kg ai/T seed and PHI 130–147 days, spring barley) clothianidin residue levels in barley grain were < 0.01, < 0.01 and < 0.01 mg/kg (n = 3).

GAP for seed treatments in Italy were not available.

Field trials involving wheat were performed in Germany, the UK, France and the USA.

The GAP for wheat in the UK is for one seed treatment at 0.50 kg ai/T seeds. For seed treatments and subsequent field trials performed in the UK, Germany and France, matching this GAP (1 × 0.38–0.63 kg ai/T seeds and PHI 130–155 days) clothianidin residues in wheat (grain) were: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 8).

GAP for wheat in the USA is for one seed treatment at 0.07 kg ai/T seeds. Trials performed in the USA did not match this GAP.

The Meeting noted that after seed treatment on maize, popcorn and sorghum according to GAP in the USA and after seed treatments on barley and wheat according to GAP in Northern EU, no residues were found in grains (< 0.01 mg/kg). Since GAP and residue levels for rice was different from other cereals, the results for barley, wheat, maize, popcorn and sorghum cannot be extrapolated to rice or vice versa. Although the USA and EU data on barley, wheat, maize, popcorn and sorghum could be used to support a cereal grains commodity group (excluding rice) recommendation, the Meeting decided to recommend maximum residue levels for individual cereals, to be in line with the thiamethoxam evaluation, where quantitative amounts of metabolite CGA 322704 differed in different cereals. The Meeting estimated a maximum residue level of 0.01* mg/kg for clothianidin on barley, maize, popcorn, sorghum and wheat and estimated an STMR of 0.01 mg/kg.

Statistical calculations using the NAFTA calculator were not possible, as all levels were below the LOQ.

Grasses for sugar and syrup production

Field trials involving sugarcane were performed in Australia.

GAP for sugarcane in Australia is for one soil directed spray application at 500 g ai/ha and PHI 147 days. In trials performed in Australia matching this GAP (1 × 500 g ai/ha and PHI 146–175 days) clothianidin residue levels in sugarcane billets were < 0.02, 0.04 and 0.14 mg/kg (n = 3) using an SC formulation and < 0.02 and 0.02 mg/kg (n = 2) using a WG formulation, on partly the same locations. In a single bridging study using a WG and SC formulation, residue levels were identical (both < 0.02 mg/kg). The datasets are too small for a Mann-Whitney U test. The Meeting agreed to combine the datasets and take only the maximum value per location. This resulted in the following dataset for sugarcane billets: < 0.02, 0.02, 0.04 and 0.14 mg/kg (n = 4).

The Meeting estimated a maximum residue level of 0.4 mg/kg for clothianidin on sugarcane and estimated an STMR of 0.03 mg/kg and an HR of 0.14 mg/kg.

The value using the NAFTA calculator (NAFTA UCL/median 95 = 0.31, no MLE used) differed from the estimate of 0.4 mg/kg made by the Meeting. The chosen level was higher to recognize the small dataset.

Oilseeds

Field trials involving undelinted cotton seed were performed in Australia and the USA.

GAP for cotton in Australia is for two foliar aerial or ground spray applications at 50 g ai/ha, with adjuvant, unstated interval and PHI 5 days. Trials performed in Australia did not match this GAP. However, foliar treatments performed at an exaggerated rate in Australia (4 × 50 g ai/ha, with adjuvant, interval 14 days, PHI 5 days) showed no residues: < 0.02$, < 0.02$ and < 0.02$ mg/kg, n = 3. However, values marked with $ cannot be used for a recommendation because of sampling deficiencies.

GAP for cotton in the USA is for one seed treatment at 2.1 kg ai/T seeds. Trials performed in the USA did not match this GAP. However, trials performed at an exaggerated dose rate of 3.5 kg ai/T seeds, showed no residues: < 0.01$, < 0.01$, < 0.01$, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 12). However, values marked with $ cannot be used for a recommendation because of sampling deficiencies.

GAP for cotton in the USA is for three foliar spray applications at 75 g ai/ha (max 224 g ai/ha per season), interval 7 days and PHI 21 days. Field trials performed in the USA did not match this GAP.

Since USA foliar treatments at exaggerated dose rates show residues, the seed treatment dataset is considered not representative for cotton GAP. The dataset for cottonseed is considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for cottonseed.

Field trials involving rape seed were performed in Germany, Sweden, the UK, France, the USA and Canada.

GAP for rape seed in the Czech Republic, Estonia, Finland, and Germany is for one seed treatment at 10 kg ai/T seeds. In field trials performed in Germany, Sweden and France matching this GAP (1 × 7.4–9.5 kg ai/T seeds and PHI 111–320 days) clothianidin residue levels in rapeseeds were < 0.01$, < 0.01$, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 9). However, values marked with $ cannot be used for a recommendation because of sampling deficiencies.

GAP for rapeseed (including canola) in the USA and Canada is for one seed treatment at 4.0 kg ai/T seeds. Field trials performed in the USA and Canada did not match this GAP. Although field trials are available at an exaggerated dose rate, the results of these trials are considered not reliable because of sampling deficiencies.

The Meeting estimated a maximum residue level of 0.01* mg/kg for clothianidin on rape seed and estimated an STMR of 0.01 mg/kg.

Statistical calculations using the NAFTA calculator were not possible, since all levels are below LOQ.

Field trials involving sunflower seed were performed in France, Italy and Spain.

GAP for sunflower seeds in Romania is for one seed treatment at 0.5 mg ai/seed. Trials performed in Italy and Spain did not match this GAP. For seed treatments and subsequent field trials performed in France matching this GAP (1 × 0.50–0.62 mg ai/seed, 115–145 days PHI) clothianidin residues in sunflower seeds were < 0.01, < 0.01 and < 0.01 mg/kg (n = 3).

The dataset for sunflower seed is considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for sunflower seed.

Legume animal feeds

Field trials involving soya bean forage and soya bean hay were not available.

Straw, fodder and forage of cereal grains and grasses

Field trials involving field corn forage were performed in the USA and Canada.

GAP for maize (field corn, popcorn and sweet corn) in the USA and Canada is for one seed treatment at 1.25 mg ai/seed. Seed treatment with subsequent field trials performed in the USA and Canada did not match this GAP.

The Meeting could not estimate an STMR or highest residue for field corn forage as there were no trials matching the GAP.

Field trials involving sweet corn forage were performed in the USA and Canada.

GAP for maize (field corn, popcorn and sweet corn) in the USA and Canada is for one seed treatment at 1.25 mg ai/seed. Seed treatment with subsequent field trials performed in the USA and Canada did not match this GAP.

The Meeting could not estimate an STMR or highest residue for sweet corn forage as there were no trials matching the GAP.

Field trials involving field corn stover were performed in the USA and Canada.

GAP for maize (field corn, popcorn and sweet corn) in the USA and Canada is for one seed treatment at 1.25 mg ai/seed. Seed treatment with subsequent field trials performed in the USA and Canada did not match this GAP.

The Meeting could not estimate an STMR or highest residue for field corn stover as there were no trials matching the GAP.

Field trials involving popcorn stover were performed in the USA and Canada.

GAP for maize (field corn, popcorn and sweet corn) in the USA and Canada is for one seed treatment at 1.25 mg ai/seed. Seed treatment with subsequent field trials performed in the USA and Canada did not match this GAP.

The Meeting could not estimate an STMR or highest residue for popcorn stover as there were no trials matching the GAP.

Field trials involving sweet corn stover were performed in the USA and Canada.

GAP for maize (field corn, popcorn and sweet corn) in the USA and Canada is for one seed treatment at 1.25 mg ai/seed. Seed treatment with subsequent field trials performed in the USA and Canada did not match this GAP.

The Meeting could not estimate an STMR or highest residue for sweet corn stover as there were no trials matching the GAP.

Field trials involving rice whole crop silage were not available.

Field trials involving rice straw were not available.

Field trials involving sorghum grain forage were performed in the USA.

GAP for sorghum in the USA is for one seed treatment at 2.5 kg ai/T seeds. In field trials performed in the USA matching this GAP (1 × 2.5 kg ai/T seeds and PHI 42–112 days) clothianidin residues in green sorghum forage were < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 12).

The Meeting estimated an STMR of 0.01 mg/kg and a highest residue of 0.01 mg/kg for clothianidin in sorghum grain forage. A maximum residue level is not required, since forage is not traded.

The NAFTA calculator is not needed here, since maximum residue levels are not proposed for livestock forage.

Field trials involving sorghum grain stover were performed in the USA.

GAP in the USA for sorghum is for one seed treatment at 2.5 kg ai/T seeds. In field trials performed in the USA matching this GAP (1 × 2.5 kg ai/T seeds and PHI 97–167 days) clothianidin

residues in dry sorghum grain stover were < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg (n = 12). After harvest, sorghum stover was left drying in the field for 0–24 days. The Meeting considered this acceptable, since it is normal practice in the USA.

The Meeting estimated a maximum residue level of 0.01* mg/kg for clothianidin in sorghum grain stover, an STMR of 0.01 mg/kg and a highest residue of 0.01 mg/kg. A correction for dry weight is not necessary here since all the values are below LOQ. The dry weight values are considered to be the same.

Statistical calculations using the NAFTA calculator were not possible, since all levels are below LOQ.

Field trials involving green barley forage were performed in Germany, the UK, France and Italy.

GAP for winter barley in the UK and Ireland is for one seed treatment at 0.50 kg ai/T seeds. For seed treatments and subsequent trials performed in Germany, the UK and France matching this GAP (1 × 0.44–0.47 kg ai/T seed and PHI 55–57 days, spring barley) clothianidin residue levels in barley forage were 0.02, 0.02 and 0.05 mg/kg (n = 3).

GAP for seed treatments in Italy are not available.

The dataset for green barley forage is considered insufficient to support a recommendation. The Meeting could not estimate an STMR or highest residue for green barley forage.

Field trials involving green wheat forage were performed in Germany, the UK, France and the USA.

GAP for wheat in the UK is for one seed treatment at 0.50 kg ai/T seeds. For seed treatments and subsequent field trials performed in the UK, Germany and France matching this GAP (1 × 0.38–0.63 kg ai/T seeds and PHI 28–61 days) clothianidin residues in wheat green wheat forage were < 0.02, 0.022$^{\$}$, 0.024$^{\$}$, 0.030$^{\$}$, 0.058, 0.15$^{\$}$, 0.19$^{\$}$ and 0.23 mg/kg (n = 8). However, values marked with $ could not be used for a recommendation because of sampling deficiencies.

GAP for wheat in the USA is for seed treatment at 0.07 kg ai/T seeds. Trials performed in the USA did not match this GAP.

The dataset for green wheat forage is considered insufficient to support a recommendation. The Meeting could not estimate an STMR or highest residue for green wheat forage.

Field trials involving barley hay were not available. However, the Meeting decided that for the purpose of dietary burden calculations, data from barley straw can be used for barley hay.

Field trials involving wheat hay were performed in the USA.

GAP for wheat in the USA is for seed treatment at 0.07 kg ai/T seeds. Trials performed in the USA did not match this GAP.

The Meeting could not estimate an STMR or highest residue for wheat hay as there were no trials matching the GAP. However, the Meeting decided that for the purpose of dietary burden calculations, data from wheat straw can be used for wheat hay.

Field trials involving barley straw were performed in Germany, the UK, France and Italy.

GAP for winter barley in the UK and Ireland is for one seed treatment at 0.50 kg ai/T seeds. For seed treatments and subsequent trials performed in Germany, the UK and France matching this GAP (1 × 0.44–0.47 kg ai/T seed; PHI 130–147 days, spring barley) clothianidin residue levels in barley straw were < 0.02, < 0.02 and < 0.02 mg/kg (n = 3).

GAP for seed treatments in Italy are not available.

Field trials involving wheat straw were performed in Germany, the UK, France and the USA.

GAP for wheat in the UK is for one seed treatment at 0.50 kg ai/T seeds. For seed treatments and subsequent field trials performed in the UK, Germany and France matching this GAP (1 × 0.38–0.63 kg ai/T seeds and PHI 130–155 days) clothianidin residues in wheat straw (dry) were < 0.02$, < 0.02$, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02 and < 0.02 mg/kg (n = 8). However, the values marked with $ cannot be used for a recommendation because of storage deficiencies.

GAP for wheat in the USA is for seed treatment at 0.07 kg ai/T seeds. Field trials performed in the USA did not match this GAP.

Since wheat straw may not always be readily distinguishable from barley straw in trade, (since residues of wheat straw and barley straw are similar and since the GAPs for barley and wheat are similar), residues from wheat straw can be combined with residues from barley straw. This resulted in the following dataset: < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02 and < 0.02 mg/kg (n = 9).

The Meeting estimated a maximum residue level of 0.02* mg/kg for clothianidin in barley and wheat straw, an STMR of 0.02 mg/kg and a highest residue of 0.02 mg/kg. A correction for dry weight is not necessary here since all the values are below LOQ. The dry weight values are considered to be the same.

Statistical calculations using the NAFTA calculator were not possible, since all levels are below LOQ.

Miscellaneous fodder and forage crops

Field trials involving cotton gin by-products were performed in Australia and the USA.

GAP for cotton in Australia is for two foliar aerial or ground spray applications at 50 g ai/ha, unstated interval and PHI 5 days. Trials performed in Australia did not match this GAP.

GAP for cotton in the USA is for one seed treatment at 2.1 kg ai/T seeds. Trials performed in the USA did not match this GAP.

GAP for cotton in the USA is for three foliar spray applications at 75 g ai/ha (max 224 g ai/ha per season), interval 7 days, PHI 21 days. Field trials performed in the USA did not match this GAP.

The Meeting could not estimate an STMR or highest residue for cotton gin by-products as there were no trials matching the GAP.

Field trials involving green rape forage were performed in Germany, Sweden, the UK, and France.

GAP for rape seed in the Czech Republic, Estonia, Finland, and Germany is for one seed treatment at 10 kg ai/T seeds. In field trials performed in Germany, Sweden and France matching this GAP (1 × 7.4–9.5 kg ai/T seeds and PHI 27–191 days) clothianidin residue levels in green rape forage were < 0.02, < 0.02, < 0.02, < 0.02, < 0.02$, < 0.02$, < 0.02$, 0.027, 0.038$ and 0.055$ mg/kg (n = 10). However, values marked with $ cannot be used for a recommendation because of sampling deficiencies.

The meeting estimated an STMR of 0.02 mg/kg and a highest residue of 0.027 mg/kg of clothianidin in green rape forage. A maximum residue level is not required, since forage is not traded.

The NAFTA calculator is not needed here, since maximum residue levels are not proposed for livestock forage.

Field trials involving sugar beet tops were performed in Belgium, Germany, the UK, France, Italy, Spain and the USA.

GAP for sugar beets in Belgium, Denmark, Finland, Germany, Netherlands, Slovakia and the UK is for one seed treatment at 0.6 mg ai/seed. For seed treatments and subsequent field trials

performed in the UK, France and Germany matching this GAP (1 × 0.6 mg ai/seed and PHI 92–148 days) clothianidin residues in sugar beet tops were < 0.02, < 0.02 and < 0.02 mg/kg (n = 3). Residue levels in immature plants were not selected, because sugar beet leaves are normally harvested when roots are mature.

GAP for sugar beet in Italy, Slovenia, and Spain is for one seed treatment at 0.6 mg ai/seed. Trials performed in Spain and Italy did not match this GAP.

GAP for sugar beets in the USA is for one seed treatment at 0.6 mg ai/seed (FS formulation). For seed treatments and subsequent field trials performed in the USA matching this GAP (1 × 0.6 mg ai/seed, PHI 109–179 days, SE formulation) clothianidin residues in sugar beet leaves were < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and 0.011 mg/kg (n = 12).

The Meeting noted that the GAP for Northern Europe is identical to the GAP for the USA. But because the LOQ of the USA dataset was lower, the Meeting decided to use only the USA dataset for a recommendation. The Meeting estimated an STMR of 0.01 mg/kg and a highest residue of 0.011 mg/kg of clothianidin in sugar beet tops. A maximum residue level is not required, since forage is not traded.

The NAFTA calculator was not used as maximum residue levels are not proposed for livestock forage.

Field trials involving sugarcane tops were performed in Australia.

GAP for sugar cane in Australia is for one soil directed spray application at 500 g ai/ha (PHI 147 days). In field trials performed in Australia matching this GAP (1 × 500 g ai/ha and a PHI 146–175 days) clothianidin residue levels in sugarcane tops were 0.08, 0.21 and 0.27 mg/kg (n = 3), expressed on dry weight (dw) for an SC formulation and 0.15 and 0.17 mg/kg dw (n = 2) for a WG formulation at similar locations. In a single bridging study using a WG and SC formulation, residue levels for the WG formulation were higher (0.15 versus 0.08 mg/kg for WG and SC formulation). The datasets are too small for a Mann-Whitney U test. The Meeting agreed to combine the datasets and take only the maximum value per location. This resulted in the following dataset for sugarcane tops: 0.15, 0.17, 0.21 and 0.27 mg/kg dw (n = 4)

The meeting estimated an STMR of 0.19 mg/kg and a highest residue of 0.27 mg/kg of clothianidin in sugarcane tops, based on dry weight basis. A maximum residue level is not required, since forage is not traded.

The NAFTA calculator is not needed here, since maximum residue levels are not proposed for livestock forage.

Field trials involving sugarcane fodder were not available.

Teas

Field trials involving dry leaves of tea were performed in Japan.

GAP for tea (green, black) in Japan is for one spray application at 12 g ai/hL and PHI 7 days. In field trials performed in Japan matching this GAP (1 × 12 g ai/hL and PHI 7 days) clothianidin residues in tea (dry leaves) were 5.3 and 18 mg/kg (n = 2).

The dataset for tea is considered insufficient to support a recommendation. The Meeting could not estimate maximum residue levels for tea.

Combination of residues from clothianidin use and thiamethoxam use

As indicated before, clothianidin residues may arise from use of clothianidin as well as from use of thiamethoxam (metabolite CGA 322704). The Meeting considered it unlikely that both pesticides are

used on the same crop and therefore the maximum estimated levels, the maximum STMR, and the maximum HR of each use is taken as recommendation.

CCN	Commodity name	Origin	Recommendation mg/kg	STMR mg/kg	HR mg/kg
FC 0001	Citrus fruits	CGA 322704	0.07	0.02	0.02
		clothianidin	no GAP		
		both uses	0.07[b]	0.02	0.02
FP 0009	Pome fruits	CGA 322704	0.1	0.025	0.04
		clothianidin	0.4	0.10	0.20
		both uses	0.4[a,b]	0.10	0.20
FS 0012	Stone fruits	CGA 322704	0.2	0.04	0.12
		clothianidin	insufficient data		
		both uses	0.2[a,b]	0.04	0.12
FB 0018	Berries and other small fruits	CGA 322704	0.07	0.01	0.05
	Cranberries	clothianidin	0.01*	0.01	0.01
	Grapes	clothianidin	0.7	0.12	0.41
	Berries and other small fruits, except grapes	both uses	0.07[a,b]	0.01	0.05
	Grapes	both uses	0.7[a,b]	0.12	0.41
FI 0327	Banana	CGA 322704	0.02*	0.02	0.02
		clothianidin	0.02	0.02	0.02
		both uses	0.02[a,b]	0.02	0.02
FI 0350	Papaya	CGA 322704	0.01*	0	0
		clothianidin	no GAP		
		both uses	0.01*[,b]	0	0
FI 0353	Pineapple	CGA 322704	0.01*	0	0
		clothianidin	no GAP		
		both uses	0.01*[,b]	0	0
VB 0040	Brassica (cole or cabbage) vegetables, Head cabbages, flowerhead Brassicas	CGA 322704	0.2	0.015	0.04
	Cabbages, head	clothianidin	insufficient data		
	Broccoli	clothianidin	insufficient data		
	Brassica (cole or cabbage) vegetables, Head cabbages, flowerhead Brassicas	both uses	0.2[b]	0.015	0.04
	Head cabbage with wrapper leaves (for livestock dietary burden)	CGA 322704	–	0.03	0.08
		clothianidin	insufficient data		
		both uses	–	0.03	0.08
VC 0045	Fruiting vegetables, Cucurbits	CGA 322704	0.02*	0.02	0.02
	Cucumber	clothianidin	insufficient data		
	Squash, summer	clothianidin	insufficient data		
	Fruiting vegetables, Cucurbits	both uses	0.02*[,b]	0.02	0.02
VO 0050	Fruiting vegetables, other than cucurbits (except sweet corn)	CGA 322704	0.05	0.02	0.03
	Egg plant	clothianidin	insufficient data		
	Tomato	clothianidin	insufficient data		
	Fruiting vegetables, other than cucurbits (except sweet corn)	both uses	0.05[b]	0.02	0.03
VO 0447	Sweet corn (corn-on-the-cob)	CGA 322704	0.01*	0.01	0.01
		clothianidin	0.01*	0.01	0.01
		both uses	0.01*[, a,b]	0.01	0.01
HS 0444	Pepper Chilli, dried	CGA 322704	0.5	0.2	0.3
		clothianidin	no GAP		
		both uses	0.5[b]	0.2	0.3
VL 0053	Leafy vegetables	CGA 322704	2	0.52	0.80
	Lettuce, Head	clothianidin	insufficient data		
	Lettuce, Leaf	clothianidin	insufficient data		
	Leafy vegetables	both uses	2[b]	0.52	0.80

CCN	Commodity name	Origin	Recommendation mg/kg	STMR mg/kg	HR mg/kg
VP 0060	Legume vegetables	CGA 322704	0.01*	0.01	0.01
		clothianidin	no GAP		
		both uses	0.01*[a,b]	0.01	0.01
VD 0070	Pulses	CGA 322704	0.02	0.02	–
	Soya bean (dry)	clothianidin	insufficient data		
	Pulses	both uses	0.02[b]	0.02	–
VR 0075	Root and tuber vegetables	CGA 322704	0.2	0.01	0.15
	Carrots	clothianidin	insufficient data		
	Chicory roots	clothianidin	insufficient data		
	Potato	clothianidin	0.05	0.02	0.033
	Sugar beet roots	clothianidin	0.03	0.01	0.019
	Root and tuber vegetables	both uses	0.2[a,b]	0.02	0.15
VS 0620	Artichoke, Globe	CGA 322704	0.05	0.024	0.029
		clothianidin	no GAP		
		both uses	0.05[b]	0.024	0.029
VS 0624	Celery	CGA 322704	0.04	0.01	0.02
		clothianidin	no GAP		
		both uses	0.04[b]	0.01	0.02
GC 0640	Barley	CGA 322704	0.04	0.01	–
		clothianidin	0.01*	0.01	–
		both uses	0.04[a,b]	0.01	–
GC 0645	Maize	CGA 322704	0.02	0.02	–
		clothianidin	0.01*	0.01	–
		both uses	0.02[a,b]	0.02	–
GC 0656	Popcorn	CGA 322704	0.01	0.01	–
		clothianidin	0.01*	0.01	–
		both uses	0.01[a,b]	0.01	–
GC 0649	Rice	CGA 322704	insufficient data		
		clothianidin	0.5[a]	0.145	–
		both uses	0.5[a]	0.145	–
GC 0651	Sorghum	CGA 322704	no GAP		
		clothianidin	0.01*	0.01	–
		both uses	0.01*[a]	0.01	–
GC 0654	Wheat	CGA 322704	0.02*	0.02	–
		clothianidin	0.01*	0.01	–
		both uses	0.02*[a,b]	0.02	–
GS 0659	Sugarcane	CGA 322704	no GAP		
		clothianidin	0.4	0.03	0.14
		both uses	0.4[a]	0.03	0.14
TN 0672	Pecan	CGA 322704	0.01*	0.01	0.01
		clothianidin	no GAP		
		both uses	0.01*[b]	0.01	0.01
SO 0088	Oilseed	CGA 322704	0.02*	0.02	–
	Cottonseed (undelinted seed)	clothianidin	insufficient data		
	Rape seed	clothianidin	0.01*	0.01	–
	Sunflower seed	clothianidin	insufficient data		
	Oilseed	both uses	0.02*[a,b]	0.02	–
SB 0715	Cacao beans	CGA 322704	0.02*	0.02	–
		clothianidin	no GAP		
		both uses	0.02*[b]	0.02	–
SB 0716	Coffee beans	CGA 322704	0.05	0.015	–
		clothianidin	no GAP		
		both uses	0.05[b]	0.015	–
AL 0528	Pea vines	CGA 322704	–	0.05	0.05
		clothianidin	no GAP		
		both uses	–	0.05	0.05

CCN	Commodity name	Origin	Recommendation mg/kg	STMR mg/kg	HR mg/kg
AL 0072	Pea hay or Pea fodder (dry)	CGA 322704	0.2, dw	0.05, dw	0.10, dw
		clothianidin	no GAP		
		both uses	0.2, dw [b]	0.05, dw	0.10, dw
AF ----	Barley forage (green)	CGA 322704	–	0.04	0.05
		clothianidin	insufficient data		
		both uses	–[b]	0.04	0.05
AF 0645	Field corn forage (maize forage)	CGA 322704	–	0.01	0.02
		clothianidin	insufficient data		
		both uses	–[b]	0.01	0.02
AF 0645	Sweet corn forage (maize forage)	CGA 322704	–	0.01	0.02
		clothianidin	insufficient data		
		both uses	–[b]	0.01	0.02
AF 0651	Sorghum grain forage (green)	CGA 322704	no GAP		
		clothianidin	not required	0.01	0.01
		both uses	–[a]	0.01	0.01
AF ----	Wheat forage (green)	CGA 322704	–	0.05	0.06
		clothianidin	insufficient data		
		both uses	–[b]	0.05	0.06
AS 0640	Barley straw and fodder, dry	CGA 322704	0.2, dw	0.05, dw	0.14, dw
		clothianidin	0.02*, dw	0.02, dw	0.02, dw
		both uses	0.2, dw [b,a]	0.05, dw	0.14, dw
AS 0645	Field corn stover (Maize fodder)	CGA 322704	0.01*	0.01	0.01
		clothianidin	insufficient data		
		both uses	0.01*[b], dw	0.01, dw	0.01, dw
AS 0645	Popcorn stover (Maize fodder)	CGA 322704	0.01*, dw	0.01, dw	0.01, dw
		clothianidin	insufficient data		
		both uses	0.01*[b], dw	0.01, dw	0.01, dw
AS 0645	Sweet corn stover (Maize fodder)	CGA 322704	0.01, dw	0.01, dw	0.01, dw
		clothianidin	insufficient data		
		both uses	0.01, dw [b]	0.01, dw	0.01, dw
AS 0651	Sorghum grain stover (sorghum straw and fodder, dry)	CGA 322704	no GAP		
		clothianidin	0.01*, dw	0.01, dw	0.01, dw
		both uses	0.01*, dw [a]	0.01, dw	0.01, dw
AS 0654	Wheat straw and fodder, dry	CGA 322704	0.2, dw	0.05, dw	0.14, dw
		clothianidin	0.02*, dw	0.02, dw	0.02, dw
		both uses	0.2, dw [b,a]	0.05, dw	0.14, dw
AV ----	Rape forage (green)	CGA 322704	–	0.05	0.05
		clothianidin	–	0.02	0.027
		both uses	–[a,b]	0.02[c]	0.027[c]
AV 0596	Sugar beet tops (Sugar beet leaves or tops)	CGA 322704	–	0.02	0.02
		clothianidin	–	0.01	0.011
		both uses	–[b]	0.02	0.02
AV 0659	Sugarcane tops (sugarcane forage)	CGA 322704	no GAP		
		clothianidin	–	0.19, dw	0.27, dw
		both uses	–[a]	0.19, dw	0.27, dw
DT 1114	Tea, Green, Black (black, fermented and dried)	CGA 322704	0.7	0.12	–
		clothianidin	insufficient data		
		both uses	0.7[b]	0.12	–

[a] based on clothianidin use as derived from 2010 clothianidin evaluation

[b] based on thiamethoxam use as derived from 2010 thiamethoxam evaluation (metabolite CGA 322704).

[c] overall residue based on trials with the lower LOQ

– not required to recommend MRL (animal forage) or HR (seeds, grains)

dw = residue value expressed as dry weight (i.e., corrected to 100% dry matter)

Residues from rotational crops

In a field rotational crop study, where the soil was treated with 162–192 g ai/ha, clothianidin levels in green crop parts ranged from < 0.01–0.025 mg/kg, < 0.01–0.017 mg/kg, and < 0.01–0.023 mg/kg at the 1, 4 and 8 month plant back intervals, respectively. Clothianidin was not found at the 12 month plant back intervals (< 0.01 mg/kg). Clothianidin was not found in turnip roots, wheat grain and wheat straw at any of the plant back intervals (< 0.01 mg/kg).

Dose rates used in the field rotational crop study are within the normal GAP ranges; therefore, residues from rotational crops need to be taken into account for the MRL recommendation. The field rotational crop study shows that residues from rotational crops are only expected in leafy crop types like Brassica vegetables (010, VB), leafy vegetables (013, VL), legume vegetables (014, VP), stalk and stem vegetables (017, VS), legume feeds (050, AL), forage of cereal grains and grasses (051, AF), and miscellaneous forage crops (052, AV).

The proposed MRL recommendation for direct treatment of Brassica vegetables, leafy vegetables, legume vegetables with clothianidin or thiamethoxam use covers the residues from rotation. However, for stalk and stem vegetables (017, VS), legume feeds (050, AL), forage of cereal grains and grasses (051, AF) and miscellaneous forage crops (052, AV) only a few of the commodities within the group are covered by the direct treatment recommendations.

At the 1 month plant back interval in the field rotational crop study, the following residues were found in different rotational leafy crops: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, 0.011, 0.014, 0.014 and 0.025 mg/kg (n = 9). For the commodities in groups 017 VS without a recommendation for direct treatment, the Meeting decided to recommend a maximum residue level of 0.04 mg/kg, an STMR of 0.01 mg/kg, and an HR of 0.025 mg/kg. For the animal forage commodities, a maximum residue level is not appropriate, since these commodities are not traded. The Meeting decided to recommend an STMR of 0.01 mg/kg and a highest residue of 0.025 mg/kg in animal forage crops (050 AL, 051 AF, 052 AV) without a recommendation for direct treatment.

Fate of residues during processing

Information on the fate of residues during processing by radioactivity studies was not available. Processing studies with clothianidin were undertaken for apples, grapes, tomatoes, potatoes, sugar beets, and cottonseed. In the table below, relevant processing factors for these commodities are summarized.

In addition, processing studies for apple, coffee beans, plums and tomatoes were available from the 2010 thiamethoxam evaluation. A hydrolysis study on thiamethoxam showed that thiamethoxam is stable under the hydrolysis conditions used in food processing. Therefore clothianidin levels do not arise from thiamethoxam hydrolysis and processing factors for CGA 322704 from the thiamethoxam evaluation can be used to estimate processing factors for clothianidin.

Processing factors obtained from high level residue levels in the RAC were considered to be more reliable than processing factors obtained from low level residues in the RAC. For this reason, the processing factors for apple pomace and apple juice from the clothianidin evaluation are considered the best estimate, while the processing factors for tomato paste and tomato puree from the thiamethoxam evaluation are considered the best estimate.

Using the $STMR_{RAC}$ obtained from both the thiamethoxam and clothianidin use, the Meeting estimated STMR-Ps for processed commodities as listed below. The Meeting considered the appropriate STMR-P to be used in the livestock dietary burden calculation or dietary intake calculation. An HR-P is not required for processed commodities.

Commodity	Processing factors	Processing factor (median or best estimate)	STMR-P mg/kg ([a,b] use)
Apple pomace (wet)	0.24[a] 1.4, 1.5, 1.5[b]	0.24[a]	0.10 × 0.24 = 0.024 (pome fruits)
Apple juice	0.14[a] 1.0, 1.0, 1.0[b]	0.14[a]	0.10 × 0.14 = 0.014 (pome fruits)
Dried plums, prunes	1.5, 2.0[b]	1.75[b]	0.04 × 1.75 = 0.07 (stone fruits)
Grape raisins	1.6, 3.6[a]	2.6[a]	0.12 × 2.6 = 0.31
Grape juice	1.1, 1.8[a]	1.45[a]	0.12 × 1.45 = 0.18
Grape pomace	1.9[a]	1.9[a]	0.12 × 1.9 = 0.23
Tomato paste	1.2[a] 2.00, 2.38, 3.33, 3.75, 5.50, 5.78, 6.0, 6.0, 6.5, 6.5, 9.7, 11.3[b]	5.9[b]	0.02 × 5.9 = 0.12 (fruiting veg)
Sugar beet dried pulp (85% dm)	1.7[a]	1.7[a]	0.02 × 1.7 = 0.034 (root and tubers)
Sugar beet molasses (62% dm)	3.2[a]	3.2[a]	0.02 × 3.2 = 0.064 (root and tubers)
Cottonseed meal (96% dm)	0.1[a]	0.1[a]	0.02 × 0.1 = 0.002 (oilseeds)
Cottonseed hulls (88% dm)	0.76[a]	0.76[a]	0.02 × 0.76 = 0.015 (oilseeds)
Cottonseed, refined oil	< 0.077[a]	< 0.077	0.02 × < 0.077 = 0.0015 (oilseeds)
Coffee beans, roasted	< 0.33, < 0.33, < 0.33, < 0.33, < 0.33, < 0.50, < 0.50, < 0.50, < 0.50, < 0.50[b]	< 0.33[b]	0.015 × < 0.33 = < 0.005

[a]: based on clothianidin use as derived from 2010 clothianidin evaluation

[b]: based on thiamethoxam use as derived from 2010 thiamethoxam evaluation (metabolite CGA 322704).

Based on a highest residue of 0.12 mg/kg for stone fruits and processing factor of 1.75, The Meeting estimated a maximum residue level of 0.2 mg/kg for dried plums, prunes (based on thiamethoxam and clothianidin use) and an HR of 0.21 mg/kg.

Based on a highest residue of 0.41 mg/kg for grapes and a processing factor of 2.6, The Meeting estimated a maximum residue level of 1 mg/kg for raisins (based on thiamethoxam and clothianidin use) and an HR of 1.066 mg/kg.

Based on an STMR of 0.12 mg/kg for grapes and a processing factor of 1.45, The Meeting estimated a maximum residue level of 0.2 mg/kg for grape juice (based on thiamethoxam and clothianidin use).

Livestock dietary burden

The Meeting estimated the dietary burden of clothianidin residues (both from thiamethoxam and clothianidin use) on the basis of the livestock diets listed in the FAO manual appendix IX (OECD feedstuff table). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values from feed is suitable for estimating STMR values for animal commodities.

Forage commodities do not appear in the Recommendations Table (because no maximum residue level is needed) but they are used in estimating livestock dietary burden. Therefore all plant commodities used in the dietary burden calculation are listed below. Also, the terminology for commodities in the OECD feed tables is not always identical to the descriptions in the original studies or Codex description and some clarification is needed. Codex groups have been assigned in the JMPR 2009 and 2010 Meeting. Despite the long list of plant commodities used in dietary burden calculation, data on pea silage, soya bean hay, soya bean silage, barley silage, sorghum grain silage,

wheat silage, barley bran fractions, sugar beet ensiled pulp, brewer's grain, canola meal, citrus dried pulp, maize aspirated grain fractions, maize milled by-products, hominy meal of field corn, sweet corn cannery waste, maize gluten, maize gluten meal, distiller's grain, cotton gin by-products, pineapple process waste, potato process waste, potato dried pulp, rape meal, rice hulls, rice bran, sorghum grain aspirated grain fractions, soya bean aspirated grain fractions, soya bean meal, soya bean hulls, soya bean okara, soya bean pollard, sugarcane molasses, sugarcane bagasse, tomato wet pomace, wheat aspirated grain fractions, wheat gluten meal, wheat milled by-products are not available and are therefore not taken into account in dietary burden calculations. Dietary burden for livestock therefore might be underestimated.

The Meeting decided that residue values for pea vines could be extrapolated to cowpea forage, that residue values for pea hay could be extrapolated to cowpea hay, that residue values for barley straw could be extrapolated to barley hay and that residue values for wheat straw could be extrapolated to wheat hay in the calculation of livestock dietary burden. Residues in cotton meal could not be extrapolated to other oilseed meals, because different processing processes are involved.

Codex Group	Codex commodity description	Crop	Feed Stuff	Highest residue	STMR or STMR-P	Residue Level	DM (%)
		Forages					
AL	Alfalfa forage (green)	Alfalfa	forage	0.025	0.01	HR	35
AF/AS		Barley	forage	0.05	0.04	HR	30
AF/AS	Barley straw and fodder, dry	Barley	hay	0.14	0.05	HR	100
AF/AS	Barley straw and fodder, dry	Barley	straw	0.14	0.05	HR	100
AL	Bean forage (green)	Bean	vines	0.025	0.01	HR	35
AM/AV	Sugar beet leaves or tops	Beet, mangel	fodder	0.02	0.02	HR	15
AM/AV	Sugar beet	Beet, sugar	tops	0.02	0.02	HR	23
AM/AV	Cabbages, head	Cabbage	heads, leaves	0.08	0.03	HR	15
AL	Clover	Clover	forage	0.025	0.01	HR	30
AF/AS	Maize forage	Corn, field	forage/silage	0.02	0.01	HR	40
AF/AS	Maize fodder	Corn, field	stover	0.01	0.01	HR	100
AF/AS		Corn, pop	stover	0.01	0.01	HR	100
AF/AS		Corn, sweet	forage	0.02	0.01	HR	48
AF/AS		Corn, sweet	stover	0.01	0.01	HR	100
AL		Cowpea	forage	0.05	0.05	HR	30
AL		Cowpea	hay	0.1	0.05	HR	100
AL		Crown vetch	forage	0.025	0.01	HR	30
AF/AS		Grass	forage (fresh)	0.025	0.01	HR	25
AM/AV	Kale forage	Kale	leaves	0.025	0.01	HR	15
AL	Lespedeza	Lespedeza	forage	0.025	0.01	HR	22
AF/AS		Millet	forage	0.025	0.01	HR	30
AF/AS	Oat forage	Oat	forage	0.025	0.01	HR	30
AL	Pea vines (green)	Pea	vines	0.05	0.05	HR	25

Codex Group	Codex commodity description	Crop	Feed Stuff	Highest residue	STMR or STMR-P	Residue Level	DM (%)
AL	Pea hay or fodder	Pea	hay	0.1	0.05	HR	100
AM/AV	Rape greens	Rape	forage	0.027	0.02	HR	30
AF/AS		Rice	whole crop silage	0.025	0.01	HR	40
AF/AS	Rye forage (green)	Rye	forage	0.025	0.01	HR	30
AF/AS		Sorghum, grain	forage	0.01	0.01	HR	35
AF/AS		Sorghum, grain	stover	0.01	0.01	HR	100
AL	Soya bean forage (green)	Soya bean	forage	0.025	0.01	HR	56
AM/AV		Sugarcane	tops	0.27	0.19	HR	100
AL		Trefoil	forage	0.025	0.01	HR	30
AF/AS		Triticale	forage	0.025	0.01	HR	30
AM/AV	Turnip leaves or tops	Turnip	tops (leaves)	0.025	0.01	HR	30
AL		Vetch	forage	0.025	0.01	HR	30
AF/AS		Wheat	forage	0.06	0.05	HR	25
AF/AS	Wheat straw and fodder, dry	Wheat	hay	0.14	0.05	HR	100
AF/AS	Wheat straw and fodder, dry	Wheat	straw	0.14	0.05	HR	100
		Roots & Tubers					
VR	Carrot	Carrot	culls	0.15	0.02	HR	12
VR	Cassava	Cassava/tapioca	roots	0.15	0.02	HR	37
VR	Potato culls	Potato	culls	0.15	0.02	HR	20
VR	Swede	Swede	roots	0.15	0.02	HR	10
VR	Turnip, Garden	Turnip	roots	0.15	0.02	HR	15
		Cereal Grains/ Crops Seeds					
GC	Barley	Barley	grain		0.01	STMR	88
VD	Beans, dry	Bean	seed		0.02	STMR	88
GC	Maize	Corn, field	grain		0.02	STMR	88
GC	Popcorn	Corn, pop	grain		0.01	STMR	88
VD	Cowpea	Cowpea	seed		0.02	STMR	88
VD	Lupin	Lupin	seed		0.02	STMR	88
VD	Field pea, (dry)	Pea	seed		0.02	STMR	90
GC	Rice	Rice	grain		0.145	STMR	88
GC	Sorghum	Sorghum, grain	grain		0.01	STMR	86
VD	Soya bean, dry	Soya bean	seed		0.02	STMR	89
VD	Vetch	Vetch	seed		0.02	STMR	89
GC	Wheat	Wheat	grain		0.02	STMR	89
		By-products					
AB	Apple pomace, dry	Apple	pomace, wet		0.024	STMR	40

Codex Group	Codex commodity description	Crop	Feed Stuff	Highest residue	STMR or STMR-P	Residue Level	DM (%)
AB	Sugar beet pulp, dry	Beet, sugar	dried pulp		0.034	STMR	85
DM	Sugar beet molasses	Beet, sugar	molasses		0.064	STMR	62
SM	Cotton meal	Cotton	meal		0.002	STMR	96
SO		Cotton	undelinted seed		0.02	STMR	88
SM	Cotton hulls	Cotton	hulls		0.015	STMR	88
AB	Grape pomace, dry	Grape	pomace, wet		0.23	STMR	15

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. A mean and maximum dietary burden for livestock, based on thiamethoxam and clothianidin use, is shown in the table below.

Animal dietary burden for clothianidin (from thiamethoxam and clothianidin use), expressed as ppm of dry matter diet

	US	EU	AU	JPN	overall	
	max	max	max	max	max	
beef cattle	0.298	0.795	0.640	0.027	0.795 (EU)	[a]
dairy cattle	0.277	0.586	0.632	0.061	0.632 (AU)	[b]
poultry broiler	0.051	0.209	0.094	0.022	0.209 (EU)	
poultry layer	0.051	0.258	0.094	0.021	0.258 (EU)	[c,d]
	mean	mean	mean	mean	mean	
beef cattle	0.089	0.170	0.465	0.024	0.465 (AU)	[a]
dairy cattle	0.119	0.170	0.459	0.033	0.459 (AU)	[b]
poultry broiler	0.051	0.040	0.094	0.020	0.094 (AU)	
poultry layer	0.051	0.070	0.094	0.021	0.094 (AU)	[c,d]

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

[b] Highest mean and maximum dairy cattle dietary burden suitable for maximum residue level and STMR estimates for milk.

[c] Highest mean and maximum poultry broiler or layer dietary burden suitable for maximum residue level and STMR estimates for poultry meat.

[d] Highest mean and maximum poultry layer suitable for maximum residue level and STMR estimates for eggs.

Livestock feeding studies

The Meeting received a feeding study on lactating cows.

Three groups of three lactating Holstein-Friesian cows were dosed once daily via capsules at levels of 0.27, 0.80 and 2.6 ppm dry weight feed for 28 consecutive days. Milk was collected throughout the study and tissues were collected on day 29 within 15–17 hrs after the last dose.

No residues of clothianidin were found in tissues at any dose level (< 0.02 mg/kg). Levels of clothianidin in milk were < 0.002 mg/kg in the 1 × dose group, < 0.002–0.003 mg/kg (mean 0.0020 mg/kg) in the 3 × dose group and < 0.002–0.012 mg/kg (mean 0.0046 mg/kg) in the 10 × dose group.

Residues in animal commodities

Cattle

In a feeding study where lactating cows were dosed with clothianidin at up to 2.6 ppm dry feed, no clothianidin was found in tissues (< 0.02 mg/kg). Therefore, no residues are to be expected in tissues at the mean and maximum calculated dietary burden of 0.465 and 0.795 ppm based on clothianidin dietary burden.

For milk MRL estimation, the highest residues in the milk resulting from dietary burden based on clothianidin were calculated by interpolating the maximum dietary burden for dairy cattle (0.632 ppm) between the relevant feeding levels (0.27 and 0.8 ppm) from the dairy cow feeding study and using the mean milk concentration from those feeding groups.

For milk STMR estimation, the median residues in the milk resulting from dietary burden were calculated by interpolating the mean dietary burden for dairy cattle (0.459 ppm) between the relevant feeding levels (0.27 and 0.80 ppm) from the dairy cow feeding study and using the mean milk concentration from those feeding groups.

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]	Milk (mg/kg residue)
	mean
MRL dairy cattle (0.632 ppm) [0.27–0.80 ppm]	< 0.0020 [< 0.0020–0.0020]
STMR dairy cattle (0.459 ppm) [0.27–0.80 ppm]	< 0.0020 [< 0.0020–0.0020]

Another route for clothianidin residues to end up in animal commodities is from dietary burden resulting from thiamethoxam use. Based on a lactating cow feeding study with thiamethoxam, the CGA 322704 residues in milk were estimated at 0.011 and 0.004 mg/kg resulting from the maximum (5.23 ppm) and mean (1.59 ppm) dietary burden from thiamethoxam use. The CGA 322704 residues in liver were estimated at 0.10 and 0.035 mg/kg resulting from the maximum (5.23 ppm) and mean (1.59 ppm) dietary burden from thiamethoxam use. The CGA 322704 residues in muscle, fat and kidney were below the LOQ of 0.01 mg/kg for the maximum (5.23 ppm) dietary burden from thiamethoxam use. These residues need to be taken into account.

The Meeting estimated a maximum residue level for clothianidin of 0.02* mg/kg in meat from mammals other than marine mammals, mammalian offal, except liver, and mammalian fat (based on clothianidin use). The Meeting estimated a maximum residue level for clothianidin of 0.2 mg/kg in liver of cattle, goats, pigs and sheep (based on thiamethoxam use). The meeting estimated a maximum residue for clothianidin of 0.02 mg/kg in milks (based on thiamethoxam use). The residue in animal commodities is considered not fat-soluble.

The Meeting estimated an STMR and HR of 0.02 mg/kg in meat from mammals other than marine mammals, mammalian offal, except liver and mammalian fat (based on clothianidin use). The Meeting estimated an STMR of 0.035 mg/kg and HR of 0.10 mg/kg in liver (based on thiamethoxam use). The Meeting estimated an STMR of 0.004 mg/kg in milks (based on thiamethoxam use).

Poultry

No poultry feeding study is available for clothianidin, but the metabolism studies in laying hens can be used to estimate residue levels resulting from dietary burden based on clothianidin in poultry

tissues or eggs from a mean and maximum dietary burden of 0.070 and 0.258 ppm. When extrapolating from a dose rate of 134 ppm in the laying hen metabolism study to 0.258 ppm as maximum dietary burden for poultry, and using the maximum total residues in liver of 5.1 mg/kg, residue levels in tissues and eggs are expected to be well below the LOQ of 0.01 mg/kg.

Another route for clothianidin residues to end up in animal commodities is from dietary burden resulting from thiamethoxam use. Based on a poultry metabolism study with thiamethoxam, CGA 322704 residues in poultry meat, fat and eggs from a thiamethoxam dietary burden of 1.59 ppm are also well below the LOQ of 0.01 mg/kg. However, CGA 322704 residues in poultry offal from thiamethoxam dietary burden of 1.59 ppm are higher than from clothianidin dietary burden. These residues need to be taken into account. Maximum residue levels from thiamethoxam dietary burden in poultry liver are 0.050 mg/kg clothianidin; mean residue levels in poultry liver are 0.018 mg/kg clothianidin.

The Meeting estimated a maximum residue level for clothianidin of 0.01* mg/kg in poultry meat, poultry fats, and eggs (based on clothianidin use). The Meeting estimated a maximum residue level for clothianidin of 0.1 mg/kg in poultry offal (based on thiamethoxam use). The residue in animal commodities is considered not fat-soluble.

The Meeting estimated an STMR and HR of 0.01 mg/kg in poultry meat, poultry fats, and eggs (based on clothianidin use). The Meeting estimated an STMR of 0.018 mg/kg in poultry offal and an HR of 0.050 mg/kg in poultry offal (based on thiamethoxam use).

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDI) of for clothianidin was calculated from recommendations for STMRs for raw and processed commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 3.

The IEDI of in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 1%–2% of the maximum ADI of 0.1 mg/kg bw. The Meeting concluded that the long-term intake of residues of clothianidin from uses considered by the Meeting is unlikely to present a public health concern.

Short-term intake

The International Estimated Short Term Intake (IESTI) for clothianidin was calculated from recommendations for STMRs and HRs for raw and processed commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 4.

5.8 CYPROCONAZOLE (239)

TOXICOLOGY

Cyproconazole is the International Organization for Standardization (ISO)–approved name for (2*RS*, 3*RS*, 2*SR*, 3*SR*)-2-(4-chlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol (International Union of Pure and Applied Chemistry [IUPAC]), for which the Chemical Abstracts Service (CAS) No. is 94361-06-5. The cyproconazole structure exists in four stereoisomeric forms as two diastereoisomeric pairs of enantiomers. Cyproconazole is a 1:1 mixture of the two diastereomeric pairs, each of which is a 1:1 mixture of the enantiomers (i.e., all four stereoisomers are present in similar amounts).

Cyproconazole is a broad-spectrum triazole fungicide. It acts by inhibiting sterol biosynthesis in fungi (demethylation inhibitor). Cyproconazole has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed at the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR). All pivotal studies with cyproconazole were certified as complying with good laboratory practice (GLP) unless otherwise stated.

Biochemical aspects

In a toxicokinetic study, male and female rats were given cyproconazole uniformly labelled with ^{14}C either in the phenyl ring or at the α-carbon position as a single dose at 10 or 130 mg/kg body weight (bw) or as 14 repeated doses of 10 mg/kg bw per day followed by a single oral dose of radioactive cyproconazole at 10 mg/kg bw. Cyproconazole was rapidly and extensively (86%) absorbed from the gastrointestinal tract and rapidly excreted from the body in urine and faeces (85% of the administered dose) within 168 h. The majority of excretion occurred in the first 48 h. The bile duct–cannulated rats excreted approximately 76% and 60% of the administered dose in the bile in males and females, respectively. Approximately 5% of the administered dose was recovered in the faeces in the cannulated rats. The absorption, distribution and excretion of cyproconazole were similar in rats administered repeated doses and single low and high doses. No significant radioactivity was detected in the exhaled air following a single oral dose of 10 mg/kg bw. Less than 0.42% of the administered dose was found in the carcass and tissues at 168 h. Tissue residues were highest in liver and adrenals (mainly cortex), followed by fat and kidney. There was no evidence of bioaccumulation in any tissues in rats. Cyproconazole was extensively metabolized, with a greater number of metabolites identified in the urine compared with the faeces. The metabolic profile revealed 35 metabolites, ranging from less than 0.1% to 4.9% and from less than 0.1% to 13.2% of the administered dose in the urine and faeces, respectively. Approximately 11% of the parent compound was detected in the faeces, and less than 0.4% in the urine. The predominant metabolic reactions of cyproconazole in the rat were 1) oxidative elimination of the triazole ring, 2) hydroxylation of the carbon bearing the methyl group, 3) oxidation of the methyl group to the carbinol and further to the carboxylic acid and 4) reductive elimination of the carbon bearing the methyl group, yielding a benzyl alcohol, which is further oxidized to the corresponding ketone.

Toxicological data

Cyproconazole has moderate acute toxicity when administered by the oral route to mice (median lethal dose [LD_{50}] of 200 mg/kg bw) and female rats (LD_{50} of 350 mg/kg bw). The LD_{50} in rats and rabbits treated dermally was greater than 2000 mg/kg bw. The median lethal concentration (LC_{50}) in rats treated by inhalation (nose only) was greater than 5.6 mg/L. Cyproconazole was slightly irritating

to the eyes and skin of rabbits. Cyproconazole was not a skin sensitizer in guinea-pigs as determined by the Magnusson and Kligman (maximization) test and the Buehler test.

The liver was the target organ for cyproconazole in short-term toxicity studies in mice, rats and dogs. Disturbances in lipid metabolism were also observed in all species studied. The no-observed-adverse-effect level (NOAEL) in a 90-day study of toxicity in mice was 15 ppm (equal to 2.2 mg/kg bw per day), based on decreased body weight gain in both sexes seen at 300 ppm (equal to 43.8 mg/kg bw per day).

The NOAEL in a 28-day study of toxicity in rats was 100 ppm (equal to 8.1 mg/kg bw per day), based on reduced body weight gain in females, changes in clinical chemistry, organ weight changes and histopathological findings in the liver seen at 300 ppm (equal to 25.3 mg/kg bw per day). Two 90-day dietary toxicity studies in rats were available, with a combined NOAEL of 80 ppm (equal to 6.4 mg/kg bw per day), based on reduced body weight gain seen at 320 ppm (equal to 23.8 mg/kg bw per day).

The NOAEL in the 90-day and 1-year toxicity studies in dogs was 100 ppm (equal to 3.2 mg/kg bw per day), based on retarded body weight gain seen at 350 ppm (equal to 12.1 mg/kg bw per day) and above.

The carcinogenic potential of cyproconazole was studied in mice and rats. In mice, the major changes following administration of cyproconazole occurred in the liver. There were a number of toxic effects (focal hepatocytic inflammation, single-cell hepatocytic necrosis and diffuse hepatocytic hypertrophy) at the two highest dose levels (100 and 200 ppm) in both sexes. The male mice were more severely affected than the females. The non-liver findings in mice were not considered treatment related. A treatment-related increase in the incidence of combined adenomas and carcinomas was found in males and females at 200 ppm and in males at 100 ppm. The NOAEL in this study was 15 ppm (equal to 1.8 mg/kg bw per day), and the lowest-observed-adverse-effect level (LOAEL) was 100 ppm (equal to 13.2 mg/kg bw per day).

To clarify the mode of action of mouse liver tumours, mechanistic studies were conducted in which the liver effects of cyproconazole and phenobarbital (PB) in various strains of mice were compared. The results of these studies indicated that cyproconazole as well as PB produced similar effects in a dose-related manner in mice. Studies using constitutive androstane receptor (CAR) null and wild-type mice treated with cyproconazole or PB for up to 7 days clearly indicated early gene expression changes in CAR regulation (*Cyp2b10, Gadd45β*), biochemical changes (induction of cytochrome P450 2B–dependent enzyme activities), hypertrophy, fat vacuolation and increased single-cell necrosis in the liver, indicating that these effects were a consequence of CAR activation by cyproconazole as well as PB. Based on these mechanistic studies, the Meeting concluded that development of liver tumours in mice administered cyproconazole depends upon CAR activation.

In the 2-year toxicity and carcinogenicity study in rats, the NOAEL was 50 ppm (equal to 2.2 mg/kg bw per day), on the basis of body weight depression at 350 ppm (equal to 15.6 mg/kg bw per day). There was no evidence of treatment-related tumorigenesis in the rat.

Cyproconazole gave a negative response in an adequate range of in vitro and in vivo genotoxicity tests.

The Meeting concluded that cyproconazole was unlikely to be genotoxic.

On the basis of the absence of genotoxicity, the absence of carcinogenicity in rats and no carcinogenicity in mice by a mode of action relevant to humans, the Meeting concluded that cyproconazole is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, reproductive parameters were not affected at the highest dose tested (120 ppm, equal to 8.3 mg/kg bw per day). The NOAEL for parental systemic toxicity was 20 ppm (equal to 1.4 mg/kg bw per day), based on a significant increase in relative liver weight and an increased incidence of slight fatty changes (vacuolated hepatocytes) in the liver at 120 ppm (equal to 8.3 mg/kg bw per day). These effects in the liver cannot

be unequivocally attributed to the activation of CAR. Toxicity was less pronounced in the F_0 females and was not seen in F_1 males and females. The NOAEL for reproductive and offspring toxicity was 120 ppm (equal to 8.3 mg/kg bw per day), the highest dose tested.

There are three developmental toxicity studies in rats: the main study, a non-GLP range-finding study and a published study. Cyproconazole caused significantly diminished body weight gain during the early phase of treatment (days 6–11) as well as reduced food consumption in all three studies. In the dose range of 20–30 mg/kg bw per day, body weight gain was 29–37% below that of control groups. Major fetal malformations in these studies were cleft palate (also reported as palatoschisis) and internal hydrocephalus. These malformations occurred at dose levels of 20 mg/kg bw per day and above. The NOAEL for maternal toxicity in the main developmental study was 6 mg/kg bw per day, based on reduced maternal body weight gain during gestation days 6–11 and decreased food consumption seen at 12 mg/kg bw per day. The developmental NOAEL in the main study in rats was 12 mg/kg bw per day, based on decreased fetal body weights, post-implantation loss, increases in supernumerary ribs and increased fetal malformations (e.g., cleft palate) seen at 20 mg/kg bw per day.

There are two developmental toxicity studies available in rabbits. In the first study, treatment of pregnant Chinchilla rabbits with cyproconazole resulted in maternal body weight loss and reduced food consumption early during treatment at the highest dose level of 50 mg/kg bw per day. A slightly increased number of post-implantation losses were also noted in this group. No treatment-related fetal abnormalities were observed. The NOAEL for maternal and developmental toxicity in Chinchilla rabbits was 10 mg/kg bw per day. In the second study, New Zealand White rabbits were treated at the same dose levels. As in the previous study, the high dose resulted in maternal toxicity in the form of body weight loss and reduced food consumption early during treatment. The incidence of post-implantation losses was not affected. In contrast to the first study, the second one revealed an increased number of fetal malformations, mainly affecting sternebrae, ribs, vertebral column, hind limbs and tail. The NOAEL for maternal and developmental toxicity was 10 mg/kg bw per day.

The Meeting concluded that cyproconazole can cause developmental toxicity, including malformations, but only at doses that are maternally toxic.

In a 90-day dietary study of toxicity in rats, five rats of each sex per dose were subjected to neuropathological examination and were also evaluated in the functional observational battery (FOB) and for the assessment of motor activity. No effects on FOB parameters, motor activity or neuropathology were observed at doses up to 1400 ppm (equal to 106.8 mg/kg bw per day).

No adverse effects due to occupational exposure to cyproconazole were reported in workers working in the production, formulation and packaging plant or in research laboratories.

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

Toxicological data on metabolites

Several toxicological studies were conducted on cyproconazole metabolites M21/M21a and M36 (also named NOA 405870 and NOA 405872, respectively). The IUPAC name for metabolite M21/M21a is 5-(4-chlorophenyl)-5-hydroxy-4-methyl-6-(1H-1,2,4-triazol-1-yl)-2-hexanoic acid. The IUPAC name for metabolite M36 is 5-(4-chlorophenyl)-3,5-dihydroxy-4-methyl-6-[1,2,4]triazol-1-yl-hexanoic acid. These metabolites were found in the rat at minor amounts only (0.02–0.06% of applied dose in urine). They were found in the milk and in the urine of lactating goats. Therefore, the toxicological profile of these metabolites was investigated.

The acute oral LD_{50} for metabolite M21/M21a (NOA 405870) was greater than 2000 mg/kg bw. The metabolite was negative for mutagenicity in a bacterial reverse mutation assay (Ames test). For metabolite M36 (NOA 405872), an oral LD_{50} value of greater than 2000 mg/kg bw was observed in mice and rats. Based on the results from three genotoxicity studies, it is concluded that M36 is

unlikely to be genotoxic in vivo. A 28-day feeding study in rats resulted in deaths at the test limit dose of 20 000 ppm and significant reductions in body weight at 5000 ppm and above. The NOAEL in this study was 1500 ppm (equal to 155 mg/kg bw per day), based on reduced body weights seen at 5000 ppm (equal to 527 mg/kg bw per day).

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.02 mg/kg bw on the basis of the overall NOAEL of 2.2 mg/kg bw per day from the 2-year study of toxicity and carcinogenicity and the multigeneration reproduction study in rats based on reduced body weight gain and liver toxicity seen at higher doses. A safety factor of 100 was applied. This ADI was supported by the NOAEL of 15 ppm (equal to 2.2 mg/kg bw per day) observed in a 90-day toxicity study in mice on the basis of reduced body weight gain observed at 300 ppm (equal to 43.8 mg/kg bw per day).

The Meeting established an acute reference dose (ARfD) of 0.06 mg/kg bw on the basis of a maternal toxicity NOAEL of 6 mg/kg bw per day in studies of developmental toxicity in rats, based on body weight loss during the early treatment period (gestation days 6–11) and reduced food consumption seen at 12 mg/kg bw per day. The ARfD is protective of developmental toxicity seen at a slightly higher dose in rabbits.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mice	Ninety-day study of toxicity[a]	Toxicity	15 ppm, equal to 2.2 mg/kg bw per day	300 ppm, equal to 43.8 mg/kg bw per day
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	50 ppm, equal to 2.2 mg/kg bw per day	350 ppm, equal to 15.6 mg/kg bw per day[b]
		Carcinogenicity	350 ppm, equal to 15.6 mg/kg bw per day[b]	—
	Multigeneration study of reproductive toxicity[a]	Parental toxicity	20 ppm, equal to 1.4 mg/kg bw per day[b]	120 ppm, equal to 8.3 mg/kg bw per day[b]
		Reproductive toxicity	120 ppm, equal to 8.3 mg/kg bw per day[b]	—
		Offspring toxicity	120 ppm, equal to 8.3 mg/kg bw per day[b]	—
	Developmental toxicity study [c,d]	Maternal toxicity	6 mg/kg bw per day	12 mg/kg bw per day
		Embryo and fetal toxicity	12 mg/kg bw per day	20 mg/kg bw per day[b]
Rabbit	Developmental toxicity study[c,d]	Maternal toxicity	10 mg/kg bw per day	50 mg/kg bw per day[b]
		Embryo and fetal toxicity	10 mg/kg bw per day	50 mg/kg bw per day[b]
Dog	Ninety-day and 1-year studies of toxicity[a,d]	Toxicity	100 ppm, equal to 3.2 mg/kg bw per day	350 ppm, equal to 12.1 mg/kg bw per day[b]

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.02 mg/kg bw

Estimate of acute reference dose

0.06 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapidly absorbed, > 86% within 144 h
Dermal absorption	Not available
Distribution	Widely distributed in tissues; highest residues in liver, adrenal, fat and kidney
Potential for accumulation	None
Rate and extent of excretion	Rapid and extensive
Metabolism in animals	Extensively metabolized (35 metabolites identified)
Toxicologically significant compounds (animals, plants and environment)	Cyproconazole and 1,2,4-triazole
Acute toxicity	
Rat, LD_{50}, oral	350 mg/kg bw (rats)
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.6 mg/L (4 h exposure, nose only)
Rabbit, dermal irritation	Slightly irritating
Rabbit, ocular irritation	Slightly irritating
Guinea-pig, dermal sensitization	Not a sensitizer (Magnusson and Kligman test, Buehler test)
Short-term studies of toxicity	
Target/critical effect	Reduced body weights in mice and rats
Lowest relevant oral NOAEL	2.2 mg/kg bw per day (90-day study of toxicity in mice)
Lowest relevant dermal NOAEL	100 mg/kg bw per day (rat, highest dose tested)
Lowest relevant inhalation NOAEL	0.017 mg/L, equal to 4.6 mg/kg bw per day (16-day inhalation study in rats)
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver
Lowest relevant NOAEL	2.2 mg/kg bw per day (2-year carcinogenicity study in rats)
Carcinogenicity	Not carcinogenic in rats; carcinogenic in mice by mode of action not relevant to humans

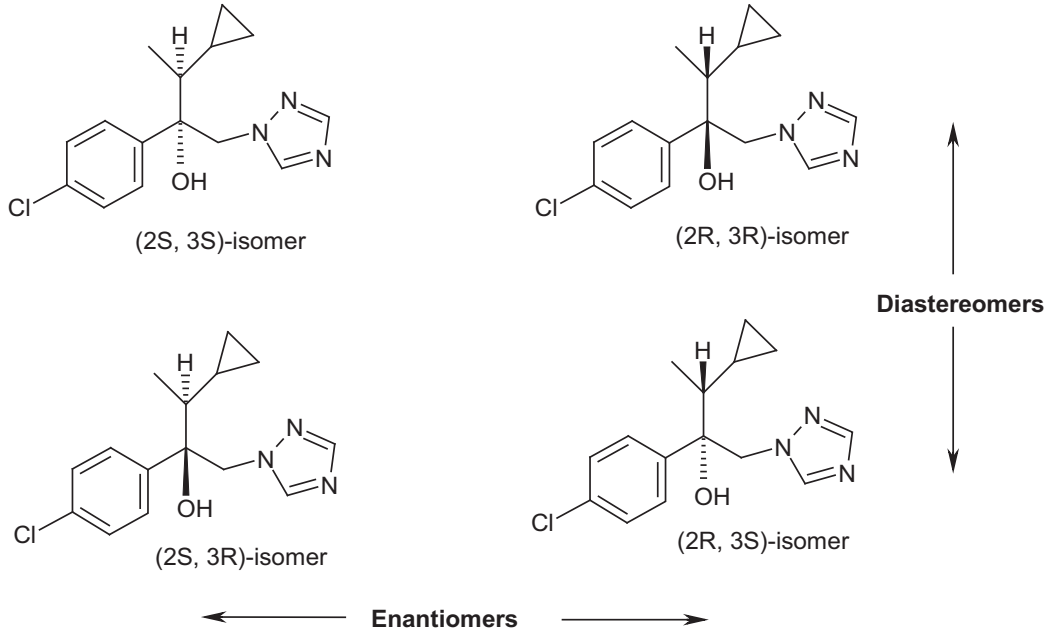
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Reproduction target/critical effect	None
Lowest relevant reproductive NOAEL	8.3 mg/kg bw per day (rats; highest dose tested)
Developmental target/critical effect	Developmental toxicity, including teratogenicity, only at maternally toxic dose in rats and rabbits
Lowest relevant developmental NOAEL	10 mg/kg bw per day (rats and rabbits)
Neurotoxicity/delayed neurotoxicity	
Subchronic neurotoxicity, 90-day rat	Not neurotoxic
Mechanistic data	
	Mechanistic studies supporting CAR-mediated liver toxicity and tumours in mice
Medical data	
	No adverse effects reported

Summary

	Value	Study	Safety factor
ADI	0–0.02 mg/kg bw	2-year study of toxicity and carcinogenicity and multigeneration reproduction study in rats	100
ARfD	0.06 mg/kg bw	Developmental studies of toxicity in rats	100

RESIDUE AND ANALYTICAL ASPECTS

Cyproconazole is an azole fungicide used to control a wide range of fungi on cereal crops, coffee, sugar beet, fruit trees, grapes, including rust on cereal crops, powdery mildew on cereal crops, fruit tree and grapes, and scab on apple. It was considered for the first time by the 2010 JMPR. Cyproconazole is an approximately 1:1 mixture of two diastereomers, each of which is exactly a 1:1 mixture of the enantiomers. All four stereoisomers are present in similar amounts.



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 (livestock feeding). Japan and the Netherlands also submitted use pattern information.

List of metabolites and degradation products

CODE OR COMMON NAME	CHEMICAL NAME
Cyproconazole (CGA 221949)	α-(4-chlorophenyl)-α-(1-cyclopropylethyl)-1*H*-1,2,4-triazole-1-ethanol
M1/M2 M9/M14 NOA 421153	2-(4-chlorophenyl)-3-cyclopropyl-1-[1,2,4]triazol-1-yl-butane-2,3-diol
M11/M18 NOA 421154	3-(4-chlorophenyl)-2-cyclopropyl-4-[1,2,4]triazol-1-yl-butane-1,3-diol
M10/M10a NOA 452154	3-(4-chlorophenyl)-2-cyclopropyl-3-hydroxy-4-[1,2,4]triazol-1-yl-butyric acid
M15 NOA 408616	1-(4-chlorophenyl)-2-[1,2,4]triazol-1-yl-ethanol
M16 CGA 123420	1-(4-chlorophenyl)-2-[1,2,4]triazol-1-yl-ethanone
M21/M21a NOA 405870	5-(4-chlorophenyl)-5-hydroxy-4-methyl-6-[1,2,4]triazol-1-yl-hex-2-enoic acid
M36 NOA 405872	δ-(4-chlorophenyl)-β,δ-dihydroxy-γ-methyl-1H-1,2,4-triazole-1-hexenoic acid
M31/M48 NOA 410714	2-chloro-5-(2-cyclopropyl-1-hydroxy-1-[1,2,4]triazol-1-ylmethyl-propyl)-phenol
M38 NOA 421155	1-[2-(4-chlorophenyl)-3-cyclopropyl-but-1-enyl]-1H-[1,2,4]triazole

CODE OR COMMON NAME	CHEMICAL NAME
M39 CGA 131013	3-(1H-1,2,4-triazol-1-yl)-alanine
M41 (C3/C5)	glucoside of 3-(4-chlorophenyl)-2-cyclopropyl)-4-(1H-1,2,4-triazol-1-yl)-1,3-butanediol
M42	glucoside of 2-(4-chlorophenyl)-3-cyclopropyl-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol
M43	glucoside of α-(4-chlorophenyl)-α-[1-(2-hydroxycyclopropyl)ethyl]-1H-1,2,4-triazole-1-ethanol
M44/M45 (C4)	glucosides of α-(4-chloro3-hydroxyphenyl)-α-(1-cyclopropylethyl)-1H-1,2,4-triazole-1-ethanol
M46	malonic acid conjugate of M42
M47	malonic acid conjugate of M41
M50	Sulfuric acid mono-[1-(4-chlorophenyl)-2-[1,2,4]triazol-1-yl-ethyl] ester
M51	Sulfuric acid mono-[3-(4-chlorophenyl)-2-cyclopropyl-2,3-dihydroxy-4-[1,2,4]triazol-1-yl-butyl] ester
M52 (M54) [stereoisomer of either M52 or M53]	Sulfuric acid mono-[3-(4-chlorophenyl)-2-cyclopropyl-3-hydroxy-4-[1,2,4]triazol-1-yl-butyl] ester
M53 (M54) [stereoisomer of either M52 or M53]	Sulfuric acid mono-[3-(4-chlorophenyl)-2-cyclopropyl-3-hydroxy-4-[1,2,4]triazol-1-yl-butyl] ester
M55 SYN 533911/SYN 533912	5-chloro-2-(1-hydroxy-2-4-[1,2,4]triazol-1-yl-ethyl) phenol or 2-chloro-5-(1-hydroxy-2-4-[1,2,4]triazol-1-yl-ethyl) phenol
M56 SYN 533921	5-[1-(4-chlorophenyl)-1-hydroxy-2-[1,2,4]triazol-1-yl-ethyl]-4-hydroxy-5-methyl-dihydro-furan-2-one
M57 NOA 405870	(E)-5-(4-chlorophenyl)-4,5-dihydroxy-4-methyl-6-[1,2,4]triazol-1-yl-hex-2-enoic acid
M58 CGA 155705	4-chlorobenozic acid
M59	2-(4-chlorophenyl)-3-methyl-1-[1,2,4]triazol-1-yl-pentane-2,4-diol
CGA71019 1,2,4-Triazole	1H-1,2,4-triazole
CGA142856 Triazole acetic acid	1,2,4-triazol-1-yl-acetic acid

Animal metabolism

The Meeting received animal metabolism studies with cyproconazole in rats, lactating goats and laying hens. The metabolism and distribution of cyproconazole in animals was investigated using the [α-carbon^{14}C]-cyproconazole in goats, hens, and rats and the [U-^{14}C-phenyl]-cyproconazole in hens. The rat studies are addressed in the Toxicology section of the Report.

Three lactating goat metabolism studies were provided in which goats were dosed with [α-carbon^{14}C]-Cyproconazole for 12 consecutive days at 1 ppm in the diet, for three consecutive days at 30 ppm in the diet, or for four consecutive days at 10 ppm in the diet. Most (> 85% TRR) of the radioactivity was extractable in milk and tissues. The TRR levels were low in muscle (about

0.01 mg/kg). Cyproconazole was a major component of the residue in liver (20% TRR), fat (27–47% TRR), kidney (24–32% TRR, of which up to 24% conjugated), and muscle (11% TRR), but minor in milk (0–9% TRR). The major metabolites in milk were NOA405872 (M36) (47–68% TRR) and NOA405870 (M21) (17–30% TRR), both of which are carboxylic acid derivatives. NOA452154 was a minor metabolite (8% TRR) in milk. Significant metabolites in liver were NOA421153/M9/M14 (27–27% TRR), NOA421155/M38 (4–16% TRR), and NOA421154/M10 (9–12% TRR). A significant metabolite in fat was NOA421155/M38 (11–36% TRR). In kidney, NOA405872/M36 was significant (12% TRR) in one study. Trace amounts of NOA408616/M15 (about 1% TRR) were found in liver, kidney, fat, and muscle, and slightly higher levels of the corresponding ketone CGA123420/M16 (1–4% TRR) were found in the same tissues.

Taken together, the studies show that cyproconazole is metabolized in goats via:

- Oxidation of the carbon bearing the methyl and cyclopropyl rings to form M14 (NOA421153);
- Oxidation of the methyl group to form M18/M11 (NOA421154) and to M10 (NOA452154);
- Elimination-reduction or removal of the cyclopropyl side chain to form M15 (NOA408616) and subsequent oxidation to the corresponding ketone M16C (GA123420) (minor);
- Elimination of water to form M38 (NOA421155);
- Oxidative opening of the cyclopropyl ring to form M36 (NOA405872) and subsequent dehydration to form M21 (NOA405870) and elimination into milk;
- Glucuronide and/or sulfate conjugation of cyproconazole (minor, except kidney, where it is 5× cyproconazole concentration).

The metabolic fate of cyproconazole was investigated in laying hens using [α-^{14}C]-cyproconazole (1 ppm for 3 days) and [U-^{14}C-phenyl]-cyproconazole (114 ppm for 4 days). Cyproconazole was a major part of the TRR in all matrices: 4% (TRR 0.07 mg/kg)–40% (TRR 3 mg/kg), muscle, 41%–67% fat, 4%–38% liver, 10–30% egg whites, 22–50% egg yolks. Conjugated cyproconazole was about 12% of the free cyproconazole concentration in eggs. NOA421153 (M9/M14) was a major metabolite in muscle (20–31% TRR), fat (15–37% TRR), liver (20–38% TRR), egg whites (35–44% TRR), and egg yolks (14–28% TRR). NOA408616 (M15) was significant in muscle (14–46% TRR), liver (10–22% TRR), egg whites (18–36% TRR), and egg yolks (4–10% TRR).

The metabolism of cyproconazole in poultry proceeds predominantly via hydroxylation, oxidation and elimination reactions. Parent compound was a major component in eggs and all tissues. The major metabolites in eggs and tissues resulted from either (i) hydroxylation of the carbon bearing the cyclopropyl group (M9 and M14) or (ii) elimination of the methyl-cyclopropyl side chain (M16) followed by reduction (M15). Hydroxylation of the methyl group (M11 and M18) was also a route of metabolism.

The metabolism of cyproconazole is qualitatively similar in ruminants and poultry. The major routes of metabolism involved either hydroxylation of the carbon bearing the cyclopropyl group to form M9 /M14 or elimination of the methyl-cyclopropyl side chain (M16) followed by reduction (M15). Hydroxylation of the methyl group (M11 and M18) was also a major route of metabolism, as was opening and modification of the cyclopropyl ring (M21, M36, M56, M57, and M59). The data (ruminant faces with NOA 421152 or M3/M4)) indicate that there is only limited cleavage of the triazole ring and that the majority of residues retain the intact phenyl and triazole rings.

Metabolites found in the ruminant and poultry metabolism studies in edible tissues, eggs, and milk were also found in the rat metabolism study. Among the more prominent fractions in urine were NOA421152 (M3 & M4), NOA408616, NOA421154 (M18) and NOA452669 (M30/33). In faeces, NOA421152 (M3 & M4) and NOA421153 (M14) were the major metabolites beside parent. Further

metabolites at significant amounts were NOA421152 (M4), NOA421153 (M9), NOA452154, NOA451353, NOA421154 (M18), and NOA452668.

Cyproconazole plant metabolism studies were considered for peanut, grape, apples, sugar beet, and wheat. The peanut study does not meet the needs of a metabolism study. Peanut vines in a glasshouse were painted with an EC formulation of [α-carbon^{14}C]-Cyproconazole and harvested 3 to 6 weeks later. The foliage contained cyproconazole (30–40% applied radioactivity) and very small amounts (1–2%) of M9/M14 and M18.

Grapes vines were treated with [α-carbon^{14}C]-Cyproconazole, and grape fruits were harvested 29 days after the last application. A portion (28% TRR) of the residue was removed by surface wash, and an additional 56% TRR was solvent extractable. The major component of the residue was cyproconazole (63% TRR). Identified metabolites were all < 2% TRR, e.g., M9/M14 and M13.

Apple trees were foliarly treated 4 times at 2 week intervals with [α-carbon^{14}C]-Cyproconazole. Apples were harvested 28 days after the last treatment. Surface residue was 17% TRR. About 60% TRR was associated with the washed fruit. Cyproconazole made up 76% of the whole fruit TRR. No metabolite exceeded 3% TRR, e.g., M9/M14 and M13 at 2.8% TRR.

[Phenyl(U)-^{14}C]-cyproconazole, and [U-triazole^{14}C]-cyproconazole were applied in separate studies in two applications at rates of 160 – 200 g ai/ha/application to wheat plants. Cyproconazole was the major component of the TRR for both labels for livestock commodities: 44% straw; 60–72% forage. Cyproconazole composed 5–45% TRR in grain. M39 (triazole alanine) was a significant grain metabolite for the [U-triazole^{14}C]cyproconazole (63% TRR), as was M9/M14 for the [Phenyl(U)-^{14}C]-cyproconazole (14% TRR).

The metabolism of [U-triazole^{14}C]-cyproconazole in sugar beets revealed that cyproconazole is the major portion of the TRR (80% roots; 76% leaves). M9/M14 comprised 2.5% TRR in leaves and 4% TRR in roots.

In all studies, levels of cyproconazole conjugates, as released by acid hydrolysis, were generally ≤ 5% TRR.

The metabolism of cyproconazole in the various plants studied is qualitatively similar. Generally cyproconazole is the major portion of the residue. The metabolism of cyproconazole in plants involves (i) hydroxylation of the methyl- and cyclopropyl-substituted carbon to form Metabolites M9/M14; (ii) oxidation of the methyl group to form Metabolites M11/M18; (iii) elimination of the cyclopropyl-substituted carbon to form the benzylic alcohol (M15) and further oxidation to the ketone (M16); (iv) hydroxylation of the cyclopropyl ring and the phenyl ring; (v) conjugation of parent and hydroxylated metabolites to form various glycosides; and (vi) oxidative elimination of the triazole ring and its subsequent conversion to triazole alanine.

Plant metabolites were also metabolites of the rat metabolism, with the exception of M39/CGA 131013 (triazolyl-alanine).

Environmental fate

Under aerobic conditions in soil cyproconazole is moderately stable. Cyproconazole ([U-triazole^{14}C]-cyproconazole) has a half-life of about 150 days, with 1,2,4-triazole and 1,2,4-tgriazol-1-yl acetic acid at about 25% of the applied radioactivity at 140 days. The half-life (first order kinetics) varied from 100 days to > 1 year with ^{14}C-benzyl cyproconazole and is about 100 days with [Phenyl(U)-^{14}C]-cyproconazole. Mineralization to carbon dioxide varied from 2% to 33% over 112 days. No other degradates were identified.

Cyproconazole is photolytically stable in soil, with no loss after 30 days of irradiation.

Cyproconazole is hydrolytically stable at pHs of 4, 5, 7, and 9 for 5 days at 50 ºC.

Residues in succeeding crops

Residues of cyproconazole are found in succeeding crops in confined rotational crop situations. Studies were reported for the application of [α-^{14}C]cyproconazole to soil followed by the planting of representative crops. [U-triazole^{14}C]cyproconazole was not studied. Cyproconazole is the major component of the residue, and TRRs typically range from < 0.01 mg/kg to 0.44 mg/kg with a 30 day plantback interval (PBI). Following a soil application of [α-^{14}C]cyproconazole at 010 kg ai/ha, rotational crops were planted at intervals (PBI) of 30 and 90 days. Cyproconazole ranged from 33% TRR (0.003 mg/kg) in wheat grain and 39% TRR (0.036 mg/kg) in sugar beet tops to 72% TRR (0.029 mg/kg) in lettuce leaves at a 30 day PBI. Metabolites detected (2–12% TRR) included M9/M14 and M18.

In field crop rotational studies following 7 applications of cyproconazole, each about 0.10 kg ai/ha (0.7 kg ai/ha total), cyproconazole residues at a 30 day PBI were < 0.01 mg/kg in wheat grain and carrot tops, 0.034 in collard greens, 0.081mg/kg in wheat straw, 0.021 mg/kg in radish root and carrot root, 0.062 mg/kg in radish tops, and 0.13 mg/kg in mustard greens. All residues were < 0.01 mg/kg at 1 year PBI. In trials following a single application at 0.082 kg ai/ha (typical 1× for primary crops), cyproconazole was < 0.01 mg/kg in spinach, radish (root and top), and wheat at a 60 day PBI.

The Meeting concluded that residues of cyproconazole in rotational crops with a minimum plantback interval of 30 days may be possible, but residues would be at or near the LOQ of the analytical method, 0.01 mg/kg. This is based on primary crop use patterns under consideration.

Methods of analysis

Adequate analytical methods exist for the determination of cyproconazole residues for data collection and enforcement purposes in both plant and livestock matrices. Early methods for crop matrices involved an optional acid hydrolysis (1 N HCl) to release cyproconazole conjugates, extraction, clean-up, and analysis by GC with NPD, ECD, or MSD. The methods determined cyproconazole only with an LOQ of 0.01–0.04 mg/kg. These methods have been validated via the analysis of spiked samples and include an independent laboratory validation for the MSD variation.

An HPLC/UV method was described for data collection for wheat commodities. Samples are extracted with aqueous methanol, cleaned-up with SPE, and analysed by HPLC with UV detection. The limit of quantitation was 0.01–0.02 mg/kg.

More recently an HPLC-MS/MS method has been developed for plant matrices. Homogenized samples are extracted with aqueous acetonitrile, filtered, and monitored for m/z 292 (Q1) and m/z 70 (Q3) for cyproconazole. The demonstrated LOQ is 0.01 mg/kg.

Analytical residue enforcement method DFG S19 has been developed (HPLC- MS/MS) and validated for a dry crop, a high-fat crop, a high-water crop, and an acidic crop. The LOQ is 0.01 mg/kg.

An HPLC-MS/MS method (RAM 499/01) has been developed and validated for the determination of cyproconazole only in livestock commodities. Major metabolites such as M36 in milk and M14 in liver are not determined currently by the method. For this method, free and conjugated cyproconazole residues are extracted with acetonitrile (ACN):water and hydrolysed using either concentrated ammonia (eggs and tissues) or 2M HCl (milk). Cyproconazole residues are then determined by LC-MS/MS using external standards. The method LOQ is 0.01 ppm for cyproconazole in each livestock commodity. The method has also undergone a successful independent laboratory validation (ILV) trial and was radiovalidated using samples from a goat dosed with [^{14}C]cyproconazole.

Analytical residue enforcement method DFG S19 has been developed (HPLC-MS/MS) for cyproconazole in livestock matrices and validated by an independent laboratory.

Stability of residues in stored analytical samples

Cyproconazole has been shown to be stable in numerous plant commodities stored frozen at ≤-12 ºC. Cyproconazole is stable (≥ 80% recovery) for at least 40–42 months in grapes, raisins, nectarines, peaches, peanut nutmeat, peanut hay, and wheat hay. It is stable (≥ 80% recovery) for at least 36 –39 months in wheat grain, wheat forage, and peanut hulls. Likewise, cyproconazole was stable in most livestock commodities fortified with cyproconazole at 0.01–10 mg/kg and stored frozen at -20 ºC. Cyproconazole was stable in milk for at least 12 months and in kidney and liver for at least 9 months. However, the percent cyproconazole remaining in fat at all fortification levels and storage intervals was variable and may be more a reflection of analytical method difficulties than actual storage stability. Some stability was indicated for up to one month in fat (60–90% remaining).

Definition of the residue

The livestock commodity analytical methods used for data collection (livestock feeding) determine cyproconazole and the metabolites M36 and M21. No hydrolyses were used to free potential conjugates. The analytical method validated for enforcement purposes determines only cyproconazole. This method uses an acid hydrolysis step (milk) or ammonia hydrolysis (eggs and tissues) to free conjugates.

Cyproconazole was the major component of the residue in all poultry commodities and all ruminant commodities except milk. Conjugated cyproconazole was found in eggs and ruminant kidney. Cyproconazole was a minor component in milk (10% TRR), whereas the major metabolites were M36 (NOA405872) and M21 (NOA405890). M36 and M21 comprised up to 80% of the TRR in milk. These two metabolites are carboxylic acids resulting from transformation of the cyclopropyl ring. Various toxicity studies with M36 reveal that this metabolite is very significantly less toxic than cyproconazole. Moreover, a feeding study with ruminants shows that M36/M21 residues are near the limit of quantitation of the analytical method at current livestock dietary burden levels. Therefore, M36/M21 need not be considered in the dietary risk assessment for milk.

While cyproconazole was a major component of the TRR in hen and goat liver, there were significant amounts of the hydroxylated cyproconazole metabolite M14, 30% TRR goat liver and 20 – 38% TRR hen liver. Cyproconazole was 27% TRR and 27%, respectively. In the feeding studies, M14 was 0.2–0.5 ppm in cow liver at a 3 ppm dietary burden and not determined in poultry liver. Cyproconazole was about 0.2 ppm in cow liver and < 0.01 mg/kg in poultry liver at a 3 ppm feeding level. M14 is considered to be less toxic than cyproconazole. Given the significant percentage of cyproconazole in the liver residue, the lower relative toxicity of M14, and the small contribution of liver to the diet, metabolite M14 need not be included in the residue definition for dietary intake.

Triazolyl-alanine was 63% TRR (0.13–0.20 mg/kg) on wheat grain in the wheat metabolism study. In livestock feeding studies, concentrations of triazole, triazolyl-alanine, and triazole acetic acid were < 0.01 mg/kg, except cattle liver (triazolyl-alanine 0.04 mg/kg).

The 2007 JMPR addressed the issue of triazole metabolites (JMPR 2007 Report, General Consideration 2.3). It was noted that 1,2,4-triazole, triazolyl-acetic acid and triazolyl-alanine may be derived from several sources. In a situation in which the metabolites arise from multiple triazole fungicides, they cannot be included in the residue definition. Since the metabolites cannot be linked to a specific triazole fungicide, they would have to be evaluated on their own. The 2007 Meeting further concluded that they did not have sufficient information to judge levels that would be without potential effect in consumers.

Cyproconazole was the major component of the residue in plant metabolism studies conducted with grape, apples, sugar beet, and wheat (except grain, 15% TRR). Concentrations of cyproconazole conjugates generally were < 5% TRR. No metabolite exceeded 10% TRR, except for M39 (triazole alanine) in wheat grain (63% TRR) and M9/M14 in wheat grain (14% TRR). Anaerobic soil metabolism studies showed that cyproconazole is relatively stable and does not form metabolites in significant concentrations. Confined rotational crop studies revealed that

cyproconazole is the major quantifiable residue in follow-on crops; metabolites were < 12% TRR. A limited rotational crop field trial (conduced at 1× for the primary crop) indicated that cyproconazole residues in follow-on crops would most likely be near the LOQ (0.01 mg/kg).

The plant commodity analytical methods used for data collection and the methods validated for enforcement of MRLs determine only cyproconazole.

The Meeting recommended that the residue definition for plant and animal commodities for compliance with MRLs should be cyproconazole. While cyproconazole is a minor component of the residue in milk, there is sufficient cyproconazole present to monitor compliance.

The Meeting recommended that the residue definition for dietary risk assessment for plant commodities should be cyproconazole.

The Meeting recommended that the residue definition for dietary risk assessment for animal commodities should be cyproconazole, free and conjugated.

The log Kow of cyproconazole (log K_{ow} 3.1) suggests that cyproconazole will show no clear preference for distribution in fat versus water. The ratio of cyproconazole residues (TRR) in muscle and fat observed in the livestock metabolism studies (lactating cow 1 muscle: 4–6 fat) indicates a slight preference for fat solubility. In the cow feeding study, cyproconazole had a slight preference for cream over skim milk (0.008 ppm vs 0.003 ppm) and a more indicative preference for fat over meat (0.052 mg/kg fat versus 0.005 mg/kg meat, or about 10 to 1).

Proposed definition of the residue (for compliance with MRL for plant commodities): *cyproconazole*.

Proposed definition of the residue (for compliance with MRL for animal commodities): *cyproconazole*.

The residue is considered fat-soluble.

Proposed definition of the residue (for estimation of dietary intake for plant commodities): *cyproconazole*.

Proposed definition of the residue (for estimation of dietary intake for animal commodities): *cyproconazole, free and conjugated.*

Results of supervised trials on crops

The NAFTA calculator was used as a tool in the estimation of the maximum residue levels from the selected residue data sets 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 with the calculator using expert judgment. Then, the NAFTA calculator was employed. If the statistical calculation spreadsheet suggested a different value than 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.

Pome fruits

Supervised residue trials on apples were provided from Spain and Brazil, but no GAP (label) was available for Brazil. Using the GAP of Italy (0.02 kg ai/hL, 7 day PHI), the trial results from Spain in ranked order are: 0.03 (2), 0.05 mg/kg.

The Meeting considered three trials insufficient for the estimation of an MRL and STMR.

Legume vegetables

Supervised field trials on succulent peas were provided from France (North and South) and the UK. A GAP was provided for France (0.06 kg ai/ha, 2 applications, 21 day PHI). The trial results for Europe in ranked order are: < 0.01 (7), 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.01 mg/kg an HR of 0.01 mg/kg, and an STMR of 0.01 mg/kg. Statistical calculation is not useful for cases with highly censored data.

Pulses

Field trials for dried pea and dried bean were reported from France (19) and the UK (10). A GAP was provided for pea and bean in the UK (0.08 kg as/ha or 0.04 kg ai/hL, 2 applications, 42 day PHI). Using this GAP, the ranked order of residues on peas (dry) in Europe for dry pea is: < 0.01 (14), 0.01 (2), < 0.02 (5). The ranked order of residues on beans (dry) in Europe were: < 0.01 (4) mg/kg. Additional bean trials at shorter PHIs (29–30) had residues of 0.01–0.05 mg/kg.

The Meeting used the dry pea and dry bean data for mutual support. The Meeting estimates a maximum residue level of 0.02 (*) mg/kg, an HR of 0.02 mg/kg, and an STMR estimate of 0.02 mg/kg for peas (dry) and beans (dry). Statistical calculation is not useful for cases with highly censored data.

Field trials on soya beans were reported from the USA. The GAP is 0.04 kg ai/ha, 2 applications, and a 30 day PHI. Nineteen trials were conducted at this GAP, and the residue results (n = 19) in ranked order are: < 0.01 (4), 0.01 (3), < 0.02 (2), 0.02 (4), 0.03 (4), 0.04, 0.05 mg/kg.

The Meeting estimated an STMR of 0.02 mg/kg, and HR of 0.05 mg/kg, and a maximum residue level of 0.07 mg/kg.

The NAFTA statistical method estimated a maximum residue level of 0.06 mg/kg, based on the mean plus three standard deviations. The statistical method is unreliable with multiple LOQ values (2) and 13 non-censored data points.

Root and tuber vegetables

Field trials for sugar beets were reported from Europe. A GAP was provided for Italy (0.08 kg ai/ha, 2 applications, 21 day PHI) and for the Netherlands (0.06 kg ai/ha, 2 applications, 45 day PHI). One trial in Switzerland, four trials in France North, and four trials in the UK meet the GAP of the Netherlands, and the results (n = 9) in ranked order are: < 0.01 (4), < 0.02 (4), and 0.02 mg/kg. Six trials in Italy, two trials in Spain, and one trial in France South meet the GAP of Italy, and the results of the trials (n = 9) in ranked order were: < 0.01, < 0.02 (5), 0.02, 0.03, 0.04 mg/kg. Using the trials matching the GAP of Italy, the Meeting estimated an STMR of 0.02 mg/kg, an HR of 0.04 mg/kg, and a maximum residue level of 0.05 mg/kg.

Statistical calculation is not useful for cases with highly censored data.

Cereal grains

Field trials for wheat were reported from Europe (12 France, 26 Germany, 2 Switzerland). A GAP for wheat was provided for Germany (0.096 kg ai/ha or 0.047 kg ai/hl, 2 applications, 35 day PHI or until BBCH 61). Three trials in France, 23 trials in Germany, and two trials in Switzerland meet the GAP of Germany, and the results of the trials (n = 28) in ranked order are: < 0.01 (8), 0.01 (4), < 0.02 (4), 0.02 (6), 0.04 (2), 0.05 (4) mg/kg.

Field trials for rye were reported from Europe (Germany 5). A GAP for rye was provided for Germany (0.096 kg ai/ha, 2 applications, 35 day PHI or application until BBCH 61) and for the Netherlands (0.08 kg ai/ha, 1 application, PHI 42 days). Note that the GAPs for wheat and rye are

identical in Germany. Using the GAP of Germany, the residue results from the German trials in ranked order are: 0.01 (2) and 0.03 mg/kg.

Field trials for barley were reported from Europe (France (12), Switzerland (5), Germany (9) and the UK (10)). A GAP for barley was provided for Germany (0.096 kg ai/ha or 0.048 kg ai/hL, 2 applications, 35 day PHI or until BBCH stage 61). Note that this GAP is identical to the GAP for wheat and rye in Germany. One trial in France (North), three trials in Switzerland, and nine trials in Germany were at the GAP of Germany. The residue results in ranked order are: 0.01, 0.02 (4), 0.03 (4), 0.04 (3), 0.07 mg/kg.

The Meeting determined that the data sets for wheat, rye, and barley are from similar populations and combined the sets. The residues (n = 44) in ranked order are < 0.01 (8), 0.01 (7), < 0.02 (4), 0.02 (10), 0.03 (5), 0.04 (5), 0.05 (4), 0.07 mg/kg. The GAPs for the various grains were identical. No cereal grain group GAP was provided, but GAPs were provided for wheat, rye, triticale, barley, and oats, which represent all major small cereal grains except rice and which justify the extension. The Meeting estimated for cereal grains except rice and maize an STMR of 0.02, an HR of 0.07 mg/kg, and a maximum residue level of 0.08 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.07 m/kg based on the mean plus 3 standard deviations, but the Meeting considered that the estimate should be above the highest residue.

Field trials for maize (field corn) were reported from the USA, where the GAP is 0.04 kg ai/ha, 2 applications, and 30 day PHI. Twenty-two trials were conducted at this GAP, and the residue results in ranked order were: < 0.01 (22) mg/kg. In three trials, samples were collected at a PHI of 7 days, and residues were < 0.01 mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg, an HR of 0.01 mg/kg, and a maximum residue level of 0.01 (*) mg/kg for maize.

Statistical method for maximum residue level estimation are not applicable where all data are < LOQ.

Oilseeds

Field trials on rape (canola) were reported from Europe. A GAP was provided for the UK (0.08 kg ai/ha, 2 applications, and a PHI of 30 days or BBCH 79, whichever occurs first). One trial from Switzerland, ten trials from France, and one trial from Germany complied with the UK GAP. The residue results (n = 12) in ranked order are: 0.01, 0.03 (3), 0.04, 0.05, 0.08 (2), 0.09, 0.10, 0.21, 0.23 mg/kg.

The Meeting estimated an STMR of 0.065, an HR of 0.23, and a maximum residue level of 0.4 mg/kg for rape seed.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.4 mg/kg, based on the UCL median 95th, which was in agreement with the Meeting's estimation.

Field trials on peanut were reported from Australia (3), Brazil (1), and the USA (4). GAP was provided for Australia (0.06 kg ai/ha, 5 applications, 14 day PHI). There is no registered use on peanuts in the USA. No GAP was provided for Brazil. The ranked orders of residues from Australian trials, corresponding to the Australian GAP, were: < 0.02 (3) mg/kg.

The Meeting considered three trials insufficient for the estimation of an STMR, HR, and maximum residue level for peanuts.

Primary animal feed commodities

Legume animal feed

Field trials on soya beans were reported from the USA. The GAP is 0.04 kg ai/ha, 2 applications, and a 30 day PHI. The PHI for forage is 14 days. Fifteen trials were at GAP for soya bean forage, and the results in ranked order were: 0.11, 0.21, 0.22, 0.31 (2), 0.33, 0.35, 0.37, 0.40, 0.41, 0.48, 0.50, 0.52, 0.80, 0.82 mg/kg.

The Meeting estimated an STMR of 0.37 mg/kg and a highest residue of 0.82 mg/kg for soya bean forage.

Fifteen trials were at GAP for soya bean fodder (hay), and the results in ranked order were: 0.17, 0.32, 0.33 (2), 0.41, 0.43, 0.44, 0.66, 0.67, 0.71, 0.75 (2), 1.3, 1.5, 1.9 mg/kg.

The Meeting estimated an STMR of 0.66 mg/kg and a highest residue of 1.9 mg/kg. The Meeting also estimated a maximum residue level of 3 mg/kg for soya bean hay.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 3.0 mg/kg, based on the 99th percentile of a log normal distribution, which was in agreement with the Meeting's estimation.

Pea Vines (Green)

Supervised field trials on succulent peas were provided from France. A GAP was provided for France (0.07 kg ai/ha, 2 applications, 21 day PHI). All trials were conducted at about 125% of the GAP maximum application rate. The residue results in ranked order for pea vines (n = 6) were: 0.02, 0.07, 0.34, 0.35, 0.43, 0.83 mg/kg.

The Meeting estimated an STMR of 0.345 and a highest residue of 0.83 mg/kg.

Pea Hay or Fodder (dry)

Field trials for dried pea fodder were reported from France and the UK. A GAP was provided for pea in the UK (0.08 kg as/ha or 0.04 kg ai/hL, 2 applications, 42 day PHI). Only two of the 17 trials were conducted at GAP, and residues in ranked order for pea fodder are: 0.12, 0.24 mg/kg.

Bean Fodder

Field trials for dried bean fodder were reported from France and the UK. A GAP was provided for bean in the UK (0.08 kg as/ha or 0.04 kg ai/hL, 2 applications, 42 day PHI). Only 1 of 8 trials was at GAP, and residues in ranked order for bean fodder are: 0.09 mg/kg.

The Meeting combined pea fodder and bean fodder results in mutual support, but decided that 3 trials were not sufficient to estimate a highest residue, STMR, and/or maximum residue level.

Sugar Beet Tops (Leaves)

Field trials for sugar beets were reported from Europe. A GAP was provided for Italy (0.08 kg ai/ha, 2 applications, 21 day PHI) and for the Netherlands (0.06 kg ai/ha, 2 applications, 45 day PHI). Using the GAP of the Netherlands to evaluate the trials of the UK, France, Germany, and Switzerland residue values (n = 5; Switzerland and France) for sugar beet tops in ranked order are: 0.07, 0.15, 0.17, 0.23, 0.35 mg/kg. Using the GAP of Italy to evaluate the trials in Spain and Italy, residue values (n = 4; Italy) for sugar beet tops in ranked order were: 0.06, 0.29, 0.34, 0.54 mg/kg.

Using the trials evaluated against the GAP of Italy, the Meeting estimated an STMR of 0.315 mg/kg and a highest residue of 0.54 mg/kg for sugar beet tops.

Cereal Grain Straw, Forage, Fodder, Silage

Field trials for wheat were reported from Europe (12 France, 26 Germany, 2 Switzerland). A GAP was provided for Germany (0.096 kg ai/ha or 0.047 kg ai/hL, 2 applications, 35 day PHI or until BBCH 61). The residue results for wheat straw (n = 30; France – (n = 3) 0.39, 1.6, 1.7; Switzerland (n = 2) – 0.09, 0.11; Germany (n = 25) – 0.15, 0.22, 0.23, 0.24, 0.36, 0.37, 0.42, 0.43, 0.76, 0.77, 0.78 (2), 0.79, 0.85 (2), 0.92 (3), 1.1, 1.3, 1.4, 1.7, 2.1, 2.4, 3.6, in ranked order were: 0.09, 0.11. 0.15, 0.22, 0.23, 0.24, 0.36, 0.37, 0.39, 0.42, 0.43, 0.76, 0.77, 0.78 (2), 0.79, 0.85 (2), 0.92 (3), 1.1, 1.3, 1.4, 1.6, 1.7 (2), 2.1, 2.4. 3.6 mg/kg.

Field trials in rye were reported from Europe (Germany n = 5). A GAP was provided for Germany (0.096 kg ai/ha, 2 applications, 35 day PHI or application until BBCH 61) and for the Netherlands (0.08 kg ai/ha, 1 application, PHI 42 days). Note that the GAPs for wheat and rye are identical in Germany. Using the GAP of Germany, trial results at GAP for rye straw in ranked order were: 0.64, 0.68, 1.2 mg/kg.

Field trials for barley were reported from Europe (France 12, Switzerland 5, Germany 9, and the UK 10). A GAP was provided for Germany (0.096 kg ai/ha or 0.048 kg ai/hL, 2 applications, 35 day PHI or until BBCH stage 61). Note that this GAP is identical to the GAP for wheat and rye in Germany. For barley straw, One trial in France North (0.16), three trials in Switzerland (0.24, 0.34, 0.42), and 13 trials in Germany were at the GAP. The results (n = 17) in ranked order were: 0.01, 0.14, 0.15, 0.16, 0.20, 0.22, 0.24, 0.28, 0.34, 0.42, 0.52 (3), 0.53, 0.56, 0.63, 0.67 mg/kg.

Noting that the GAPs for wheat, rye, and barley were identical and that the residue values were similar, the Meeting decided to estimate values for the cereal grain straws group (except rice and maize). The residue values for wheat straw were used, as this set is the largest and contains the highest high residue.

The Meeting estimated an STMR of 0.785 mg/kg, and a highest residue of 3.6 mg/kg. The Meeting also estimated a maximum residue level of 5 mg/kg for cereal grain straws (except rice and maize).

The NAFTA statistical spreadsheet provided a maximum residue level estimate of 5.1 mg/kg, based on the 95th percentile at the 99th UCL.

Field trials for maize (field corn) were reported from the USA, where the GAP is 0.04 kg ai/ha, 2 applications, and 30 day PHI for grain and fodder/straw and a 21 day PHI for forage/silage. Twenty-three trials for maize fodder were at the GAP, and the results in ranked order were: < 0.01 (2), 0.08 (2), 0.12 (2), 0.21, 0.22, 0.23, 0.24, 0.27, 0.28 (2), 0.33, 0.34, 0.35 (3), 0.45, 0.46, 0.74, 0.80, 1.5 mg/kg.

The Meeting estimated an STMR of 0.28 and a highest residue of 1.5 mg/kg. The Meeting also estimates a maximum residue level of 2 mg/kg for maize fodder.

The NAFTA statistical calculation estimates a maximum residue level of 1.4 mg/kg. However, JMPR (FAO) guidance specifies that an estimate shall not be below the highest result (1.5 mg/kg).

Twenty-two trials for maize forage are at the GAP, and the results in ranked order were: < 0.01, 0.03, 0.05, 0.06 (2), 0.07, 0.08 (2), 0.09, 0.10 (2), 0.12, 0.13, 0.14, 0.16, 0.19, 0.20, 0.23, 0.24, 0.29, 0.31, 0.44 mg/kg.

The Meeting estimated an STMR of 0.11 and a highest residue of 0.44 mg/kg.

Oilseed forages and fodders

Field trials on rape (canola) were reported from Europe. A GAP was provided for the UK (0.08 kg ai/ha, 2 applications, and a PHI of 30 days). Six trials for rape forage from France were at GAP, and the results in ranked order were: 0.24, 0.28, 0.48, 0.52, 1.2, 1.9 mg/kg.

The Meeting estimated an STMR of 0.50 and a highest residue of 1.9 mg/kg for rape forage.

Field trials on peanut were reported from Australia (3), Brazil (1), and the USA (4). GAP was provided for Australia (0.06 kg ai/ha, 5 applications, 14 day PHI). There is no registered use on peanuts in the USA. For two trials at GAP in Australia, residues on peanut fodder were 5.3 and 14 mg/kg. For two trials at GAP in Australia, residues on peanut forage (green) were 1.3 and 5.3 mg/kg.

The Meeting considered two trials insufficient for the estimation of an STMR or highest residue for peanut fodder or peanut forage.

Fate of residue during processing

The effects of processing on the nature of residues in processed commodities were investigated in buffer solutions under conditions simulating pasteurization, boiling, and sterilization. Radio-labelled cyproconazole was demonstrated to be stable under these conditions.

The fate of cyproconazole residues has been studied in processing studies for apples, maize, rape seed (canola), soya bean, and peanuts. Estimated relevant processing factors and STMR-Ps are summarized below.

Commodity	Number of Studies (n)	Median Cyproconazole Transfer Factors	Cyproconazole RAC-STMR (mg/kg)	Cyproconazole STMR-P (mg/kg)
Oilseed rape – press cake	1	0.83	0.065	0.054
Oilseed rape – crude oil	4	0.86	0.065	0.056
Oilseed rape – solvent extracted meal	1	0.25	0.065	0.016
Oilseed rape – refined oil	4	0.08	0.065	0.0052
Soya bean – meal	4	0.64	0.02	0.013
Soya bean – hulls	4	0.75	0.02	0.015
Soya bean – refined oil	4	1.8	0.02	0.036

The Meeting decided to estimate a maximum residue level of 0.1 mg/kg for refined soya bean oil based on a highest residue of 0.05 mg/kg for soya beans and a processing factor of 1.8 (0.05 mg/kg × 1.8 = 0.09 mg/kg).

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of cyproconazole in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual (2009 Edition). Calculation from highest residues, STMR (some bulk blended commodities), and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable foe estimating STMR values for animal commodities. The percentage dry matter is assumed to be 100% when the highest residue levels and STMRs are expressed on a dry weight basis.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, chicken broilers, and laying poultry are provided in Annex 6 of the 2010 JMPR Report. The calculations were made according to the animal diets from the US/CAN, EU, and Australia in Appendix IX of the FAO Manual (2009 Edition).

Commodity	Level	Animal Dietary Burden, Cyproconazole, ppm of dry matter diet.			
		US/CAN	EU	Australia	Japan
Beef cattle	Max	0.644	3.08	6.33[a]	0.022
	Mean	0.153	0.929	1.67[c]	0.022
Dairy cattle	Max	2.88	3.21	5.05[b]	0.711
	Mean	0.764	1.04	1.40[d]	0.180
Poultry – broiler	Max	0.022	0.022	0.022	0.014
	Mean	0.022	0.022	0.022	0.014
Poultry – layer	Max	0.022	1.40 [e,g]	0.022	0.013
	Mean	0.022	0.413 [f,h]	0.022	0.013

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian tissues

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

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

[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 tissues.

[f] Highest mean poultry dietary burden suitable for STMR estimates for poultry tissues.

[g] Highest maximum poultry dietary burden suitable for MRL estimates for poultry eggs.

[h] Highest mean poultry dietary burden suitable for STMR estimates for poultry eggs.

Farm animal feeding studies

A cow feeding study involved Friesian dairy cows dosed orally with cyproconazole for 35 days at levels equivalent to 1, 3, 10, and 30 ppm in the diet. Aside for one usually high value (0.025 ppm) from the 1-ppm dose group on day 14, cyproconazole residues in milk were≤ 0.006 ppm for the 1, 3 and 10 ppm dose groups and were < 0.003–0.014 ppm for the 30 ppm dose group, with the maximum values occurring on days 7 or 14. At intervals in excess of 14 days, cyproconazole was found (> 0.003 ppm) in the 30 ppm dosing level only.

In tissues, cyproconazole was found at the following levels at dosing levels of 1, 2, 10, and 30 ppm, respectively: liver 0.090 (avg 0.082), 0.218 (avg 0.214), 0.604 (avg 0.514), 0.930 (avg 0.748); fat < 0.003; 0.003; 0.024 (avg 0.017), 0.052 (avg 0.022); kidney < 0.003, 0.009 (avg 0.007), 0.031 (avg 0.016, 0.038 (avg 0.028); muscle < 0.003, < 0.003, 0.003, 0.005 mg/kg.

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.

Cattle Dietary Burden [a] (ppm)						
Feeding Level [ppm]	Cream	Milk	Muscle	Liver	Kidney	Fat
MAXIMUM RESIDUE LEVEL	Mean	Mean	Highest	Highest	Highest	Highest
MAXIMUM RESIDUE LEVEL beef cattle (6.33) [3/10]			0.003 [< 0.003/0.003]	0.46 [0.218/0.604]	0.115 [0.054/0.1861]	0.015 [0.003/0.024]
MAXIMUM RESIDUE LEVEL dairy cattle (5.05) [3/10]	- -	0.006 [0.005/0.006]	0.003 [< 0.003/0.003]	0.36 [0.218/0.604]	0.092 [0.054/0.186]	0.012 [0.003/0.024]
STMR	Mean	Mean	Mean	Mean	Mean	Mean
STMR beef cattle			0.003	0.14	0.026	0.003

Cattle Dietary Burden [a] (ppm)						
Feeding Level [ppm]	Cream	Milk	Muscle	Liver	Kidney	Fat
(1.67) [1/3]			[< 0.003/< 0.003]	[0.082/0.214]	[< 0.018/0.042]	[< 0.003/ 0.003]
STMR dairy Cattle (1.40) [1/3]	- -	0.009 [0.009/0.004]	0.003 [< 0.003/< 0.003]	0.11 [0.082/0.214]]	0.023 [< 0.018/0.042]	0.003 [< 0.003/0.003]

[a] Data from the first cattle feeding study (Oakes, 1994, T021566-04).

The data from the lactating dairy cow feeding study was used to support mammalian (except marine) milk and meat maximum residue levels. In this study only free cyproconazole was determined. The ruminant metabolism study showed that conjugated cyproconazole was about 5× the free cyproconazole concentration in kidney. Therefore, the measured cyproconazole concentration in kidney was multiplied by 6 for the dietary intake calculation.

Insufficient data were provided in the dairy cow feeding study to allow estimation of milk fat levels.

The Meeting estimated the following STMR values: milk 0.009 mg/kg; muscle 0.003 mg/kg; edible offal 0.14 mg/kg; fat 0.003 mg/kg. The HR values are: muscle 0.003 mg/kg, edible offal 0.46 mg/kg, fat 0.020 mg/kg.

The Meeting estimated the following maximum residue levels for mammalian commodities (except marine): milk at 0.01 mg/kg; meat (fat) at 0.02 mg/kg and edible offal at 0.5 mg/kg.

A poultry feeding study was also available, in which 15 hens/treatment group were dosed for 29 days with cyproconazole at feed concentrations of 0.12, 0.45, and 1.87 ppm. Cyproconazole was < 0.01 mg/kg in eggs and all tissues at all feeding levels. Noting that the mean and maximum dietary burden for poultry for meat and eggs are 0.44 ppm and 1.6 ppm, respectively, the Meeting concluded that cyproconazole residues are unlikely in poultry commodities.

The Meeting estimated the following STMR values: eggs, 0.01 mg/kg; muscle, 0.01 mg/kg fat, 0.01 mg/kg; edible offal, 0.01 mg/kg. The Meeting estimated the following maximum residue levels: eggs, 0.01 mg/kg meat, 0.01 (*) mg/kg; edible offal, 0.01 (*) mg/kg. The HR values are eggs, 0.01 mg/kg; muscle, 0.01 mg/kg; fat, 0.01 mg/kg; edible offal, 0.01 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of cyproconazole were calculated for the 13 GEMS/Food Consumption Cluster Diets using STMRs and STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.02 mg/kg bw and the calculated IEDIs were 0.5–2% of the maximum ADI. The Meeting concluded that the long-term intake of residues of cyproconazole resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intakes (IESTI) of cyproconazole were calculated for food commodities and their processed commodities using HRs/HR-Ps or STMRs/STMR-Ps estimated by the current Meeting (see Annex 4). The ARfD is 0.06 mg/kg and the calculated IESTIs were 0–5% of the ARfD for the general population and 0–4% of the ARfD for children. The Meeting concluded that

the short-term intake of residues of cyproconazole, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.

5.9 DICAMBA (240)

TOXICOLOGY

Dicamba is the International Organization for Standardization (ISO)–approved name for 3,6-dichloro-2-methoxybenzoic acid (International Union of Pure and Applied Chemistry [IUPAC]) and has the Chemical Abstracts Service (CAS) No. 1918-00-9. Dicamba is a benzoic acid auxin herbicide, mimicking the action of indolyl acetic acid in regulating plant growth.

Dicamba has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed at the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR).

All pivotal studies contained certificates of compliance with good laboratory practice (GLP).

Biochemical aspects

The absorption, distribution, metabolism and excretion of dicamba after oral dosing were investigated in several studies in rats and one study using mice, rabbits and dogs. Generally, there were no differences in the toxicokinetics of dicamba between species and sexes. Furthermore, it was shown that the anionic counter-ion of dicamba salts did not influence the absorption, metabolism or elimination of dicamba. Dicamba was rapidly absorbed, with peak levels occurring within the first hour after administration. The absorption was not saturated at doses up to 1000 mg/kg body weight (bw). Between 2 and 4 h after the first absorption peak, a second peak was observed, indicative of enterohepatic recirculation of dicamba. At doses greater than 125 mg/kg bw, the elimination half-life of dicamba equivalents increased, and the area under the curve (AUC) increased disproportionately with dose, indicating saturation of elimination at higher doses. Only 3% of a low or high dose (0.5 or 200 mg/kg bw) was found in the tissues 4 h post-dosing, with highest residues in the kidneys, plasma and uterus. After 7 days, only 0.2% of the administered dose was found in the tissues. More than 95% of the administered dose is excreted in the urine, with less than 5% in the faeces. Excretion by expired air is negligible. In urine and faeces, more than 90% of the radioactivity found was accounted for by unchanged dicamba. In urine, very low amounts of glucuronidated dicamba (M1), 3,6-dichlorosalicylic acid (DCSA; NOA 414746), 5-hydroxy-dicamba (NOA 405873) and M2 (NOA 414746) were found. In the liver and kidneys, 84–91% of total radioactive residues was identified as dicamba. In summary, dicamba is poorly metabolized, and the pathways involved include demethylation, hydroxylation and glucuronic acid conjugation.

Toxicological data

Dicamba is of low acute toxicity. The lowest oral median lethal dose (LD_{50}) was approximately 1600 mg/kg bw in female rats. By dermal application, the LD_{50} was greater than 2000 mg/kg bw, and the median lethal concentration (LC_{50}) in an inhalation study was greater than 9.6 mg/L. Dicamba was only slightly irritating to the skin but severely irritating to the eye. Dicamba did not show skin sensitizing potential.

In repeated-dose studies in rats and dogs, the mostly mild effects observed included lower body weight gains, haematological and clinical chemistry effects and clinical signs of toxicity.

In a 13-week rat feeding study with dietary concentrations up to 12 000 ppm, reduced activity, lower body weight development and reduced food consumption were observed. Animals had significantly lower platelet counts and partial thromboplastin times; females also had reduced red cell parameters and increased white blood cell and lymphocyte counts, and clinical chemistry parameters were changed. After a recovery period, most of the haematological and clinical chemistry parameters were similar to those in control animals. Relative liver weights were statistically significantly increased. Histological findings were restricted to high-dose females, which showed reversible

centrilobular hepatocyte hypertrophy and hepatocellular pigmentation. The no-observed-adverse-effect level (NOAEL) was 6000 ppm (equal to 479.3 mg/kg bw per day), based on haematological and biochemical effects at 12 000 ppm. In a 13-week dog study with administration in capsules of doses up to 300 mg/kg bw per day, including a high-dose recovery group, behavioural changes (i.e., ataxia, stiff gait and sporadic transient collapses approximately 2 h after dosing) at 300 mg/kg bw per day were observed, and body weight gain was decreased by 26% in males and by 44% in females. In the high-dose recovery group, body weight development was similar to that in the controls. Red blood cell parameters were reduced and the partial thromboplastin time was slightly elevated in males and females receiving 300 mg/kg bw per day. These effects were partially reversible within 4 weeks. The NOAEL in this study was 50 mg/kg bw per day, based on behavioural effects at 300 mg/kg bw per day. In a 52-week feeding study in dogs with dietary concentrations up to 2500 ppm, animals in the 500 ppm and 2500 ppm groups showed initially lower food consumption and lower body weight gain. This effect was transient and is not considered to be adverse. The NOAEL was 2500 ppm (equal to 52 mg/kg bw per day), the highest dose tested.

In a 24-month feeding study (89 weeks for males) in mice with dietary concentrations up to 3000 ppm, the onset of mortality was early in the study, and the overall mortality was increased in males. At 3000 ppm, body weights in females were lower from week 25 onwards. The NOAEL was 1000 ppm (equal to 108 mg/kg bw per day), based on reduced body weight gain in females at the highest dose.

Dicamba was not carcinogenic in mice.

A carcinogenicity study in rats with dietary concentrations up to 2500 ppm was considered adequate to assess carcinogenicity at 104 weeks, although survival was low at study termination (week 117). The incidences of mixed malignant lymphoma (8% versus 0% in all other groups) and thyroid C-cell carcinoma were increased in the high dose group males, although not statistically significantly. Although the incidence of malignant lymphoma was higher than the historical control range of 0–1.8%, it was at the upper bound of the historical control ranges aggregated for all types of malignant lymphoreticular lymphoma (0–8.6% and 0–8.4% in another historical control group data set). There was no increase in the incidence of C-cell hyperplasia or adenoma, which are part of the progression to carcinoma. The NOAEL for general toxicity was 2500 ppm (equal to 107 mg/kg bw per day), the highest dose tested.

Dicamba was an equivocal carcinogen in rats.

The potential genotoxicity of dicamba was tested in an adequate battery of in vitro and in vivo studies, providing no evidence of genotoxic potential.

The Meeting concluded that dicamba was unlikely to be genotoxic.

On the basis of the absence of genotoxicity and the absence of carcinogenicity in mice and the fact that an equivocal increase in the incidences of lymphoid tumours and of thyroid C-cell carcinoma in male rats occurred only at the highest dose, the Meeting concluded that dicamba is unlikely to be carcinogenic at human dietary exposure levels.

In a two-generation study of reproductive toxicity in rats at dietary concentrations up to 5000 ppm, high-dose females showed increased body tone and slow righting reflex, and high-dose F_1 and F_2 pups had lower body weights throughout the lactation phase. At weaning, their body weights were lower by more than 20%. Thereafter, body weight gain was not affected. At 1500 ppm, pup weights were also slightly reduced, attaining statistical significance at several time points in the lactation phase. There were no effects on mating performance or pregnancy at any dose level. At the high dose, balano-preputial separation was delayed statistically significantly (45.6 days versus 43.7 days in controls). The NOAEL for parental toxicity was 1500 ppm (equal to 105 mg/kg bw per day), based on behavioural effects at 5000 ppm. The NOAEL for reproductive toxicity was 5000 ppm (equal to 347 mg/kg bw per day), the highest dose tested. The NOAEL for effects on postnatal development was 500 ppm (equal to 35.1 mg/kg bw per day), based on reduced pup body weights.

In a study on developmental toxicity in rats at dose levels up to 400 mg/kg bw per day, 3 of 25 females died on treatment day 2 or 3. The mean body weight on gestation day (GD) 20 was lower (by 8%) in high-dose animals. Food consumption was reduced by approximately 20%, and animals showed behavioural changes, such as ataxia and stiffening of the body. The body weights of high-dose fetuses were statistically not significantly reduced by 6%. There were no treatment-related skeletal anomalies. The maternal NOAEL was 160 mg/kg bw per day, based on mortality and behavioural changes at 400 mg/kg bw per day, and the developmental NOAEL was 400 mg/kg bw per day, the highest dose tested.

In a study on developmental toxicity in rabbits at dose levels up to 300 mg/kg bw per day, one 150 mg/kg bw per day doe aborted on GD 22, and four does in the high dose group aborted between GD 19 and GD 24. All animals aborting showed body weight loss accompanied by reduced food consumption and ataxia. On necropsy, no lesions were observed. Generally, the mid- and high-dose dams showed decreased motor activity and ataxia, and the high-dose animals also had rales, laboured breathing and impaired righting reflex. These clinical signs were observed first on GD 9. The body weights and the food consumption of high-dose dams were reduced. There were no effects of treatment on the litter data. The NOAEL for dams was 30 mg/kg bw per day, based on behavioural changes at 150 mg/kg bw per day. The developmental NOAEL was 300 mg/kg bw per day, the highest dose tested.

The Meeting concluded that dicamba was not teratogenic.

In an acute neurotoxicity study in rats at doses ranging from 300 to 1200 mg/kg bw, nonspecific and transient neurobehavioural effects were apparent within 1.5 h after dosing in all dose groups, with a dose-dependent incidence and severity of rigidity.

In a 13-week rat feeding study of neurotoxicity with dietary concentrations up to 12 000 ppm (equal to 767.9 mg/kg bw per day), no behavioural or histological evidence for neurotoxicity was observed.

Toxicological studies for three metabolites were submitted. DCSA and 3,6-dichlorogentisic acid (DCGA) have been identified as metabolites of dicamba in soya beans, sugarcane, wheat and cotton and are also environmental metabolites of dicamba. DCSA has been identified in rats, cows, goats and hens, and 5-hydroxy-dicamba was found in rats.

In a poorly described 13-week feeding study in rats and dogs, 5-hydroxy-dicamba showed no toxicity up to 250 ppm (equivalent to 25 mg/kg bw per day in rats and 6.25 mg/kg bw per day in dogs), the highest dietary concentration tested. 5-Hydroxy-dicamba gave positive results in mouse lymphoma assays and in a Chinese hamster ovary chromosomal aberration test at cytotoxic levels, in the absence and presence of metabolic activation (S9). 5-Hydroxy-dicamba was negative in a mouse micronucleus test.

DCSA showed pharmacokinetic behaviour very similar to that of the parent dicamba and was excreted mainly unchanged and to a minor extent as DCSA carboxyl glucuronide and DCSA phenolic glucuronide (M2, also identified as a rat metabolite of dicamba). In a 13-week feeding study in rats at dietary DCSA concentrations up to 12 000 ppm, reduced body weight gain and haematological and clinical chemistry effects were observed at 6000 ppm and 12 000 ppm. The NOAEL was 3000 ppm (equal to 195 mg/kg bw per day), based on reduced body weight gain at 6000 ppm. In a 13-week study in dogs administered up to 150 mg/kg bw per day by capsule, the NOAEL was 50 mg/kg bw per day, based on reduced (by 11%) body weight gain and liver effects at 150 mg/kg bw per day. In a 52-week feeding study in rats, the NOAEL was 3000 ppm (equal to 171.2 mg/kg bw per day), the highest dose tested. In a two-generation study in rats at dietary concentrations of DCSA up to 5000 ppm, the NOAEL for parental toxicity was 500 ppm (equal to 37 mg/kg bw per day), based on lower body weight gain and reduced food consumption in both sexes at 5000 ppm. The NOAEL for offspring toxicity was 500 ppm (equal to 37 mg/kg bw per day), based on severe toxicity, including mortality, in pups during lactation. The NOAEL for reproductive performance was 5000 ppm (equal to 323 mg/kg bw per day), the highest dose tested. In a pilot and a definitive rat developmental study

on DCSA, the overall NOAEL for maternal and developmental toxicity was 100 mg/kg bw per day, based on severe dam toxicity, including mortality and lower fetal body weight, at 200 mg/kg bw per day. In a pilot and a definitive rabbit developmental study on DCSA, the overall NOAEL for maternal toxicity was 30 mg/kg bw per day, based on reduced food consumption and lower body weight gain at 65 mg/kg bw per day. The NOAEL for developmental toxicity was 65 mg/kg bw per day, the highest dose tested. In genotoxicity studies, including a mouse micronucleus test, DCSA was negative. However, in human peripheral lymphocytes, DCSA increased the number of cells with chromosomal aberrations in the presence and absence of metabolic activation by S9 after 3 or 22 h of exposure at cytotoxic levels.

The metabolite DCGA was evaluated in a 4-week feeding study in rats at dietary concentrations up to 12 000 ppm. The NOAEL was 6000 ppm (equal to 474 mg/kg bw per day), based on reduced body weight gain and lower lymphocyte counts in animals at 12 000 ppm. In a pilot rat developmental study with doses up to 1000 mg/kg bw per day, the maternal NOAEL was 50 mg/kg bw per day, based on increased incidences of rales at 200 mg/kg bw per day, and the developmental NOAEL was 1000 mg/kg bw per day, the highest dose tested. DCGA was negative in an Ames and a rat chromosomal aberration test.

It was concluded that DCSA and DCGA have toxicity similar to or lower than that of dicamba. Based on available data, 5-hydroxy-dicamba appears to be of lower toxicity than the parent.

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.3 mg/kg bw on the basis of a NOAEL of 30 mg/kg bw per day in a rabbit developmental toxicity study, based on maternal toxicity (behavioural changes) at 150 mg/kg bw per day. A safety factor of 100 was applied. The ADI is supported by a postnatal developmental NOAEL of 35.1 mg/kg bw per day in the rat multigeneration study, on the basis of reduced pup body weights at 105 mg/kg bw per day. This ADI would also be protective against the equivocal increase in the incidences of malignant lymphoma and thyroid parafollicular cell carcinoma in male rats at 107 mg/kg bw per day.

The Meeting established an acute reference dose (ARfD) of 0.5 mg/kg bw based on a NOAEL of 50 mg/kg bw per day in the 13-week dog study, based on behavioural effects observed shortly after dosing at 300 mg/kg bw per day. A safety factor of 100 was applied.

The behavioural effects seen in a study on developmental toxicity in rabbits at dose levels of 150 mg/kg bw per day and above are not considered to be an adequate basis for an ARfD because the clinical signs were observed first after four applied doses.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	1000 ppm, equal to 108 mg/kg bw per day	3000 ppm, equal to 358 mg/kg bw per day
		Carcinogenicity	3000 ppm, equal to 358 mg/kg bw per day[b]	—

Species	Study	Effect	NOAEL	LOAEL
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	2500 ppm, equal to 107 mg/kg bw per day[b]	—
		Carcinogenicity	250 ppm, equal to 11 mg/kg bw per day	2500 ppm, equal to 107 mg/kg bw per day[b]
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	5000 ppm, equal to 347 mg/kg bw per day[b]	—
		Parental toxicity	1500 ppm, equal to 105 mg/kg bw per day	5000 ppm, equal to 347 mg/kg bw per day
		Offspring toxicity	500 ppm, equal to 35.1 mg/kg bw per day	1500 ppm, equal to 105 mg/kg bw per day
	Developmental toxicity study[d]	Maternal toxicity	160 mg/kg bw per day	400 mg/kg bw per day
		Embryo and fetal toxicity	400 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity study[d]	Maternal toxicity	30 mg/kg bw per day	150 mg/kg bw per day
		Embryo and fetal toxicity	300 mg/kg bw per day[b]	—
Dog	Thirteen-week study of toxicity[d]	Toxicity	50 mg/kg bw per day	300 mg/kg bw per day
	One-year study of toxicity[a]	Toxicity	2500 ppm, equal to 52 mg/kg bw per day[b]	—

[a] Dietary administration.

[b] Highest dose tested.

[c] Equivocal increase in the incidences of malignant lymphoma and thyroid parafollicular cell carcinoma in male rats.

[d] Gavage administration.

Estimate of acceptable daily intake for humans

0–0.3 mg/kg bw

Estimate of acute reference dose

0.5 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, > 90% within 24 h
Distribution	Extensive, highest levels in kidneys, plasma and uterus
Potential for accumulation	None
Rate and extent of excretion	Rapid, close to 100% within 48 h, mainly via urine

Metabolism in animals	Poorly metabolized, primarily via demethylation, hydroxylation and glucuronidation
Toxicologically significant compounds in animals, plants and the environment	Dicamba, DCSA, DCGA
Acute toxicity	
Rat, LD_{50}, oral	1600 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 9.6 mg/L
Rabbit, dermal irritation	Slightly irritating
Rabbit, ocular irritation	Severely irritating
Guinea-pig, dermal sensitization	Not a sensitizer (Magnusson and Kligman test)
Short-term studies of toxicity	
Target/critical effect	Body weight reduction, haematology and clinical chemistry (dogs)
Lowest relevant oral NOAEL	50 mg/kg bw per day (dogs)
Lowest relevant dermal NOAEL	2500 mg/kg bw per day, the highest dose tested (rabbits)
Lowest relevant inhalation NOAEL	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Reduced body weight gain
Lowest relevant NOAEL	1000 ppm, equal to 108 mg/kg bw per day (mice)
Carcinogenicity	Equivocal increase in malignant lymphoma and thyroid C-cell carcinoma (rats) at 2500 ppm (equal to 107 mg/kg bw per day); unlikely to be carcinogenic at human dietary exposure levels
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects, offspring toxicity (rats)
Lowest relevant reproductive NOAEL	347 mg/kg bw per day, the highest dose tested (rats); 30 mg/kg bw per day (maternal toxicity in rabbits)
Lowest relevant offspring NOAEL	35.1 mg/kg bw per day (rats)
Developmental target/critical effect	No developmental effects (rats, rabbits)
Lowest relevant developmental NOAEL	300 mg/kg bw per day (rabbits), the highest dose tested
Neurotoxicity/delayed neurotoxicity	
	Not neurotoxic
Other toxicological studies	
	Metabolism, pharmacokinetic, toxicity and genotoxicity studies with metabolites
Medical data	
	No data

Summary

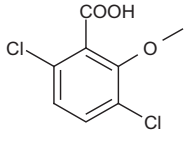
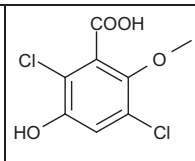
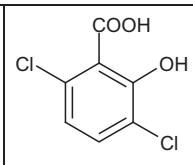
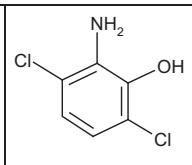
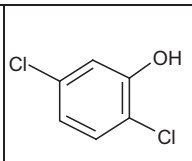
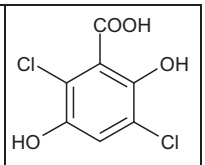
	Value	Study	Safety factor
ADI	0–0.3 mg/kg bw	Developmental toxicity study in rabbit	100
ARfD	0.5 mg/kg bw	Thirteen-week study of toxicity in dog	100

RESIDUE AND ANALYTICAL ASPECTS

Dicamba, a systemic broad-spectrum herbicide, is used in a variety of crops. Its mode of action is similar to that of endogenous auxin (IAA) and other auxin-type herbicides and appears to involve cell wall plasticity and nucleic acid metabolism.

It was identified as a priority new compound at the Forty-second Session of the CCPR in 2009 (ALINORM 09/30/24, para. 193) for evaluation for the first time by the 2010 JMPR. The Meeting received information on physical and chemical properties, animal and plant metabolism, environmental fate, analytical methods, storage stability, use patterns, supervised trials, processing and farm animal feeding.

The structures of dicamba, along with those of metabolites referred to in this appraisal, are shown below.

					
Dicamba	5-OH Dicamba	DCSA	2A36DCP	DCP	DCGA

Animal metabolism

The Meeting received information on the fate of orally-dosed dicamba in lactating goats and cow, and laying hens.

When ^{14}C-dicamba, uniformly labelled with ^{14}C in the phenyl ring, was administered orally at a dose equivalent to a dietary concentration of 10 ppm to a lactating goat daily for four consecutive days, 83%, 8.5% and 0.019% of the total administered radioactivity (TAR) was eliminated via urine, faeces and milk respectively, indicating that the majority of administered radioactivity was rapidly incorporated and excreted in urine. Total recovered radioactivity was 93% of the TAR.

Radioactivity in milk was low throughout the 4 day study period with the cumulative radioactivity of only 0.019% of the TAR. The maximum radioactive residues were 0.002 mg/kg in dicamba equivalents.

Total radioactive residues (TRR) in tissues after sacrifice (24 hours after the last dose) were also low at 0.014 mg/kg (0.023% of TAR), 0.054 mg/kg (0.014% of TAR), 0.011 mg/kg (0.033% of TAR) and 0.004 mg/kg (0.12% of TAR) in parent equivalents in liver, kidney, fat and muscle respectively.

Dicamba was rapidly incorporated into body of lactating goat after oral administration but poorly metabolized. The primary residue was the parent compound (63–93% of TRR) in all tissues

analysed with much smaller amounts of DCSA (1.2–12% of TRR). An unidentified metabolite was found at 0.10% of TRR.

Acid hydrolysis of unextracted radioactivity of liver, kidney and fat released 26–30% of TRR into ethyl acetate fraction which contained metabolites identical to dicamba and DCSA.

Radioactive residues in milk and muscle were not characterized due to their extremely low levels (maximum 0.002 mg/kg in milk and 0.004 mg/kg in muscle expressed in dicamba equivalents).

The result indicates that the major metabolism of dicamba involves O-demethylation to form DCSA although the parent compound was the predominant residue observed in excreta and tissues.

When [phenyl-U-^{14}C]-dicamba was administered orally at a dose equivalent to a dietary concentration of 60 ppm to a lactating cow twice a day for five consecutive days, 89%, 1.5% and 0.018% of TAR were recovered from urine, faeces and milk, respectively. This indicates that the administered radioactive carbon was rapidly incorporated and excreted into urine.

Radioactivity in milk was very low throughout the 5 day study period with the cumulative radioactivity of only 0.018% of the TAR. The maximum radioactive residues were 0.004 mg/kg in dicamba equivalents.

The TRR in tissues after sacrifice (6 hours after the last dose) were also low at 0.30 mg/kg, 2.59 mg/kg, 0.02 mg/kg and 0.03 mg/kg in parent equivalents in liver, kidney, fat and muscle respectively.

Unchanged dicamba was the major radioactive residue found in excreta (75–84% of TRR) and also tissues (51% of TRR in liver, and 70% of TRR in kidney). Much smaller amount of DCSA was found in urine (14–18% of TRR), faeces (8–13% of TRR), liver (21% of TRR) and kidney (11% of TRR). DCSA was the only detected metabolite in milk but its too low level did not allow confirmation of the structure. Radioactive residues in muscle were not characterized due to their low level.

The only other metabolites detected were DCSA glucuronide and DCP in urine but both were less than 4% of TRR.

The above result indicates that the metabolism of dicamba in cow occurs primarily through O-demethylation. It also involves conjugation of DCSA with glucuronic acid and decarboxylation of DCSA to produce DCP.

When [phenyl-U-^{14}C]-dicamba was administered orally at a dose equivalent to a dietary concentration of 10 ppm to a group of laying hens once a day for four consecutive days, 89% and 0.014% of TAR were eliminated in excreta and eggs, respectively. The total recovered radioactivity was 89% of the TAR.

The TRR in tissues after sacrifice (24 hours after the last dose) were very low at 0.0029 mg/kg (0.003% of TAR), 0.0003 mg/kg (0.004% of TAR), 0.0005 mg/kg (0.004% of TAR) and 0.0002 mg/kg (0.001% of TAR) in parent equivalents in liver, breast muscle, leg muscle and fat, respectively, showing little transfer to edible portion of chicken. The radioactive residues in egg white and yolk were also low and never exceeded 0.0035 mg/kg in dicamba equivalents or 0.001% of TAR.

Almost the entire radioactivity found in excreta was attributed to unchanged dicamba and 61% of the TRR in liver and 95% of the TRR in eggs were also attributed to dicamba. 2A36DCP was identified from liver at 36% of the TRR but not from excreta. DCSA and 5-OH dicamba were only identified from urine at 1.6% and 0.0004% of the TRR, respectively. Radioactive residues in muscle and fat were not characterized due to their extremely low level (< 0.0005 mg/kg in dicamba equivalents).

When laying hens were given [phenyl-U-^{14}C]-dicamba as a single oral dose (equivalent to 1 ppm and 100 ppm in the diet) or intravenously (equivalent to 1 ppm in the diet), radioactivity was rapidly incorporated and then eliminated in excreta (78–87% of TAR).

Soon after administration, radioactivity appeared in blood, reached the maximum only 30 min after dose, and decreased rapidly. The half-life of 1.1 hours in blood was calculated.

Only very low amounts of radioactivity were found in the tissues. A total of about 0.06% of the intravenously administered radioactivity was found in eleven tissues 24 hour after administration while 0.7–0.8% of the orally administered radioactivity (1 mg/kg bw) was found in these tissues after the same period. Most of the recovered radioactivity was found in kidney in both experiments.

Dicamba is almost only radioactive compound found in excreta and kidney (≥ 94% of TRR) with small amounts of DCSA (0–4.9%). There are a number of unidentified metabolites found but none exceeded 1.1% of TRR except in kidney one unidentified metabolite accounted for 5.8% of TRR.

Limited metabolism of dicamba was observed in ruminants and hens as the unchanged parent compound was the primary residue component in milk and all ruminant tissues as well as eggs and all avian tissues. Metabolism of dicamba appears to follow the same pathway in goat, cow, hen and rat. The metabolic pathway involves O-demethylation to give DCSA; hydroxylation to produce 5-OH dicamba; decarboxylation of DCSA to give DCP; substitution of carboxyl group of DCSA with amino group to form 2A36DCP; and conjugation of DCSA with glucuronic acid.

Plant metabolism

The Meeting received information on the fate of dicamba after foliar applications or treatment simulating foliar application of [phenyl-U-^{14}C]-dicamba on soya bean, wheat, sugar cane and cotton for which residue trial data were submitted to the present Meeting. Soya bean, wheat and cotton were treated and grown in the field while sugar cane was treated and grown in glasshouse.

[^{14}C]-Dicamba was applied at a sub-toxic rate of 5.17 µg/plant to soya bean plants (foliar application) grown on untreated soil at two different timings.

With the early podfill growth stage application, radioactivity rapidly decreased from 85% to 4.6% of the total applied radioactivity (TAR) in treated leaves in the first seven days after application. After 14 days, the total recovered radioactivity averaged 42% of the TAR, about a half of which was found in immature beans. This indicates rapid and significant incorporation and translocation from leaf to beans.

Over 64% and 94% of respective TRR were attributed to unchanged dicamba in treated leaves and immature beans 14 days after treatment. About 17% of the TRR in the leaf samples collected 14 days after treatment (DAT) was attributed to DCSA while only 0.6% of the TRR in the 14-DAT immature bean samples was DCSA. No di-hydroxylated metabolites were observed.

The result indicates that dicamba is translocated without metabolization or conjugation while at the site of application, dicamba goes through gradual O-demethylation.

With late senescent growth stage application, also rapid decline of radioactivity from 77% to 11% of TRR was observed in treated leaves 6 days after application. Only 63% of the TAR was recovered in the plant 6 days after treatment, among which 26% was found in the intact plant while another 24% was recovered from abscised leaves.

Untreated leaves, stems, roots, pods and immature beans 6 days after treatment contained similar radioactivity. Their radioactivity levels were similar also to those of the same tissues after early podfill stage application except immature beans. With late senescent growth stage application, there was far less translocation of dicamba to beans compared to early podfill stage application. Only 2.1% of TAR or 8% of the TRR remained in immature beans 6 days after treatment.

About 64% and 44% of respective TRR were attributed to unchanged dicamba in treated leaves (not abscised) and beans 6 days after treatment. Only 0.3% and 0.7% of the respective TRR were attributed to DCSA in 6-DAT bean sample and treated leaves (not abscised). Similarly small amounts of 5-OH dicamba and DCGA were also found in treated leaves and immature beans but neither exceeded 1.0% of TRR.

Foliar application of [^{14}C]-dicamba to spring wheat resulted in the majority of radioactivity recovered from leaves and stems and later from straw (1.1–1.9 mg/kg in dicamba equivalents). On the other hand, there was little translocation to grain at 0.056 mg/kg in dicamba equivalents.

In grain, forage and straw samples, none of free individual metabolites were > 5% of TRR and > 0.01 mg/kg, except free dicamba in grain (16% of TRR but 0.009 mg/kg). Including conjugated forms, 5-OH dicamba was the most predominant radioactive residue in straw at 3.7% of TRR and 0.70 mg/kg, and dicamba in grain as described above.

Significant amounts of radioactivity were incorporated into unextracted plant matrix constituents, such as protein, cellulose, pectin and lignin.

The above result indicates that metabolism of dicamba in wheat was extensive and includes hydroxylation at 5-position of dicamba to form 5-OH dicamba and its O-demethylation to form DCGA; O-demethylation of dicamba to form DCSA; O-demethylation of dicamba and hydroxylation at 5-position to form DCGA; and conjugation and incorporation into plant matrix constituents.

After foliar application of [^{14}C]-dicamba to 6-week old sugar cane plants grown in untreated soil at a rate of 3.06 mg/plant, dicamba was rapidly taken up by leaves with 46% of TAR recovered from plant 28 days after treatment. More than 90% of the incorporated radioactivity remained in treated leaves with about 6% TAR translocated to other parts of the plant 28 days after treatment.

Dicamba was predominant radioactive residue in treated leaves at 0 DAT (more than 90% of TRR) but decreased to less than half of TRR by 12 DAT. Over time 5-OH dicamba was formed and reached 49% of TRR by 12 DAT. At 28 DAT, the total extractable amount of 5-OH dicamba was greater than that of dicamba itself. Small amount of DCGA was also found at a total of about 2% of TRR. Amounts of unextracted radioactivity were also significant indicating incorporation of radioactivity into plant matrix. β-Glucosidase treatment released significant amount of DCSA.

Metabolism of dicamba in sugar cane seems to involve as primary pathway, hydroxylation to form 5-OH dicamba. Other pathway may include O-demethylation to form DCSA and its conjugation to form β-D-glucosides; and O-demethylation of 5-OH dicamba and hydroxylation of DCSA to form DCGA.

[^{14}C]-Dicamba was applied to cotton grown in untreated soil at a rate of 60 μg/plant, a sub-toxic rate, at the green-boll growth stage. Radioactivity in treated plants rapidly declined from 16% to 1.9% of TAR in 14 days after foliar application. On the other hand, the 14 DAT untreated leaf, stem root and boll samples contained comparable radioactivity; in particular, bolls contained 22% of TAR. This indicates significant translocation to bolls.

Among parts of the 14 DAT bolls, the majority of radioactivity (17% of TAR) is located in carpels with 2.5% and 2.6% of TAR in seed and lint respectively.

Dicamba was the predominant radioactive residue in ether fractions of treated seed (14 DAT) at 2.2% of TAR. Further analysis indicated that dicamba was poorly metabolized or not conjugated in cotton seed.

Dicamba was the predominant residue in all analysed cotton parts with very slow metabolization showing minor amounts of 5-OH dicamba.

In summary, in wheat and sugar cane, there is little translocation and dicamba was rapidly metabolized after foliar application of dicamba. In these plants, hydroxylation to form 5-OH dicamba appears to be the primary metabolic pathway. Conjugation of 5-OH dicamba is also observed.

In soya beans and cotton, which are susceptible to dicamba, metabolism of dicamba appears to be slow and limited to occur in treated leaves. However, significant translocation was observed.

Despite some differences in the rate of metabolism and translocation, there seems to be a common metabolic pathway of dicamba after its foliar application to these four plant species. The metabolism of dicamba appear to follow: hydroxylation of dicamba at the 5-position to form 5-OH dicamba; O-demethylation of 5-OH dicamba to form DCGA; O-demethylation of dicamba to form DCSA; O-demethylation of dicamba and hydroxylation to form DCGA; and conjugation of 5-OH dicamba and DCSA with glucose to form the β-D-glucosides.

Environmental fate in soil

The Meeting reviewed information on aerobic soil metabolism, aqueous photolysis and rotational crop study.

Aerobic soil metabolism

Aerobic soil metabolism studies were conducted using ^{14}C-dicamba applied to various soils and incubated under aerobic conditions at 20–25 °C. Under aerobic conditions, dicamba applied to soil was degraded very rapidly with O-demethylation, which was induced by microorganisms. DCSA was the predominant degradate in soil with its maximum level at 14–59% of the applied radioactivity. It is further degraded to 0.1–15% of the applied radioactivity at the termination of studies. A small amount of 2,5-diOH dicamba was also observed indicating possible hydroxylation of DCSA. Mineralization in the presence of microorganism was also rapid and amounting to 27–67% of the applied radioactivity at the termination of studies.

Components associated with fulvic acid were low with the maximum at 1.4–11% of applied radioactivity. However those associated with humic acid were higher with the maximum at 16–34% of the applied radioactivity.

Calculated half-life of dicamba ranged between 2.1 day and 26 days under laboratory conditions at 20–25 °C. That of DCSA ranged between 1.7 days and 45 days. These values indicate that dicamba is not persistent in soil under laboratory conditions.

Field dissipation studies with the application rate of 480 g ai/ ha confirmed fast degradation. Only the 0-10 cm soil layer contained significant amount of dicamba at the beginning of the study and the 10-20 cm and 20-30 cam soil layers contained trace amounts of dicamba. Dicamba was rapidly degraded to < 0.01 mg/kg within 21 days.

DCSA was found only in the top 0–10 cm soil layer at a maximum of 0.03 mg/kg between 6 days and 14 days after treatment. After 28 days, it also decreased to 0.01 mg/kg or less.

Dicamba and DCSA were shown to be not persistent in soil in the field.

In the other field studies with application rate of 360 g/ha, dicamba applied to soil surface decreased rapidly to < 0.01–0.29 mg/kg in the top 10 cm soil in 2–3 days after application. Within 30–60 days after treatment, dicamba decreased to 0.01 mg/kg or below.

DCSA was formed during the test period. In one study it, reached its maximum between 7 days and 15 days after application at 0.09 mg/kg and decreased thereafter to 0.02–0.05 mg/kg 120 days after application.

Calculated half-life of dicamba ranged between 1.4 and 11 days under the field condition and that for DCSA was about 10 days. These results also confirm that neither dicamba nor DCSA is persistent in soil.

Degradation pathway of dicamba in aerobic soil appears to involve O-demethylation of dicamba to form DCSA; hydroxylation of DCSA to form 2,5-diOH dicamba; hydroxylation of

dicamba to form 5-OH dicamba followed by O-demethylation to form 2,5-diOH dicamba; incorporation of further degradates into soil matrix: and mineralization.

Photolysis on dry soil

Under xenon arc (simulating 40°N latitude summer sunlight) at 25 °C, dicamba degraded slowly on dry soil surface with about 20% of dicamba photo-degraded in 30 days. Without irradiation, no significant loss of dicamba was observed in 30 days. This indicates that photolysis on soil surface by light is not regarded as an important degradation pathway for dicamba.

Residues in succeeding crops

In an outdoor confined rotation study, mustard, turnip and wheat were planted at 32, 131 and 369 days after the application of ^{14}C-dicamba at a rate of 560 g ai/ha to soil.

Only samples from rotational crops planted 32 days after soil treatment contained detectable radioactive residues. No radioactive residues were detected in samples from crops planted 131 or 369 days after soil treatment. These results indicate negligible uptake of dicamba by rotational crops from soil. Crops planted 32 days after treatment contained 0.0015 mg/kg (turnip tops) to 0.21 mg/kg (mustard tops) in dicamba equivalents. Wheat forage contained 0.033 mg/kg in dicamba equivalents.

DCSA or 5-OH dicamba was not detected in these crops from all plant back intervals.

These results indicate rapid degradation of dicamba in soil and limited uptake of dicamba into plants. Analysis of soil confirmed the rapid degradation and dissipation of both dicamba and DCSA in soil.

In another rotational crop study with plant back intervals of 214, 301 and 542 days after treatment at a rate of 2.24 kg ai/ha, similar results were observed with the maximum at 0.043 mg/kg in dicamba equivalents in turnip tops from 214 day plant back interval. Analysis of soil also showed rapid degradation and dissipation of dicamba and DCSA in soil.

In the third rotational crop study, collard greens, carrot and barley were planted 30, 120 and 365 days after treatment at a rate of 840 g ai/ha. While these crops planted 30 days after treatment contained radioactive residues at 0.026–9.5 mg/kg in dicamba equivalents, those planted 120 days after treatment contained radioactive residues at < 0.01–0.036 mg/kg and no crop planted 365 days after treatment contained detectable radioactive residues.

It is concluded that no or little dicamba residues were expected to occur in rotational crops.

Methods of analysis

Analytical methods for determination of residues of dicamba and its metabolites were developed for a wide range of matrices of plant and animal origin. In general, these methods employ homogenization, hydrolysis at 95 °C for 1.5 hours and extraction with 1N HCl, neutralization, and re-acidification, extraction with ethyl ether, methylation with diazomethane, clean-up, and analysis using GC/ECD. Confirmation was done using GC/MSD. The HCl hydrolysis process releases conjugated dicamba and its metabolites.

The methods for plant matrices were validated for each analyte at 0.01–1.0 mg/kg, and in case of pasture grass and hay at 20–100 mg/kg.

Method AM-0-766A was successfully validated at the fortification levels of 0.01–0.50 mg/kg for dicamba and DCSA in asparagus.

Method AM-069B and its better presented method AM-0691B-0297-4 were successfully validated (recovery 70–120%) at the fortification levels of 0.05–5.0 mg/kg for dicamba and 5-OH dicamba in barley grain and straw; maize grain, silage, stalk and stover; cotton seed, trash, seed hull, seed meal, crude seed oil and refined seed oil; peanut hay (green); sorghum grain and silage; soya

bean seed, forage, stalk and straw; sugar cane leaf and stalk; tomato, tomato juice, tomato pomace and tomato sauce; and wheat grain, silage, straw, bran, germ and flour. It was also validated at fortification levels of 20–100 mg/kg for dicamba and 5-OH dicamba in pasture grass and hay. However, the overall mean relative standard deviation was slightly higher than 20% (21–23%) for 5-OH dicamba in soya bean seed and forage, and wheat silage.

Method AM-0691B-0297-3 was also successfully validated for the same fortification levels as above for dicamba and 5-OH dicamba in barley grain and straw: maize forage, grain, silage and fodder; wheat grain, and pasture grass and hay. However, the relative standard deviation was slightly higher than 20% (23 and 26%) for 0.10 mg/kg 5-OH dicamba in barley grain and wheat grain.

Method AM-766A-1093-2 involving butylation with diazobutane, was validated successfully for 0.01–3 mg/kg of dicamba and 0.01–0.1 mg/kg of DCSA in asparagus.

Method AM-0941-1094-0, using butylation, rather than methylation, was successfully validated for 0.02–5.0 mg/kg of dicamba and DCSA and 5-OH dicamba in asparagus and soya bean except fortification level of 0.10 mg/kg in soya bean which showed a recovery of 63%. However, overall relative standard deviation of fortified soya bean samples were higher than 20% (25% for dicamba, 28% for DCSA and 25% for 5-OH dicamba.

Method REM 193.01 was successfully validated for the purpose of enforcement for 0.01 and 0.10 mg/kg of dicamba and 5-OH dicamba in maize, whole plant, grain and straw; rape seed; pasture and oranges.

The multiresidue methods described in the FDA PAM were tested for DCSA and 5-OH dicamba. After screening, Protocols C, A and B were tested. While GPC test resulted in recoveries of 5-OH dicamba and DCSA within acceptable range, recoveries of 5-OH dicamba and DCSA in soya bean forage through complete Protocol B were at or below 6%. From the soya bean seed, 5-OH dicamba showed 0% of recovery at all fortified levels.

The methods for animal matrices employ very similar procedures as the methods for plant matrices described above. They were validated for dicamba and DCSA at 0.01–3.0 mg/kg in bovine tissues, milk and eggs.

Method AM-0938-0994-0, using butylation with diazobutane, was successfully validated for 0.01–0.50 mg/kg of dicamba in beef fat, kidney, liver, muscle and milk except that for 0.01 mg/kg fortification to liver, the recovery was 65%. For 0.01–0.50 mg/kg of DCSA, the recoveries of around 65% were seen for beef fat and liver. On the contrary, the recovery of 140% was seen for kidney. Relatively high relative standard deviations (25–47%) were seen for fat, liver and milk. It was successfully validated for muscle. In the confirmatory trial, it was again successfully validated for 0.1–3.0 mg/kg dicamba in beef fat and liver and for 0.10–0.50 mg/kg DCSA in fat. However, in the confirmatory trial, recoveries of 0.75–3.0 mg/kg DCSA in liver were in a range of 50–56%.

Method GRM022.03A using N-(tert-butyldimethylsilyl)-N-methyl-trifluoroacetamide to produce tertiary butyl demethyl silyl esters was successfully validated as enforcement method for 0.01 and 0.10 mg/kg of dicamba and DCSA in eggs, milk, beef muscle, fat, liver and kidney. However, in the second validation study, the method was successfully validated only for 0.01 and 0.10 mg/kg dicamba in eggs, milk, beef muscle, liver and kidney and 0.01 and 0.10 mg/kg DCSA in muscle and liver.

In most methods, limit of quantitation was 0.01 mg/kg. For some matrices, such as asparagus, soya beans and cotton, the LOQs were higher at 0.02 mg/kg.

The methods used in cattle feeding studies were not described among the analytical methods. The method used in the 1979 studies determined dicamba and DCSA inseparably as methyl ester of dicamba using GC/ECD.

Stability of residues in stored analytical samples

Stability of dicamba and its metabolites (fortification level of 0.1–0.5 mg/kg) in homogenised asparagus, soya bean, maize and sorghum stored in deep freezer was investigated 3–36 months reflecting the sample storage periods in residue trials.

In asparagus, remaining dicamba and DCSA were 75% and 81% respectively after 104 days of frozen storage, and remaining 5-OH dicamba was 87% (unadjusted for procedural recovery) after 119 days frozen storage. In these specified time, dicamba, DCSA and 5-OH dicamba are stable in the frozen storage.

After frozen storage for 81 days, residues of dicamba and 5-OH dicamba were stable in sugar cane, and for 60 days in bagasse and final molasses with more than 95% of the original residues remaining.

After frozen storage for 3 months, residues of dicamba and 5-OH dicamba were stable in soya bean with 79% and 91% of the original residues remaining respectively. They were similarly stable in refined soya bean oil with 79% and 86% remaining respectively. However, 63% and 65% of DCSA were remaining after 3 month frozen storage in seeds and refined oil showing some degradation but procedural recoveries were also low at 68% and 71% in seeds and refined oil respectively.

Dicamba in maize grain, forage, fodder and silage was stable frozen up to 36 months. 5-OH dicamba was stable frozen for up to 36 months in maize grain and forage but up to only 3 months in fodder and silage.

Dicamba and 5-OH dicamba were stable up to 5 months in sorghum grain and up to 2 months in grain dust.

Dicamba was demonstrated to be stable frozen up to 18 months in animal tissues. DCSA was generally stable for the same period in animal tissues but, in liver and muscle, showed to be unstable beyond 3 months.

Definition of the residue

In goats, cows and hens, metabolism of dicamba was limited. The parent compound remained as major components in ruminant and avian tissues. In goats and cows, much smaller amount of DCSA was found in liver and kidney. In hen metabolism studies after oral administration of dicamba at a dose level equivalent to 10 ppm, 2A36DCP was identified from liver extract at 0.001 mg/kg (36% of TRR) while DCSA was not detected from analysed matrices, liver, kidney or eggs.

In soya bean and cotton, the predominant residue was dicamba. In soya bean much less amount of 5-OH dicamba was detected. While DCSA was not found after early podfill stage foliar treatment, it was found at a very small amount after late senescent stage foliar application.

In sugar cane, major residues were 5-OH dicamba and dicamba with a very small amount of DCGA after foliar application.

In wheat grain, forage and straw, free metabolites were all < 0.01 mg/kg. Dicamba was predominant in grain while 5-OH dicamba was the predominant residue in straw.

Sufficiently validated GC/ECD methods were available for determining the parent compound, 5-OH dicamba and DCSA in a wide range of plant commodities and animal tissues, milk and eggs.

Based on the above findings, the Meeting considered that the parent dicamba was suitable residue for enforcement.

However, as DCSA is a major metabolite in goats and cows and in the cattle feeding study DCSA was not separately determined from dicamba, the Meeting decided to include DCSA in the

residue definition for both enforcement and estimation of dietary intake for animal commodities. In many trials on crops, DCSA was not determined.

5-OH dicamba, a major metabolite in plants, is formed in significant amounts in some plant species, the Meeting decided to include this compound in the residue definition for plant commodities for estimation of dietary intake.

Dicamba has logPow of –0.5 and –1.8 at pH 5 and 7, respectively, at 25°C, indicating that dicamba is not fat-soluble. In animal metabolism studies, there was no specific residue concentration found in tissues with higher fat content.

The Meeting recommended the following residue definition for plant and animal commodities:

Definition of the residue for plant commodities (for compliance with the MRL): *Dicamba*

Definition of the residue (for estimation of dietary intake) for plant commodities: *Sum of dicamba and 5-OH dicamba expressed as dicamba*

Definition of the residue (for compliance with the MRL and for estimation of dietary intake) for animal commodities: *Sum of dicamba and DCSA*

Residue is not fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised trial data for dicamba on sweet corn, soya bean, asparagus, barley, maize (field corn), sorghum, wheat, sugar cane, cotton and pasture grasses. All trials were conducted in the USA.

For all analytes and matrices, generally the LOQ was 0.01 mg/kg unless as otherwise stated.

For summing up the total residues, if dicamba, 5-OH dicamba and DCSA were below the LOQ, the LOQ value of each was used for calculation.

Sweet corn

Nine supervised trials were conducted. Two treatments were applied side-by-side consisting of two applications of 0.14 kg ai/ha (total 0.28 kg as/ha; 50% WG) and two applications of 0.28 kg ai/ha (total 0.56 kg ai/ha; 480 g/L SL). The timings for the sequential applications were early post-emergence (12 inch tall corn plant) and mid post-emergence (24 inch tall corn plant). The LOQ was 0.02 mg/kg for dicamba and 5-OH dicamba. DCSA was not determined.

The US GAP allows one application at a rate of 0. 14 kg ai/ha with a PHI of 72 days.

The trials were conducted with 2 applications at a rate of 0.14 kg ai/ha with PHI of 21–60 days. Under this condition, that would lead to higher residues, resulting dicamba residues were < 0.02 (8) and 0.02 mg/kg.

Taking into consideration, the trial condition, the Meeting estimated a maximum residue level of 0.02 mg/kg for sweet corn.

Corresponding total residues of dicamba and 5-OH dicamba in rank order were: < 0.04 (8) and 0.04mg/kg.

The Meeting estimated an STMR and HR at 0.04 and 0.04 mg/kg.

Because residues were mostly below the limit of quantitation the NAFTA calculator was not used.

Soya bean

A total of 23 trials were conducted.

Each formulation was applied at the maximum proposed label rate according to the methods and conditions representing U.S. soybean production.

US GAP allow two different applications: application of 0.56 kg as/ha as a broadcast made to the soil surface approximately 14 prior to planting and application of 2.24 kg ai/ha applied approximately 14 days prior to harvest. The PHI is 14 days for the latter use. .

In all the trials, the second application was carried out 7 days before normal harvest, shorter than GAP PHI. In addition, the total applied rate exceeded the maximum seasonal rate. There were significant residues found in soya bean seeds but it is not possible to estimate residue levels at 14 day PHI.

The Meeting concluded that since no trial matched the GAP, no maximum residue level could be recommended.

Asparagus

US GAP allows the use of dicamba in asparagus with one application of 0.56 kg as/ha (0.56 kg ai/ha total maximum seasonal application) and PHI of one day.

A total of eight supervised field residue trials were conducted. The formulations used at each site were the dimethylamine salt (DMA^+), the diglycolamine salt (DGA^+), and the sodium salt (Na^+) of dicamba. Each formulation was applied at the maximum proposed label rate according to the methods and conditions representing U.S. asparagus production. There was no statistically significant difference in residues after application with different salt type.

Residues from trials matching the GAP were: 0.45, 0.49, 0.58, 0.78, 0.96, 1.1, 2.3 and 3.3 mg/kg.

The Meeting estimated a maximum residue level of 5 mg/kg.

Corresponding total residues of dicamba were: 0.46, 0.50, 0.59, 0.79, 0.97, 1.11, 2.34 and 3.28 mg/kg.

The Meeting estimated an STMR and HR at 0.87 mg/kg and 3.3 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 6 mg/kg, which differed from the estimate made by the Meeting.

Barley

US GAP allows two applications: one application of 0.14 kg as/ha immediately prior to the first joint stage and one application of 0.28 kg ai/ha. The PHI is 7 days.

A total of 11 supervised field residue trials were conducted. The dimethylamine salt (DMA^+) of dicamba was applied in five trial locations. Side by side trials with three formulations (the dimethylamine salt (DMA^+), the diglycolamine salt (DGA^+), and the sodium salt (Na^+) of dicamba) were conducted at four locations to determine the similarity of residues from the different salts. The statistical analysis indicated different salt type did not influence residue levels.

Residues of dicamba from trials matching US GAP were: 0.78, 1.1, 1.1, 1.5, 1.6, 1.6, 1.8, 2.7, 2.9 and 5.0 mg/kg.

The Meeting estimated a maximum residue level of 7 mg/kg. An STMR for the estimation of animal dietary burden was estimated to be 1.6 mg/kg.

Corresponding total residues of dicamba in rank order were: 0.83, 1.1, 1.1, 1.7, 1.7, 1.7, 1.9, 2.8, 2.9 and 5.1 mg/kg.

The Meeting estimated an STMR at 1.7 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 7 mg/kg, which was in agreement with the Meetings estimate.

Maize (field corn)

US GAP allows one to two applications per season, for a maximum seasonal application of 0.84 kg ai/ha. The normal use pattern consists of one application of 0.56 kg ai/ha applied pre-plant, pre-emergence or early post-emergence (up to the 5 leaf stage) and, if required, one application of 0.28 kg ai/ha applied late post-emergence (20–90 cm tall or 15 days before tassel emergence). No PHI was specified.

A total of 19 supervised field residue trials were conducted. The dimethylamine salt (DMA^+) of dicamba was applied in 11 trial locations. Side by side trials with three formulations (the dimethylamine salt (DMA^+), the diglycolamine salt (DGA^+), and the sodium salt (Na^+) of dicamba) were conducted at eight locations resulting in no significant effect of salt type on residues.

There was a fallow application in the previous fall. Since in the USA one season for maize is specified to be from March to October, this application is not regarded to be included in the maximum seasonal rate

Residues of dicamba from trials matching GAP were all < 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.01(*) mg/kg for maize. An STMR for the estimation of animal dietary burden was estimated to be 0.01mg/kg.

Corresponding total residues of dicamba in rank order were: < 0.02 (16), 0.02, (2) and 0.03 mg/kg.

The Meeting estimated an STMR at 0.02 mg/kg.

Sorghum

US GAP allows two applications: one application of 0.28 kg ai/ha immediately prior to the first joint stage and one application of 0.28 kg ai/ha applied at the soft dough stage. The PHI is 30 days.

A total of 11 supervised field residue trials were conducted.

Residues of dicamba from trials matching GAP were: 0.39, 0.41, 0.78, 0.97, 1.0, 1.2, 1.2, 1.3 and 2.0 mg/kg.

The Meeting estimated a maximum residue level of 4 mg/kg. An STMR for the estimation of animal dietary burden was estimated to be 1.0 mg/kg.

Corresponding total residues of dicamba in rank order were: 0.54, 0.85, 1.3, 1.7, 2.0, 2.2, 2.4, 2.7 and 3.2 mg/kg.

The Meeting estimated an STMR at 2.0 mg/kg.

The maximum residue level estimate derived from use of the NAFTA calculator was 3.5 mg/kg, which was in agreement with the Meetings estimate (after rounding up to one figure).

Wheat

US GAP allows two applications: one spring application of 0.28 kg ai/ha immediately prior to the first joint stage and one broadcast application of 0.28 kg ai/ha. The PHI is 7 days.

A total of 20 supervised field residue trials were conducted,

Residues of dicamba from trials matching GAP were: 0.05, 0.07, 0.08, 0.11, 0.11, 0.11, 0.16, 0.19, 0.19, 0.25, 0.29, 0.34, 0.35, 0.47, 0.53, 0.81, 0.84 and 1.1 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg. An STMR for the estimation of animal dietary burden was estimated to be 0.22 mg/kg.

Corresponding total residues of dicamba were: 0.06, 0.09, 0.09, 0.12, 0.12, 0.16, 0.17, 0.20, 0.22, 0.30, 0.35, 0.37, 0.39, 0.50, 0.63, 1.1, 1.2 and 1.3 mg/kg.

The Meeting estimated an STMR at 0.26 mg/kg.

The maximum residue level estimate derived from use of the NAFTA calculator was 2 mg/kg, which was in agreement with the Meetings estimate.

Sugar cane

US GAP allows one application at 2.24 kg as/ha (2.24 kg as/ha total maximum seasonal application) applied at lay-by. Under these conditions, a PHI is not necessary.

A total of eight supervised field residue trials were conducted.

Residues of dicamba from trials matching GAP were: < 0.01, 0.01, 0.02, 0.03, 0.03, 0.05, 0.05, 0.96 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg. An STMR for the estimation of STMR-P was estimated to be 0.03 mg/kg.

Corresponding total residues of dicamba were: 0.02, 0.03, 0.05, 0.08, 0.11, 0.13, 0.20 and 1.1 mg/kg.

The Meeting estimated an STMR and HR at 0.095 mg/kg and 1.1 mg/kg

The maximum residue level estimate derived from use of the NAFTA calculator was 1.3 mg/kg.

Cotton

The GAP of the USA allows a single pre-plant application at 0.28 kg as/ha. Residue trials were conducted at 0.56 kg ai/ha, which was the originally proposed application rate. Under this use condition, a PHI is not necessary.

A total of 12 supervised field residue trials were conducted. The LOQ was 0.04 mg/kg due to interference.

With the double rate, residues of dicamba were all < 0.04 mg/kg.

The Meeting therefore decided to estimate a maximum residue level of 0.04 (*) mg/kg for cotton seed.

As the LOQ is higher than those in other trials and application was made pre-plant possibly leading to nil residue situation, when both dicamba and 5-OH dicamba were < 0.04 mg/kg, the total residues were calculated to be < 0.04 mg/kg. When either dicamba or 5-OH dicamba was < 0.04 mg/kg and the other was higher than 0.04 mg/kg, residues at < 0.04 mg/kg were assumed to be zero in calculating the total residues.

Corresponding total residues of dicamba were: < 0.04 (11) and 0.05 mg/kg.

Since the trials were conducted at double rate with relatively high LOQ, the Meeting estimated both an STMR at 0.04 mg/kg.

Soya bean forage and hay

Soya bean forage and hay samples were collected before the second application is made to avoid abscission. Therefore, residues in these commodities came from pre-plant application.

Since the residues from the pre-plant application were expected to be very low and harvesting soya bean plants before harvesting soya bean seeds does not seem to be a common practice, the Meeting did not estimate a maximum residue level for soya bean forage and hay.

Barley and wheat straw

Since they are not distinguishable in trade, their trial results were evaluated together. US GAP for barley and wheat were similar.

Residues of dicamba in barley straw were: 1.0, 2.5, 3.1, 3.6, 3.6, 3.7, 5.5, 6.6, 10 and 30 mg/kg.

Residues of dicamba in wheat straw were: 0.40, 0.60, 1.1, 1.4, 2.2, 2.4, 2.4, 3.2, 3.6, 4.0, 4.4, 5.2, 5.3, 5.7, 7.1, 7.3, 21 and 23 mg/kg.

The Meeting concluded that the residue populations are similar and estimated a maximum residue level of 50 mg/kg. The highest dicamba residue and median residue for the estimation of animal dietary burden were 30 and 3.65 mg/kg for barley straw and 23 and 3.8 mg/kg for wheat straw.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 25 mg/kg based on barley straw data and 40 mg/kg based on wheat straw data.

Grasses forage and hay

The GAP of the USA allows one application of dicamba at 0.56 kg ai/ha. PHI for hay is 37 days and the shortest PHI for forage is 7 days.

The Meeting received trials data for various kinds of grasses, which are reviewed together in this evaluation.

Residues of dicamba in hay from those trials conducted according to GAP were: 1.4, 2.9, 3.1, 3.2, 3.4, 4.0, 6.3, 6.8, 6.9, 8.3, 8.6, 16 and 19 mg/kg.

The Meeting estimated a maximum residue level of 30 mg/kg for hay. The highest dicamba residue and median residue for the estimation of animal dietary burden were 19 and 6.3 mg/kg.

T The maximum residue level estimate derived from use of the NAFTA statistical calculator was 30 mg/kg, which was in agreement with the estimate of the Meeting.

Residues of dicamba in forage from those trials conducted according to GAP were: 2.2, 2.4, 6.6, 6.6, 6.9, 9.8, 11, 11, 12, 15, 15, 25 and 35 mg/kg.

The Meeting estimated the highest residue of 35 mg/kg and median residue of 11 mg/kg (fresh weight basis) for the calculation of animal dietary burden. These are equivalent to 140 mg/kg and 44 mg/kg on a dry weight basis after applying the dry matter of 25%.

Maize forage and fodder

Residues of dicamba in maize fodder from trials according to GAP were: 0.01, 0.01, 0.03, 0.04, 0.05, 0.06, 0.06, 0.06, 0.06, 0.06, 0.08, 0.08, 0.10, 0.10, 0.13, 0.24, 0.18, 0.20 and 0.33 mg/kg.

For trials on sweet corn, dicamba was applied twice instead of once as specified in GAP. However, even with two applications, residues of dicamba were mostly < 0.02 mg/kg and the highest residue was 0.05 mg/kg.

Based on trials on maize, the Meeting estimated a maximum residue level of 0.6 mg/kg for maize fodder. The highest dicamba residue and median residue for the estimation of animal burden were 0.33 and 0.06 mg/kg, respectively using the dry matter of 40%.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.60 mg/kg, which was in agreement with the estimate of the Meeting.

Residues of dicamba in forage from trials matching GAP were: 0.02, 0.06, 0.07, 0.07, 0.08, 0.09, 0.10, 0.12, 0.14, 0.16, 0.16, 0.18, 0.18, 0.19, 0.20, 0.25, 0.30, 0.30 and 0.31 mg/kg.

The Meeting estimated the highest residue and median residue for calculating animal dietary burden to be 0.31 and 0.16 mg/kg for maize forage on a fresh weight basis which are equivalent to 0.775 mg/kg and 0.40 mg/kg respectively.

Sorghum fodder

Residues of dicamba in sorghum fodder were: 0.57, 0.64, 0.81, 1.3, 1.3, 1.4, 1.6, 4.3 and 5.4 mg/kg.

The Meeting estimated a maximum residue level of 8 mg/kg. The highest dicamba residue and median residue for the estimation of animal dietary burden were 5.4 and 1.3 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 9 mg/kg.

Cotton gin trash

Residues of dicamba were even at double rate mostly < 0.04 mg/kg. In two trials residues of 0.05 and 0.06 mg/kg were observed. Since cotton gin trash is not an important trade item, no maximum residue level was recommended. The highest dicamba residue and median residue were 0.06 and 0.04 mg/kg. Although the trials were not in compliance with the current US GAP, the above mentioned values can be used for calculation of animal burden as an STMR and highest residue.

Fate of residues during processing

The Meeting received information on processing of soya beans to meal and oil; maize to flour, grits, meal, starch and oil; sugar cane to molasses and sugar; and cotton to meal and oil.

Processing factors were calculated for the processed commodities of the above and STMR-Ps for these commodities are shown below:

Processed Orange Product	Processing factor		STMR/STMR-P (mg/kg)
	Dicamba	Total residues	
Soya bean			
Refined oil	< 0.019	< 0.036	
Maize			0.02
Flour	0.26	0.28	0.0056
Large grits	0.20	0.22	0.0044
Meal	0.069	0.095	0.0019
Crude oil	< 0.029	< 0.058	0.00116
Wheat			0.26
Bran	0.99	1.0	0.26
Flour	0.052	< 0.070	0.02
Sugar cane			0.14
Molasses	42	24	3.4
White sugar	< 0.77	< 0.37	0.05
Cotton seed			0.04
Refined oil	< 0.01	< 0.02	0.008

As there is no concentration of dicamba and 5-OH dicamba observed in these processed commodities, no maximum residue levels are necessary for these commodities.

For the purpose of calculating animal dietary burden for estimating maximum residue levels for commodities of animal origin, STMR-P for maize hull and gluten, wheat bran and grain dust, sugar cane molasses and bagasse, and cotton seed meal were calculated based on dicamba residues only to be 0.0033, 0.014, 0.26, 2.3, 4.0, 0.198 and 0.07 mg/kg respectively..

Residues in Animal Products

Estimation of dietary burdens

Barley, maize, sorghum and wheat grains; soya bean forage and hay; straw of barley and wheat; grass forage and hay; processed maize byproducts; processed wheat byproducts; processed sugar cane products: and cotton gin trash and processed cotton byproducts may be fed to dairy cattle, beef cattle, broilers and layers. The maximum and dietary burdens were calculated using the highest residue or STMR/STMR-Ps of dicamba in commodities for which maximum residue levels were recommended on a basis of the OECD Animal Feeding Table.

5-OH Dicamba was not included in the calculation of animal burden as the feeding study with 5-OH dicamba resulted in very low uptake of 5-OH (< 0.01 mg/kg) into tissues, milk or blood of cattle at a dose equivalent to 59 ppm in the diet.

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

	US/CAN		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle	6.0	2.6	71.2	23.2	140[a]	44.0[b]	15.7	5.8
Dairy cattle	64.3	21.1	85.0	27.4	140[c]	44.0[d]	27.5	9.2
Broilers	1.4	1.4	1.3	1.3	1.0	1.0	0.84	0.84
Layers	1.4	1.4	15.6[e]	6.0[f]	1.0	1.0	0.73	0.73

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

[b d] Suitable for estimating STMRs for milk, meat, fat and edible offal of cattle.

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

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

Residues in milk and cattle tissues

Lactating dairy cows were dosed daily for 30 consecutive days via gelatin capsules containing dicamba (40–400 ppm in diet).

Significant residues of dicamba and DCSA were found in kidney in all dose groups. However, in muscle, residues of dicamba and DCSA were generally low and < 0.01 mg/kg in the 40 ppm dose group. Residues in all tissues declined after withdrawal period to < 0.01 mg/kg in the 40 and 120 ppm dose groups. However, in kidney residues of 0.056 mg/kg was found in the 120 ppm group. Tissues from the 400 dose group contained significant amount of residues (0.01–0.28 mg/kg).

The maximum residues in milk were 0.023–0.039 mg/g in the 40 ppm dose group, 0.041–0.069 mg/kg in the 120 ppm dose group, and 0.21–0.34 mg/kg in the 400 ppm dose group. Residues in milk declined to < 0.01 mg/kg one day after termination of feeding dicamba.

In another study with 1000 ppm dose for 31 days, significant levels of residues were observed in liver (2.4–5.1 mg/kg) and kidney (9.8–47 mg/kg) . However, after 5 day withdrawal period, residues were reduced to 0.03 mg/kg in kidney and 0.22 mg/kg in liver. Muscle contained 0.11–0.39 mg/kg after 31 days of feeding period.

Milk contained up to 0.51 mg/kg of residues but within two days of withdrawal the concentration declined to < 0.01 mg/kg.

In a third study with 19, 59 and 183 ppm dose groups, no tissues contained residues above 0.01 mg/kg with an exception of 0.02–0.04 mg/kg occasionally found in kidney.

In the 183 ppm dose group, kidney contained up to 0.54 mg/kg of residues. In other tissues, residues above 0.01 mg/kg (up to 0.04 mg/kg) were found.

5-OH dicamba was fed to lactating cows at a dose rate equivalent to 19 ppm in the diet. However, the incorporation of 5-OH dicamba was minimal showing residues mostly below 0.005 mg/kg with occasional observation of 0.005 mg/kg.

Using the dietary burdens for beef and dairy cattle and the results in the lactating cattle feeding study, the maximum residue levels and STMRs were estimated. The calculated residues in cattle tissues and milk are summarized below.

Dietary burden mg/kg Feeding level [mg/kg]	Dicamba and DCSA residues, mg/kg				
	Milk	Muscle	Liver	Kidney	Fat
MRL	highest	highest	highest	highest	highest
140.0	0.071	0.016	0.082	0.331	0.036
[120/400]	[0.06/0.31]	[0.014/0.037]	[0.072/ 0.207]	[0.288/ 0.885]	[0.034/0.059]
STMR	mean	mean	mean	mean	mean
44.0	0.021	0.010	0.028	0.160	0.023
[40/120]	[0.02/0.04]	[< 0.01/0.012]	[0.026/0.066]	[0.154/0.282]	[0.023/0.025]

The Meeting estimated a maximum residue level for dicamba and DCSA in milks, mammalian meat, liver, kidney and fat at 0.2, 0.03, 0.2, 0.7 and 0.07 mg/kg. Based on the maximum residue levels for liver and kidney, the Meeting agreed to recommend a maximum residue level of 0.7 mg/kg for edible offal (mammalian).

STMRs were estimated to be 0.021, 0.010, 0.028 0.160 and 0.023 mg/kg for milks, mammalian meat, liver, kidney and fat. HRs were estimated to be 0.016, 0.082, 0.331 and 0.036 mg/kg for mammalian meat, liver, kidney and fat.

Residues in eggs and poultry tissues

Laying hens were fed with dicamba at a rate equivalent to 2, 6 and 20 ppm in the diet for 28 consecutive days. Tissues from the 2 and 6 ppm group, no residues above 0.01 mg/kg were observed except in liver up to 0.023 mg/kg of residues were found. In the 20 ppm dose group, up to 0.068 mg/kg of residues were found in liver, fat, skin and breast muscle. The residue concentration was lower in muscle than in other tissues.

Residues in pooled egg samples were < 0.01 mg/kg.

Using the dietary burdens for poultry broiler and layer and the results in the laying hen feeding study, the maximum residue levels and STMRs were estimated. The calculated residues in cattle tissues and milk are summarized below.

Dietary burden mg/kg Feeding level [mg/kg]	Dicamba residues, mg/kg			
	Eggs	Muscle	Liver	Fat
MRL	highest	highest	highest	highest
15.6	< 0.01	0.012	0.044	0.020
[6/20]	[< 0.01/< 0.01]	[< 0.01/0.013]	[0.023/0.053]	[< 0.01/0.025]
STMR	Mean	Mean	Mean	mean

Dietary burden mg/kg Feeding level [mg/kg]	Dicamba residues, mg/kg			
	Eggs	Muscle	Liver	Fat
6	< 0.01	< 0.01	< 0.01	< 0.01
[6]	[< 0.01]	[< 0.01]	[< 0.01]	[< 0.01]

The Meeting estimated a maximum residue level for dicamba and DCSA in eggs, poultry meat, liver and fat at 0.01*, 0.02, 0.07 and 0.04 mg/kg. Based on the maximum residue level for liver, the Meeting recommended a maximum residue level of 0.07 mg/kg for edible offal of poultry.

STMRs were estimated to be 0.01, 0.01, 0.01 and 0.01 mg/kg for eggs, poultry meat, liver and fat. HRs were estimated to be 0.01, 0.012, 0.044 and 0.01 mg/kg for these commodities.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) of dicamba were calculated for the 13 GEMS/Food cluster diets using STMRs and STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.3 mg/kg bw and the calculated IEDIs were 0–1% of the maximum ADI. The Meeting concluded that the long-term intake of residues of dicamba resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intakes (IESTI) of dicamba were calculated for food commodities and their processed commodities using HRs/HR-Ps or STMRs/STMR-Ps estimated by the current Meeting (Annex 4). The ARfD is 0.5 mg/kg and the calculated IESTIs were 0–4% of the ARfD for the general population and 0–9% of the ARfD for children. The Meeting concluded that the short-term intake of residues of dicamba, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.

5.10 DIFENOCONAZOLE (224)

RESIDUE AND ANALYTICAL ASPECTS

Difenoconazole was evaluated by the JMPR for the first time in 2007 when an ADI of 0–0.01 mg/kg bw and an ARfD of 0.3 mg/kg bw were established, and maximum, supervised trial median and high residue levels were recommended for a range of commodities. Additional studies on residues in banana, passion fruits, beans with pods, papaya, ginseng and almonds were evaluated by the present Meeting.

Methods of analysis

The analytical methods used for the determination of difenoconazole residues in samples derived from supervised trials, submitted for evaluation to the present Meeting, had already been considered by the 2007 JMPR. These methods are based on GC separation and pulse flame photometric detection (PFPD), ECD or MS detection. The validity of the results was supported by validation data on representative crops and results of concurrent recovery studies.

Fresh ginseng root and ginseng processed products were extracted with acetonitrile, partitioned either with dichloromethane or n-hexane, cleaned up on Florisil or silica gel column, and determined applying capillary column GC and ECD. The methods were validated before the analysis of the samples. Additional recovery studies were performed at the same time when the treated or processed samples were analysed. The average recoveries based on minimum 5 replicates ranged between 89 and 105% with repeatability of ≤ 7.4%. The limits of quantification were between 0.002–0.007 mg/kg for fresh ginseng root, and 0.007–0.04 for various ginseng products.

The freezer storage stability studies carried out with fresh ginseng and ginseng processed products showed that the residue was stable for the longest period (135 days) for which the samples were stored at or below -20 ºC. The studies reported by the 2007 JMPR cover the other sample materials evaluated by the present Meeting.

Results of supervised trials on crops

The original labels with translation were provided only for the countries where the trials had been carried out.

The reports on supervised trials were made available for the Meeting. Some of the trials had not been conducted according to GLP. However, the documentation of the trials was sufficient for evaluation of the results.

Banana

A national use pattern in China permits a foliar application of difenoconazole EC 25 (250 g/L) on bananas at a dilution rate of 2000 to 3000 which equates to spray solution concentrations of 8.33 to 12.5 g ai/hL with a PHI of 42 days. Multiple applications are permitted with a maximum of three treatments at 10-day intervals.

Difenoconazole formulated as a 250 g/L EC was applied to banana plants (four trials) as a foliar application 3 or 4 times at the maximum GAP rate of 12.5 g ai/hL (2000× dilution) and 3 or 4 times at a spray rate of 25 g ai/hL (double rate) in China. Samples were taken at 35 and 42 days. According to the typical practice in China, the applications were performed by spraying, from the ground using manual knapsack or mechanised equipment, directly upwards to the banana plants.

The difenoconazole residues in whole fruit samples treated according to the maximum GAP rate, in ranked order, were: 0.12, 0.18, 0.33 and 0.41 mg/kg.

Residues from 4 treatments at 12.5 g ai/hL rate were: 0.25, 0.29, 0.3, and 0.47 mg/kg. The residues from 3 or 4 treatments were not significantly different indicating that the first treatment made at least 82 days before sampling did not influence the final residue level. The trials performed with 3 and 4 applications were conducted side-by–side, therefore they are not independent and the results cannot be combined.

The residues in banana pulp derived from the same trials were substantially lower. For the 3 application trials the residues were: 0.045, 0.051, 0.052, and 0.11 mg/kg.

No correlation between the residue in pulp and whole banana could be established based on the results.

The 2007 JMPR evaluated residue data derived from ground and aerial treatments carried out with much lower dosage rate (GAP 8 × 0.1 kg/ha, PHI 0 day) than the Chinese trials, and resulted in lower residue values: < 0.02 (6), 0.02, 0.03, 0.04, 0.06, 0.07 and 0.13 mg/kg.

The two residue populations are significantly different and could not be combined.

The Meeting concluded that four residue trials, reflecting the Chinese GAP and growing conditions, was not sufficient for the estimation of residue levels.

Papaya

To protect fruits from pests and diseases a 3-day PHI is required during harvesting period for continuously fruiting crops like papaya in the Equatorial countries of Africa.

As part of the field trials conducted within the Pesticide Initiative Programme, aiming to provide data for the establishment of import tolerance in the European Union, difenoconazole was applied 6 times during the growing season at 60 g ai/ha at about 14-day intervals at two sites in Côte d'Ivoire. The application conditions (dosage, interval between applications and PHI) were based on the requirement to achieve adequate control of papaya diseases, but were not supported by a label or official declaration of approved use. Samples were collected at 3 and 7 days after the last three applications. The residues measured in samples taken at day 3 were: < 0.05, 0.05, 0.06, 0.07, 0.12 and 0.13 mg/kg.

Residues in samples taken 7 days after the last treatment were: < 0.05, < 0.05, < 0.05; 0.06, < 0.05 and 0.10 mg/kg.

Taking into account the rapid decrease of residues it is most likely that only the last application affects the residue levels in fruits. The residues taken from the same site after repeated treatments can be considered independent.

Based on the 3-day PHI and 0.06 kg ai/ha application rate which provided efficient control of diseases to protect the crop, the Meeting estimated a maximum residue level, STMR and HR values of 0.3, 0.065 and 0.13 mg/kg, respectively.

Passion fruit

A national use pattern in Brazil permits up to four foliar applications of difenoconazole EC 25 (250 g/L) on passion fruit at a rate of 5 g ai/hL or between 0.01 and 0.04 kg ai/ha with a PHI of 14 days.

In four Brazilian trials the applications were performed within GAP (1 treatment with −25% dosage rate) and the samples taken at 7 days after the treatment contained residues below the LOQ of 0.01 mg/kg with one exception (0.04 mg/kg).

Where the trials were conducted at 2.5–5 times maximum GAP rate the residues in all samples taken at 7 or 14 days were below the limit of quantification (0.01–0.05 mg/kg).

The difenoconazole residues in whole fruit collected at 7 or 14 days PHI were, in ranked order: < 0.01 (6), < 0.02 (2), 0.04, < 0.05 (2) mg/kg.

Taking into account that up to 5 times GAP dose rate did not lead to residues at or above 0.05 mg/kg at shorter intervals than the recommended PHI, the Meeting estimated a maximum residue level, an STMR value and HR value of 0.05, 0.01 and 0.04 mg/kg, respectively.

Legume vegetables

National use pattern in Portugal permits 2 foliar applications of difenoconazole EC 25 (250 g/L) at 12 to 14 days intervals on beans at a rate of 0.125 kg ai/ha with a PHI of 7 days. Eight trials in beans and one in peas were conducted in Italy and South France.

The results were evaluated against the Portugal GAP. The difenoconazole residues in beans or peas with pods were, in ranked order: 0.01, 0.03, 0.04, 0.05, 0.07, 0.09, 0.17, 0.31 and 0.50 mg/kg.

The Meeting estimated a maximum residue level, STMR value and an HR value for difenoconazole in beans and peas of 0.7, 0.07 and 0.5 mg/kg, respectively.

Ginseng

The GAP in Korea permits 4 or 5 foliar applications at 10 day intervals with 0.027 kg ai/hL or 0.053 kg ai/hL spray concentration and 7 or 14 days PHI, respectively.

Ready to harvest ginseng plantations of 4–6 years old were treated with difenoconazole EC formulation (0.053 kg ai/hL) 4 times at 10-day intervals in three typical ginseng growing areas in the Republic of Korea.

Three root samples were collected 14 days after the last application from each field. The residues in fresh ginseng root were: 0.0063, 0.011, < 0.02 (3), 0.038, 0.04, 0.10, and 0.36 mg/kg.

The Meeting estimated a maximum residue level, HR and STMR of 0.5 mg/kg, 0.36 mg/kg and 0.02 mg/kg, respectively.

Tree nuts

The US GAP permits up to two foliar applications of difenoconazole EC 250 (232 g/L) on almonds at a rate of 91 to 128 g ai/ha with a PHI of 14 days.

Six trials were conducted with four foliar applications at a rate of 127 g ai/ha. Samples of mature almond were collected at 14 days after the last application. Residues in all almond nutmeat samples were below the limit of quantification (0.01 mg/kg).

The US GAP permits up to two foliar applications of difenoconazole EC 250 (232 g/L) on pecans s at a rate of 91 to 128 g ai/ha with a PHI of 14 days.

Trials were conducted with four applications at a rate of 0.129 kg ai/ha. Residues in 6 pecan nutmeat samples were < 0.01 (5) and 0.02 mg/kg.

Based on the mutually supporting residue data, the Meeting estimated a maximum residue level, STMR value and an HR value for difenoconazole in tree nuts of 0.03, 0.01 and 0.02 mg/kg, respectively.

Animal feed

Beans and peas forage

Residues in bean forage following the treatments according to GAP (2 × 0.125 kg/ha, PHI 7 days) were: 0.28, 0.31, 0.75, 0.76, and 0.85 mg/kg.

The Meeting estimated an STMR value and high residue for difenoconazole in bean forage 0.75 and 0.85 mg/kg, respectively.

Almond hulls

The residues in almond hulls derived from trials complying with the total seasonal rate as specified by US GAP (0.51 kg/ha) in ranked order, were: 0.53, 0.83, 1.04, 1.44, 1.93 and 3.22 mg/kg.

The Meeting estimated a maximum reside level, an STMR value and high residue for difenoconazole in almond hulls of 6, 1.24 and 3.22 mg/kg, respectively. Estimated derived from use of the NAFTA and OECD calculators was 6 mg/kg.

Fate of residues during processing

Fresh ginseng roots were dried or extracted with ethanol to produce powdery material. The processing was carried out independently from samples obtained from three plots treated at each of the three different sites. The average processing factors were calculated from the results obtained from the three replicate plots. The best estimate for the processing factor for dried ginseng is 3.28. The ethanol extract of dried ginseng resulted in a wide range of processing factors (2.7–18.44) which made the obtaining of a single best estimate impossible. The apparent numerical processing factor for the water extract is 2. However, this estimate is very uncertain as it is based on the LOQ values of processed and fresh ginseng. In one study where the LOQ value was sufficiently low the results indicated a processing factor of 1.1

Consequently the Meeting could only estimate a processing factor of 3.3 for dried ginseng.

Residues in animal commodities

The 2007 JMPR evaluated two animal transfer studies carried out with Holstein dairy cows administering difenoconazole at 1 ppm (1×), 3 ppm (3×), 5 ppm (5×), 10 ppm (10×) and 15 ppm (15×) in the dry-weight diet for 29–30 consecutive days. The Meeting concluded that the two feeding studies were generally in good agreement of transfer factors, and decided to use the study with the 1 and 3 ppm feeding levels as most closely bracketing the dietary burdens.

Livestock dietary burden

The residues in almond hull and bean forage evaluated by the present Meeting contributed substantially to the beef and dairy cattle dietary burden calculation based on the maximum portion of agricultural commodities in animal feed (FAO, 2009). Dietary burden calculations for beef cattle, and dairy cattle are provided in Annex 6. The Japanese animal diet contained only soya bean seed of those commodities for which the JMPR estimated highest and median residues. The residues in soya been seed resulted in an animal dietary burden of 0.00 ppm on dry matter bases, therefore those values are not included in the summary below.

	Livestock dietary burden, difenoconazole, ppm of dry matter diet					
	US/CAN		EU		Australia	
	max	mean	max	mean	max	mean
Beef cattle	0.62	0.48	1.85	0.81	2.0	1.77 [b]
Dairy cattle	0.80	0.31	2.42 [a]	1.15	2.14	1.82 [c]

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat and milk.

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

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

Animal commodities, MRL estimation

For MRL estimation, the residues in the animal commodities are the sum of difenoconazole and CGA 205375 (1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanol)) expressed as difenoconazole.

Cattle

For maximum residue level estimation, the high residues in the tissues were calculated by interpolating the maximum dietary burden of 2.42 ppm (in 2007 it was 2.10 ppm) between the relevant feeding levels (1 and 3 ppm) from the dairy cow feeding study and using the highest tissue concentrations from individual animals within those feeding groups.

The STMR values for the tissues were calculated by taking the STMR dietary burden (1.82 ppm) between the relevant feeding levels (1 and 3 ppm) from the dairy cow feeding study and using mean residue of the 3 animals.

In the following table, 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]	Milk	Muscle	Liver	Kidney	Fat
MRL					
MRL dairy cattle (2.42) [1, 3]	Mean < 0.005 [< 0.005, < 0.005]	highest 0.021 [< 0.01, 0.026]	highest 0.121 [0.051, 0.15]	highest 0.0178 [< 0.01, 0.021]	highest 0.031 [0.015, 0.038]
STMR					
STMR dairy cattle (1.82) [0, 1, 3]	Mean < 0.005 [0, < 0.005, < 0.005)]	mean < 0.01 [0, < 0.01]	mean 0.041 [0, 0.045]	mean < 0.01 [0, < 0.01]	mean 0.012 [0, 0.013]

The data from the cattle feeding studies were used to support mammalian meat and milk maximum residue levels.

Residues in the milk were below LOQ (0.005 mg/kg) for all samples from the 1 ppm and 3 ppm feeding groups, so the dietary burdens (2.42 and 1.82 ppm) were taken as a proportion of the 3 ppm to calculate the residues resulting from the dietary burdens.

For muscle, the residue arising from a dietary burden of 2.42 ppm was 0.021 mg/kg, while the residue resulting from a dietary burden of 1.82 ppm was < 0.01 mg/kg. For fat, the residue arising from a dietary burden of 2.42 ppm was 0.031 mg/kg, while the residue resulting from a dietary burden of 1.82 ppm was 0.012 mg/kg.

The Meeting confirmed its previous recommendation for a maximum residue level for difenoconazole in mammalian meat (fat) of 0.05 mg/kg. The Meeting estimated STMR and HR values for meat (fat) of 0.012 and 0.031 mg/kg respectively. The Meeting estimated STMR and HR values for meat (muscle) of 0.01 and 0.021 mg/kg respectively.

The residues in milk were below the limit of quantification at 1 and 3 ppm feeding level. The Meeting estimated a maximum residue level of 0.005* mg/kg and STMR value of 0.005 mg/kg for milk.

For liver, the residue arising from a dietary burden of 2.42 ppm was 0.121 mg/kg, while the residue resulting from a dietary burden of 1.82 ppm was 0.041 mg/kg. The Meeting confirmed its

recommendation for a maximum residue level of 0.2 mg/kg, and estimated an STMR value and an HR value for difenoconazole in liver of 0.041 and 0.12 mg/kg, respectively.

For kidney, the residue arising from a dietary burden of 2.42 ppm was 0.018 mg/kg, while the residue resulting from a dietary burden of 1.82 ppm was < 0.01 mg/kg. Although the residue levels in kidney were somewhat below those in liver, the Meeting decided that it was preferable to have an animal offal MRL which would be supported by the liver data.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in mammalian edible offal of 0.2, 0.041 and 0.12 mg/kg, respectively.

The Meeting withdrew its previous recommendations for STMR values of 0.043 mg/kg and HR values of 0.11 mg/kg for edible offal (mammalian), and HR values of 0.019 for meat (muscle) and 0.028 mg/kg meat (fat).

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of difenoconazole resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the thirteen Cluster Diets, based on estimated STMRs were 1–10% of the maximum ADI (0.01 mg/kg bw). The Meeting concluded that the long-term intake of residues of difenoconazole from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The IESTI of difenoconazole calculated on the basis of the recommendations made by the JMPR represented 0–3 % of the maximum ARfD (0.3 mg/kg bw) for children and 0–2 % for the general population.

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

5.11 DITHIANON (180)

TOXICOLOGY

Dithianon ($C_{14}H_4N_2O_2S_2$) is the International Organization for Standardization (ISO)–approved name for 5,10-dihydro-5,10-dioxonaphtho[2,3-b]-1,4-dithiine-2,3-dicarbonitrile (International Union of Pure and Applied Chemistry [IUPAC]), with Chemical Abstracts Service (CAS) No. 3347-22-6. Dithianon is used on a range of fruits and vegetables as a multi-site contact fungicide that inhibits spore germination.

Dithianon was evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1992, when an acceptable daily intake (ADI) of 0–0.01 mg/kg body weight (bw) was established. It is being reviewed at the present Meeting as part of the periodic re-evaluation programme of the Codex Committee on Pesticide Residues (CCPR). All the pivotal studies met the basic requirement of the relevant guideline and contained certificates of compliance with good laboratory practice (GLP) or quality assurance.

Biochemical aspects

At tested doses of 10 and 50 mg/kg bw, orally administered dithianon was about 40–50% absorbed in rats, with a time to maximum concentration in blood of approximately 6 h. There were no substantial dose- or sex-related differences in the absorption, elimination or distribution of radioactivity following oral administration of [^{14}C]dithianon. The majority of the administered dose was recovered in faeces (64.0–72.2%) and urine (26.7–31.4%).

The material balance from a preliminary study showed that dithianon was not metabolized to volatile compounds, including carbon dioxide. The elimination half-life was between 46 and 57 h. There was no bioaccumulation of dithianon in tissues. The parent compound was extensively metabolized by the following key transformation steps: oxidation of the sulfur atoms, cleavage of the dithiine ring, reduction of the 1,4-naphthoquinone moiety and further glucuronidation, as well as substitution of the carbonitrile moieties by amino and carboxy groups. The only metabolite in rat urine at a level greater than 2% was M216F020 (glucuronic acid conjugate of 1,4-dihydroxynaphthalene). All other identified metabolites were present in insignificant amounts. The metabolic pathways were similar in male and female rats.

Toxicological data

Dithianon technical has moderate acute toxicity in rats (oral median lethal dose [LD_{50}] approximately 300 mg/kg bw). The dermal LD_{50} in rats was greater than 2000 mg/kg bw. Dithianon is slightly to moderately toxic by acute inhalation in rats, with a median lethal concentration (LC_{50}) between 0.31 and 2.1 mg/L, depending on particle size. Dithianon is non-irritating to rabbit skin but is a severe eye irritant. It was found to be a skin sensitizer (guinea-pig maximization test).

Short-term oral toxicity studies were conducted in mice, rats and dogs. These studies indicate that the kidney is the main target organ. A 4-week (range-finding) study in mice with dithianon administered in the diet resulted in slight anaemia and haemosiderin deposition in the liver of females at 500 ppm, with a no-observed-adverse-effect level (NOAEL) of 100 ppm (equivalent to 15 mg/kg bw per day). A 90-day rat oral toxicity study revealed slight anaemia (both sexes) as well as histopathological findings of renal tubular epithelial cell degeneration and regenerative hyperplasia (females only) at 1080 ppm, with a NOAEL of 180 ppm (equal to 14.6 mg/kg bw per day).

Studies in dogs included a 90-day dietary study and a 1-year dietary study. In the 90-day study, the doses used were 0, 40, 200 and 1000 ppm (equal to 0, 0.63, 2.95 and 12.6 mg/kg bw per day). In the 1-year study, the same dietary doses were used, but the compound intakes were 0, 1.6, 7.3 and 37.1 mg/kg bw per day. In the 90-day study, the NOAEL was 2.95 mg/kg bw per day, based on

decreases in body weight (females), decreased body weight gain (males), decreased food consumption, increases in alkaline phosphatase activity and increased kidney weights (males and females) and increased thromboplastin time (females) at 12.6 mg/kg bw per day. Oral administration of dithianon for 1 year resulted in slight anaemia, liver impairment and effects on kidney and thyroid. The NOAEL for dithianon fed to dogs in their diets for 1 year was 200 ppm (equal to 7.3 mg/kg bw per day), based on increases in kidney and liver weights in both sexes at 1000 ppm (equal to 37.1 mg/kg bw per day).

Long-term toxicity and carcinogenicity studies were undertaken in mice (80 weeks) and rats (104 weeks). In male mice at 500 ppm in the diet, there was an association between the observed kidney damage (chronic nephropathy) and an increased incidence of early mortality, indicating that the maximum tolerated dose (MTD) was exceeded at 500 ppm. No increases in tumour incidence were noted in any of the treatment groups. The NOAEL for chronic toxicity in mice was 20 ppm (equivalent to 3 mg/kg bw per day), based on increased absolute and relative kidney weights for males and females and an exacerbation of spontaneous chronic nephropathy in females at 100 ppm. Dithianon was not carcinogenic in mice at a dietary concentration of 500 ppm, the highest dose tested. In the rat study, the NOAEL for chronic toxicity was 20 ppm (equivalent to 1 mg/kg bw per day), based on histopathological kidney lesions (females) at 120 ppm. Increased incidences of renal tubule adenomas and carcinomas in kidney were observed in female rats at 600 ppm (equivalent to 30 mg/kg bw per day). The highest dietary concentration (600 ppm) also resulted in a consistently significant lower body weight (19.8–20.5%) in female rats compared with controls at weeks 72, 84 and 104. Moreover, only the highest dose (i.e., 600 ppm) in female rats demonstrated severe glomerulonephropathy with sclerosis. The tumours in rat kidneys were associated with severe nephrotoxicity in proximal tubular cells. This dose exceeded the MTD in females.

In a 7-day dietary study in rats, hydropic degeneration of the proximal tubular epithelial cells was seen in both males and females receiving 600 ppm (equivalent to 60 mg/kg bw per day) or 1080 ppm (equivalent to 108 mg/kg bw per day) at 4 and 7 days, with significantly greater incidence and severity in females. In females at day 7, the newly regenerated tubular epithelial cells with signs of hydropic degeneration demonstrated the susceptibility of renal tubules to damage. In contrast, males showed no evidence of further degeneration, suggesting adaptation to the toxic effects by day 7. Electron microscopy suggested that the mitochondria in the proximal tubular cells were the target. The NOAEL for this study was 120 ppm (equivalent to 12 mg/kg bw per day) in females.

These findings were further substantiated by a 28-day dietary renal turnover study in female rats. Continuous labelling techniques using bromodeoxyuridine (BrdU) showed an increase in tubular cell turnover at 600 ppm (equivalent to 60 mg/kg bw per day), consistent with the histopathological results. The NOAEL for the repeated cellular degenerative/regenerative responses was 120 ppm (equivalent to 12 mg/kg bw per day). It appears that persistent cellular damage to proximal tubular epithelial cells triggers a regenerative response in basophilic tubules, which is the basis for the development of proliferative lesions following long-term (2-year) dietary exposure of female rats to 600 ppm. Neither the degenerative/regenerative (cell turnover) responses nor renal tumours (in the carcinogenicity study) were observed at concentrations of 20 or 120 ppm. The high susceptibility of female rats to renal effects (proximal tubular degeneration, regeneration and tumours) might be related to the involvement of cyclooxygenase-2 (COX-2), but experimental evidence for this as an explanation for the sex difference is not available.

Dithianon was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. The majority of results were negative, including in vivo studies. There were some positive results in vitro that occurred only at cytotoxic doses.

The Meeting concluded that dithianon is unlikely to be genotoxic in vivo.

In view of the lack of in vivo genotoxicity, the lack of any tumorigenic response in mice and male rats and the fact that the kidney tumours in female rats occurred only at doses that were cytotoxic, the Meeting concluded that dithianon is unlikely to pose a carcinogenic risk at human dietary exposure levels.

In a multigeneration study in rats, the NOAEL for fertility and reproductive functions was 600 ppm (equal to 27.6 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity was 200 ppm (equal to 9 mg/kg bw per day), based on reductions in food consumption and body weight gain in parental animals of both generations at 600 ppm.

Developmental toxicity studies have been carried out in rats and rabbits. In a rat developmental study, the NOAEL for maternal toxicity and embryo and fetal toxicity was 20 mg/kg bw per day, based on decreases in body weight gain and food consumption in the dams and increased number of resorptions and a subsequent reduction in the mean number of fetuses per dam at 50 mg/kg bw per day and above. In a rabbit developmental toxicity study, the NOAEL for maternal toxicity was 10 mg/kg bw per day, based on reductions in body weight gain and food consumption at 25 mg/kg bw per day. The NOAEL for developmental effects was 25 mg/kg bw per day, based on an increased incidence of post-implantation loss resulting from an increase in abortions and resorptions and a subsequent reduction in the mean number of fetuses per doe at 40 mg/kg bw per day. There were no developmental effects in the absence of maternal toxicity.

The Meeting concluded that dithianon did not cause developmental toxicity at doses that were not toxic to the dams and that it was not teratogenic.

In a 4-week neurotoxicity study in rats, a NOAEL of 15 mg/kg bw per day was identified based on clinical observations of smeared anogenital region with urine and dark discoloured urine at 30 mg/kg bw per day. There were no signs of neurotoxicity in any other study.

Skin and eye irritation have been repeatedly observed in dithianon-exposed workers. In operators spraying dithianon-containing products, erythema, swelling, itching, blistering and peeling of the skin have been reported.

The Meeting concluded that the existing database on dithianon was adequate to characterize the potential for hazard to fetuses, infants and children.

Toxicological evaluation

The Meeting reaffirmed the ADI of 0–0.01 mg/kg bw for dithianon based on a NOAEL of 1 mg/kg bw per day for histopathological kidney lesions in females at 6 mg/kg bw per day in a 2-year toxicity study of rats and using a 100-fold safety factor.

The Meeting established an acute reference dose (ARfD) of 0.1 mg/kg bw for dithianon, taking into account a NOAEL of 12 mg/kg bw and using a safety factor of 100. The NOAEL was based on a mechanistic study in which nephrotoxicity was assessed in rats following 4 and 7 days of dosing. At these time points, a dietary intake of 60 mg/kg bw per day of dithianon induced repeated cellular degenerative/regenerative responses in kidney tubular cells of female rats.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighty-week study of toxicity and carcinogenicity[a]	Toxicity	20 ppm, equivalent to 3 mg/kg bw per day	100 ppm, equivalent to 15 mg/kg bw per day
		Carcinogenicity	500 ppm, equivalent to 75 mg/kg bw per day[b]	—
Rat	Seven-day study of toxicity[a]	Nephrotoxicity	120 ppm, equivalent to 12 mg/kg bw per day	600 ppm, equivalent to 60 mg/kg bw per day
	Ninety-day study of	Toxicity	180 ppm, equal to 14.6	1080 ppm, equal to 86.7

Species	Study	Effect	NOAEL	LOAEL
	toxicity[a]		mg/kg bw per day	mg/kg bw per day
	Twenty-four-month study of toxicity and carcinogenicity[a]	Toxicity	20 ppm, equivalent to 1 mg/kg bw per day	120 ppm, equivalent to 6 mg/kg bw per day
		Carcinogenicity	120 ppm, equivalent to 6 mg/kg bw per day	600 ppm, equivalent to 30 mg/kg bw per day
	Two-generation study of reproductive toxicity[a]	Offspring	600 ppm, equal to 27.6 mg/kg bw per day[b]	—
		Parental toxicity	200 ppm, equal to 9 mg/kg bw per day	600 ppm, equal to 27.6 mg/kg bw per day
Rabbit	Developmental toxicity study[c]	Maternal toxicity	10 mg/kg bw per day	25 mg/kg bw per day
		Embryo and fetal toxicity	25 mg/kg bw per day	40 mg/kg bw per day
Dog	Twelve-month study of toxicity[a]	Toxicity	200 ppm, equal to 7.3 mg/kg bw per day	1000 ppm, equal to 37.1 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.1 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	T_{max} approximately 6 h, 42–52% absorbed
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Excreted in faeces (64.0–72.2%) and urine (26.7–31.4%)
	Half-life 46–57 h
Metabolism in animals	Extensive
Toxicologically significant compounds in animals, plants and the environment	Dithianon
Acute toxicity	
Rat, LD_{50}, oral	300 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw

Rat, LC_{50}, inhalation	0.31 mg/L
Rabbit, dermal irritation	Non-irritant
Rabbit, ocular irritation	Severely irritant
Guinea-pig, dermal sensitization	Sensitizer (Magnusson and Kligman test)
Short-term studies of toxicity	
Target/critical effect	Kidney, tubular damage
Lowest relevant oral NOAEL	12 mg/kg bw per day (7-day study in rats)
	7.3 mg/kg bw per day (1-year study in dogs)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Kidney, tubular damage
Lowest relevant NOAEL	1 mg/kg bw per day (24-month study in rats)
Carcinogenicity	Only in kidneys of female rats at cytotoxic doses
Genotoxicity	
	Not genotoxic in vivo
Reproductive toxicity	
Reproduction target/critical effect	None
Lowest relevant reproductive NOAEL	27.6 mg/kg bw per day, the highest dose tested, in rats
Developmental target/critical effect	Increase in post-implantation loss in the presence of maternal toxicity; not teratogenic
Lowest relevant developmental NOAEL	25 mg/kg bw per day in rabbits
Neurotoxicity/delayed neurotoxicity	
	Not neurotoxic
Other toxicological studies	
	Mechanistic studies on kidney toxicity
Medical data	
	Local skin and eye irritation effects in exposed plant workers and operators

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.01 mg/kg bw	Two-year dietary toxicity study in rats	100
ARfD	0.1 mg/kg bw	Four/seven-day nephrotoxicity study in rats	100

5.12 ENDOSULFAN (032)

RESIDUE AND ANALYTICAL ASPECTS

Endosulfan is a synthetic cyclodiene non-systemic insecticide and acaricide with both contact and stomach activity. It is has been widely used in agriculture to control a range of insects and mites on a broad spectrum of crops. It has been evaluated several times by the JMPR; the initial evaluation for residues was in 1967 and the latest in 2006. Under the CCPR Periodic Review Programme the toxicology was re-evaluated in 1998. The Meeting established an ADI of 0–0.006 mg/kg bw and an acute reference dose (ARfD) of 0.02 mg/kg bw. In 2006, a Periodic Review of the residue-analytical aspects was completed.

In the 2006 review, the Meeting was not able to recommend a maximum residue level for tea, as trials from India could not be matched against the provided GAPs from China, Japan or Malaysia. At the Thirty-ninth Session of CCPR in 2007, on the proposal of the delegations of China and India the CXL for tea (green, black) was retained for four years under the Periodic Review Programme. The Forty-first Session of CCPR in 2009 scheduled the review of data on tea from China by the 2010 JMPR. GAP for tea in China and new trials in tea performed over several years (2004–2007) were submitted by the Government of China.

Methods of analysis

The Meeting received a description and validation data of a GC-ECD analytical method for residues of total endosulfan (alpha endosulfan, beta endosulfan and endosulfan sulphate) in fresh leaves of tea. in made tea, and in tea infusions. The recoveries of the method for endosulfan (total residue) are satisfactorily over a range of 0.01–50 mg/kg in made tea.

Results of supervised trials on tea

The present Meeting received 17 decay trials and 30 residue trials (2-point decline) on tea, green and black, which were performed over a period of four years in four different provinces within China. GAP in China is one treatment at an application rate of 0.668 kg ai/ha (0.089 kg ai/hL, 750 L water/ha) with a pre-harvest interval of 7 days.

Ten of the decay trials were at GAP. Total endosulfan residue levels in ‘made tea’, were, in ranked order: 2.0 (2), 2.3, 2.5, 2.5, 3.2, 3.4, 4.1, 4.2 and 4.3 mg/kg.

Seven of the 2-point decline trials were at GAP. Total endosulfan residue levels in ‘made tea’, in ranked order, were: 1.9, 2.2, 4.1(2), 4.3(2), 4.7 mg/kg. Since the decay trials and the decline trials appear not to be independent, the Meeting decided to estimate a maximum residue level based on the data set yielding the highest STMR, the terminal residue trials.

The Meeting estimated a maximum residue level of 10 mg/kg for ‘made tea’, and an STMR of 4.1 mg/kg.

The maximum residue level estimate derived from use of the NAFTA calculator was 6 mg/kg.

Fate of residues during processing

The Meeting received information on the extraction rate of endosulfan residue during tea infusion. Tea infusions were prepared by adding boiling water to dried and processed tea leaves (‘made tea’) and allowed to stand for 20 minutes. This was repeated twice. The infusion was filtered and the % infusion (% of residue extracted in the boiling water) was calculated. This was done 4× for Hangzhou Green Tea, 4× for Fujian Oolong Tea, 3× for Hunan Black Tea, 4× for Anhui Baked Tea. After 3

infusions for endosulfan (total residue) the mean %infusion (or extraction rate) was 8.3%, range 7.1–9.7%, n = 15.

The Meeting estimated an STMR-P in tea infusion of 0.34 mg/kg.

Residues in animal commodities

Since tea is not an animal feed item, the recommendations for animal commodities as made by the 2006 Meeting are still valid.

DIETARY RISK ASSESSMENT

Long-term intake

In 2006 the Meeting concluded that the long term intake of residues of endosulfan from uses that have been considered by the JMPR is unlikely to present a public health concern. The IEDI in the thirteen GEMS/Food regional diets, on the basis of the estimated STMRs, represented 2–20% of the maximum ADI of 0.006 mg/kg bw.

Due to the low contribution of tea in the entire diet, no revision of the chronic dietary exposure assessment has been carried out.

Short-term intake

In the 2006 evaluation no short-term intake for tea was calculated.

Based on the STMR-P of 0.34 mg/kg for tea (green, black), the short-term intake for both children ≤ 6 years and for the general population represented 1% of the ARfD. The Meeting concluded that the short-term intake of endosulfan from its use on tea (green, black) was unlikely to present a public health concern.

5.13 ETOXAZOLE (241)

TOXICOLOGY

Etoxazole is the International Organization for Standardization (ISO)–approved name for (*RS*)-5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazol-4-yl]phenetole (International Union of Pure and Applied Chemistry [IUPAC]), with Chemical Abstracts Service (CAS) No. 153233-91-1. Etoxazole is a new acaricide that belongs to the diphenyloxazole class of miticides/ovicides, possibly acting by inhibiting chitin biosynthesis and causing adults to lay sterile eggs. Etoxazole has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed at the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR).

All the pivotal studies contained certificates of compliance with good laboratory practice (GLP).

Biochemical aspects

The absorption, distribution, metabolism and excretion of etoxazole were investigated in rats. ^{14}C-labelled etoxazole was rapidly but only moderately absorbed from the gastrointestinal tract of rats following oral dosing. Maximum concentrations of radioactivity in plasma were observed within 2–4 h of dosing for the low dose group (5 mg/kg body weight [bw]) and within 4–6 h for the high dose group (500 mg/kg bw). At the low dose, the degree of absorption in males (50–54%) was less than that in females (63–70%), but there were no major sex-related differences in the pattern of excretion. Saturation of absorption occurred at a high dose (500 mg/kg bw per day), with less than 30% absorbed. Faecal excretion was the primary route of elimination, and excretion was essentially complete within 120 h after dosing. Very little etoxazole was retained in the tissues. By 168 h post-dose, concentrations of radioactivity remaining in liver, thyroid and fat of rats were 3.9–7.8 times higher in the repeated-dose experiment than in the same tissues from the single-dose group.

The parent compound was the major component in the faeces, at 17.8–29.1% in the low dose groups and 74.7–80.2% in the high dose groups. Based on the analyses of excreta, bile and liver, the biotransformation of etoxazole in rats primarily involves the hydroxylation of the 4,5-dihydrooxazole ring, followed by cleavage of the metabolite and hydroxylation of the *tert*-butyl side-chain.

Toxicological data

Etoxazole had low acute toxicity in rats, causing no mortality at the limit dose after oral (median lethal dose [LD_{50}] > 5000 mg/kg bw), dermal (LD_{50} > 2000 mg/kg bw) or inhalation (median lethal concentration [LC_{50}] > 1.09 mg/L air, highest attainable concentration) exposure. Etoxazole was not irritating to the skin or eyes of rabbits and not sensitizing under the conditions of the Magnusson and Kligman maximization test in guinea-pigs.

Following repeated dietary dosing, the liver was the main target organ in mice, rats and dogs. Hepatotoxicity was manifest as increased liver weight, liver enlargement and centrilobular hepatocellular hypertrophy, as well as alterations in clinical chemistry (elevated serum levels of liver enzymes, cholesterol, triglycerides and protein). In several studies, effects on the liver were mild and considered to be non-adverse, reflecting an adaptive response of the liver rather than overt hepatotoxicity. The spectrum of liver effects and the doses eliciting hepatotoxicity did not change significantly with duration of dosing, although the severity of the histopathological lesions observed in the liver did increase slightly with longer-term dosing. For example, fatty change of the liver was observed in mice only after exposure to doses of 2285 ppm (equal to 241 mg/kg bw per day) and higher for 18 months and in rats in the second generation of a multigeneration reproduction study at 2000 ppm (equal to 157 mg/kg bw per day), and the degree of centrilobular hepatocellular

hypertrophy was graded as severe only in high-dose dogs after 12 months of dosing at 5000 ppm (equal to 116 mg/kg bw per day). Generally, the macroscopic observation of liver enlargement was more evident in females than in males, whereas the microscopic observation of hepatocellular hypertrophy was more prominent in males. Periportal necrosis of the liver was observed only in mice at 6400 ppm (equal to 878 mg/kg bw per day), the highest dose tested. An increased incidence of hyperplasia of the bile duct was observed at high doses in female rats only after dosing for 2 years. A special study revealed that drug metabolizing enzymes were not induced following exposure of rats to etoxazole for 4 or 13 weeks.

Dental and bone abnormalities were observed in rats after repeated dosing. The dental abnormalities included elongation of the upper incisors after subchronic dosing and elongation, whitening and abrasion of the upper and lower incisors as well as abnormal amelogenesis (formation of tooth enamel) of the upper incisor after longer-term dosing. It should be noted that the molecule contains fluorine. Although there are no specific studies on the release of fluoride from the molecule, these dental and bone effects would be consistent with the presence of free fluoride. The no-observed-adverse-effect level (NOAEL) for elongation of incisors in the 90-day study was 5000 ppm (equal to 300 mg/kg bw per day). In the 2-year study conducted at higher doses, the dental effects occurred at the lowest-observed-adverse-effect level (LOAEL) of 5000 ppm (equal to 187 mg/kg bw per day), and the NOAEL was 50 ppm (equal to 1.83 mg/kg bw per day). Thickening and hyperplasia of the parietal bone were observed in rats only after chronic dosing at the highest dose tested, 10 000 ppm (equal to 386 mg/kg bw per day). In the 2-year rat study conducted at lower doses, no dental or bone effects were observed at the highest dose tested (64 mg/kg bw per day). An overall NOAEL for dental and bone abnormalities and liver effects from the two long-term rat studies combined is 64 mg/kg bw per day.

The dog was the most sensitive species following short-term dosing. The NOAEL in the 90-day study was 200 ppm (equal to 5.33 mg/kg bw per day) based on liver effects (increased serum levels of triglycerides and alkaline phosphatase [AP], absolute and relative weights and incidence of centrilobular hepatocellular hypertrophy), as well as mucous stool (observed after repeated dosing), and decreased absolute and relative prostate weights and slight to moderate prostate acinar cell atrophy. The NOAEL in the 1-year dog study was also 200 ppm (equal to 4.62 mg/kg bw per day) based on liver effects (increased serum level of AP, incidence of liver enlargement and incidence of centrilobular hepatocellular hypertrophy) at the LOAEL of 1000 ppm (equal to 23.5 mg/kg bw per day). In contrast, the NOAEL in the 90-day mouse study was 1600 ppm (equal to 214 mg/kg bw per day), and the NOAEL in the 90-day rat study was 1000 ppm (equal to 61.8 mg/kg bw per day), in both cases based on liver effects.

Two carcinogenicity studies each were conducted in the rat and the mouse due to inadequate dosing in the initial studies. In the first mouse study, animals were dosed at 0, 15.1, 60.1 or 241 mg/kg bw per day (average concentrations in the diet were 0, 143, 564 and 2285 ppm), and no adverse effects were observed at any dose. In the second mouse carcinogenicity study, the animals were dosed at 0, 2250 or 4500 ppm (equal to 0, 242 and 482 mg/kg bw per day), and these doses were still not sufficient to produce adverse effects in females. In males, liver effects (increased incidence of fatty change) were observed at the highest dose. However, based on a weight of evidence evaluation, the study was considered acceptable for the assessment of carcinogenicity in mice. In the first rat study, animals were dosed at 0, 4, 16 or 64 mg/kg bw per day (approximately 0, 112, 449 and 1786 ppm). Testicular interstitial cell tumours were increased in all dose groups compared with controls (1/80, 10/80, 10/80 and 11/78, respectively); however, this was not considered to be treatment related, as it was not dose related, the incidence in the control group in this study was very low compared with historical control data for the laboratory and the strain, and an increase in the tumours was not observed in the second study at higher doses (5/50, 2/50, 4/50 and 1/50 at 0, 1.83, 187 and 386 mg/kg bw per day, respectively). Furthermore, special studies were conducted to examine testicular effects in the rat. These studies showed that etoxazole did not affect the proliferative activity of testicular interstitial cells after 4 or 13 weeks of dosing, nor did it have a significant impact on circulating levels of male reproductive hormones, the histology of the testis or

epididymides or spermatogenesis after 13 weeks of dosing. An increased incidence of pancreatic islet cell adenomas was observed in the females at 64 mg/kg bw per day; however, this was not considered to be treatment related in the absence of an increase in carcinomas in the same study or an increase in adenomas at higher doses in the second study. Therefore, no adverse effects were observed at any dose. In the second rat study, the animals were dosed at 0, 50, 5000 or 10 000 ppm (equal to 0, 1.83, 187 and 386 mg/kg bw per day), and no increase in tumours was observed. Overall, there was no evidence of carcinogenicity in either the rat or the mouse when the results from all of these studies are considered.

Etoxazole was adequately tested for genotoxicity in vitro and in vivo in a range of assays. Several negative results were obtained in a battery of in vitro and in vivo genotoxicity studies. A positive response was obtained at cytotoxic doses in a study with human lymphocytes. In the mouse lymphoma assay with metabolic activation, a weakly positive response occurred at a dose approaching cytotoxic doses, and an inconclusive result was found without metabolic activation.

The Meeting concluded that etoxazole was unlikely to be genotoxic.

On the basis of the absence of treatment-related carcinogenicity in rodents and the lack of genotoxicity, the Meeting concluded that etoxazole is unlikely to pose a carcinogenic risk to humans.

No effects on reproduction were noted in a multigeneration reproduction study in the rat. However, there was an increase in mortality of the offspring during early lactation in both generations at 2000 ppm (equal to 139 mg/kg bw per day), the highest dose tested. Increases in the number of pup deaths as well as the number of litters with pup deaths were observed. Furthermore, at this dose, the viability index on lactation day 4 was below historical control values. Effects in parental animals at the high dose were limited to non-adverse changes in organ weights (increased absolute and relative liver weights in males and increased relative weight in adrenal gland in females, with no corresponding histopathology noted in these tissues) in the first generation and slight hepatotoxicity in males (increased absolute and relative liver weights, slight centrilobular hepatocellular fatty change in two males) of the second generation. The NOAEL for parental and offspring toxicity was 400 ppm (equal to 28.2 mg/kg bw per day), and the NOAEL for reproductive toxicity was 2000 ppm (equal to 139 mg/kg bw per day), the highest dose tested.

No developmental toxicity was observed when pregnant rats were dosed up to 1000 mg/kg bw per day over the period of major organogenesis. Slight reductions in body weight and food consumption were observed in maternal animals at this dose. The NOAEL for maternal toxicity was 200 mg/kg bw per day, and the NOAEL for developmental toxicity was 1000 mg/kg bw per day, the highest dose tested. In rabbits, the fetal and litter incidence of skeletal variations was increased following prenatal exposure to etoxazole at 1000 mg/kg bw per day, in the presence of maternal toxicity (i.e., liver enlargement as well as body weight reduction). The NOAEL for maternal and developmental toxicity was 200 mg/kg bw per day.

The Meeting concluded that etoxazole induced developmental toxicity only in the presence of maternal toxicity and that it was not teratogenic.

The clinical observations of the repeated-dose studies did not reveal any evidence of neurotoxicity. In addition, a functional observational battery, which included an assessment of motor activity, grip strength and sensorimotor reaction to stimuli, conducted at 1 year in the 2-year study in rats, yielded negative results for neurotoxicity.

There were no reports of adverse health effects in manufacturing plant personnel or in operators and workers exposed to etoxazole formulations during their use. Also, there was no evidence to support any findings in relation to poisoning with etoxazole.

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.05 mg/kg bw on the basis of an overall NOAEL of 5.33 mg/kg bw per day in the 90-day and 1-year studies in dogs for liver effects (e.g., increases in serum levels of AP and triglycerides, absolute and relative liver weights and incidence of centrilobular hepatocyte hypertrophy). A safety factor of 100 was applied.

The Meeting concluded that it was not necessary to establish an acute reference dose (ARfD) for etoxazole in view of its low acute toxicity, the absence of relevant developmental toxicity in rats and rabbits that could have occurred as a consequence of an acute exposure, and the absence of any other toxicological effect that would be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	2250 ppm, equal to 242 mg/kg bw per day	4500 ppm, equal to 482 mg/kg bw per day
Rat	Two-year studies of toxicity and carcinogenicity[a,b]	Toxicity	1786 ppm, equal to 64 mg/kg bw per day	5000 ppm, equal to 187 mg/kg bw per day
		Carcinogenicity	10 000 ppm, equal to 386 mg/kg bw per day[c]	—
	Two-generation study of reproductive toxicity[a]	Parental toxicity	400 ppm, equal to 28.2 mg/kg bw per day	2000 ppm, equal to 139 mg/kg bw per day[c]
		Offspring toxicity	400 ppm, equal to 28.2 mg/kg bw per day	2000 ppm, equal to 139 mg/kg bw per day[c]
		Reproductive toxicity	2000 ppm, equal to 139 mg/kg bw per day[c]	—
	Developmental toxicity[d]	Maternal toxicity	200 mg/kg bw per day	1000 mg/kg bw per day
		Embryo and fetal toxicity	1000 mg/kg bw per day[c]	—
Rabbit	Developmental toxicity[d]	Maternal toxicity	200 mg/kg bw per day	1000 mg/kg bw per day
		Embryo and fetal toxicity	200 mg/kg bw per day	1000 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity[a,b]	Toxicity	200 ppm, equal to 5.33 mg/kg bw per day	1000 ppm, equal to 23.5 mg/kg bw per day

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested.

[d] Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.05 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 etoxazole

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid; approximately 60%
Distribution	Wide; highest concentrations in liver
Potential for accumulation	None
Rate and extent of excretion	Largely complete within 48 h; primarily via faeces (77–88%, bile 30–54%) and to a lesser extent via urine (8–17%)
Metabolism in animals	Extensive; mainly by hydroxylation of the 4,5-dihydrooxazole ring followed by cleavage of the molecule and hydroxylation of the *tert*-butyl side-chain
Toxicologically significant compounds in animals, plants and the environment	Parent compound
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 1.09 mg/L (highest attainable concentration)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman test)
Short-term studies of toxicity	
Target/critical effect	Increased absolute and relative liver weights, clinical chemistry changes, centrilobular hepatocyte hypertrophy, prostate atrophy
Lowest relevant oral NOAEL	5.33 mg/kg bw per day (13-week study in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (28-day study in rats)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Increased absolute and relative liver weights, clinical chemistry changes, histopathological changes in liver, dental and bone abnormalities
Lowest relevant NOAEL	64 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Not carcinogenic in rats or mice
Genotoxicity	
	Unlikely to be genotoxic

Reproductive toxicity	
Reproduction target/critical effect	No effect on fertility at highest dose tested; slight decrease in viability of pups and pup body weight at parentally toxic dose
Lowest relevant reproductive NOAEL	28.2 mg/kg bw per day for offspring toxicity in two-generation reproduction study in rats
Developmental target/critical effect	Increased incidence of skeletal variations at maternally toxic dose
Lowest relevant developmental NOAEL	200 mg/kg bw per day in rabbits
Neurotoxicity/delayed neurotoxicity	
	No evidence of neurotoxicity
Other toxicological studies	
	Special studies on testicular function in rats revealed no effect on proliferative activity of interstitial cells, changes in circulating male hormones or histopathology
Medical data	
	No data

Summary

	Value	Study	Safety factor
ADI	0–0.05 mg/kg bw	Dog, 90-day and 1-year study	100
ARfD	Unnecessary		

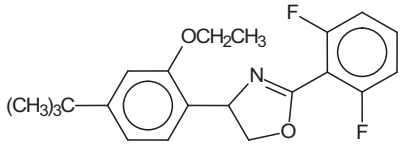
RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of etoxazole were considered for the first time by the present Meeting. The residue evaluation was scheduled for the 2010 JMPR by the Forty-first Session of the CCPR (ALINORM 09/32/24).

Etoxazole is an acaricide which belongs to the diphenyloxazoline group of chemicals, and controls mites by causing adults to lay sterile eggs and also inhibition of chitin biosynthesis. The Meeting received information on identity, animal and plant metabolism, environment fate in soil, rotational crops, analytical methods, storage stability, use patterns, supervised trials, farm animal feeding studies and fates of residues in processing.

The 2010 JMPR established an ADI for etoxazole of 0–0.05 mg/kg bw. For etoxazole the ARfD is unnecessary.

(*RS*)-5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazol-4-yl]phenetole



Etoxazole is a 1:1 mixture of the enantiomers.

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

R-2	2-(2,6-difluorophenyl)-4-[2-ethoxy-4-(1-hydroxymethyl-1-methylethyl)phenyl]-4,5-dihydrooxazole
R-3	*N*-(2,6-difluorobenzoyl)-4-*tert*- butyl-2-ethoxybenzamide
R-4	*N*-(2,6-difluorobenzoyl)-2-amino- 2-(4-*tert*-butyl-2-ethoxyphenyl) ethanol
R-7	2-amino-2-(4-*tert*-butyl-2- ethoxyphenyl)ethyl 2,6-difluorobenzoate hydrochloride
R-7-CO_2H	2-amino-2-[2-ethoxy-4-(1-carboxy-1-methylethyl)phenyl]ethyl 2,6- difluorobenzoate hydrochloride
R-8	2-amino-2-(4-*tert*-butyl-2-ethoxy- phenyl)ethanol
R-10	*N*-(2,6-difluorobenzoyl)glycine
R-11	2,6-difluorobenzoic acid
R-12	4-*tert*-butyl-2-ethoxybenzoic acid
R-13	4-(4-*tert*-butyl-2-ethoxyphenyl)-2- (2,6-difluorophenyl)oxazole
R-15	4-*tert*-butyl-2-ethoxybenzamide
R-16	2-(2,6-difluorophenyl)-4-[2-ethoxy-4-(1-carboxy-1-methylethyl)phenyl]-4,5- dihydrooxazole
R-20	2-ethoxy-4-(1-hydroxymethyl-1- methylethyl)benzoic acid
R-24	2-amino-2-(2-ethoxy-4-[1'- hydroxymethyl-1'- methylethyl]phenyl)ethanol
DFB	2,6-difluorobenzamide
Metabolite 1	2-amino-2-(2-ethoxy-4-[1'-hydroxycarbonyl-1'-methyl-ethyl]phenyl)ethanol

Animal metabolism

The Meeting received animal metabolism studies with etoxazole in rats, lactating goats and laying hens. The metabolism and distribution of etoxazole in animals were investigated using the [U-^{14}C-difluorophenyl] and [U-^{14}C-*tert* butylphenyl]-labelled etoxazole.

Etoxazole was metabolised in rats principally by hydroxylation of the 4,5-dihydrooxazole ring followed by cleavage of the molecule and hydroxylation of the tertiary-butyl side chain. There was a significant difference in the proportions of metabolites excreted in the urine of male and female rats. The major component in male rat urine was Metabolite 1 and in female urine was R-24. Metabolism in rats was summarized and evaluated by the WHO panel of the JMPR in 2010.

When lactating goats were orally dosed with [^{14}C-*tert* butylphenyl]- and [^{14}C-difluorophenyl]-etoxazole at 20 mg/animal/day, equivalent to approximately 10 ppm in the feed for 4 consecutive days, most of the administered radioactivity was recovered in the gastro-intestinal contents (80% and 29%). Radioactivity was excreted in urine (1.9% and 1.5%) and faeces (17% and 54%). Overall recoveries of the administered dose were 99% and 85%. The Meeting considered that the result of studies using [^{14}C-*tert* butylphenyl]-etoxazole was unreliable, since most of radioactivity was recovered from the gastro-intestinal tracts. The result of studies using [^{14}C-difluorophenyl]-etoxazole are summarized below.

Radioactive residues were highest in the bile (0.317 mg/kg) and livers (0.063 mg/kg). Total radioactive residues in all other tissues and milk were < 0.008 mg/kg. Parent etoxazole accounted for a total of 63–65% dose in the faeces and gastro-intestinal tracts. The major urinary metabolites corresponded to R-11 (0.5% dose) and R-10 (0.8% dose).

Laying hens were orally dosed with [^{14}C-*tert*-butylphenyl]- or [^{14}C-difluorophenyl]-etoxazole at doses equivalent to 12 or 11 ppm in the feed for 8 consecutive days. The majority (84.4–99.8%) of

the radioactive residues were extracted in egg yolk, egg white, abdominal and skin fat, thigh muscle, breast muscle and liver.

Parent etoxazole was the major ^{14}C residue in egg yolk, abdominal and skin fat, thigh muscle, and breast muscle. Its concentration in isolated egg yolk was approximately 0.1 mg/kg. It accounted for only about 3% of TRR in liver (0.057–0.078 mg/kg), but 90–92% of TRR in the composite fat (0.55–0.69 mg/kg). Most of ^{14}C residue in liver was metabolite R-16 (59–66% of TRR), a *tert*-butyl methyl group oxidation product of etoxazole. R-16 was also observed in minor quantities in all tissues except egg white. The analogous dihydrooxazole ring-opened product of R-16, designated as R-7-CO_2H, was observed only in liver. The liver contained unextracted ^{14}C residues in both radiolabel treatments (0.29 mg/kg or 12–15% of TRR). The majority (about 80%) was protein-bound and could be solubilised by treatment with protease.

Etoxazole was metabolized to several metabolites and the metabolic routes are similar in goats and hens. The major metabolic processes were oxidation of the *tert*-butyl moiety, and the hydrolysis of the hydrooxazole ring. Ruminant and poultry metabolism studies demonstrated that transfer of administered ^{14}C residues to milk, eggs, and tissues is low.

The metabolic pathway proposed for goats and hens is similar to that for rats. Some metabolites such as R-8 (0.7% TRR in poultry liver), R-10 (0.8% dose in goat urine), R-20 (11.5% TRR in goat liver) were observed in goat and hen metabolism studies, but not in rat studies.

Plant metabolism

The Meeting received plant metabolism studies performed on apples, oranges and egg plants using the tert-butylphenyl- and oxazole- U-[^{14}C] labelled etoxazole, and on cotton using the tert-butylphenyl-and difluorophenyl-U-[^{14}C] labelled etoxazole.

In an apple metabolism study, apple trees were treated once at a rate of 0.15 kg ai/ha. Samples of fruit and leaves were taken at Day 0, 14 or 15, 21 and 30 after application. The TRR in fruit declined from 0.46 to 0.13 mg/kg and 0.18 to 0.09 mg/kg from treatment with the tert-butylphenyl- and oxazole-labelled etoxazole, respectively. Similarly, the TRR in leaves declined from 14.9 to 2.5 mg/kg and 11.8 to 0.7 mg/kg. Parent etoxazole was the only component that exceeded 10% of the TRR in fruit (42% of TRR at harvest) and leaves (30% of TRR at harvest) at all sampling times. Metabolites accounting for 0.001–0.010 mg/kg (0.4–8.2% of TRR in fruit) were identified as R-3, R-7, R-13, R-11 (oxazole label), R-12 (tert-butylphenyl label), and R-15 (tert-butylphenyl label).

In an orange metabolism study, orange trees were treated at a rate of 0.4 kg ai/ha. Samples of fruit and leaves were taken immediately after application and at 21, 30, 60 and 90 days after application. The TRR in fruit declined from 0.25 to 0.11 mg/kg and 0.27 to 0.07 mg/kg from treatment with the tert-butylphenyl- and oxazole- labelled etoxazole, respectively. Similarly, the TRR in leaves declined from 9.3 to 0.81 mg/kg and 17.9 to 2.7 mg/kg from treatment. Parent etoxazole was the only component that exceeded 10% of the TRR in fruit (48% of TRR at harvest) and leaves (52% of TRR at harvest) at all sampling times. Etoxazole and metabolites R-3, R-7, R-13, R-14 and R-15 were identified by co-chromatography. The residue was a surface residue and translocation was minimal.

In an egg plant metabolism study, egg plants maintained under controlled conditions in a plant growth room were treated at a rate of 0.2 kg ai/ha. Samples of fruit were taken immediately after applications at 1 day, and 2 and 4 weeks. Samples of leaves were taken immediately after application at 1 day and 4 weeks. The TRR in fruit declined from 0.20 to 0.10 mg/kg from treatment with the tert-butylphenyl-labelled etoxazole, but for fruit-treated oxazole-labelled etoxazole the TRR did not decline (0.16 to 0.20 mg/kg). Parent etoxazole was the only component that exceeded 10% of the TRR in fruit (69–74% of TRR at harvest) and leaves (70–75% of TRR at harvest) at all sampling times. Metabolites accounting for 0.001–0.004 mg/kg (0.3–1.8% fruit radioactivity) were identified as R-2, R-3, R-7, R-13 (both radiolabels), R-11 (oxazole radiolabel), and R-12 (tert-butylphenyl radiolabel). Again, the residue was a surface residue and translocation was minimal.

In a cotton metabolism study, two foliar treatments were applied to cotton plants at a rate of 0.1 kg ai/ha at 42 and 21 days prior to harvest. Cottonseed (ginned from open cotton bolls) and gin trash was harvested for analysis. Cottonseed contained low amounts of radioactivity, with TRR values of 0.031 and 0.020 mg/kg for difluorophenyl and tert-butylphenyl cottonseed, respectively. Cotton gin trash samples contained TRR values of 6.9 and 5.3 mg/kg for the difluorophenyl- and tert-butylphenyl-labelled etoxazole. The major residues identified in gin trash were parent etoxazole (36–44% of TRR) and R-3 (16–18% of TRR).

In the plant metabolism studies on apples, oranges, egg plants and cotton, the metabolic pathways were similar. Etoxazole was metabolized to several metabolites. In all plants investigated, the parent etoxazole was identified as the major component (30–75% of TRR). Metabolites were detected in concentrations < 10% of TRR in apples, oranges and egg plants. In cotton gin trash, the component (R-3) exceeded 10% of TRR. In all studies, the residue remained mainly in the surface, penetration into fruit was minimal and translocation was also minimal. The major metabolic processes were the hydrolysis and cleavage of the oxazole ring.

All plant metabolites identified except R-14 were found in rats, goats or hens. The structure of R-14 is similar to that of R-7 which was identified in rats and hens. These metabolites may be generated during the hydrolysis and cleavage of hydrooxazole ring.

The stabilities of metabolites in plant metabolism studies during freezer storage were determined by re-extraction and comparison of radioresidue profiles to chromatographic profiles. The amounts of radioactivity extracted and the percentages of the major metabolites identified were similar after freezer storage intervals (5–13 months).

Environmental fate in soil

The Meeting received information on aerobic soil metabolism and rotational crop study.

Aerobic soil metabolism and degradation study was conducted using [^{14}C-*tert*-butylphenyl] and [^{14}C-difluorophenyl]-etoxazole in a sand loam soil under aerobic conditions at a nominal average temperature of 20 °C for 269 days. Etoxazole declined rapidly from 95.7–97.8% of total applied radioactivity (TAR) at 0 day to 11.2–12.6% of TAR at 30 days. Totals of 15.8–56.4% of TAR were evolved as CO_2 during 269 days. Several degradates were observed during the incubation period. The degradate R-13 rose to 10.9–11.7% of TAR at 60 days, declining to about 7% of TAR at 269 days. The degradate R-7 reached a maximum proportion of 11.5–21.6% of TAR after 7 days, declined to 5.5–5.9% of TAR at 60 days. The degradate R-8 reached a peak level of 44.8% TAR at 60 days and was still relatively great (28.6% TAR) at 269 days. The minor components R-3, R-4, R-12 and R-15 were never greater than 1.5, 4.4, 4.0 and 3.2% TAR respectively. ^{14}C-etoxazole was degradated with a DT_{50} of 9.9 to 10.6 days.

In confined rotational crop study, radish, lettuce and wheat were designated for planting at 30, 120 and 360 days after treatment (DAT) at an application rate of 0.11 kg ai/ha with [^{14}C-*tert*-butylphenyl] and [^{14}C-difluorophenyl]-etoxazole. The TRR in the 30 DAT rotational crop samples from the treated plots were below the significant residue level of 0.01 mg/kg. Uptake and accumulation of etoxazole-related radioactive residues is very low (< 0.005 mg/kg) in rotational crops of radish, lettuce and wheat planted at the earliest plant-back interval (30 DAT).

Etoxazole residues are not expected to occur in succeeding crops.

Environmental fate in water systems

In the hydrolysis study with [^{14}C-*tert*-butylphenyl]-etoxazole conducted using sterile aqueous buffer solutions, the hydrolytic half-lives at 20 °C were found to be about 10 days at pH 5, 161 days at pH 7 and 165 days at pH 9. In pH 1.2 buffer at 37 °C and in pH 5 buffer at 20 °C, etoxazole was hydrolyzed to R-7, while in pH 7 and pH 9 buffer, it was hydrolyzed to R-4. No other radioactive products were detected in quantities greater than 6% of the recovered radioactivity. At 20 °C the

hydrolytic stability of etoxazole in aqueous buffer is of the order pH 9 > pH 7 > pH 5. In buffers of acidic pH, etoxazole is hydrolyzed to R-7 and in neutral or basic pH to R-4.

The photolysis study with [^{14}C-*tert*-butylphenyl] and [^{14}C-oxazole]-etoxazole was conducted using pH 9 buffer containing 10% acetonitrile. The photolytic half-life of etoxazole in pH 9 buffer was found to be 15.9–17.4 days summer sunlight equivalents at latitude 40 °N. The major degradates were identified as R-3, R-11, R-12 and R-15.

Methods of analysis

The Meeting received description and validation data for analytical methods for residues of parent etoxazole in raw agricultural commodities, processed commodities, feed commodities and animal commodities. In most of the methods for determination of etoxazole, homogenized samples were extracted with acetone (for plant materials) and ethyl acetate (for animal commodities), and the extract was cleaned up with liquid–liquid partition followed by column chromatography using SPE. Residues were determined by gas chromatography with FTD, NPD or MSD. The methods of analysis for a range of substrates were validated with LOQs of the 0.002–0.01 mg/kg range for etoxazole.

The multiresidue method DFG Method S19 (modified version) with GC-MS detection was validated for etoxazole in plant materials. LOQs were 0.01 mg/kg for etoxazole.

The Meeting received LC-MS/MS method of analysis for Metabolite 1 and R-20 in bovine liver and kidney. The method was validated with an LOQ of 0.02 mg/kg for both analytes.

Stability of residues in stored analytical samples

The Meeting received information on the freezer storage stability of etoxazole residues in plant commodities (apples, mandarin peel/pulp, strawberries, cantaloupes, grapes, almond hulls, hops, cotton seed/gin trash, cherries, plums fresh/dried, peaches, cucumbers, tomatoes, mint tops/oil and tea). The Meeting noted that the residue might be degradating during sample preparation. Spiking of chopped samples would not reveal this degradation. Nevertheless the Meeting decided to evaluate the results of residue trials, where the storage stability studies show adequate recoveries. Enforcement laboratories should be aware that special precautions may be necessary during sample preparations.

The Meeting received information on the freezer storage stability of etoxazole in milk cream, metabolite R-20 in liver, and Metabolite 1 in liver and kidney. The results of the studies showed that each compound is stable in each animal commodity tested for at least 2 months in frozen storage.

Definition of the residue

In the lactating goat metabolism study, TRRs in kidney (0.94 mg/kg) and liver (0.06–0.23 mg/kg) were higher than those in other tissues. Metabolite 1 is the major component of the residues in liver (12% TRR) and kidney (81% TRR). In the laying hen study, the major residue components are parent etoxazole (in all tissues) and R-16 (in muscle and liver). However, according to farm animal feeding studies, the parent, Metabolite 1 and R-20 are expected to be present at below the LOQ.

The Meeting decided that parent etoxazole is a suitable analyte for enforcement purposes and dietary risk assessment in animal commodities.

The octanol/water coefficient (log P_{ow}) of 5.5 for etoxazole suggests that etoxazole might be fat soluble. In the laying hen metabolism study, etoxazole found in the composite fat was 0.55–0.69 mg/kg and that in muscle was 0.01–0.08 mg/kg. In the dairy cow feeding study, the residue of etoxazole in fat was higher than that in other tissues. The ratio of etoxazole residues in muscle and fat observed in the laying hen metabolism study and the dairy cow feeding study indicates that etoxazole is fat soluble.

The plant metabolism studies of etoxazole were conducted with fruiting vegetables (egg plants), fruit crops (apples and oranges) and oilseed (cotton). Each study was conducted with both

tert-butylphenyl- and oxazole-radio-labelled etoxazole for apples, oranges and egg plants, and with both tert-butylphenyl- and difluorophenyl-radio-labelled etoxazole for cotton. Parent etoxazole was always the major component (30–75% TRR). Metabolite R-14 was found in oranges and cotton at low levels (< 3.2% TRR) but not in rat metabolism studies. In cotton seed, DFB and R-3 were also identified as the major residue components, but the concentration of each residue was less than 0.01 mg/kg.

The Meeting decided that parent etoxazole is a suitable analyte for enforcement purposes and dietary risk assessment in plant commodities.

The Meeting recommended the following residue definition for plants and animals (for compliance with the MRL and for estimation of dietary intake): *etoxazole.*

The residue is fat-soluble.

Residues of supervised trials on crops

The Meeting received supervised trial data for the foliar application of etoxazole on citrus fruits (mandarins and oranges), apples, pears, cherries, plums, nectarines, peaches, grapes, strawberries, cantaloupes, cucumbers, peppers, tomatoes, almonds, pecans, cotton seed, mints, hops and tea. Residue trial data was made available from Australia, member states of the European Union, Japan and the USA.

Labels (or translation of labels) were available from Australia, Brazil, France, Greece, Italy, Japan, Spain, the UK and the USA describing the registered uses of etoxazole, and GAP information was also provided from Australia and the Netherlands.

The Meeting decided that an ARfD for etoxazole is unnecessary. Therefore, it is not necessary to estimate HR values for etoxazole in the commodities.

As noted above, the Meeting decided to use the results of only these residue trials, for which the storage stability of etoxazole during the respective storage interval was demonstrated, to estimate a maximum residue level. The Meeting therefore recommended the maximum residue levels for citrus, grapes, cucumbers, tree nuts, mint, hops and tea.

Citrus fruits

Data were available from supervised trials on mandarins and oranges in Italy and Spain.

In Italy and Spain, etoxazole is registered for use on citrus at a foliar application of 5.5 g ai/hL (a maximum rate of 0.055 kg ai/ha) with a PHI of 14 days. Residues in whole fruit of mandarins from trials matching GAP of Italy and Spain were (n = 8): 0.01, 0.02 (2), 0.04 and 0.05 (4) mg/kg. Residues in whole fruit of oranges from trials matching GAP of Italy and Spain were (n = 6): 0.01 (2), 0.02 (3) and 0.05 mg/kg. The residue populations for trials conducted on mandarins and oranges were not similar (Mann-Whitney U test). The Meeting decided to use the data on the crop with the highest residues (mandarins) to estimate a maximum residue level for the group. Residues in mandarin pulp from trials of Italy and Spain were (n = 8): < 0.01 (7) and 0.01 mg/kg. Residues in orange pulp from trials of Italy and Spain were (n = 6): < 0.01 (6) mg/kg.

Based on the trials for mandarins in Italy and Spain, the Meeting estimated a maximum residue level and an STMR value for etoxazole in citrus of 0.1 and 0.01 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 0.09 mg/kg (Mean + 3SD). Rounding-up of the value to 0.1 mg/kg coincides with the recommendation of the current Meeting.

Pome fruits

Data were available from supervised trials on apples in member states of the EU and the USA.

According to the freezer storage stability study on apples conducted in 2001, etoxazole is declining even after 41days storage interval. Insufficient data was available to demonstrate storage stability of pome fruits.

The Meeting could not estimate maximum residue levels for etoxazole in pome fruit.

Stone fruits

Cherries

Data were available from supervised trials on cherries in Spain and the USA.

Trials from the USA on cherries were reported for the foliar application of a WG formulation. However, the storage stability of etoxazole residues in the trials was unstable (60–68% remaining for 193 days storage interval). The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in cherries.

Residue trials were provided from Spain for use of etoxazole on cherries but no GAP was available.

The Meeting decided not to recommend a maxiumum residue level for etoxazole in cherries.

Plums

Trials were reported for plums from member states of the EU and the USA.

Trials from France on plums were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in plums.

Trials from the USA on plums were reported for the foliar application of a WG formulation. However, the storage stability of etoxazole residues in the trials was unstable (41–45% remaining for 207 days storage interval). The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in plums.

Nectarines

Trials on nectarines were reported from Australia (1 × 3.9 g ai/hL and PHI of 21 days). However, storage stability information was insufficient and the residue trials conducted in Australia did not match the GAP of Australia.

Peaches

Trials were reported for peaches from Australia, member states of the EU and the USA.

In Australia, etoxazole is registered for use on stone fruits at a foliar application of 3.9 g ai/hL with a PHI of 21 days. However, the residue trials on peaches conducted in Australia did not match the GAP of Australia.

Trials from France, Greece, Italy and Spain on peaches were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in peaches.

Trials from the USA on peaches were reported for the foliar application of a WG formulation. However, the storage stability of etoxazole residues in the trials was unstable (45–53% remaining for 278 days storage interval). The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in peaches.

Berries and other small fruits

Grapes

Data were available from supervised trials on grapes in France and the USA.

Trials from France on grapes were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in grapes.

Etoxazole is registered in the USA for use on grapes at a foliar application of a maximum rate of 0.15 kg ai/ha with a PHI of 14 days. Etoxazole residues in grapes from trials in the USA matching GAP were (n = 12): < 0.01, 0.01, 0.03, 0.04 (4), 0.05 (2), 0.06, 0.10 and 0.33 mg/kg. Adequate storage stability studies were available in the US trials.

Based on the US trials, the Meeting estimated a maximum residue level and an STMR value for etoxazole in grapes of 0.5 and 0.04 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 0.25 mg/kg (UCLMedian 95th), but this value was below the HR value and therefore disregarded.

Strawberry

Trials on strawberries were reported from the USA (GAP: one foliar application of a maximum rate of 0.15 kg ai/ha and PHI of 1 day). However, the storage stability of etoxazole residues in the trials was unstable (63% remaining for 32 days storage interval). The Meeting decided not to recommend a maximum residue level for etoxazole in strawberries

Fruiting vegetables—Cucurbits

Data were available from supervised trials on cantaloupe and cucumber in the USA.

Melons

Trials on cantaloupes were reported from the USA (two foliar applications of a maximum rate of 0.15 kg ai/ha and PHI of 7 days). However, the storage stability of etoxazole residues in the trials was unstable (55% remaining for 50 days storage interval). The Meeting decided not to recommend a maximum residue level for etoxazole in melons

Cucumber

The GAP on cucumbers of the USA is a maximum two foliar applications at a maximum rate of 0.15 kg ai/ha with a PHI of 7 days. Etoxazole residues in cucumbers from trials in the USA matching GAP were (n = 9): < 0.01 (7) and 0.01 (2) mg/kg. Adequate storage stability studies were available in the US trials.

Based on the US trials for cucumbers, the Meeting estimated a maximum residue level and an STMR value for etoxazole in cucumbers of 0.02 and 0.01 mg/kg respectively.

The NAFTA calculator could not be used, as residues from seven of the nine trials, matching GAP, were below the LOQs.

Fruiting vegetables, other than Cucurbits

Peppers

Trials from Australia on peppers were reported for the foliar application of a SC formulation. However, the residue trials conducted did not match the GAP on peppers in Australia. The Meeting could not estimate a maximum residue level for peppers.

Tomatoes

Data were available from supervised trials on tomatoes in Australia, member states of the EU and the USA.

Trials from France, Greece, Italy, Netherlands and Spain on tomatoes were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in tomatoes.

Trials from the USA on tomatoes were reported for the foliar application of a WG formulation (GAP: two foliar applications of a maximum rate of 0.14 kg ai/ha and PHI of 1 day). Etoxazole residues in tomatoes from trials in the USA matching GAP were (n = 3): 0.01 and 0.05 (2) mg/kg. Adequate storage stability studies were available in the US trials. However, the trials for tomatoes matching the US GAP were insufficient to estimate a maximum residue level for the commodity.

Trials from Australia on tomatoes were reported for the foliar application of a SC formulation. However, the residue trials conducted did not match the GAP on tomatoes in Australia.

The Meeting could not estimate a maximum residue level for etoxazole in tomatoes.

Tree nuts

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

Etoxazole is registered in the USA for use on tree nuts at a foliar application of a maximum rate of 0.15 kg ai/ha with a PHI of 28 days. Etoxazole residues in almond nutmeat from trials in the USA matching GAP were (n = 5): < 0.01 (5) mg/kg. Etoxazole residues in pecans from trials in the USA matching GAP were (n = 5): < 0.01 (5) mg/kg. Adequate storage stability studies were available in the US trials.

The use pattern in the USA is for tree nuts and the Meeting decided that trials in almonds and pecans could be used to support a group maximum residue level for tree nuts. The Meeting decided to combine the data for the purpose of estimating a maximum residue level for the group.

Based on the US trials for almond nutmeat and pecans, the Meeting estimated a maximum residue level of 0.01 (*) mg/kg, and an STMR value of 0 mg/kg for etoxazole in tree nuts.

The NAFTA statistical calculator was not used as all residues were below the LOQ.

Cotton seed

Data were available from supervised trials on cotton seeds in Australia, member states of the EU and the USA.

Trials from Greece and Spain on cotton seeds were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in cotton seeds.

Trials from the USA on cotton seeds were reported for the foliar application of a SC formulation or a WP formulation. Adequate storage stability studies were available in the US trials. However, the residue trials conducted in the USA did not match the GAP on cotton seeds in the USA.

Trials from Australia on cotton seeds were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in cotton seeds.

Mints

Data from the USA on mints were reported for the foliar application of a WG formulation.

Etoxazole is registered in the USA for use on mint at a maximum rate of 0.20 kg ai/ha and PHI 7 days with a maximum seasonal application of 0.40 kg ai/ha. Etoxazole residues in mints from trials in the USA matching GAP were (n = 5): 3.1, 3.2, 4.9, 5.6 and 7.6 mg/kg. Adequate storage stability studies were available in the US trials.

Based on the US trials, the Meeting estimated a maximum residue level and an STMR value for etoxazole in mints of 15 and 4.9 mg/kg respectively.

The normal Meeting procedure is to round values to the nearest units of 5 for maximum residue levels between 10 and 30 mg/kg. The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 12 mg/kg (95/99 Rule). Rounding of the value to 15 mg/kg coincides with the recommendation of the current Meeting.

Hops

Data were available from supervised residue trials on hops in Germany and the USA.

Trials from Germany on hops were reported for the foliar application of a SC formulation. However, there was no approved GAP/label provided for hops.

Etoxazole is registered in the USA for use on hops at a foliar application of a maximum rate of 0.20 kg ai/ha with a PHI of 7 days. Etoxazole residues in dried cones of hops from trials in the USA matching GAP were (n = 3): 2.5, 4.2 and 4.3 mg/kg. Adequate storage stability studies were available in the US trials.

Based on the US trials, the Meeting estimated a maximum residue level and an STMR value for etoxazole in hops of 15 and 4.2 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 8.0 mg/kg (95/99 Rule), however, due to the small number of trials (n = 3) this value was considered unreliable.

Tea

Data from Japan on tea were reported for the foliar application of a SC formulation and a WP formulation.

Etoxazole is registered in Japan for use on tea at a foliar application of 10 g ai/hL (a maximum rate of 0.4 kg ai/ha) with a PHI of 14 days. Etoxazole residues in green tea from trials in Japan matching GAP were (n = 8): 2.4, 3.1, 4.1, 4.7, 4.8, 6.4, 7.3 and 8.0 mg/kg. Adequate storage stability studies were available in Japanese trials.

Based on Japanese trials, the Meeting estimated a maximum residue level and an STMR value for etoxazole in tea of 15 and 4.75 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 13 mg/kg (95/99 Rule). With rounding the value coincides with the recommendation of the current Meeting. The normal Meeting procedure is to round the value to the nearest units of 5 for maximum residue levels between 10 and 30 mg/kg.

Animal feedstuffs

Almond hulls

Trials on almond hulls were reported from the USA (GAP: a foliar application of a maximum rate of 0.15 kg ai/ha with a PHI of 28 days). Etoxazole residues in almond hulls from trials in the USA matching GAP were (n = 5): 0.14, 0.17, 0.23, 0.39 and 1.8 mg/kg. Adequate storage stability studies were available in the US trials.

The Meeting estimated a maximum residue level and an STMR value for etoxazole in almond hulls of 3 and 0.23 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was of 2.5 mg/kg (UCLMedian 95th), which when rounded-up is in agreement with the Meeting's estimation.

Cotton gin trash

Data were available from supervised residue trials on cotton gin trash in Australia and the USA

Trials from the USA on cotton gin trash were reported for the foliar application of a SC formulation or a WP formulation. However, storage stability information was insufficient and the residue trials conducted in the USA did not match the GAP on cotton gin trash in the USA.

Trials from Australia on cotton gin trash were reported for the foliar application of a SC formulation or a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate an STMR value for etoxazole in cotton gin trash.

Fate of residues during processing

The fate of etoxazole residues has been examined in oranges, apples, grapes, cotton seeds and mints processing studies. Processing studies were conducted for apples and grapes in France. However, RAC samples were below the LOQ (0.010 mg/kg), and no residues were found in any processed commodities. Based on the results of processing studies conducted in the USA, processing factors were calculated for apples and grapes. Estimated processing factors and the derived STMR-Ps are summarized in the Table below.

Processing factors and STMR-P for food and feed

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors[a]	PF (Mean or best estimate)	RAC STMR (mg/kg)	STMR-P (mg/kg)
Orange	Wet pomace	1.5	1.5	0.01 (for citrus)	0.015
	Dry pomace	1.5	1.5		0.015
	Juice	< 0.5	0.5		0.005
Grape	Juice	1.7	1.7	0.04	0.068
	Raisin	1.1	1.1		0.044
Mint	Oil	3.0, 0.19	1.6	4.9	7.8

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

The Meeting estimated an STMR-P of 0.015 mg/kg (0.01 × 1.5 = 0.015 mg/kg) for citrus dried pulp, 0.005 mg/kg (0.01 × 0.5 = 0.005 mg/kg) for citrus juice, 0.068 mg/kg (0.04 × 1.7 = 0.068 mg/kg) for grape juice, 0.044 mg/kg (0.04 × 1.1 = 0.044 mg/kg) for dried grapes and 7.8 mg/kg (4.9 × 1.6 = 7.8 mg/kg) for mint oil

Residue in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of etoxazole in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual 2009. Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed in a dry weight basis.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Appendix IX of the FAO manual. The calculations were made according to the animal diets from US/CAN, EU, Australia and Japan in the Table (Appendix IX of the FAO manual).

Livestock dietary burden, etoxazole, ppm of dry matter diet								
	US/CAN		EU		Australia		Japan	
	Max	mean	max	mean	Max	mean	max	Mean
Beef cattle	0.03	0.03	0.00	0.00	0.03[a]	0.03[b]	0.00	0.00
Dairy cattle	0.03	0.03	0.00	0.00	0.03[a]	0.03[bc]	0.00	0.00
Poultry-broiler	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Poultry-layer	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat and milk

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

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

Farm animal feeding studies

The Meeting received a lactating dairy cow feeding study, which provided information on likely residues resulting in animal commodities and milk from etoxazole residues in the animals' diets.

Lactating dairy cows

Holstein dairy cows were dosed with etoxazole for 28 days at the equivalent of 1, 3 and 10 ppm in the diet. Residues of etoxazole were below the LOQ (0.01 mg/kg) in whole milk at the 1 and 3 ppm feeding levels. At the 10 ppm level, etoxazole residues in milk were the LOQ level from day 3 to day 27. Cream (day 27) from the 3 ppm level contained at the LOQ (0.02 mg/kg) level of etoxazole residues. Kidney and muscle contained no residue (< 0.005 mg/kg) of etoxazole at 1 and 3 ppm feeding levels, and the LOQ level from only one cow at the 10 ppm level. Liver contained etoxazole residues of the LOQ at the 3 ppm level, and 0.01–0.02 mg/kg at the 10 ppm level. Fat contained etoxazole residues of 0.01–0.02 mg/kg at the 1 ppm, 0.02–0.03 mg/kg at the 3 ppm and 0.06–0.11 mg/kg at the 10 ppm level respectively.

At the 10 ppm feeding level at day 27, etoxazole residue levels in milk were approximately 10% of the levels in cream.

Animal commodities maximum residue levels

For the estimation of maximum residue levels, the residue in the animal commodities is etoxazole.

The maximum dietary burden for beef and dairy cattle is 0.03 ppm, allowing residue levels to be obtained from the 1 ppm feeding level. In a feeding study, in which etoxazole equivalent to 1 ppm in the diet was dosed to lactating cows for 28 consecutive days, no etoxazole residues were detected in liver, kidney and muscle (< 0.01 mg/kg) and milk (< 0.01 mg/kg). Etoxazole residues in fat were < 0.01, 0.014 and 0.015 mg/kg at the 1 ppm level. Therefore no residues (< LOQ) are to be expected at the maximum estimated dietary burden of 0.03 ppm feed for beef cattle and dairy cattle.

The Meeting estimated a maximum residue level of 0.01 (*) mg/kg in mammalian meat and mammalian edible offal, and 0.01 (*) mg/kg in milk.

The mean estimated dietary burden for dairy cattle is 0.03 ppm. No etoxazole residues (< 0.01 mg/kg) were found in any samples of milk at the 1 ppm feeding level. Therefore the Meeting estimated an STMR of 0 mg/kg in milk.

The mean estimated dietary burden for cattle is 0.03 ppm. In muscle, kidney and liver, no etoxazole residues (< 0.01 mg/kg) were detectable at the 1 ppm feeding level. In fat, etoxazole residues above the LOQ (0.01 mg/kg) were found at the 1 ppm level, but no residues (0.015 × 0.03 = 0.0005 mg/kg; LOD: 0.005 mg/kg) are expected to be detected in fat at the mean estimated dietary burden of 0.03 ppm. The Meeting estimated STMRs of 0 mg/kg in meat and offal and 0.0005 mg/kg of fat.

On the fat basis, the Meeting estimated a maximum residue level of 0.01 (*) mg/kg for meat (fat) from mammals (other than marine mammals) and an STMR value of 0.0005 mg/kg.

The maximum and mean dietary burden for broiler and layer poultry are 0.00 ppm. Therefore, no residues are to be expected at the estimated dietary burden for poultry.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) of etoxazole were calculated for the 13 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.05 mg/kg bw and the calculated IEDIs were 0–1% of the maximum ADI (0.05 mg/kg bw). The Meeting concluded that the long-term intakes of residues of etoxazole, resulting from the uses considered by current JMPR, are unlikely to present a public health concern.

Short-term intake

The 2010 JMPR decided that an ARfD was unnecessary. The Meeting therefore concluded that the short-term intake of residues of etoxazole is unlikely to present a public health concern.

5.14 FENPYROXIMATE (193)

RESIDUE AND ANALYTICAL ASPECTS

Fenpyroximate was evaluated by JMPR in 1995 for the first time and then again in 1999. The 1995 JMPR allocated an ADI of 0–0.01 mg/kg bw. The 2007 JMPR established an ARfD of 0.02 mg/kg.

The 1999 JMPR concluded that the residue definition for compliance with the MRL and for estimation of dietary intake, both for animal and plant commodities should be fenpyroximate and recommended the maximum residue levels for apples, grapes, hops, oranges, cattle kidney, cattle liver, cattle meat and cattle milk.

Following the establishment of an ARfD of 0.02 mg/kg, the Fortieth CCPR decided to advance the MRL for apples to Step 8. Because of acute intake concern, the MRL for grapes was retained at Step 7.

The Meeting received information on the residue analysis, storage stability, use patterns, supervised field trials and fates of residues during processing of citrus, grapes and tomatoes. The supervised field trial information included data on citrus, apples, pears, grapes, cantaloupes, cucumbers, tomatoes, peppers (bell and non-bell) and tree nuts.

Methods of analysis

The analytical methods for fenpyroximate and its Z-isomer were evaluated both in 1995 and in 1999. GC, HPLC and HLPC-MS were suitable for the residues determination in plant materials. HLPC-MS/MS is suitable for animal products.

The Meeting received information on multi-residue analytical methods based on DFG S19 for the determination of fenpyroximate and it's Z-isomer in a range of commodities, processed fractions and some livestock feeds. The limits of quantification being 0.005 mg/kg (apples, citrus, cotton, hops, grapes, peppers, tomatoes, okra, melons and cucumbers); 0.01 mg/kg (apples, grapes, oranges, cotton seed, strawberries, peaches, pears, plums, beans, cucumbers, peppers and tomatoes); 0.02 mg/kg (oranges, orange juice, dry orange pulp and orange oil); 0.05 mg/kg (melons, tomatoes, tomato paste, tomato puree, peppers, pears, almonds and almond hulls) for fenpyroximate and its Z-isomer. Recoveries were within acceptable limits of 70 to 120%, with the exception of some reported recoveries for fenpyroximate in dry orange pulp and orange oil.

Stability of residues in stored analytical samples

The meeting received information on the frozen storage stability of residues of fenpyroximate and its Z-isomer in citrus, cantaloupes, pears, grapes, tomatoes and peppers in the corresponding supervised residues trials. The storage stability data covered the period of storage of field samples for residue analysis.

Incurred residues of fenpyroximate and its Z-isomer were stable under frozen storage conditions in orange RAC for up to 132 days, in orange juice for up to 210 days, in orange dry pulp for up to 196 days and up to 191 days in orange oil. In melons (cantaloupe), fenpyroximate was shown to be stable for up to 12 months and in apples and pears up to 100 days.

Fenpyroximate and its Z-isomer residues were shown to be stable under frozen storage conditions in grapes up to 268 days, in raisins up to 195 days, in raisin waste up to 195 days, in wet and dry pomace up to 177 days, and in grape juice for up to 165 days.

Fenpyroximate residues fortified in peppers were stable under frozen storage (< –20 °C) up to 403 days.

Incurred fenpyroximate and Z-isomer residues were stable under frozen storage conditions (–29 to –10 °C) in tomato whole fruit for up to 626 days, in tomato paste for up to 547 days and in tomato puree for up to 546 days.

Results of supervised field trials on crops

The Meeting received supervised residue trial data following foliar application of fenpyroximate on citrus fruits, cucumbers, melons (cantaloupes), tomatoes, peppers, apples, pears, grapes, and tree nuts.

Residues of fenpyroximate and its Z-isomer were reported in most studies. However as the Z-isomer is not included in the residue definition, it is not included in the estimation of maximum residue levels and not discussed further in this appraisal. Supervised field trials conducted with different formulations at identical varieties, locations and dates were not considered as independent. The highest result according to the corresponding GAP was selected in these cases. Where multiple samples were taken from a single plot, individual results are reported, amongst which the highest result is used for estimation of maximum residue level. Where results from separate plots with distinct characteristics such as different varieties or treatment schedules were reported, results are listed for each plot.

The NAFTA calculator was used as a tool in the estimation of the maximum residue level 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 using expert judgment. 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 fruits

Data were available from supervised trials on oranges, lemons and grapefruits conducted in the USA.

The GAP of fenpyroximate on citrus in the USA is a maximum of two foliar applications at a rate of 0.22 kg ai/ha (not exceeding 0.45 kg ai/ha per growing season), with a PHI of 14 days.

Residues in oranges (whole fruit) from trials in the USA matching critical GAP in rank order were: 0.07, 0.11, 0.18and 0.28 mg/kg.

Residues in lemons (whole fruit) from trials matching critical GAP in the USA in rank order were: 0.17, 0.21 and 0.23 mg/kg.

Residues in grapefruit (whole fruit) from trials matching critical GAP in the USA in rank order were: 0.02, 0.04 and 0.09 mg/kg.

On the basis of the foliar application in the USA, the combined data (whole fruit) in rank order were (n = 10): 0.02, 0.04, 0.07, 0.09, 0.11, 0.17, 0.18, 0.21, 0.23 and 0.28 mg/kg. The Meeting estimated a maximum residue level for the citrus fruit group of 0.5 mg/kg. The previous recommendation of 0.2 mg/kg for fenpyroximate in oranges, sweet and sour, was withdrawn.

The Meeting noted that in trials reported in the evaluation of 1999 JMPR, a reduction factor for residues in whole fruit to pulp of 0.24 can be derived. Taking into account this factor, the Meeting estimated an STMR and HR value of 0.034 and 0.067 mg/kg, respectively.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 0.45 mg/kg, which, when rounded up, was in agreement with the Meeting's estimation.

Apples and pears

Data were available from supervised trials on apples in the EU and pears in the USA and EU.

For apples, the GAP from France, a single application at 8 g ai/100L PHI 21 days, was considered against the field trials from France and Italy from 2001 and 2006. Only one new trial from Germany matched the GAP, with residues of 0.03 mg/kg.

For pears, the critical GAP in the USA is up to two applications at a maximum application rate of 0.11 kg ai/ha (not exceeding 0.11 kg ai/ha per growing season) with a PHI of 14 days. The new data point for pear trials that matched GAP were in rank order: 0.029, < 0.05, 0.052 and 0.10 mg/kg.

From the EU trials, conducted in France, only one trial matched the GAP from Italy, which is a single application at 7 g ai/100L with a PHI of 14 days. This gave a residue value of 0.04 mg/kg.

In the 1999 evaluation of fenpyroximate, the same GAP from France was used to consider residues in apples from French trials, German trials and one Belgian trial which gave the following data in rank order: 0.03, < 0.05, 0.06, 0.06, 0.08, 0.09, 0.09, 0.09, 0.10, 0.11, 0.12, 0.12, 0.15, 0.16, and 0.16 mg/kg. Including the single value from a 2006 trial gives the following data for apples (n = 16): 0.03, 0.03, < 0.05, 0.06, 0.06, 0.08, 0.09, 0.09, 0.09, 0.10, 0.11, 0.12, 0.12, 0.15, 0.16, and 0.16 mg/kg.

The Meeting considered that the EU data from the 1999 evaluation and the residue of 0.04 mg/kg in pears could be combined to recommend a pome fruit MRL of 0.3 mg/kg, with STMR of 0.09 mg/kg and HR of 0.16 mg/kg for apples, also to be used for pears. Use of the NAFTA calculator gives a maximum residue level of 0.31 mg/kg.

The Meeting recommended a maximum residue level of 0.3 mg/kg for pome fruit to replace the current CXL of 0.3 mg/kg for apples.

Grapes

Data were available from supervised field trials on grapes conducted in Southern regions of the EU to support a review of alternative GAP.

The alternative GAP is from Italy which is a single application at a spray concentration of 0.0051 kg ai/hL with a PHI of 28 days.

Eight trials conducted in Italy, France and Spain matched with the GAP from Italy. Residues found in ranked order were (n = 8): < 0.01, < 0.01, 0.01, 0.02, 0.02, 0.03, 0.05 and 0.05 mg/kg. Including data from the 1995 and 1999 evaluations of fenpyroximate with the current data set, with trials from Italy and France matching the same GAP gives residues in rank order (n = 11): < 0.01, < 0.01, 0.01, < 0.02, 0.02, 0.02, 0.03, 0.04, 0.04, 0.05, and 0.05 mg/kg.

The Meeting considered a value of 0.1 mg/kg to be appropriate as a maximum residue level. Use of the NAFTA calculator resulted in a value of 0.1 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg, an STMR of 0.02 mg/kg and HR of 0.05 mg/kg for fenpyroximate in grapes.

The Meeting agreed to withdraw its previous recommendation of a maximum residue level of 1 mg/kg in grapes.

Fruiting vegetables, Cucurbits

Data were available from supervised trials on cucumbers grown under protected cover in the EU and melons (cantaloupes), grown in the field in the USA.

Cucumber

The GAP of fenpyroximate on greenhouse cucumbers in the USA is a single foliar application at maximum rate of 0.11 kg ai/ha with a PHI of 7 days (not exceeding 0.11 kg ai/ha per growing season).

Residues on greenhouse cucumbers in Europe matching representative GAP in the USA were in ranked order: (n = 9): < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, 0.01, 0.02, 0.02 and 0.02 mg/kg.

The Meeting recommended 0.03 mg/kg as a maximum residue level for cucumbers. Using the NAFTA calculator gave an estimate of 0.03 mg/kg. The corresponding STMR is 0.01 mg/kg and HR value is 0.02 mg/kg.

Melons

The GAP of fenpyroximate on melons in the USA is up to two foliar applications at a maximum rate of 0.11 kg ai/ha with a PHI of 3 days (not exceeding 0.22 kg ai/ha per growing season).

Data from eight residue trials on melons in the USA matched this GAP giving residues in rank order: (n = 8): < 0.05, < 0.05, < 0.05, < 0.05, < 0.05, < 0.05, < 0.05 and < 0.05 mg/kg.

The Meeting agreed to recommend a maximum residue level of 0.05(*) mg/kg for melons. The corresponding STMR and HR values are 0.05 (*) mg/kg.

The NAFTA calculator was not used to derive an estimate as all residue values were below the LOQ, making its application unsuitable.

Fruiting vegetables, other than Cucurbits

Data were available from supervised trials (field and greenhouse) on tomatoes conducted in the USA, Spain, Greece, the UK and France and on peppers in the USA.

Tomatoes

The critical GAP in the USA is up to two sprays at an application rate of 0.11 kg ai/ha (not exceeding 0.22 kg ai/ha per growing season) with a PHI of 1 day for both field and greenhouse tomatoes.

Nineteen trials (16 fields including two cherry tomatoes and three greenhouses) were conducted in the USA which matched USA GAP. Residues from fields in rank order were: < 0.05(7), 0.05, 0.05, 0.06, 0.07, 0.07, 0.08, 0.09, 0.11 and 0.12 mg/kg. Residues from greenhouses were: 0.08, 0.08 and 0.14 mg/kg. This combined data set was used for maximum residue level estimation.

Nine trials (four fields and five greenhouses) were conducted in EU (Greece—one, Spain—five, the UK and France—one) matched Spain GAP. Residues from fields were: 0.02, 0.02, 0.04 and 0.04 mg/kg. Residues from greenhouses were: 0.03, 0.04, 0.04, 0.04 and 0.09 mg/kg.

The Meeting recommended 0.2 mg/kg as a maximum residue level using USA data. Using the NAFTA calculator gives an estimate of 0.15 mg/kg using the USA data. The corresponding STMR is 0.06 mg/kg and HR value is 0.14 mg/kg.

Peppers

The critical GAP in the USA is up to two applications at a rate of 0.11 kg ai/ha (not exceeding 0.22 kg ai/ha per growing season) with a PHI of 1 day.

Matching the USA GAP, residues for 13 field trials in rank order were (n = 13): < 0.05(7), 0.057, 0.058, 0.074, 0.075, 0.12 and 0.13 mg/kg, and residues for three greenhouses in rank order were < 0.05, 0.056 and 0.069 mg/kg. This data set was used for maximum residue level estimation.

The Meeting considered a value of 0.2 mg/kg as a maximum residue level. Use of the NAFTA calculator yielded a value of 0.14 mg/kg. The corresponding STMR is 0.053 mg/kg and HR value is 0.13 mg/kg.

On the basis of the STMR and HR for peppers and the default dehydration factor of 7, an STMR and HR for chilli peppers (dry) were calculated to be 0.37 and 0.9 mg/kg respectively. Based on the HR, the Meeting recommended a maximum residue level for chilli peppers (dry) at 1 mg/kg.

On the basis of estimations on tomatoes and peppers, The Meeting agreed to recommend the group MRL 0.2 mg/kg for fruiting vegetables other than cucurbits, except sweet corn and mushroom.

Tree nuts

Data were available from the supervised field trials conducted in the US.

The critical GAP in the USA is two spray applications at a rate of 0.22 kg ai/ha with a PHI of 14 days.

None of the trials matched the GAP as they were conducted at twice the maximum rate. However, all residues (five on almonds, three on walnuts and five on pecans) in nut meat were less than 0.05 mg/kg.

Based on the US residue data for almonds, walnuts and pecans, the Meeting estimated a maximum residue level of 0.05(*) mg/kg, and a STMR value and HR value of 0.05(*) mg/kg for fenpyroximate in tree nuts.

The NAFTA calculator was not used to derive an estimate as all residue values were below the LOQ, making its application unsuitable.

Animal feed commodities

Almond hulls

As the residue data for tree nuts did not match the USA GAP, the data for hulls were not considered appropriate for estimation of a maximum residue level. The Meeting did not make a recommendation for almond hulls.

Fate of residues in processing

The Meeting received information on the fate of incurred residues of fenpyroximate during the processing of citrus, grapes and tomatoes. The processing factors and STMR-P are summarized in Table 1.

Orange dry pulp, apple wet pomace, grape wet/dry pomace and raisins are expected to contain higher residues than respective raw agricultural commodities. The Meeting estimated processing factors of 0.13 for orange juice and 5.3 for orange dry pulp, giving STMR-P values of 0.018 and 0.74 mg/kg for orange juice and dry pulp, respectively. Using the highest residue value of 0.28 mg/kg for oranges and the PF of 5.3 gives a highest value (P) of 1.5 mg/kg.

Multiplying the HR of grapes found in the supervised trials 0.05 mg/kg by the processing factor of 2.7 resulted in an HR-P and proposed MRL estimate of 0.14 and 0.3 mg/kg for dried grapes. The Meeting estimated processing factors of 0.11, 2.8, 9.6 and 2.7 for grape juice, wet pomace, dry pomace and raisins, respectively. Using the HR of 0.05 mg/kg and the PF of 9.6 for dry pomace gives an HR-P of 0.48.

The Meeting estimated processing factors of 0.54 and 0.44 for tomato paste and puree, respectively.

Table 1 Summary of calculated processing factors

Commodity	Processed fraction	Calculated processing factor	Processing factor	STMR/ STMR-P, mg/kg
Orange[a]	RAC			0.14
	Juice	< 0.13, < 0.02, < 0.02	0.13	0.018
	Dry pulp	6.9, 4.75, 5.3	5.3	0.74
Grape	RAC			0.02
	Juice	< 0.11	0.11	0.0022
	Wet pomace	2.8	2.8	0.056
	Dry pomace	9.6	9.6	0.19
	Raisin	2.7	2.7	0.054
Tomato/US	RAC			0.06
	Paste	0.69, 0.38	0.54	0.032
	Puree	0.44, 0.44	0.44	0.026

[a] Based on whole fruit data

Residues of animal commodities

Farm animal studies on dairy cattle were considered by the 1999 JMPR.

The dietary burden of fenpyroximate residues in farm animals was estimated from the diets listed in OECD Feedstuff derived from field crops. Among commodities reviewed by the 1999 JMPR and 2010 JMPR, apple wet pomace (STMR-P, 0.05 mg/kg), citrus pulp, dry (STMR-P, 0.64 mg/kg), grape pomace, wet (STMR-P, 0.06 mg/kg) and tomato pomace, wet (STMR-P, 0.03 mg/kg) can be fed to beef and dairy cattle. Poultry were not exposed to fenpyroximate through treated feed items.

The maximum dietary burden of beef cattle and dairy cattle was estimated using apple pomace, wet and citrus pulp, dry, and provided in Annex table 1 and 2 of the present meeting report. The summary of livestock dietary burdens of fenpyroximate is shown in Table 2.

As reported in 1999 JMPR, the animal feeding study was conducted at a level equivalent to 1, 3 or 10 ppm in the feed. The maximum and mean dietary burdens in beef cattle and dairy cattle are 0.24 and 0.24 ppm of dry matter diet, which is below the lowest feeding level in the animal feeding study. So the maximum residue levels and STMR values for relevant animal commodities are estimated by applying the transfer factor at the lowest feeding level to the dietary burden. The results are summarized in Table 3.

Table 2 Summary of livestock dietary burdens (ppm of dry matter diet)

	US/CAN		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle	0.08	0.08	0.06	0.06	0.24[a]	0.24[a]	-	-
Dairy cattle	0.08	0.08	0.16	0.16	0.24[b]	0.24[b]	-	-

[a] suitable for estimating maximum residue levels and STMRs for meat and edible offal.

[b] suitable for estimating a maximum residue level and STMRs for milk.

Table 3 Summary of residues corresponding to the estimated dietary burden

Dietary burden (ppm) Feeding level[ppm]	Milk	Muscle	Liver	Kidney	Fat
MRL					
	mean	highest	highest	highest	highest
MRL beef or dairy cattle					
(0.24)	0.005*F	0.01*	0.01*	0.01*	0.004
[0, 1] for other than milk [0, 3] for milk	[0, 0.011]	[0, < 0.01]	[0, < 0.003]	[0, < 0.003]	[0, 0.018]

Dietary burden (ppm) Feeding level[ppm]	Milk	Muscle	Liver	Kidney	Fat
STMR					
	mean	mean	mean	mean	mean
STMR beef or dairy cattle					
(0.24)	0.001	0	0	0	0.006
[0, 1] for other than milk [0, 3] for milk	[0, 0.011]	[0, < 0.01]	[0, < 0.003]	[0, < 0.003]	[0, 0.015]

The Meeting confirmed the current CXL 0.01 (*) mg/kg for cattle kidney, 0.01(*) mg/kg for cattle liver, 0.02 mg/kg for cattle liver and 0.005(*) mg/kg for cattle milk.

DIETARY RISK ASSESSMENT

Long-term intake

The acceptable daily intake (ADI) of 0–0.01 mg/kg bw/day based on the NOAEL for reduced body weight gain in a 2-year study in rats was allocated by 1995 JMPR.

International Estimated Daily Intake (IEDI) was calculated for commodities of human consumption for which STMRs for fenpyroximate were estimated. Results are presented in Annex Table 3. The IEDI for the 13 GEMS/Food cluster diets were 6% or less of the maximum ADI. The intake of residues of fenpyroximate resulting from its proposed uses is unlikely to present a public health concern.

Short-term intake

The acute reference dose (ARfD) of 0.02 mg/kg bw was established by the 2007 JMPR.

International Estimates of Short-term Intake (IESTI) have been calculated for the general population (Annex 4) and for children aged 1 to 6 years (Annex 4). The results compared to the proposed ARfD of 0.02 mg/kg bw/day show short-term intakes of 20% and 60% for the general population and for children, respectively. The results indicate that short-term intake of fenpyroximate resulting from proposed uses is unlikely to present a public health concern.

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

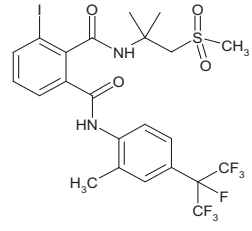
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 0.0685 mg/L (highest achievable concentration)
Rabbit, dermal irritation	Not an irritant
Rabbit, ocular irritation	Not an irritant
Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman test)
Short-term studies of toxicity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

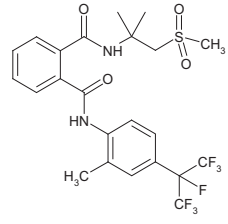
	Value	Study	Safety factor
ADI	0–0.02 mg/kg bw	Two-year study in rat, one-year study in dog	100
ARfD	0.2 mg/kg bw	One- and two-generation studies of reproductive toxicity, developmental neurotoxicity study in rat	100

RESIDUE AND ANALYTICAL ASPECTS

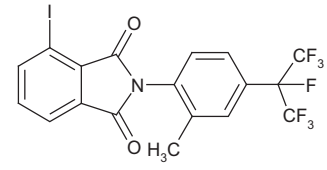
Flubendiamide is an insecticide for use in a broad number of annual and perennial crops against a wide range of lepidopteran pests. The compound is being evaluated by the 2010 JMPR as a new compound, for both residue and toxicological aspects. Data was provided on metabolism of flubendiamide in farm 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

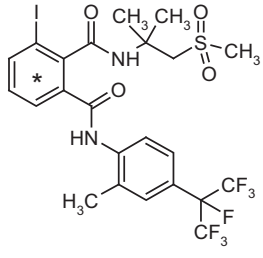


Flubendiamide-iodophthalimide

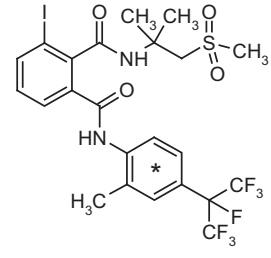
Metabolism in animals

The metabolism of flubendiamide in rats 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 laying hens 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 apples 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 sweet corn 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 rice 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 plant material (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 animal commodities (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 apples and pears 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 apples 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 pears 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 apples and pears 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, 0.23 (3), 0.27, 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 stone fruits 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 cherries according to US GAP. Residues of flubendiamide at 7 days PHI were 0.19, 0.25, 0.48, 0.57, 0.60, 0.63, 0.99 and 1.0 mg/kg.

Peaches and Nectarines

Nine trials were conducted in the USA and Canada in peaches 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 plums. 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 grapes 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, 0.40, 0.43, 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 Brassica vegetables 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 broccoli; 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 cabbages 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, 0.27, 0.43, 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 Brussels sprouts in Australia in 2006. In four trials conducted according to GAP residues of flubendiamide at 3 days PHI were 0.08, 0.23, 0.50 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 cucurbit vegetables 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), 0.04, 0.05, 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 sweet corn 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 leaf and head lettuce, 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, 0.78, 0.97, 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 leaf lettuce trials conducted in 2006 according to GAP, residues of flubendiamide at a 1 day PHI were 0.95, 1.6 (2), 1.8, 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 legume vegetables 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 green beans.

Trials were conducted with beans and peas 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, 0.43, 0.45, and 0.90 mg/kg in peas with pods.

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 soya beans 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, 0.08 (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 shelled beans (six trials) and shelled peas (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 < 0.01 (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 cowpeas and dry peas 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, 0.18 (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, 1.3, 2.1, 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 soya bean forage and hay 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, 7.9, 8.0, 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, 26, 29 (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 forage and hay from cowpeas and vines and hay from peas in the USA according to GAP.

Residues at 3 days PHI from six trials in cowpea forage were: 3.9, 4.2, 5.5, 6.6, 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), 3.1, 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, 12, 15, 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 maize forage 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), 3.8 (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 almonds in the USA according to GAP, residues in almond hulls at 14 days PHI were 0.98, 1.4, 1.4, 2.1, 2.4, 2.5, 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 cotton gin trash at a 28 day PHI were 2.3, 3.5, 6.8, 8.1 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

Laying hens 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).

Lactating cows 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 poultry 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.

5.16 FLUDIOXONIL (211)

RESIDUE AND ANALYTICAL ASPECTS

Fludioxonil, a fungicide to control plant-pathogenic fungi such as *Botrytis cinerea,* was first evaluated at the 2004 JMPR Meeting. That Meeting established an ADI of 0–0.4 mg/kg bw and considered that an ARfD was unnecessary. The Meeting concluded that the residue definition for plant commodities for compliance with the MRL and for consumer risk assessment was fludioxonil only. A number of maximum residue levels were proposed, but in 2004, no maximum residue level was recommended for the post-harvest use on pomegranate or yam. At that time no GAP was available for pomegranate and the number of trials at the critical GAP for yams was insufficient. A maximum residue level for citrus fruit was recommended based on post-harvest uses. However, since the last evaluation a new GAP has been introduced for post-harvest applications of fludioxonil to citrus fruits, in which the maximum application rate has been doubled and further residue studies have been carried out. Furthermore, additional data has been submitted by the manufacturer to support the use of fludioxonil on pomegranate and root & tuber vegetables.

Methods of analysis

In the newly submitted supervised residue trials, fludioxonil (parent only) was analysed by either method REM 133.04 or AG-597B, or slight modifications thereof. JMPR 2004 concluded the following on these methods: 'Methods REM-133/AG631A and AG-597 are suitable for the determination of fludioxonil in samples of plant origin. The methods are fully validated for a range of crops and crop types.'

In the current trials, the methods were validated for the range of LOQ to at least the highest residue value measured, with an LOQ of 0.02 mg/kg for citrus fruits, sweet potato and pomegranate, 0.03 mg/kg for older pomegranate studies and 0.04 mg/kg for yams.

Stability of pesticide residues in stored analytical samples

The 2004 Meeting concluded that fludioxonil is stable in an array of stored frozen commodities. No degradation of fludioxonil was observed in any frozen commodity throughout the duration of the studies. Fludioxonil is stable for at least 24 months in frozen samples of the following commodities: cereal grains, cereal straw, apple, tomato, grape, pea, rape-seed, maize grain, maize meal, sorghum hay, potato tuber and potato flake. Fludioxonil is stable for at least 12 months in frozen broccoli, cabbage and carrots and for 9 months in frozen chives. Fludioxonil is also stable for at least 3 months in frozen peach, plum, cherry and blueberry.

Additional storage stability studies on citrus, sweet potato and yam were available to the Meeting. Fludioxonil is stable for at least 14 months in frozen samples of citrus, and at least 10 months in lemon juice and pulp. Fludioxonil is also stable for at least 10 months in sweet potato and for 5 months in yam. Based on these data, the Meeting concluded, that no storage stability problems are to be expected in these commodities since samples were stored for less than the period tested for in the storage stability studies. Storage of pomegranate samples is covered by results for citrus fruits.

Results of supervised trials on crops

Supervised trials with fludioxonil were conducted with post-harvest treatment of citrus fruit, pomegranate, sweet potato and yam.

Citrus fruits

Since 2004, 27 new trials have been carried out in the USA and in the EU. Citrus fruit was treated with fludioxonil in post-harvest residue trials in oranges (10), lemons (5), grapefruit (4) and mandarins (8). Citrus fruits were treated once, twice or three times by post-harvest dip or drench (30-240 g ai/hL) or spray (1-4 g ai/tonne fruit).

The critical GAP in the US is 2 applications of dip or drench at 120 g ai/hL and/or spray at 4 mg ai/kg fruit. No minimum time for interval between applications is given. As residue decline studies show that the residue is stable in time, interval duration does not significantly influence final residue values. For compliance with worst case GAP, all trials conducted with two applications at worst case GAP-rate (± 25% of overall application rate) were considered, regardless the length of interval between applications.

The selected residue levels on orange (seven trials; two treatments at GAP rate) in ranked order, were: 2.9, 3.5, 4.0, 4.4, 4.6, 5.0 and 7.2 mg/kg. The levels on mandarin (seven trials; two treatments at GAP rate) were: 2.9, 5.6 (2), 5.8, 7.0, 7.3 and 7.8 mg/kg. The residue level on lemon (two trials at 75% of GAP rate) were: 2.5 and 3.9 mg/kg.

No trials that were summarised in JMPR 2004 complied with the newly introduced critical GAP. The Meeting decided to estimate a maximum residue level based on the data from mandarin; the data from orange and lemon are used for support. The Meeting estimated a maximum residue level for whole citrus of 10 mg/kg. In the selected trials, residue in the pulp was not measured. However, in 47 of the other citrus trials residues in peel and pulp were determined and a processing factor of 0.07 for residue in citrus pulp could be derived. An STMR-P of 0.41 (5.8×0.07) mg/kg was estimated, for citrus pulp.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 11 mg/kg. Since the total dose is 8 mg/kg (post-harvest), the Meeting considered that 10 mg/kg was sufficient.

Pomegranates

Since 2004, four post-harvest trials on pomegranate have been conducted according to the critical GAP in the USA, i.e. a single dip or drench application at 60 g ai/hL. Another two trials with the same applications were summarised in JMPR 2004. All trials are considered appropriate to be included in MRL setting and calculation of STMR.

The residue levels on pomegranate (six trials) in ranked order, were: 0.65, 0.80, 0.95, 1.1, 1.2 and 1.3 mg/kg. The Meeting estimated a maximum residue level for pomegranate 2 mg/kg and an STMR of 1 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 2 mg/kg.

Root and tuber vegetables

Four post-harvest trials on sweet potato tubers have been conducted in the USA and two trials on yam tubers have been conducted in Puerto Rico (also summarised in JMPR 2004, but with some errors). All trials were conducted according to the range specified in the recommended GAP. Two sweet potato trials in the USA (2.5 and 2.8 mg/kg) and two yam trials in Puerto Rico (4.2 and 5.7 mg/kg) comply with the critical GAP, i.e., a single application at 60 g ai/hL.

The residue levels on yams and sweet potatoes (four trials) were used in mutual support. The Meeting estimated a maximum residue level for yams and sweet potatoes of 10 mg/kg and an STMR of 3.5 mg/kg.

The maximum residue level estimate derived from use of the NAFTA statistical calculator was 9 mg/kg,

Fate of residues during processing

Post-harvest treatments are normally reserved for high value commodities and it is therefore unlikely that treated crops will undergo industrial processing. However, information on the fate of incurred residues of fludioxonil during the processing of citrus fruits was submitted to the Meeting for completeness. The processed commodities obtained from industrial processing are juice, marmalade, and wet and dry pomace from orange (one trial), and juice, oil, and pomace from lemon (one trial). For household processing (peeling and washing), data on residues in peel, pulp and washed fruit was available in most of the supervised residue trials.

For pulp, the calculated processing factor is very low (0.07) due to the fact that the fruit was peeled on the same day as the day of last application. Therefore, time for translocation of fludioxonil from the peel to the pulp was very limited, explaining the low processing factor for pulp. Only in 3 samples, another application was made 2 days before, as in all other samples, no other application was performed or it was performed at the same day as the last application. If the fruit is stored for longer periods before peeling, the processing factor for pulp will likely be higher. The other way around is the processing factor of 3.2 for peel derived from a worst-case scenario and this factor will likely be lower if fruit is stored for longer periods before peeling. For washed fruit, it can be concluded that the processing factor is not influenced by the period between last treatment and the washing of the fruit. Therefore, all trials are included in the calculation of the overall processing factor for washing (0.67).

Data on different kinds of citrus fruit (lemon, mandarin, orange and grapefruit) can be combined to derive one processing factor for each processed commodity of citrus fruit.

Processing factors and STMR-P values in citrus fruit

Commodity	Processed commodity	PF (mean)	STMR-P
Citrus fruit (STMR = 5.8)	pulp	0.07	0.41
	juice	0.11	0.64
	dry pomace	6.4	37

Residues in animal commodities

Waste pulp (pomace) from processed citrus fruits can contribute to animal diets and is listed on the OECD Dietary Burden Calculator. However, in commercial practice, post-harvest treatment is normally reserved for high value commodities and it is therefore unlikely that pomace from treated fruits would be fed to livestock. As a result of this, the Meeting considered that the proposed MRL and STMR for fludioxonil in citrus crops will not change the dietary burden calculation which was evaluated at the 2004 JMPR meeting.

Pomegranate and tropical root and tuber vegetables are not regarded as crops contributing significantly to animal diets and do not appear on the OECD Dietary Burden Calculator. Therefore the Meeting retained the recommendations for animal commodities as reported in 2004.

DIETARY RISK ASSESSMENT

Long-term intake

The IEDI of fludioxonil based on the STMRs for 48 commodities for the 13 GEMS/Food regional diets were 1–2% of the maximum ADI of 0.4 mg/kg bw (see Annex 3 of the Report). The Meeting

concluded that the long-term dietary intake of residues of fludioxonil is unlikely to present a public health concern.

Short--term intake

The 2004 JMPR decided that an ARfD for fludioxonil is unnecessary. The Meeting therefore concluded that the short-term dietary intake of fludioxonil residues is unlikely to present a public health concern.

5.17 FLUOPYRAM (243)

TOXICOLOGY

Fluopyram is the International Organization for Standardization (ISO)–approved common name for *N*-(2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl)-2-(trifluoromethyl)benzamide (International Union of Pure and Applied Chemistry [IUPAC]) (Chemical Abstracts Service [CAS] No. 658066-35-4), a novel broad-spectrum fungicide from the pyridinyl-ethyl-benzamide class. Fluopyram acts by inhibiting the enzyme succinate dehydrogenase (SDH, so-called complex II in the mitochondrial respiratory chain), which is a functional part of the tricarboxylic acid cycle, linked to mitochondrial electron transport. SDH consists of four subunits (A, B, C and D), and fluopyram, like a number of SDH inhibitors, acts by blocking the enzyme binding site for ubiquinone, which is formed by the subunits B, C and D. Fluopyram has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed at the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR).

All pivotal studies were certified as complying with good laboratory practice (GLP) or an approved quality assurance programme.

Biochemical aspects

In rats given [^{14}C]phenyl ring–labelled or [^{14}C]pyridyl ring-labelled fluopyram orally by gavage, absorption was rapid and accounted for 93% of the total recovered radioactivity after a single dose of 5 mg/kg body weight (bw) (both labels) or 250 mg/kg bw (phenyl ring label). The maximum plasma concentrations of radio-labelled material were reached after 0.7–3 h with the pyridyl ring label and after 8–48 h with the phenyl ring label. Radiolabel was widely distributed throughout the body. Residues in tissues 168 h after a single dose of 5 mg/kg bw accounted for less than 0.5% (pyridyl ring label) or 3–5% (phenyl ring label) of the administered dose, with liver and kidney containing the highest concentrations of residues. Elimination of the radiolabel was via the faeces (39–64%) and the urine (35–60%), with evidence of significant enterohepatic circulation. In bile duct–cannulated rats, extensive biliary excretion (79–87%) was demonstrated. The terminal elimination half-lives of radio-labelled material ranged from 24 to 53 h for the phenyl ring–labelled fluopyram and from 56 to 73 h for the pyridyl ring–labelled fluopyram.

Fluopyram was extensively metabolized, and more than 20 metabolites were identified. The metabolism was principally oxidative and took place mainly at the ethylene bridge of the molecule. Hydrolytic cleavage of the molecule and subsequent oxidation were also observed, as was conjugation of several hydroxylated metabolites with glucuronic acid and, to a lesser extent, sulfate.

Toxicological data

Fluopyram was of low toxicity after oral and dermal exposure in rats (median lethal dose [LD_{50}] > 2000 mg/kg bw), and neither mortality nor systemic toxicity occurred at this limit dose. After inhalation exposure in rats, fluopyram was also of low toxicity (median lethal concentration [LC_{50}] > 5.1 mg/L), and the clinical signs observed were nonspecific and reversible within 1–5 days. Fluopyram was not a skin irritant in rabbits was only minimally irritating to the eye of rabbits and was not a skin sensitizer in the local lymph node assay in mice.

Following repeated administration of fluopyram to mice, rats and dogs, the liver was the major target organ in all species tested. The effects noted at lower doses (increased liver weights, hepatocellular hypertrophy) were consistent with the induction of hepatic cytochrome P450 (CYP), whereas effects observed at higher doses included hepatocellular degeneration or necrosis and related clinical chemistry findings (e.g., increased serum levels of liver enzymes, cholesterol and triglycerides). In mice, the adrenals were an additional target. The thyroid effects seen in mice and

rats were considered to be secondary to the enhanced hepatic clearance of thyroid hormones. The hyaline droplet nephropathy observed in male rats was considered not to be relevant to humans, as this effect is due to an accumulation of α_{2u}-globulin in the proximal tubules, a protein that is found only in trace amounts in humans.

In a 28-day range-finding study in mice, the no-observed-adverse-effect level (NOAEL) was 150 ppm (equal to 24.7 mg/kg bw per day), based on effects in liver (hepatocellular necrosis) and adrenals (hypertrophy of the zona fasciculata) at 1000 ppm and above. In a 90-day study in mice, the NOAEL was 150 ppm (equal to 26.6 mg/kg bw per day), based on effects in liver (hepatocellular necrosis) and adrenals (cortical vacuolation) at 1000 ppm.

In a 28-day range-finding study in rats, the NOAEL was 400 ppm (equal to 31 mg/kg bw per day), based on effects in the liver (increased liver weight, hepatocellular hypertrophy, enzyme induction) and the thyroid (hypertrophy of follicular cells, colloid depletion) at 3200 ppm. In a 90-day study in rats, the NOAEL was 200 ppm (equal to 12.5 mg/kg bw per day), based on effects in the liver (hepatocellular hypertrophy and vacuolation) and the thyroid (hypertrophy of follicular cells) at 1000 ppm and above. Effects at higher doses (3200 ppm, equal to 204 mg/kg bw per day) included decreased body weight gain and food consumption, decreased haemoglobin and haematocrit, clinical chemistry changes and increased levels of triiodothyronine (T_3), thyroxine (T_4) and thyroid stimulating hormone (TSH). It was noted that levels of these hormones more often change in opposite directions, with decreases in T_3 and/or T_4 being associated with increases in TSH. This pattern was subsequently observed in mechanistic studies described below.

In a 28-day range-finding study in dogs, the NOAEL was 150 mg/kg bw per day, based on treatment-related clinical signs (liquid faeces) and liver toxicity (increased liver weight, clinical chemistry changes, histopathological findings) at 750 mg/kg bw per day. In a 90-day study in dogs, the NOAEL was 800 ppm (equal to 28.5 mg/kg bw per day), based on liver toxicity (increased liver weight, histopathological findings, including necrosis, related clinical chemistry changes) at 5000 ppm and above. In a 1-year study in dogs, the NOAEL was 400 ppm (equal to 13.2 mg/kg bw per day), based on liver toxicity (hepatocellular hypertrophy, increased serum levels of alkaline phosphatase) at 2000 ppm. The overall NOAEL for the 90-day and 1-year dog studies was 28.5 mg/kg bw per day.

Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. In an 18-month study of carcinogenicity in mice, the NOAEL for oncogenicity was 150 ppm (equal to 20.9 mg/kg bw per day), based on an increased incidence of follicular cell adenoma in the thyroid in males at 750 ppm. The NOAEL for non-neoplastic changes was 30 ppm (equal to 4.2 mg/kg bw per day), based on liver toxicity (hepatocellular single-cell degeneration/necrosis) and thyroid changes (follicular cell hyperplasia) in males at 150 ppm and above.

In a mechanistic study on thyroid tumorigenesis in male mice, increased liver weights, hepatocellular hypertrophy, increased hepatic CYP content and marked increases in hepatic activities of pentoxyresorufin *O*-dealkylase (PROD) (CYP2B) and benzyloxyresorufin *O*-dealkylase (BROD) (CYP3A) were observed after 3 and 14 days of exposure to fluopyram at 2000 ppm (equal to 308–314 mg/kg bw per day), whereas ethoxyresorufin *O*-deethylase (EROD) (CYP1A2) activity was only slightly increased and uridine diphosphate-glucuronosyltransferase (UDPGT) activity (using 4-nitrophenol as a substrate) was unaffected. However, decreased T_4 and increased TSH levels were noted after 3 and 14 days. The pattern of changes in the liver and thyroid end-points was similar to the profile observed in male mice treated with phenobarbital at 80 mg/kg bw per day in a parallel study.

In a 3-day study of effects on gene expression in the liver of male mice, quantitative polymerase chain reaction (PCR) analyses demonstrated that both fluopyram (2000 ppm, equivalent to approximately 286 mg/kg bw per day) and phenobarbital (80 mg/kg bw per day) induced an upregulation of the sulfotransferase and UDPGT gene transcripts. For most genes, at the doses used, effects were more pronounced with fluopyram than with phenobarbital. Further mechanistic studies in male mice demonstrated that both fluopyram (2000 ppm, equivalent to approximately

286 mg/kg bw per day) and phenobarbital (80 mg/kg bw per day) significantly increased the clearance of intravenously administered T_4. In vitro studies showed that fluopyram did not affect the thyroid peroxidase-catalysed oxidation of guaiacol.

The Meeting concluded that for the thyroid tumours in male mice, there was evidence that the mode of action was likely to be secondary to enhanced hepatic clearance of thyroxine, leading to hormone imbalance. The marked quantitative species differences in the inherent susceptibility for neoplasia in response to thyroid hormone imbalance allowed for the conclusion that the fluopyram-induced thyroid tumours in mice are not relevant to humans.

In a 24-month study of toxicity and carcinogenicity in rats, the NOAEL for oncogenicity was 150 ppm (equal to 8.6 mg/kg bw per day), based on an increased incidence of liver cell tumours (adenoma and carcinoma) in females at 1500 ppm (equal to 89 mg/kg bw per day). The NOAEL for non-neoplastic changes was 30 ppm (equal to 1.2 mg/kg bw per day), based on increased incidences of findings in the liver (hepatocellular hypertrophy and eosinophilic foci in males) at 150 ppm and above. The changes in the thyroid (follicular cell hypertrophy, colloid alteration) at 150 ppm and above were attributable to the apparent susceptibility of rats to thyroid hormone imbalance and were therefore not considered relevant to humans.

In a mechanistic study on liver tumorigenesis in female rats, increased liver weights, hepatocellular hypertrophy, increased cell proliferation in the centrilobular and periportal zones of the hepatic lobules, increased hepatic CYP content and moderate to marked increases in hepatic activities of EROD, PROD, BROD and UDPGT were observed after 7 days of exposure to fluopyram (3000 ppm, equal to 193 mg/kg bw per day). The pattern of changes was similar to the profile observed in female rats treated with phenobarbital at 80 mg/kg bw per day in a parallel study.

The Meeting concluded that the relevance of the liver tumours in female rats to humans could not be discounted, as the results of the mechanistic studies were only partly sufficient to support the proposed phenobarbital-like mode of action. In particular, activation of the constitutive androstane receptor (CAR) by fluopyram has not been clearly demonstrated, and there is a lack of dose–response concordance with key precursor events and tumour incidence. However, the Meeting noted that the mode of action for the observed liver tumours is a high-dose phenomenon that would be anticipated to exhibit a threshold.

Fluopyram was tested for genotoxicity in vitro and in vivo in an adequate range of assays. It was not found to be genotoxic in mammalian and microbial test systems.

The Meeting concluded that fluopyram was unlikely to be genotoxic.

On the basis of the absence of genotoxicity, the human non-relevance of the thyroid tumours in mice and the fact that the dose–response relationship for the liver tumours in rats would be anticipated to exhibit a threshold, the Meeting concluded that fluopyram is unlikely to pose a carcinogenic risk to humans at dietary exposure levels.

In a two-generation reproductive toxicity study in rats, the NOAEL for effects on fertility was 1200 ppm (equal to 82.4 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity was 220 ppm (equal to 13.9 mg/kg bw per day), based on decreased body weight and/or body weight gain in females and liver toxicity in both sexes at 1200 ppm. The NOAEL for offspring toxicity was 220 ppm (equal to 13.9 mg/kg bw per day), based on decreased body weight gain and decreased spleen and thymus weights at 1200 ppm.

In a prenatal developmental toxicity study in rats, the NOAEL for maternal toxicity was 30 mg/kg bw per day, based on decreased body weight gain and food consumption and increased liver weights and hepatocellular hypertrophy at 150 mg/kg bw per day and above. The NOAEL for prenatal developmental toxicity was 150 mg/kg bw per day, based on lower fetal body weights and an increased incidence of visceral and skeletal variations at 450 mg/kg bw per day.

In a prenatal developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 25 mg/kg bw per day, based on reduced body weight gain and food consumption at 75 mg/kg bw per

day. The NOAEL for prenatal developmental toxicity was 25 mg/kg bw per day, based on reduced fetal body weights and an increased number of small fetuses ("runts") at 75 mg/kg bw per day.

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

In an acute neurotoxicity study in rats, the NOAEL for neurotoxicity was 50 mg/kg bw, based on decreased motor and locomotor activity at 100 mg/kg bw and above. In a subchronic study of neurotoxicity in rats, the NOAEL for neurotoxicity was 2500 ppm (equal to 164.2 mg/kg bw per day), the highest dose tested. The NOAEL for general toxicity was 500 ppm (equal to 33.2 mg/kg bw per day), based on decreased body weight, body weight gain and food consumption and increased liver weight at 2500 ppm.

Fluopyram-pyridyl-carboxylic acid (AE C657188), a plant metabolite of fluopyram, was of low acute oral toxicity in rats (LD_{50} > 2000 mg/kg bw) and showed no genotoxic potential in vitro in mammalian or microbial test systems. In a 28-day oral toxicity study in rats, there was no evidence of toxicity up to dietary concentrations of 20 000 ppm (equal to 1574 mg/kg bw per day), the highest dose tested.

Fluopyram-methyl-sulfoxide (AE 1344122), a plant metabolite of fluopyram, was of low acute oral toxicity in rats (LD_{50} > 2000 mg/kg bw) and showed no genotoxic potential in vitro in mammalian or microbial test systems. In a 28-day oral toxicity study in rats, the NOAEL was 2000 ppm (equal to 152 mg/kg bw per day), based on reduced body weight gain and food consumption in both sexes and kidney toxicity (tubular degeneration and single-cell necrosis, urinalysis findings) in females at 20 000 ppm.

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

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) for fluopyram of 0–0.01 mg/kg bw, based on a NOAEL of 1.2 mg/kg bw per day for changes in liver (hepatocellular hypertrophy, eosinophilic foci) at 6.0 mg/kg bw per day in a 2-year rat study. A safety factor of 100 was applied. The ADI provides a margin of at least 860-fold relative to the NOAEL for liver tumours in rats.

The Meeting established an acute reference dose (ARfD) for fluopyram of 0.5 mg/kg bw, based on the NOAEL of 50 mg/kg bw for decreases in measures of motor and locomotor activity at 100 mg/kg bw in an acute neurotoxicity study in rats. A 100-fold safety factor was applied.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Thirteen-week study of toxicity	Toxicity	150 ppm, equal to 26.6 mg/kg bw per day	1000 ppm, equal to 188 mg/kg bw per day
	Eighteen-month study of toxicity and carcinogenicity	Toxicity	30 ppm, equal to 4.2 mg/kg bw per day	150 ppm, equal to 20.9 mg/kg bw per day
		Carcinogenicity	150 ppm, equal to 20.9 mg/kg bw per day	750 ppm, equal to 105 mg/kg bw per day
Rat	Thirteen-week study of toxicity	Toxicity	200 ppm, equal to 12.5 mg/kg bw per day	1000 ppm, equal to 60.5 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
	Two-year study of toxicity and carcinogenicity	Toxicity	30 ppm, equal to 1.2 mg/kg bw per day	150 ppm, equal to 6.0 mg/kg bw per day
		Carcinogenicity	150 ppm, equal to 8.6 mg/kg bw per day	1500 ppm, equal to 89 mg/kg bw per day
	Multigeneration study of reproductive toxicity	Fertility	1200 ppm, equal to 82.4 mg/kg bw per day[a]	—
		Parental toxicity	220 ppm, equal to 13.9 mg/kg bw per day	1200 ppm, equal to 82.4 mg/kg bw per day
		Offspring toxicity	220 ppm, equal to 13.9 mg/kg bw per day	1200 ppm, equal to 82.4 mg/kg bw per day
	Developmental toxicity study[b]	Maternal toxicity	30 mg/kg bw per day	150 mg/kg bw per day
		Embryo and fetal toxicity	150 mg/kg bw per day	450 mg/kg bw per day
	Acute neurotoxicity study[b]	Neurotoxicity	50 mg/kg bw	100 mg/kg bw
	Subchronic neurotoxicity study	Neurotoxicity	2500 ppm, equal to 164.2 mg/kg bw per day[a]	—
Rabbit	Developmental toxicity study[b]	Maternal toxicity	25 mg/kg bw per day	75 mg/kg bw per day
		Embryo and fetal toxicity	25 mg/kg bw per day	75 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity[c]	Toxicity	800 ppm, equal to 28.5 mg/kg bw per day	2000 ppm, equal to 66.1 mg/kg bw per day

[a] Highest dose tested.

[b] Gavage administration.

[c] Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.5 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	Rapid; approximately 93%
Distribution	Wide; highest concentrations in liver and kidney
Rate and extent of excretion	> 95% within 168 h (35–60% in urine; 39–64% in faeces; up to 79–87% in bile)

Potential for accumulation	None
Metabolism in animals	Extensive; hydroxylation, oxidation and hydrolytic cleavage of the molecule, followed by conjugation (glucuronic acid, sulfate)
Toxicologically significant compounds (animals, plants and the environment)	Fluopyram
Acute toxicity	
Rat, LD_{50}, oral	> 2000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.1 mg/L (4 h, nose-only exposure)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Minimally irritating
Mouse, dermal sensitization	Not sensitizing (local lymph node assay)
Short-term studies of toxicity	
Target/critical effect	Liver (enzyme induction, hypertrophy, single-cell necrosis) in mice, rats and dogs, adrenals (cortical hypertrophy and vacuolation) in mice
Lowest relevant oral NOAEL	12.5 mg/kg bw per day (90-day study in rats)
Lowest relevant dermal NOAEL	300 mg/kg bw per day (28-day study in rats)
Lowest relevant inhalation NOAEC	No data
Long-term toxicity and carcinogenicity	
Target/critical effect	Liver (hypertrophy, single-cell degeneration/necrosis) in mice and rats
Lowest relevant NOAEL	1.2 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Unlikely to pose a carcinogenic risk to humans at levels of dietary exposure
Genotoxicity	
	No genotoxic potential
Reproductive toxicity	
Reproductive target/critical effect	No effects on fertility at highest dose tested; decreased body weight gain in pups at parentally toxic dose
Lowest relevant reproductive NOAEL	13.9 mg/kg bw per day for offspring toxicity (two-generation study in rats)
Developmental target/critical effect	Decreased fetal weight and increased number of small fetuses at maternally toxic dose
Lowest relevant developmental NOAEL	25 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity	Decrease in motor and locomotor activity; NOAEL: 50 mg/kg bw
Subchronic neurotoxicity	No evidence of neurotoxicity at highest dose tested
Other toxicological studies	
Mechanistic studies	Studies on liver enzyme induction (rats, mice) and thyroid hormone levels (mice) suggest a non-genotoxic threshold

	mechanism for carcinogenicity
Studies on plant metabolites	Fluopyram-pyridyl-carboxylic acid (AE C657188): lower toxicity than parent compound, not genotoxic in vitro
	Fluopyram-methyl-sulfoxide (AE 1344122): lower toxicity than parent compound, not genotoxic in vitro
Medical data	
	Limited data; no adverse health effects reported in manufacturing plant personnel

Summary

	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Two-year study of toxicity in rat	100
ARfD	0.5 mg/kg bw	Acute neurotoxicity study in rat	100

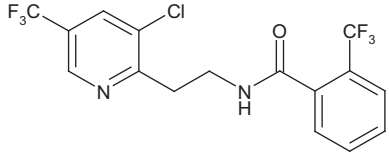
RESIDUE AND ANALYTICAL ASPECTS

Fluopyram, a pyridylethylamide broad spectrum fungicide, is being developed for protection against a range of Ascomycete and Deuteromycete diseases in many horticultural and arable crops. Fungicidal action is by the inhibition of succinate dehydrogenase (complex II) within the fungal mitochondrial respiratory chain, thus blocking electron transport. Fluopyram inhibits spore germination, germ tube elongation, mycelium growth and sporulation. Within plants, fluopyram shows translaminar activity and some upwards movement within the xylem.

Authorisations exist for the use of fluopyram (SC formulation) in China and registration has recently been granted in Romania for use on grapes. Other uses are currently being progressed in Europe and North America.

Residue and analytical aspects of fluopyram were considered for the first time by the present meeting. The manufacturer submitted studies on metabolism, analytical methods, supervised field trials, processing, freezer storage stability, environmental fate in soil and rotational crop residues.

Fluopyram is N-{2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethyl}-2-(trifluoromethyl)benzamide. It is relatively insoluble in water (15 mg/L), stable to hydrolysis, of low volatility (1.2 x 10^{-6} Pa at 20 °C), has a log P_{OW} of 3.3 and is soluble (> 250 g/L) in methanol, dichloromethane, acetone, ethyl acetate and dimethyl sulfoxide.



Fluopyram (AE C656948)

The following abbreviations are used for the metabolites discussed below:

BZM	-benzamide	2-(trifluoromethyl)benzamide
PAA	-pyridyl-acetic acid	[3-chloro-5-(trifluoromethyl)pyridin-2-yl]acetic acid
PCA [a]	-pyridyl-carboxylic acid	3-chloro-5-(trifluoromethyl)pyridine-2-carboxylic acid
7-OH	-7-hydroxy	N-{2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-2-hydroxyethyl}-2-trifluoromethyl) benzamide
8-OH	-8-hydroxy	N-{2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1-hydroxyethyl}-2-

	trifluoromethyl) benzamide
E-olefine	N-{(E)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl}-2-trifluoromethyl) benzamide
Z-olefine	N-{(Z)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide
GA	glucuronic acid
glyc	glycoside
glc	glucoside

[a] Also a metabolite of fluopicolide (M05)

Animal metabolism

The Meeting received information on the metabolism of radio-labelled fluopyram (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings) in rats, lactating goats and laying hens.

In rats, absorption was rapid and residues in tissues at 168 h accounted for < 0.5% (pyridyl ring-label) or 3–5% (phenyl ring-label) of the administered dose, with liver and kidney containing the highest concentrations of residues. Elimination of the radiolabel was via the faeces (39–64%) and the urine (35–60%).

The metabolism of fluopyram in rats was principally oxidative and took place mainly at the ethylene bridge of the molecule. Also, hydrolytic cleavage of the molecule and subsequent oxidation was observed, as was conjugation of several hydroxylated metabolites with glucuronic acid and to a lesser extent with sulphate. Somewhat higher levels of unchanged parent compound in tissues of female rats compared to male rats indicated that the metabolic transformation of the parent compound was generally more pronounced in males.

Lactating goats were orally dosed with [pyridyl-2,6-^{14}C]- or [phenyl-U-^{14}C]-fluopyram at doses equivalent to approximately 45 ppm in the feed for 5 consecutive days and sacrificed 24 hours after the last dose.

The majority of the administered dose was recovered in excreta (29–36% in faeces, 52–53% in urine) with an estimated 7–18% assumed to have remained in the gastro-intestinal tract. Radioactivity retained in tissues or secreted in milk accounted for about 5% (phenyl-label) and less than 1% (pyridyl-label) of the administered dose. Overall 82–93% of administered radioactivity was accounted for.

Radio-labelled residues (fluopyram equivalents) in the phenyl-label study were highest in liver (8.4 mg/kg) and kidney (2.3 mg/kg) and were 0.74 mg/kg in muscle, 0.4 mg/kg in fat and 0.25 mg/kg in milk. Except for fat, much lower residues (but a similar distribution) occurred in the pyridyl-label study, with highest residues in liver (1.4 mg/kg) and kidney (0.4 mg/kg) and were 0.04 mg/kg in muscle and 0.05 mg/kg in milk. In fat, residues reported in the two studies were comparable (0.37–0.4 mg/kg).

In the phenyl-label study, the TRR-values in milk increased continuously over the 5 day dosing period without reaching a plateau, suggesting ongoing absorption, rapid distribution and delayed excretion. The equivalent concentrations in milk samples ranged from 0.05 (8 hours after the first dose) to 0.45 mg/kg (24 hours after the last of 5 doses), with a cumulative total representing 0.56% of the total applied dose. However, in the pyridyl-label study, TRR-values increased during the 8 hour period after each dosing and then decreased (suggesting rapid absorption, distribution and elimination) and reached plateau-levels within 24 hours. The highest TRR-value in milk (0.063 mg/kg) was detected 32 hours after the first dose, with a cumulative total TRR of 0.08% of the total applied dose.

The two metabolism studies were combined using appropriate scaling to obtain an overall picture of the metabolism and the scaled results indicated that residues of BZM represented 98% of the TRR in muscle, 89% TRR in milk, 81% TRR in liver, 73% TRR in kidney and 48% in fat. The Z- and E-olefine isomers made up about 13% and 8% TRR in fat respectively. Residues of the parent compound were about 18% TRR in fat and were less than 1% TRR in all other matrices. Other metabolites were present at less than 10% in any matrix.

Laying hens were orally dosed with [pyridyl-2,6-^{14}C]- or [phenyl-U-^{14}C]-fluopyram at doses equivalent to approximately 26 ppm in the feed for 14 consecutive days and sacrificed 24 hours after the last dose.

The majority of the administered dose was recovered in excreta (83–95%) with an estimated 4–5% assumed to have remained in the gastro-intestinal tract. Radioactivity retained in tissues or found in eggs accounted for about 12% (phenyl-label) and less than 1% (pyridyl-label) of the administered dose. Overall 95–96% of administered radioactivity was accounted for.

Radio-labelled residues in the pyridyl-label study were considerably lower than those in the phenyl-label study (consistent with the results of the goat metabolism studies). Total residues were highest in liver (9.5 mg/kg in the phenyl-label study, 0.54 mg/kg in the pyridyl-label study). In kidney, the phenyl-label residues were 5.8mg/kg and the pyridyl-label residues were 0.24 mg/kg. In muscle, total radioactive residues were 3.3 mg/kg (phenyl-label) and 0.05 mg/kg (pyridyl-label) and were 2.5 mg/kg (phenyl-label) and 0.15 mg/kg (pyridyl-label) in skin. Residues in fat were 1.7 mg/kg in the phenyl-label study and 0.5 mg/kg in the pyridyl-label study.

In eggs, after 8 days, the TRR values in eggs increased to 3.2 mg/kg (phenyl-label study) and to 0.32 mg/kg (pyridyl-label study), reaching a plateau after 8–10 days. The residue-level in the eggs collected from the ovary and oviduct were about 1.5× (phenyl-label) and about 3× (pyridyl-label) higher than those in the laid eggs at the test end, suggesting that the egg yolk was probably the preferred site for the secretion.

The two metabolism studies were combined using appropriate scaling to obtain an overall picture of the metabolism and the scaled results indicated that the BZM metabolite was the major component of the extracted radioactivity identified in muscle (98% TRR), liver (89% TRR), eggs (90% TRR) and fat (68% TRR). The only other metabolite found above 10% TRR was the Z-olefine isomer, found in fat at about 26% TRR. Fluopyram was found in fat at about 2.5% TRR and made up less than 1% TRR in other matrices.

In summary, BZM was the main residue component in edible livestock matrices, making up more than about 90% of the residues in milk, eggs and muscle, about 80–90% of the residues in liver and about 73% of the residues in kidney. The predominant residues in fat were the BZM metabolite (48–68%), the E-/Z-olefine isomers (21–26%) and to a lesser extent fluopyram (18% of the residues in ruminant fat).

The proposed metabolic pathway in livestock (hen and goat) includes hydroxylation of the parent compound to the 7-OH and 8-OH metabolites, the formation of the Z/E-olefines, cleavage of the fluopyram molecule to produce BZM (from the phenyl-label) and PAA (from the pyridyl-label) and conjugation of the hydroxylated parent compound, mainly with glucuronic acid.

These main metabolic reactions are also observed in the rat metabolism studies.

Plant metabolism

The Meeting received information on the metabolism of radio-labelled fluopyram (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings) in grapes, potatoes, and beans after two or three spray applications at a maximum annual application rate of 0.5 kg ai/ha and on red bell pepper applying 5 mg ai/plant through the drip irrigation system. To facilitate metabolite identification in bell pepper a 4× overdose experiment was also performed at an application rate of 20 mg ai/plant.

In grapes treated three times at 42–49 day intervals up to the start of ripening (total 0.5 kg ai/ha) and sampled 18–19 days later, 77–80% (1.3–1.5 mg/kg fluopyram equivalents) of the radioactive residue in grapes was found in the acetonitrile surface wash and a further 19–20% (0.34 mg/kg) was obtained by triple-extraction in acetonitrile/water. Residues in leaves sampled immediately after the second application were 28–64 mg/kg and were 43–48 mg/kg at harvest 19 days after the third application.

Between 94% and 99% of the TRR was identified, mostly as the unchanged fluopyram (96–98% in grapes and 91–92% in leaves) with minor components being the BZM, the 7-OH (and its glycoside), the 8-OH and the PCA metabolites, all present in grapes or leaves at 1% TRR or less.

In potatoes foliar treated three times at 11–16 day intervals up to berry development (total 0.5 kg ai/ha) and sampled 51 days later, total radioactive residues in tubers were very low (0.008–0.012 mg/kg) and were 22–48 mg/kg in leaves.

Between 74% and 99% of the TRR was identified, mostly as the unchanged fluopyram (23–69% in tubers and 98% in leaves) with the PCA metabolite (pyridyl-label) also present in tubers at about 50% TRR (0.006 mg/kg) and 0.5% (0.11 mg/kg) in leaves. Minor residue components were the BZM and the 7-OH metabolites, present in tubers or leaves at 7% TRR or less.

In beans treated twice at the equivalent of 0.25–0.27 kg ai/ha, 28 days apart (total 0.5 kg ai/ha) and sampled as green beans and foliage (4 days after the last application), as succulent beans (without pods) and straw (29 days after the last application) and as dry beans (29 days after the last application and a further 11 days drying), total radioactive residues were 1.4–3.9 mg/kg (green beans), 0.07–0.17 mg/kg (succulent beans), 0.12–0.31 mg/kg (dry beans), 37–39 mg/kg (foliage) and 17–19 mg/kg in straw (vines and empty pods).

Between 76% and 99% of the TRR was identified, mostly as the unchanged fluopyram (92–99% in green beans and foliage and 87–90% in straw), as the BZM metabolite (52% in succulent beans and 64% in dry beans) or as the PAA and PCA metabolites (30–31% in succulent beans and 23–33% in dry beans). Glycoside-glucuronic acid conjugates of the hydroxylated fluopyram were also found at up to 10% TRR in dry and succulent beans.

In sweet peppers treated with a single drip irrigation application of 5 mg ai/plant and harvested at fruit maturity, 55–96 days later, total radioactive residues were 0.04–0.06 mg/kg (fruit) and 2.3–3.5 mg/kg (plants without fruit). In plants treated at 20 mg ai/plant (4×), TRRs were 6.2–18 mg/kg in plants sampled 33 days after treatment.

Between 78% and 98% of the TRR was identified, mostly as the unchanged fluopyram (16–49% in fruit, 64–70% in plants (without fruits) and 87–88% in the 4× plants), as the BZM metabolite (16% TRR in fruit and 10% in plants or as the PCA metabolite (20–44% TRR) and PAA-glycoside isomers (individually ranging from 13–24% TRR).

In summary, residues of unchanged fluopyram account for the major part of the residues in grapes and green beans and also occur at lower levels in potatoes, drip-irrigated red peppers, dry and succulent beans (without pods), where the commodities are not directly exposed to fluopyram spray applications. In these latter commodities, significant levels of the cleavage products BZM and to a lesser extent the PCA and PAA metabolites also occur, generally at concentrations close to the combined fluopyram plus BZM levels. The PCA metabolite residues were up to 0.1 mg/kg in dry beans, less than 0.05 mg/kg in succulent beans (without pods) and peppers (drip irrigated) and less than 0.01 mg/kg in potatoes. Residues of the PAA metabolite in beans were 0.05–0.07 mg/kg in both the fresh and dry beans (without pods).

The proposed metabolic pathway in plants involves hydroxylation of the parent compound to the 7-OH and 8-OH metabolites and subsequent conjugation (mainly with sugars), cleavage of the parent molecule to produce the BZM, PAA and PCA metabolites.

With the exception of PCA and its methyl-sulfoxide derivative, the main metabolites in plants are also observed in the rat, goat and poultry metabolism studies.

Environmental fate in soil

The Meeting received information the environmental fate and behaviour of fluopyram, including hydrolytic stability, aerobic degradation in soil, photolysis on the soil surface, field dissipation and confined and field rotational crop studies. Radio-labelled fluopyram (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings) were used in the confined soil degradation and rotational crop studies.

Hydrolysis

Fluopyram was stable in sterile aqueous buffered solutions at pH 4, 7 and 9 when stored at 50 °C in the dark for 5 days. One minor degradate was measured, at up to 1.6% applied radiolabel, in the pH 7 and pH 9 solutions at the end of the test period.

Photolysis

After exposure to continuous artificial sunlight for 13 days, radio-labelled fluopyram residues in sterile buffer solutions decreased to 64–72% of the applied phenyl and pyridyl ring radiolabels. In both studies, the one major degradation product was the lactame degradate, comprising 12–13% of the applied radiolabel. A number of minor degradation products were reported, all at less than 4.2% of the applied amount. Based on simple first order degradation kinetics, experimental DT_{50} values of 21–25 days and DT_{90} values of 70–83 days were calculated.

In soil treated with the equivalent of 0.25 kg ai/ha and exposed to artificial irradiation for 23 days, phenyl ring radio-labelled fluopyram was stable, with no organic volatiles or degradation products being detected, about 0.2% of the applied radio-label being mineralised to $^{14}CO_2$ and non-extractable residues increasing to a maximum of 2.3%.

Aerobic soil metabolism

Studies were conducted in four European soils (2 loam soils, a silt-loam and a sandy-loam) with radio-labelled (phenyl ring) fluopyram at a target rate of 0.67 mg/kg soil (equivalent to 250 g/ha, mixed to 2.5 cm depth). In these studies, soils were incubated in the dark for 121–128 days at 20 °C and samples were collected at intervals up to 128 days after application.

Fluopyram was slowly degraded with an estimated single first order (SFO) half-lives of 165–339 day (mean 239 days). The identified soil metabolites were BZM (maximum 1.1%TARafter 30 days), 7-OH (maximum 3.3–4.2%TARafter 30–60 days), PCA (maximum 0.7%TARafter 30 days) and the methyl sulfoxide (maximum 1%TARat 128 days). The estimated single first order half-lives for the 7-OH metabolite ranged from 7.5–16 days..

In two US soils (silty clay loam and sandy loam), radio-labelled fluopyram was applied to soil at 0.11–0.13 mg ai/kg (equivalent to 250 g/ha mixed to 15 cm depth), the soils were incubated in the dark at 25 °C for 365 days and sampled at 12 regular intervals during the 1 year study period.

Fluopyram (parent) residues decreased to 60–71 % in the two soils and the SFO model half-lives were 922 days and 484 days. Apart from CO_2, no metabolite of significance was detected in either soil and volatile residues were insignificant. No intermediate metabolites accumulated in the aerobic soil system.

The proposed metabolic pathway of fluopyram in soil includes hydroxylation to form the 7-OH metabolite, cleavage of the parent molecule and the formation of the BZM and the PCA metabolites, the latter being further metabolized to the methyl-sulfoxide. Microbial breakdown leads to the formation of carbon dioxide and soil bound residues and all degradation products were either further transformed to their metabolic downstream products, mineralized (5–24% AR), or substantially integrated into the soil matrix as non-extractable residues (9–15%) after 128 days incubation.

Soil dissipation

In six European field studies involving bare soil (pre-emergent - grass) treatments equivalent to 0.25 kg ai/ha, about 50% of the total applied fluopyram disappearing within 21 to 347 days after treatment in the different soils. Dissipation then proceeded more slowly until the end of the 2-year study when residues remaining were 3–27% of the total applied amount. The time required for dissipation of 90% of the initial concentration of fluopyram ranged from 497 to more than 1000 days.

Interim results of a 4-year soil dissipation study in Europe (two sites) involving annual applications of 0.25 kg ai/ha report an increase in fluopyram residues at the end of each year, from 23–47% of the annual application rate just before the 2nd application to 46–66% of the annual application rate just before the 3rd application.

Five field dissipation studies were conducted in USA with fluopyram (0.5 kg ai/ha) being applied to bare soil. Fluopyram showed biphasic degradation behaviour (double first order in parallel (DFOP) kinetics model) with estimated DT_{50} values of 24 days, 87 days and 166–537 days with 21–44% of the applied residue remaining after 18–22 months. DT_{75} values in these studies ranged from 500 to more than 1000 days.

The observed transformation products were 7-OH, BZM, and PCA metabolites, only found above the LOQ (1.0 µg/kg) in the top 15 cm segment. The highest concentrations found were 3.0 µg/kg (7-OH), 9.7 µg/kg (BZM) and 10 µg/kg (PCA). Residues of BZM and PCA were below the LOQ (1 µg/kg) at all sites within 30 days after treatment. In four of the sites, residues of 7-OH were below the LOQ after 9 months and at one site, were present at about 1.6 µg/kg (mostly in the top 15 cm segment) at the end of the 22-month study period.

Residues in succeeding crops

In rotational crop metabolism studies involving wheat, Swiss chard and turnips as representative crops (small grains, leafy crops and root crops respectively), 1st, 2nd and 3rd rotation crops were planted 30, 139 and 280 days after a single bare-soil spray treatment at a nominal rate of 0.5 kg ai/ha radio-labelled fluopyram (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings).

Total radioactive residues (fluopyram equivalents) were found in all matrices from the 1st rotation crops, at levels ranging from 0.04–0.07 mg/kg (turnip roots) to 6.1–6.7 mg/kg (wheat straw). Total residues decreased in the 2nd rotation crops (0.01–3.5 mg/kg) and decreased further to < 0.01–1.6 mg/kg in the 3rd rotation crops.

Fluopyram was the major residue in most commodities, accounting for 20–95% of the TRR in wheat matrices, Swiss chard, turnip leaves and roots.

The 7-OH metabolite was a significant residue in Swiss chard (21–39% TRR in all rotations), with the BZM metabolite occurring at close to 10% TRR in Swiss chard and turnip leaves of the first rotation. In all other commodities the BZM metabolite was only a minor component. The PCA metabolite was the main residue component in wheat grains from the first rotation, accounting for about half the TRR and the methyl-sulfoxide metabolite, a degradation product of PCA, was a significant residue in wheat grains in the second rotation (49% TRR).

Rotational crop field studies were conducted in Europe where wheat, turnip/carrot and lettuce were planted as representative crops in bare soil treated with 0.5 kg ai/ha or following harvest of lettuce (primary crop) treated with 0.5 kg ai/ha. Plant-back intervals in these trials were 28–49 days (1st rotation), 90–240 days (2nd rotation) and 286–320 days (3rd rotation).

Fluopyram was found in all commodities with highest residues present in wheat straw and forage (0.28 mg/kg and 0.12 mg/kg respectively). Residues were also present in wheat grain, lettuce, turnip and carrot tops and roots at levels of 0.01–0.05 mg/kg.

Residues of the 7-OH metabolite were only found in wheat straw at levels of 0.11–0.08 mg/kg with residues of the BZM and the methyl-sulfoxide metabolites also present at 0.14 mg/kg and 0.07 mg/kg respectively.

In rotational crop studies in North America where alfalfa and cotton were planted 12–14 days after the last of two applications of fluopyram (total 0.5 kg ai/ha), fluopyram residues were not found in cotton seed, were less than 0.02 mg/kg in cotton gin trash and were generally less than 0.1 mg/kg in alfalfa forage (except in 2 of the 12 sites where residues in 1st cut forage were up to 0.39 mg/kg and up to 0.19 mg/kg in 3rd cut forage). Residues in alfalfa hay, sampled at the same times as the forage showed a similar pattern (taking into account the increased dry matter content).

In a limited rotational crop study in North America where wheat, turnip and mustard greens were planted in rotation with cover crops treated with 2× 0.25 kg ai/ha fluopyram (plant-back interval of about 240 days), residues of fluopyram were found in all commodities except wheat grain and turnip roots. Maximum residues found were 0.12 mg/kg in wheat straw, 0.09 mg/kg in wheat hay, 0.05 mg/kg in wheat forage and 0.04 mg/kg in turnip tops and in fresh mustard leaves.

In summary, at plant-back intervals of more than 28 days, residues of fluopyram can be expected at low levels (0.01–0.05 mg/kg) in root crops, cereal grain crops and in leafy vegetables grown as rotational crops, with higher levels likely to occur in cereal forage (up to 0.12 mg/kg) and feed commodities (up to 0.28 mg/kg in straw). Levels of up to 0.11 mg/kg of the 7-OH metabolite and up to 0.14 mg/kg of the BZM metabolite could occur in cereal straw and residues of the methyl-sulfoxide metabolite may also occur in cereal grain (up to 0.09 mg/kg), cereal forage (up to 0.06 mg/kg) and cereal straw (up to 0.07 mg/kg).

Methods of analysis

Several analytical methods have been reported for the analysis of fluopyram and for selected metabolites and in animal commodities. The basic approach employs extraction by homogenisation with acetonitrile/water and in some methods, additional clean-up using SPE or liquid/liquid partition. Residues are determined by liquid chromatography with mass spectrometric detection.

The methods for fluopyram and selected metabolites have been validated for a range of substrates with LOQs of 0.01 mg/kg for each analyte (0.05 mg/kg for wheat straw). Studies on extraction efficiency indicated that in most matrices, greater than 80% of the residue can be extracted with acetonitrile/water with single and double extraction and that comparable results can be achieved for fluopyram using acetone/water extraction (as used in the DFG S19 multi-residue method).

In the methods used to measure fluopyram metabolites in plant commodities, dilution under acid conditions allowed the determination of the PCA metabolite and its methyl-sulfoxide derivative while a parallel dilution under basic conditions allowed the determination of fluopyram and the BZM, 7-OH and PAA metabolites.

For analysis of animal commodities, extracts are cleaned-up on a C18 cartridge and further diluted with methanol/water (containing the corresponding internal standards) before analysis for fluopyram, the BZM metabolite and the sum of the two olefine isomers (because of internal inter-conversion between the E-isomer and the Z-isomer).

Based on the results of validation studies and the concurrent recovery rates achieved in the supervised field trials, the available analytical methods fulfilled the following criteria:-

- 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 European multi-residue method DFG S19 method used in combination with GC/MS was validated as a multi-residue enforcement method to monitor residues of fluopyram in both plant and animal matrices, but is not applicable as an enforcement method for the BZM metabolite. The US-FDA PAM 1 multi-residue methods (E1 extraction and DG17 detection without Florisil cleanup) are also suitable for detection and enforcement of fluopyram in non-fatty matrices but are also not suitable for measuring the BZM residues. For animal tissues, milk and eggs, a modification of the data collection method was validated as an enforcement method for measuring fluopyram and its BZM metabolite.

Stability of residues in stored analytical samples

Freezer storage stability was tested for a range of representative substrates covering those with a high water content (lettuce), a high starch content (wheat grain), a high protein content (dry pea seed), a high oil content (rape seed) and a high acid content (orange).

Fluopyram and major metabolites (BZM, PAA and PCA) are stable in these representative substrates for at least 24 months in frozen storage. Residues of the PCA metabolite are stable in grapes potato tubers, cabbage leaves and wheat grain for at least 30 months in frozen storage and residues of the methyl-sulfoxide metabolite in wheat forage, straw and grain are stable for at least 25 months in frozen storage.

Definition of the residue

In animal commodities, BZM is the main residue in edible animal tissues, milk and eggs, with the combined E/Z olefine isomers and the parent compound being major components only in fat of ruminants and poultry.

Although a suitable multi-residue method was not available to measure these components, an HPLC-MS/MS method measuring fluopyram and the BZM metabolite has been validated for MRL-compliance and the Meeting recommended that for MRL-compliance, the residue definition should be fluopyram and its BZM metabolite.

For animal commodity dietary intake estimation, in addition to the parent compound and the BZM metabolite, the E/Z olefine isomers contributes about 30% to the final residue in ruminant and poultry fat.

Both BZM (2-(trifluoromethyl)benzamide) and to a much lesser extent the E/Z olefine isomers (N-{(E)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide and N-{(Z)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide) also occur in rats and are adequately covered in the derived toxicological reference doses and the Meeting agreed that these metabolites should be included in the residue definition.

The compound fluopyram has a log K_{ow} of 3.3, suggesting that it is fat-soluble, and this is supported by the preferential partitioning into milk fat (cream) and fat reported in a cow feeding study. Analysis of skim milk and heavy cream in the cow feeding study also indicated that the combined E/Z olefine isomers also show preferential partitioning into fat (0.12:1). However the BZM metabolite (the major component of the residue in eggs, milk and animal tissues) is not fat-soluble. The Meeting therefore concluded that fluopyram (as defined in the residue definitions for animal commodities) is not fat-soluble.

Fluopyram is the major residue in treated plant commodities and where residues occur in rotational crops, fluopyram is also the major residue. The Meeting also noted that multi-residue analytical methods exist to measure the parent residues and agreed that for MRL-compliance, the residue definition for plant commodities should be fluopyram.

Metabolites identified in the plant metabolism studies at more than 10% TRR are BZM, PCA and PAA. While these metabolites were generally present at not more than 1% TRR and below

0.02 mg/kg in most edible commodities, higher percentages (up to 60% TRR but at relatively low concentrations up to 0.1 mg/kg) were found in commodities not directly exposed to spray applications (drip irrigated peppers, potato tubers and beans without pods). In wheat grown as a rotational crop, PCA was found in grain at up to 56% TRR and 0.23 mg/kg.

In supervised crop field trials, residues of BZM, PCA and to a lesser extent PAA were sometimes detected in a number of commodities, mostly at longer PHIs of 10–21 days and generally at levels below 0.02 mg/kg. Higher levels of BZM and less frequently, PCA and its methyl sulfoxide (up to about 0.1 mg/kg) and PAA (rarely more than 0.05 mg/kg) were found occasionally in some legumes and brassicas, rape seed, grapes, lettuce and strawberries. The related parent residues are usually more than twice the metabolite levels.

Two of the main metabolites in plants (BZM and PAA) are also observed in the animal metabolism studies and the toxicology of these metabolites are addressed in the rat studies and are covered by the derived reference doses. Sufficient toxicology information is available to confirm that the PCA metabolite and its methyl sulfoxide, common metabolites with fluopicolide, are significantly less toxic than fluopyram

The Meeting therefore agreed that the BZM, PCA and PAA metabolites need not be included in the plant commodity residue definitions for MRL enforcement or estimation of dietary intake.

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

Proposed definition of the residue (for compliance with the MRL for animal commodities): *sum of fluopyram and 2-(trifluoromethyl) benzamide, expressed as fluopyram.*

Proposed definition of the residue (for estimation of dietary intake for animal commodities: *sum of fluopyram, 2-(trifluoromethyl)benzamide and the combined residues of N-{(E)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide and N-{(Z)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide, all expressed as fluopyram.*

The residue is not fat-soluble.

Results of supervised trials on crops

The Meeting received supervised trial data for foliar applications of fluopyram (SC formulations) on a wide range of fruit, vegetable, cereal, tree nut, oilseed, hops and herb crops and for drip-line irrigation treatments to strawberries and cucurbits and for seed treatment to cereals. These trials were conducted mainly in Europe and/or North America.

The NAFTA calculator was used as a tool in the estimation the maximum residue level 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 with the calculator using expert judgement. Then, the NAFTA calculator was employed. If the statistical calculation spreadsheet suggested a different value than 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.

The Meeting noted that GAP has been authorised for the use of fluopyram (500 SC) on table and wine grapes in Romania and on cucumbers in China.

Grapes

GAP for fluopyram in Romania is 2× 0.25 kg ai/ha (max), PHI 21 days for wine grapes and 3 days for table grapes. Residues in trials in South Europe matching the Romanian wine grape GAP (i.e., PHI 21 days) in wine grapes were: 0.26, 0.34, 0.35, 0.36, 0.44, 0.46 and 0.56 mg/kg (n = 7) and in table

grapes were: 0.13, 0.22, 0.28, 0.41, 0.44, 0.61 and 0.63 mg/kg (n = 7). As these data sets were not from different populations, the Meeting agreed to combine the results, giving a data set of: 0.13, 0.22, 0.26, 0.28, 0.34, 0.35, 0.36, 0.41, 0.44, 0.44, 0.46, 0.56, 0.61 and 0.63 mg/kg (n = 14).

In trials matching the GAP for table grapes in Romania (i.e., PHI of 3 days), residues in trials from Europe (on table grapes) were: 0.3, 0.34, 0.55, 0.6, 0.66, 0.96 and 1 mg/kg (n = 7) and on wine grapes were: 0.36, 0.51, 0.57, 0.58, 0.58, 0.63 and 0.63 mg/kg (n = 7). As these data sets were not from different populations, the Meeting agreed to combine the results, giving a data set of: 0.3, 0.34, 0.36, 0.51, 0.55, 0.57, 0.58, 0.58, 0.6, 0.63, 0.63, 0.66, 0.96 and 1 mg/kg (n = 14).

The Meeting agreed to use the data from the European trials on grapes matching the Romanian GAP for table grapes (PHI 3 days) and estimated a maximum residue level of 2 mg/kg, an STMR of 0.58 mg/kg and an HR of 1 mg/kg for fluopyram on grapes. The value derived from use of the NAFTA Calculator was 1.3 mg/kg (unrounded).

Cucumber

Supervised residue trial data and GAP information on the use of fluopyram as a foliar spray on cucumber in China were provided to the Meeting. The GAP for use in China is for up to 3 foliar applications of 0.075 kg ai/ha at 7–10 day intervals and the PHI is 2 days.

In six trials matching this GAP, fluopyram residues were 0.05, 0.07, 0.08, 0.14, 0.17 and 0.19 mg/kg.

The Meeting estimated an STMR of 0.11 mg/kg, an HR of 0.19 mg/kg and recommended a maximum residue level of 0.5 mg/kg. The value derived from use of the NAFTA Calculator was 0.36 mg/kg (unrounded).

Estimation of residues in plant commodities grown as potential succeeding crops

Although the results of the rotational crop studies indicate that potential residues could occur in root crops, cereals and leafy vegetables planted in rotation with cucumbers, the Meeting noted that interim soil accumulation studies suggested that residues could build up following repeat applications and concluded there was insufficient information to estimate a residue plateau level for fluopyram in soil. As this is a prerequisite for estimating possible residues in rotational crops (according to the principles outlined in the JMPR Report 2008, General consideration 2.9), the Meeting was not able to recommend maximum residue levels for fluopyram in rotational crops.

Fate of residues during processing

The effect of processing on the nature of residues was investigated in buffer solutions under conditions simulating pasteurisation, boiling and sterilisation. Fluopyram was shown to be stable under these conditions.

The fate of fluopyram residues has been examined in a number of studies reflecting household washing, peeling and cooking practices and also simulated commercial processing. Estimated processing factors and STMR-Ps for the commodities considered at this Meeting are summarised below.

Summary of relevant processing factors and STMR-P values for fluopyram residues.

Raw agricultural commodity	Processed commodity	Calculated processing factors [a]	Processing factor (mean or median)	RAC STMR (mg/kg)	STMR-P (mg/kg)
Grape	Juice	< 0.02, < 0.02, < 0.02, < 0.03,	< 0.02 (median)	0.58	< 0.012
	Red wine (young)	0.1, 0.14, 0.16, 0.22	0.16	0.58	0.093
	Red wine [b]	0.14, 0.17, 0.2, 0.2	0.18	0.58	0.104
	Pomace (wet)	2.2, 3.1, 3.6, 3.9	3.2	0.58	1.86

Raw agricultural commodity	Processed commodity	Calculated processing factors [a]	Processing factor (mean or median)	RAC STMR (mg/kg)	STMR-P (mg/kg)
	Raisins	2.0, 2.4, 2.9, 3.2, 6.6	2.9 (median)	0.58	1.68

[a] Each value represents a separate study where residues were above the LOQ in the RAC. The factor is the ratio of the total residue in the processed item divided by the total residue in the RAC.

[b] Wine at first taste (approximately 132 days bottled storage)

In four grape processing studies conducted in Europe, fluopyram residues decreased in juice median processing factor of < 0.02) and in wine (mean processing factor of 0.18) with residues increasing about 3-fold in raisins and wet pomace.

The Meeting agreed to estimate a maximum residue level for dried grapes of 5 mg/kg based on a highest residue for grapes of 1 mg/kg and a median processing factor of 2.9 (1 mg/kg × 2.9 PF). The STMR-P for residues of fluopyram in dried grapes is 1.68 mg/kg and the HR-P is 2.9 mg/kg.

The STMR-P for grape pomace (wet) is 1.86 mg/kg and assuming a default 15% dry matter content, the STMR-P for grape pomace (dry) is 12.4 mg/kg.

The STMR-P for grape juice is 0.012 mg/kg and is 0.1 mg/kg for wine.

The Meeting agreed that for commodities not being considered for maximum residue levels at this meeting, the relevant processing studies would not be reviewed and processing factors would not be estimated at this meeting.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of fluopyram in farm animals on the basis of the diets listed in Annex 6 of the 2009 JMPR Report (OECD Feedstuffs Derived from Field Crops). Based on the estimated STMR-P of 12.4 mg/kg for grape pomace (dry) and the 20% contribution to the Australian dairy and beef cattle diets, the maximum and mean residue contribution is 2.48 mg/kg. Grape pomace is not a significant component of poultry diets.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef and dairy cattle, calculated using the animal diets from US/CAN, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report) are summarised below.

		Animal dietary burden, fluopyram, ppm of dry matter diet		
		US/CAN	EU	Australia
Beef cattle	max	0.0	0.0	2.48 [a]
	mean	0.0	0.0	2.48 [c]
Dairy cattle	max	0.0	0.0	2.48 [b]
	mean	0.0	0.0	2.48 [d]
Poultry – broiler	max	0.0	0.0 [e]	0.0
	mean	0.0	0.0 [f]	0.0
Poultry – layer	max	0.0	0.0 [g]	0.0
	mean	0.0	0.0 [h]	0.0

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian tissues

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

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

[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 tissues.

[f] Highest mean poultry dietary burden suitable for STMR estimates for poultry tissues.

[g] Highest maximum poultry dietary burden suitable for MRL estimates for poultry eggs.

[h] Highest mean poultry dietary burden suitable for STMR estimates for poultry eggs.

The fluopyram dietary burdens for animal commodity MRL and STMR estimation (residue levels in animal feeds expressed on dry weight) are: 2.48 ppm for beef and dairy cattle and 0.0 ppm for poultry.

Farm animal feeding studies

The Meeting received information on the residue levels arising in animal tissues and milk when dairy cows were dosed with fluopyram for 29 days at the equivalent of 1.5, 14.4, 44 and 133 ppm in the diet. A separate dose group (146 ppm) was used to estimate residue depuration of fluopyram and its major metabolites.

In milk, average residues of fluopyram were not detectable in the 1.5 ppm dose group and increased to 0.12 mg/kg in the highest dose group (133 ppm). In skim milk, fluopyram residues were 0.02 mg/kg and 1.3 mg/kg in centrifuged 'cream' (71–78% milk fat). Residues of BZM, the predominant residue component in milk, increased from 0.04–1.7 mg/kg over the four dose groups while residues of the total-olefine metabolites were above the LOQ only in the two higher dose groups (0.03 mg/kg and 0.12 mg/kg respectively).

In muscle, residues of fluopyram did not exceed 0.03 mg/kg at any dose level and the predominant residue was the BZM metabolite, found at up to 1.4 mg/kg. Residues of the total-olefine metabolites were found above the LOQ (0.02 mg/kg) only in the two higher dose groups, up to 0.04 mg/kg.

In fat, residues of fluopyram were < LOQ in the lowest dose group and increased to 0.58 mg/kg in the 133 ppm dose group and a similar pattern was observed with BZM (up to 0.86 mg/kg). Total-olefine residues were found at up to 0.77 mg/kg.

In liver, fluopyram residues were found in all dose groups, up to 4.0 mg/kg with higher residues of the BZM metabolite also being found in the top three dose groups (1.2–6.9 mg/kg). Residues of the total-olefine isomers were found in the top three dose groups at levels of 0.04–0.5 mg/kg.

In kidney, fluopyram residues were above the LOQ in the two higher dose groups (44 ppm and 133 ppm) at levels of 0.03 mg/kg and 0.07 mg/kg respectively. The predominant residue was the BZM metabolite, present at 0.03–1.6 mg/kg over the four dose groups and residues of the total-olefine metabolites above the LOQ were found in the two higher dose groups at 0.04 mg/kg and 0.13 mg/kg respectively.

Residue depletion was studied in cows dosed orally for 29 days with the equivalent of 146 ppm fluopyram. Fluopyram residues in milk had depleted to < 0.01 mg/kg within 2 days after the last dose and were not detectable after 5 days with residues of BZM and the total-olefine metabolites being < LOQ within 21 days. In tissues, fluopyram residues decreased to less than the LOQ within 7 days (muscle) and within 14 days (fat, liver and kidney). Tissue residues of BZM decreased to less than the LOQ within 14 days in fat and within 21 days in milk with residues of 0.42 mg/kg (liver), 0.19 mg/kg (muscle) and 0.05 mg/kg (kidney) remaining at the end of the study period (21 days after the last dose). Residues of the total-olefine metabolites also remained in fat (0.17 mg/kg) and liver (0.04 mg/kg) at the end of the study period and were < 0.02 mg/kg (LOQ) in muscle within 7 days and within 21 days in kidney.

The Meeting also received information on the residues in tissues and eggs when laying hens were dosed with fluopyram for 28 days at levels equivalent to 0.05, 0.49, 1.6 and 4.8 ppm in the diet.

Fluopyram residues were not detected in eggs or any tissues from any dose groups and residues of the total-olefine metabolites were either not detectable or were at or below 0.02 mg/kg (LOQ) except in skin/fat from the highest (4.8ppm) dose group. The BZM metabolite was the predominant residue and was found in eggs and all tissues up to 1.4 mg/kg in liver, 0.72 mg/kg in eggs, 0.41 mg/kg in skin/fat and 0.29 mg/kg in muscle from the highest dose group.

In the residue depuration dose group (4.8 ppm), residues of the total-olefine metabolites in skin/fat were not detectable within 21 days after the last dose and residues of the BZM metabolite decreased to 0.01 mg/kg in muscle, 0.02 mg/kg in skin/fat, 0.03 mg/kg in eggs and 0.05 mg/kg in liver at the end of the study (21 days after the last dose).

Animal commodity maximum residue levels

The maximum and the mean dietary burden for beef and dairy cattle is 2.48 ppm and residue levels in tissues were obtained by interpolation between the 1.5 ppm and the 14.4 ppm feeding levels.

Dietary burden (mg/kg)[a]		Combined Fluopyram, BZM and Total olefine residues, mg/kg (fluopyram equivalents)[c]								
Feeding level [ppm][b]		Milk	Fat		Muscle		Liver		Kidney	
		mean	high	mean	high	mean	high	mean	high	mean
MRL beef	2.48		*< 0.049*		*< 0.053*		*0.551*		*< 0.057*	
	[1.5:14.4] F [1.5:14.4] B		< 0.01:0.07 0.01:0.33		0:< 0.01 0.02:0.44		0.26:0.98 0.1:1.9		0:< 0.01 0.03:0.38	
MRL dairy	2.48	*0.037*								
	[1.5:14.4] F [1.5:14.4] B	0:0.01 0.02:0.24								
Hi-res cattle			*< 0.076*		*< 0.054*		*< 0.574*		*< 0.059*	
	[1.5:14.4] F [1.5:14.4] B [1.5:14.4] O		< 0.01:0.07 0.01:0.33 < 0.02:0.12		0:< 0.01 0.02:0.44 0:< 0.02		0.26:0.98 0.1:1.9 < 0.02:0.06		0:< 0.01 0.03:0.38 0:< 0.02	
STMR beef	2.48			*< 0.061*		*< 0.043*		*0.472*		*< 0.051*
	[1.5:14.4] F [1.5:14.4] B [1.5:14.4] O			< 0.01:0.04 0.01:0.18 < 0.02:0.09		0:< 0.01 0.02:0.29 0:< 0.02		0.25:0.71 0.1:1.21 0:0.04		0:< 0.01 0.03:0.28 0:< 0.02
STMR dairy	2.48	*< 0.039*								
	[1.5:14.4] F [1.5:14.4] B [1.5:14.4] O	0:0.01 0.02:0.24 0:< 0.02								

[a] Values in parentheses are the estimated dietary burdens

[b] Values in square brackets are the actual feeding levels in the transfer study

[c] Residue values in italics are interpolated from the dietary burden, feeding levels and the residues found in the transfer studies (F = fluopyram, B = BZM, O = total olefins)

High is the highest individual animal tissue residue in the relevant feeding group.

Mean is mean animal tissue residue in the relevant feeding group.

Combined residues of fluopyram and BZM (expressed as fluopyram equivalents) expected in cattle milk and tissues for use in estimating maximum residue levels are: < 0.049 mg/kg (fat), < 0.053 mg/kg (muscle), 0.551 mg/kg (liver) and < 0.057 mg/kg (kidney) and the mean residue for milk is 0.037 mg/kg.

The Meeting estimated maximum residue levels of 0.1 mg/kg for fluopyram in meat (from mammals other than marine mammals), 0.7 mg/kg for edible offal (mammalian), 0.1 mg/kg for fat and 0.07 mg/kg for milks.

Estimated HRs for dietary intake estimation for fluopyram (and including residues of BZM and total olefins) are 0.076 mg/kg for mammalian fat, 0.054 mg/kg for mammalian muscle, 0.574 mg/kg for liver and 0.059 mg/kg for kidney.

Estimated STMRs for dietary intake estimation for fluopyram (and including residues of BZM and total olefins) are 0.061 mg/kg for mammalian fat, 0.043 mg/kg for mammalian muscle, 0.472 mg/kg for mammalian liver, 0.051 mg/kg for mammalian kidney and 0.039 mg/kg for milks.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intake (IEDI) for fluopyram was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available. The results are shown in Annex 3.

The International Estimated Daily Intakes of fluopyram for the 13 GEMS/Food regional diets, based on estimated STMRs were 1–6% of the maximum ADI of 0.01 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of fluopyram from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The International Estimated Short-term Intake (IESTI) for fluopyram was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available (Annex 4).

For fluopyram the IESTI varied from 0–4% of the ARfD (0.5 mg/kg bw) for the general population and 0–10% for children. The Meeting concluded that the short-term intake of residues of fluopyram from uses considered by the Meeting is unlikely to present a public health concern.

5.18 MEPTYLDINOCAP (244)

TOXICOLOGY

Meptyldinocap is the International Organization for Standardization (ISO)–approved name for 2-(1-methylheptyl)-4,6-dinitrophenyl crotonate (International Union of Pure and Applied Chemistry [IUPAC]), with Chemical Abstracts Service (CAS) No. 131-72-6. Meptyldinocap is a new dinitrophenolic fungicidal compound, which acts by uncoupling mitochondrial oxidative phosphorylation. Meptyldinocap was reviewed for the first time by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) on the request of the Codex Committee on Pesticide Residues (CCPR).

Meptyldinocap is one of the six structural analogues present in the existing active substance dinocap. Dinocap was evaluated previously by the JMPR in 1969, 1974, 1989, 1998 and 2000. In 1998, the acceptable daily intake (ADI) and the acute reference dose (ARfD) for dinocap were established at 0–0.008 mg/kg body weight (bw) and 0.008 mg/kg bw, respectively. In 2000, two ARfDs were established for dinocap, one for women of childbearing age, at 0.008 mg/kg bw, and another for the general population, at 0.03 mg/kg bw. Dinocap contains approximately 22% meptyldinocap.

The database supporting meptyldinocap consists of some new studies performed with meptyldinocap together with earlier studies performed with dinocap. Previously evaluated studies with dinocap were reviewed at the Meeting but are summarized only briefly. Most of the pivotal studies met the basic requirements of the relevant Organisation for Economic Co-operation and Development (OECD) or national test guidelines, although the level of detail in some of the older reports of studies performed with dinocap did not always meet current requirements. A number of studies using dinocap did not contain certificates of compliance with good laboratory practice (GLP).

Biochemical aspects

No new absorption, distribution, metabolism and excretion (ADME) studies on meptyldinocap in mammals have been conducted. However, in a number of the ADME studies with dinocap, the radiolabel was present on the methylheptyl analogue, which is the primary component of meptyldinocap. The Meeting considered that these ADME studies were applicable to meptyldinocap.

Meptyldinocap is relatively well absorbed, with approximately 60–70% of the radiolabel absorbed in rabbits. Absorption is rapid, with peak plasma radioactivity seen 1–6 h after oral administration. Radiolabel was widely distributed, with tissue levels generally low and below those in blood. The compound did not tend to concentrate in any particular organ or tissue; highest levels were found in the liver, kidneys and skin. Metabolism was extensive, consisting of hydrolytic cleavage to release the crotonate moiety and subsequent oxidation of the methylheptyl chain. The basic metabolic pathways are similar in rats and mice. Excretion of radiolabel was extensive via urine (39–58% in mice; 31–50% in rats) and faeces and mainly occurred within 48 h.

Toxicological data

Meptyldinocap is of low acute toxicity when administered orally or dermally (median lethal dose [LD_{50}] > 2000 mg/kg bw) but is of moderate toxicity by inhalation (median lethal concentration [LC_{50}] 1.2 mg/L). Meptyldinocap is a slight irritant to skin and a moderate irritant to the eye; it has been found to produce skin sensitization in a local lymph node assay in mice.

Short-term studies of toxicity with meptyldinocap were performed in mice, rats and dogs. Yellow urine staining was a consistent finding, but this is considered not to be adverse, as it is associated with the excretion of coloured metabolites of meptyldinocap. In a 28-day dietary study of meptyldinocap in mice, there were increases in liver weight (approximately 10–15%) at 750 ppm (equal to 126 mg/kg bw per day), with a NOAEL of 200 ppm (equal to 33 mg/kg bw per day). In a

90-day dietary study of meptyldinocap in rats, altered clinical chemistry parameters and mononuclear cell infiltration of the lacrimal glands were seen at 2000 ppm (equal to 122 mg/kg bw per day), with a NOAEL of 650 ppm (equal to 40 mg/kg bw per day).

In a 90-day dietary study, groups of dogs were exposed to meptyldinocap at 0, 15, 60 or 120 ppm, with a positive control group receiving 60 ppm dinocap. Reduced body weight gain was seen in males after the first week of dosing with 120 ppm (equal to 3.9 mg/kg bw per day), following a gradual introduction to the treated diets. These initial body weight effects showed no consistency between animals or with food consumption patterns. The body weight gain over 90 days was 41% lower in males receiving 120 ppm than in controls. Ocular changes seen in the dinocap-exposed group were not evident in the meptyldinocap-treated groups. The NOAEL for meptyldinocap was 60 ppm (equal to 1.6 mg/kg bw per day), based on the effects on body weight gain over the duration of the study. In an extension to this 90-day study, a satellite group was exposed to meptyldinocap for 1 year at 120 ppm (equal to 3.5 mg/kg bw per day). The examinations were limited to tibial nerves, eyes and heart. This segment of the study showed that there were no significant eye, heart or nerve lesions evident after exposure to meptyldinocap for 1 year. The reduced body weight gain seen in the 90-day phase was not evident over the extended dosing period. The 1-year study was not designed to permit the identification of a NOAEL.

No evidence of carcinogenicity was seen in long-term studies of toxicity and carcinogenicity with dinocap at the highest doses tested, 150 ppm (equal to 23 mg/kg bw per day) in mice and 2000 ppm (equal to 71 mg/kg bw per day) in rats. The NOAEL for general toxicity in the chronic study in mice with dinocap was 15 ppm (equivalent to 2.8 mg/kg bw per day), based on body weight deficits in females. In the 30-month study of dinocap in rats, there was a significant increase in survival in both sexes at the top dose of 2000 ppm (equal to 71 mg/kg bw per day), which had an impact on the incidences of a number of age-related changes. The NOAEL for general toxicity of dinocap was 200 ppm (equal to 6.4 mg/kg bw per day).

The potential genotoxicity of meptyldinocap has been investigated in an adequate range of tests in vitro and in vivo. No evidence of mutagenicity or clastogenicity was noted.

The Meeting concluded that meptyldinocap is unlikely to be genotoxic.

The Meeting concluded that dinocap is not carcinogenic and that this conclusion could be extrapolated to meptyldinocap.

No effects on fertility, reproductive parameters, sperm or reproductive tissues were seen in a two-generation dietary study with dinocap at doses up to 400 ppm (equal to 27 mg/kg bw per day), the highest dose tested over both generations. At 1000 ppm (equal to 65 mg/kg bw per day), reduced pup survival in the first generation led to a reduction in the dose level to 400 ppm, which was without effect on pups in the second generation. The NOAEL for pup development and parental toxicity was 200 ppm (equal to 13 mg/kg bw per day).

In a developmental toxicity study in mice investigating effects on the palate and inner ear, meptyldinocap did not produce any such effects on fetuses at the highest dose of 500 mg/kg bw per day, whereas a dinocap dose of 25 mg/kg bw per day produced cleft palate in nearly all fetuses and had marked effects on otoconia formation. Additional studies showed that the teratogenicity of dinocap in mice was associated with the 4-propylpentyl analogue and not the methylheptyl analogue present in meptyldinocap. In a developmental study in rats, marked maternal toxicity and marked reductions (approximately 50%) in food consumption were seen with a meptyldinocap dose of 500 mg/kg bw per day, such that this dose level had to be terminated by gestation day 11. At the next highest dose level of 150 mg/kg bw per day, there were reductions from gestation days 6 to 9 in food consumption (approximately 18 g per rat) and maternal body weight gain (approximately 14 g per rat) at the start of the dosing period. The body weight deficit and increased absolute liver weights (23%) were evident at the end of the study, but there were no indications of fetotoxicity. The NOAEL for maternal toxicity was 50 mg/kg bw per day, with the NOAEL for fetotoxicity being 150 mg/kg bw per day. In a rabbit developmental toxicity study with meptyldinocap, maternal body weight loss was

seen in several dams before dosing commenced and in half the dams exposed at 48 mg/kg bw per day early in the dosing period. From gestation days 7 to 10, dams in the top dose group had a mean deficit of 44 g in body weight gain relative to controls; although this was similar in magnitude to the decrease in food consumption over the same period, there was no apparent consistency in individual body weight gains or food consumption. Over the remainder of the study, the body weight gain in the top dose group was similar to that in controls, and from gestation days 20 to 28 (during which dosing continued), the body weight gain was greater than that in controls. There were no effects on the fetuses at any dose level. The maternal NOAEL was 12 mg/kg bw per day, and the NOAEL for fetotoxicity was 48 mg/kg bw per day.

The Meeting concluded that meptyldinocap did not induce developmental toxicity and that it was not teratogenic.

There are no specific neurotoxicity studies on meptyldinocap, but there were no indications of neurotoxicity in routine studies, including a 90-day study in rats that included a functional observational battery.

No information on medical surveillance or poisoning incidents was available.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.02 mg/kg bw on the basis of the NOAEL of 1.6 mg/kg bw per day in the 90-day dietary study in dogs, based on reduced body weight gain in males at 3.9 mg/kg bw per day. A safety factor of 100 was applied.

The Meeting concluded that an ARfD was unnecessary, as there were no effects that could be attributed to a single exposure. Meptyldinocap did not produce neurotoxicity, fetotoxicity or reproductive effects and has an oral LD_{50} of greater than 2000 mg/kg bw. The Meeting reviewed in depth the reduced body weight gains and food consumption seen in the early stages of the 90-day study in dogs and the developmental toxicity studies in rats and rabbits. In the rat developmental toxicity study, the body weight deficits were considered secondary to reduced food consumption, which was probably associated with palatability issues. The Meeting concluded that the body weight and food consumption patterns seen in the early stages of the dog and rabbit studies were not consistent between individual animals. The findings in these three studies did not provide an appropriate basis for establishing an ARfD for meptyldinocap.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Twenty-eight-day study of toxicity with meptyldinocap[a]	Toxicity	200 ppm, equal to 33 mg/kg bw per day	750 ppm, equal to 126 mg/kg bw per day
	Seventy-eight-week study of toxicity and carcinogenicity with dinocap[a]	Toxicity	15 ppm, equal to 2.8 mg/kg bw per day	100 ppm, equal to 18 mg/kg bw per day
		Carcinogenicity	150 ppm, equal to 23 mg/kg bw per day[b]	—
Rat	Ninety-day study of toxicity with meptyldinocap[a]	Toxicity	650 ppm, equal to 40 mg/kg bw per day	2000 ppm, equal to 122 mg/kg bw per day
	Thirty-month study of toxicity and carcinogenicity	Toxicity	200 ppm, equal to 6.4 mg/kg bw per day	2000 ppm, equal to 71 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
	with dinocap[a]	Carcinogenicity	2000 ppm, equal to 71 mg/kg bw per day[b]	—
	Multigeneration study of reproductive toxicity with dinocap[a]	Reproductive toxicity	400 ppm, equal to 27 mg/kg bw per day[b]	—
		Parental toxicity	200 ppm, equal to 13 mg/kg bw per day	400 ppm, equal to 27 mg/kg bw per day
		Offspring toxicity	200 ppm, equal to 13 mg/kg bw per day	400 ppm, equal to 27 mg/kg bw per day
	Developmental toxicity study with meptyldinocap[c]	Maternal toxicity	50 mg/kg bw per day	150 mg/kg bw per day
		Embryo and fetal toxicity	150 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity study with meptyldinocap[c]	Maternal toxicity	12 mg/kg bw per day	48 mg/kg bw per day
		Embryo and fetal toxicity	48 mg/kg bw per day[b]	—
Dog	Ninety-day study of toxicity with meptyldinocap[a]	Toxicity	60 ppm, equal to 1.6 mg/kg bw per day	120 ppm, equal to 3.9 mg/kg bw per day[b]

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

Estimate of acceptable daily intake for humans

0–0.02 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 meptyldinocap

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid; moderately well absorbed (60–70%)
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Relatively rapid
Metabolism in animals	Extensively metabolized, initially hydrolysis to remove the crotonate side-chain and then via oxidation of the methylheptyl chain
Toxicologically significant compounds (animals, plants and the environment)	Meptyldinocap
Acute toxicity	
Rat, LD_{50}, oral	> 2000 mg/kg bw

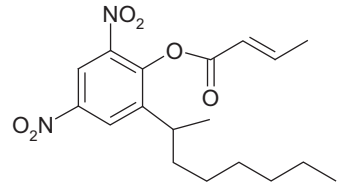
Rat, LD_{50}, dermal	> 5000 mg/kg bw
Rat, LC_{50}, inhalation	1.2 mg/L (4 h, nose only)
Rabbit, dermal irritation	Slight
Rabbit, ocular irritation	Moderate
Mouse, dermal sensitization	Sensitizer (local lymph node assay)
Short-term studies of toxicity	
Target/critical effect	Body weight gain (males)
Lowest relevant oral NOAEL	Dog: 1.6 mg/kg bw per day (meptyldinocap)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Body weight
Lowest relevant NOAEL	Mouse: 2.8 mg/kg bw per day (dinocap)
Carcinogenicity	Not carcinogenic in rats or mice
Genotoxicity	
	Not genotoxic in vitro or in vivo
Reproductive toxicity	
Reproduction target/critical effect	Pup survival
Lowest relevant reproductive NOAEL	Rat: 13 mg/kg bw per day (dinocap)
Developmental target/critical effect	None
Lowest relevant developmental NOAEL	Rabbit: 48 mg/kg bw per day (meptyldinocap)
Neurotoxicity/delayed neurotoxicity	
	No indications in routine studies
Other toxicological studies	
	No data
Medical data	
	No data

Summary

	Value	Study	Safety factor
ADI	0–0.02 mg/kg bw	Ninety-day study of toxicity in dogs	100
ARfD	Unnecessary		

RESIDUE AND ANALYTICAL ASPECTS

Meptyldinocap is a protectant and curative fungicide for the control of powdery mildew diseases. As a new compound it is evaluated at the first time by the JMPR. The meptyldinocap is the single isomer [2,4-dinitro-6-(1-methylheptyl)phenyl crotonate] of the existing active substance dinocap.



The 2,4-dinitro-6-(1-ethylhexyl)phenyl crotonate, present in the technical meptyldinocap in 1.5% concentration, is considered as impurity. The dinocap is a mixture of 2,4-dinitro-6-octylphenyl crotonates and 2,6-dinitro-4-octylphenyl crotonates. The 'octyl' being a mixture of 1-methylheptyl, 1-ethylhexyl and 1-propylpentyl groups. Approximately 22% of dinocap is meptyldinocap. Dinocap was last evaluated as new compound by the 1998 (R) and for some additional commodities by the 2001 Meetings of the JMPR. Presently both dinocap and meptyldinocap are marketed, but the manufacturers intend to gradually replace dinocap with meptyldinocap.

The manufacturer submitted information on metabolism in plants, analytical methods and residues in/on pome fruits, stone fruits, grapes, strawberries, cucurbits with edible and inedible peel which were evaluated by the present Meeting.

The studies evaluated by the present Meeting were conducted either with meptyldinocap or dinocap. The typical composition of the test substances are given below:

Isomers	Meptyldinocap	Dinocap
Meptyldinocap, 2,4-dinitro-6-(1-methylheptyl)phenyl crotonate	98.5 %	22 %
2,6-dinitro-4-(1-methylheptyl)phenyl crotonate	0 %	11 %
2,4-dinitro-6-(1-ethylhexyl)phenyl crotonate[1]	1.5 %	22 %
2,6-dinitro-4-(1-ethylhexyl)phenyl crotonate	0 %	11 %
2,4-dinitro-6-(1-propylpentyl)phenyl crotonate	0 %	22 %
2,6-dinitro-4-(1-propylpentyl)phenyl crotonate	0 %	11 %

Animal metabolism

The intended use for meptyldinocap is on vines, cucurbits and strawberries, which are not fed to animals. Therefore, no animal metabolism studies were provided for evaluation.

Farm animal metabolism studies evaluated by previous Meetings of the JMPR indicated that no radioactive residues were detectable in milk or tissues when lactating caws were fed with dinocap at 0.1, 0.3 and 1 ppm dose levels.

Plant metabolism

The plant metabolism studies on apples, cucumber and squash submitted to the current meeting had already been evaluated by the 1998 JMPR, and they were a re-evaluated by the present Meeting. The metabolism studies were carried out with meptyldinocap. A single major metabolite [2, 4-dinitro-6-(1-methylheptyl) phenol] was identified and it is referred to as 2,4-DNOP.

An apple tree was treated with a single foliar application of an EC formulation containing 45.6% ai at a rate equivalent to 1.96 kg ai/ha, four times the normal maximum application rate (0.49 kg ai/ha). Apple and leaf samples were taken on the day of application, both before and after treatment, and after 7, 14, and 21 days. Half of each fruit sample was analysed as whole fruit, and the other half peeled and the peel and pulp analysed separately.

The samples were extracted with methanol which recovered more than 90% of the radioactivity from the day 0 samples and 40–60 % from the aged samples. More than 92% of the radioactivity at each PHI was associated with the peel. The total radioactivity recovered in the neutral and alkaline methanolic extracts was more than 80% in all cases.

Two compounds present in the apple fruit have been identified by coelution with standards in both normal phase TLC and reversed phase HPLC. These are the parent meptyldinocap and its corresponding phenol, 2,4-DNOP. The parent compound was present in all of the treated samples, On the day of treatment, meptyldinocap was present at 2.12 mg/kg. After seven days the level had fallen to 0.52 mg/kg, representing 23% of the total radioactivity. After 14 days, the concentration of meptyldinocap had decreased to 0.25 mg/kg (11% of the total radioactivity), and after 21 days it was present at 0.12 mg/kg (8% of the total radioactivity). The half-life of meptyldinocap was calculated to be 5.2 days, The single major metabolite, 2,4-DNOP, was present at lower levels: it comprised roughly 24% of the total radioactivity in the aged samples (0.03–0.08 mg/kg, expressed as parent equivalent).

Five minor metabolites could be identified by gas chromatography with mass spectrometric detection: [2-methyl-5-nitro-7-(2-octyl) benzoxazole, 2-(hydroxymethyl)-5-nitro-7-(2-octyl) benzoxazole, 4-(1-propenyl)-5-nitro-7-(2-octyl)benzoxazole, 5-nitro-7-(octyl) benzoxazole and 2-hydroxymethyl-5-nitro-(2-octyl)-phenyl crotonamide]. The corresponding concentrations ranged from 0.001–0.007 mg/kg.

In cucumber, the distribution and rate of decrease of residues after a single treatment with ^{14}C-meptyldinocap at 0.56 kg ai/ha were studied. The residues of ^{14}C-meptyldinocap dissipated rapidly from the cucumber leaves and stems. The half lives of radioactive residues on leaves and stems were 11.8 days and 18.8 days, respectively. The ^{14}C residues on the leaves decreased from 38.2 mg/kg immediately after application to 1.4 mg/kg at final harvest. The ^{14}C residues in the stems decreased from 3.6 mg/kg immediately after application to 0.5 mg/kg at final harvest, 65 days after last application.

The whole mature fruit harvested 48 days after application contained ^{14}C residues of 0.16 mg/kg and whole mature fruit harvested 63 days after application contained 0.09 mg/kg. Of the whole mature fruit harvested 48 days after application, the peels contained 0.15 mg/kg and the flesh contained 0.11 mg/kg. The proportion of parent compound and 2, 4-DNOP was about the same in cucumber fruits at days 48 and 63.

Of the residues extracted from the leaves by acetone, only one metabolite (2,4-DNOP) occurred in significant (> 10%) quantity. The metabolism of ^{l4}C-meptyldinocap in cucumber leaves was extensive, leading to 18 minor metabolites. Only 2,4-DNOP could be identified amounting to 2.4% of TRR at day 8, while the unextractable residues accounted for 58% of TRR.

The half-life of the radioactivity was 8 days in the squash leaves treated with ^{14}C-meptyldinocap two times at a rate of 0.56 kg ai/ha. 2,4-DNOP was the main metabolite in the leaves and was also found in the fruit. About 6 unidentified metabolites were found in the fruit and 10 in the leaves, none of which individually accounted for more than 10% of the TRR. The 2,4-DNOP, meptyldinocap, organic soluble metabolites and water soluble polar metabolites and unextractable ^{14}C-residues amounted to 1.3%, 5.9%, 5.5%, 21% and 57.6% of TRR, respectively.

Photolysis, under natural daylight conditions, played a major role in the rapid dissipation of meptyldinocap from plant foliage. The concentration of meptyldinocap did not change on covered leaves over 27 hours following the foliar treatment with ^{14}C-meptyldinocap, while it decreased to 39% on leaves exposed to natural light. The extract of 27-hour uncovered leaves contained 53% polar photoproducts.

In summary, the metabolism of meptyldinocap is complex resulting in a large number of metabolites present at low concentrations. The metabolism of 2, 4- meptyldinocap appears to proceed by relatively rapid hydrolysis of the crotonate ester (half lives are about 5, 8 and 11.8 days on apple fruits, quash and cucumber leaves, respectively) to the corresponding phenol (2,4-DNOP). The

phenol is then further metabolised rapidly to a large number of more polar compounds, none of which is present in a significant amount. The proposed pathway for the formation of minor metabolites involves reduction of a nitro group to the amine. Metabolites are then formed by reaction of the amine with formic or acetic acid to form amides, or by intramolecular transfer of the crotonyl group to form the crotonamide. Ring closure of the amides then forms benzoxazoles. Individual metabolites could not be isolated. The amines could readily form conjugates with acids to form amides. Further degradation led to small carbon units which were subsequently incorporated into a number of natural products including cutin, lignin and other constituents that make up the acid detergent fibre.

Environmental fate in soil

Soil metabolism, degradation, leaching, rotational crop studies are not requires for compounds with intended use of foliar application only on permanent crops with no crops planted in rotation.

As part of the plant metabolism studies soil samples were also taken and analysed for meptyldinocap residues.

The ^{14}C residues in the top 2.5 cm of soil of cucumber plot decreased from 0.45 mg/kg immediately after application to 0.31 mg/kg after 63 days. The ^{14}C residues in the 2.5–7.6 cm soil depth never exceeded 0.02 mg/kg and the 7.6–15.2 cm soil depth residues never exceeded 0.007 mg/kg.

The ^{14}C residues in the top section of the soil (0–2.5 cm) of quash plot decreased from 0.43 mg/kg after the last treatment to 0.40 mg/kg 63 days later. The ^{14}C residues in the other soil sections were low.

The residues of [^{14}C]meptyldinocap in the soil in which the cucumber or squash were grown dissipate at a much slower rate than from the plants. There appeared to be no significant leaching of [^{14}C]-meptyldinocap residues into the lower depths of the soil.

Metabolism in rotational crops

The studies evaluated by the 1998 JMPR indicated that when beans, oats and turnips were grown in soil in which cucumber and squash were treated with [^{14}C]meptyldinocap 250 days earlier, the radioactive residues in samples taken until maturity of crops were at or below 0.02 mg/kg. Consequently, residues in follow up crops are unlikely to occur in measurable concentration.

Methods of analysis

The analytical methods used for determination of meptyldinocap residues in supervised trials were principally the same as those evaluated by the 1998 JMPR. Following the solvent extraction, the residues are converted to the corresponding phenols and determined by GC after methylation or analysed directly by HPLC-MS/MS. The validated limit of quantification for the meptyldinocap was 0.025 mg/kg and for combined residues 0.05 mg/kg. The average recoveries ranged from 80 to 104% with relative standard deviation of 7–14%. The concurrent recoveries obtained during the analysis of samples were in the same range.

The DFG S-19 multi residue method was found to be suitable for the determination of meptyldinocap residues in apples, barley grain, grapes and soya bean flour over in the concentration range from 0.05 mg/kg to 1.0 mg/kg with a validated limit of quantitation (LOQ) of 0.025 mg/kg for parent compound. The meptyldinocap peak was well separated from the dinocap isomers under the gas chromatographic conditions applied. The independent laboratory validation trials were conducted to satisfy the relevant requirements of the European Commission and the US EPA Guidelines.

Stability of residues in stored analytical samples

The stability of residues were tested in apples and grapes using 97.5% pure 2,4-dinitro-6-octylphenyl crotonates (2,4-DNOPC isomers) and 2,6-dinitro-4-octylphenyl crotonate isomer mixtures. The 'octyl' being a mixture of 1-methylheptyl, 1-ethylhexyl and 1-propylpentyl groups. In separate set of experiments the untreated samples were spiked at 1 mg/kg level. The overall mean procedural recoveries for 2,4-dinitro-6-octylphenyl crotonates in grapes and apples were 94.5% (RSD: 5.25%) and 88.6% (RSD: 10.3%) the average of residues remained over the period of 24 months were 89.8% (RSD: 10.13%) 71.5% (RSD: 10.5%), respectively. The results indicate that residues of the 2,4-DNOPC isomers are stable in apples, grapes, tomatoes, peaches and strawberries stored frozen up to 24 months. The stability of the meptyldinocap alone during deep-frozen storage could not be determined from these studies. However, it may be assumed to be similar to the other isomers.

Definition of the residue

Results of metabolism studies on fruits and fruiting vegetables indicate that the parent compound, meptyldinocap, forms the main residue remaining in the plant tissues at harvest. The major metabolite, the corresponding phenol, 2,4-DNOP, showed concentrations of 2–10% of total radioactivity only. The concentration of the major metabolite, the corresponding phenol (2, 4-DNOP) had not changed with time after application of the pesticide, indicating that that further metabolism to a number of minor compounds occurred relatively quickly. Initially the meptyldinocap amounted to the major portion of the TRR. The proportion of 2, 4-DNOP gradually increased with time and it was present in about the same concentration as meptyldinocap 48–63 days after the treatment of cucumber. The parent/2, 4-DNOP ratio was about 4 in apples 21 days after application.

The analytical method, which is used in the residue trials, determined meptyldinocap residues as a sum of the parent and the corresponding phenol. Multi residue methods, based on gas chromatographic and HPLC-MS/MS detection are available for the determination of meptyldinocap alone and have been validated for four representative commodities. Residues deriving from the use of dinocap could be identified based on the presence of 2,6-DNOP isomers provided that the chromatographic system used has sufficient resolution.

The current residue definition of dinocap is dinocap. As meptyldinocap is one isomer of dinocap, it is covered by the current residue definition. Non-selective methods cannot distinguish meptyldinocap from dinocap, but selective methods are available. While meptyldinocap and dinocap are both registered for crop uses, it is preferable, for enforcement purposes, to maintain a single residue definition.

It follows that, at least while dinocap MRLs are maintained, the residue definition for meptyldinocap as "dinocap, sum of all isomers" would be a practical solution.

The present Meeting established an ADI of 0–0.02 mg/kg/bw day. The new ADI is applicable for the sum of meptyldinocap and its corresponding phenol, when only they are present in the commodities analysed.

The Meeting recommended that while dinocap MRLs are maintained, the residue definition for meptyldinocap enforcement purposes should be dinocap, sum of all isomers.

Definition of the residue for dietary exposure assessment: the sum of meptyldinocap and the corresponding phenol, 2,4-DNOP, expressed as the parent meptyldinocap.

A residue definition for animal products is not required as no residue is expected to occur in animal products from the targeted use of meptyldinocap.

Results of supervised trials on crops

All trials were conducted according to GAP and the samples were analysed within the tested deep-frozen storage period. The methods applied for the analyses of samples determine meptyldinocap

residues as a sum of the parent and the corresponding phenol. The validity of the results was confirmed with concurrent recovery tests performed in the same analytical batch.

Cucumber and courgettes

GAP in France, Italy and Slovenia permits maximum 3 applications at 10 days with maximum dosage of 0.21 kg ai/ha and a PHI of 3 days. A total of eight supervised field trials on cucumbers/courgette were conducted according to maximum GAP in greenhouses located in the North and South European zones. Samples collected 3 days after the last application contained residues of < 0.005 (2), 0.01, 0.02 (4) and 0.04 mg/kg.

The Meeting estimated a maximum residue level, STMR value and HP value for Fruiting vegetables, Cucurbits, except melons of 0.07, 0.02 and 0.04 mg/kg.

Melons

GAP in France, Italy and Slovenia permits a maximum of 3 applications at 10 days with a maximum rate of 0.21 kg ai/ha and PHI of 3 days. A total of eight supervised field trials on melons were conducted according to maximum GAP in the North and South European zones. Whole fruit samples collected 3 days after the last application contained residues: < 0.005, 0.008, 0.02 (4), 0.05 and 0.28 mg/kg. No detectable residues were found in pulp samples.

The Meeting estimated a maximum residue level, STMR value and HP value for melons of 0.5, 0.005 and 0.28 mg/kg, respectively. Note: there is no information on pulp residues at high whole fruit residue.

The Meeting recommended to re-evaluate the current CXL of 0.05* for dinocap in fruiting vegetables cucurbits.

Grapes

GAP in France, Greece, Hungary and the UK permits a maximum of 4 applications with a maximum rate of 0.21 kg ai/ha and a PHI of 21 days. A total of eighteen trials were conducted on Grapes in Europe between 2005 and 2007. Eight trials with two formulations side by side containing meptyldinocap alone and the mixture of 2,4-DNPOC and 2,6-DOPOC (three isomers of each compound). In addition, eight trials were conducted in 2006 with a formulation containing meptyldinocap. All trials were performed with the permitted maximum application rate and frequency.

Samples collected at day 21 following the last application of meptyldinocap contained residues: < 0.01 (5), < 0.025 (6), 0.03 (3), 0.06 (2), 0.08, and 0.12 mg/kg.

The Meeting estimated a maximum residue level, STMR value and HP value for grapes 0.2, 0.025 and 0.12 mg/kg, respectively.

The Meeting noted that the current CXL of 0.5 mg/kg for dinocap in grapes covers the residues deriving from the use of meptyldinocap.

Strawberry

The GAP of France, Italy and Slovenia permits a maximum of 3 applications at 10 day intervals with a maximum rate of 0.21 kg ai/ha and a PHI of 3 days. A total of eight supervised field trials on strawberries were conducted according to the maximum GAP in greenhouses located in Northern and Southern Europe. The pesticide treatment was made with a formulation containing meptyldinocap.

Residues in samples collected 3 days after the final application of meptyldinocap, in ranked order, were: 0.03, 0.06, 0.07, 0.08, 0.09, 0.11, 0.12, 0.13 mg/kg.

The Meeting estimated a maximum residue level, STMR value and HP value for grapes 0.3, 0.085 and 0.13 mg/kg, respectively

The Meeting noted that the current CXL of 0.5 mg/kg for dinocap in strawberries covers the residues derived from the use of meptyldinocap.

The Meeting also noted that the current CXL for dinocap in strawberries included a note that it excludes the glasshouse use. The recommended maximum residue level for meptyldinocap is applicable for both uses.

Fate of residues during processing

Grapes

Dinocap was applied 6–8 times to both red and white grape varieties during the growing season at the recommended or 1.5× rate. Samples were collected for processing at intervals of 14–21 days after the final application. A portion of the collected grape bunches were subjected to vinification similar to commercial practice. The must from the white grape was divided into two equal portions: one of which was processed further without heating, the other was pasteurized for 2 minutes at approximately 85 °C.

The must of the white wine grapes, both pasteurized and non pasteurized, as well as the must of the red wine grapes was processed into wine following the same processing steps: fermentation; clarification (first racking and second racking); filtration, bottling and maturation. The residues were analysed with methods having LOQs of 0.04 and 0.05 mg/kg and an LOD of 0.01 mg/kg. The average recoveries in grapes, must and wine were in the 70–120% range.

Six grape samples taken 20–21 days or at shorter intervals after the last treatment did not contain residues above the LOQ. These trials could not be used for estimation of the processing factor. Other trials on red and white grapes resulted in measurable residues in grapes harvested 14–21 days after last pesticide treatment. The results of processing studies are summarised below:

PHI (days)	14	21	21	21[a]	21[a]
Grape	0.1	0.59	0.33	0.347	0.67
Must	< 0.04	< 0.05	< 0.01	< 0.05	< 0.05
Wine	< 0.04	< 0.01	< 0.01	< 0.01	< 0.01
Pf must/juice	< 0.4	< 0.085	< 0.030	< 0.144	< 0.075
Pf wine	< 0.4	< 0.017	< 0.030	< 0.029	< 0.015

[a] White grapes

The median processing factors for must and wine are < 0.08 and < 0.023 based on samples collected at the recommended PHI. The Meeting estimated STMR values of 0.0020 mg/kg and 0.00072 mg/kg for must and wine, respectively.

Raisins were prepared from the harvested grapes in two trials. However, the results are contradictory (the calculated processing factors were 2.26 and 0.417) and a processing factor could not be calculated.

Strawberry

Strawberry samples, taken 3 days after last pesticide treatment with dinocap, were processed to jam and preserve with a procedure resembling commercial practice. The residues measured in RAC and processed products are summarised below.

Dosage kg ai/ha & appl. No	0.4–0.41 × 6	0.39–0.42 × 6	0.21–0.22 × 3	0.20–0.21 ×3
Strawberry fruits (unwashed)	0.23	0.31	0.07	0.13
Jam	0.079	0.07	< 0.01	0.06
Preserve	< 0.05	0.11	< 0.01	0.11
Pf for jam	0.34	0.23	< 0.14	0.46
Pf for preserve	< 0.22	0.35	< 0.14	0.85

The calculated median processing factor for both jam and preserve is 0.285. The Meeting estimated an STMR value of 0.024 for strawberry jam and preserve.

Residues in animal commodities

Animal metabolism studies performed with dinocap evaluated by previous Meetings of the JMPR revealed that no radioactive residues were detectable in milk or tissues at any dose level (0.1-1 ppm). Consequently animal feeding studies are not required.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of meptyldinocap resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the thirteen Cluster Diets, based on estimated STMRs were 0 % of the maximum ADI (0.02 mg/kg bw). The Meeting concluded that the long-term intake of residues of difenoconazole from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

As the establishment of an ARfD was previously considered unnecessary, the Meeting concluded that the short-term intake of meptyldinocap residues is unlikely to present a public health concern.

5.19 NOVALURON (217)

RESIDUE AND ANALYTICAL ASPECTS

Novaluron is an insecticide of the class diflubenzoylureas. It was evaluated for the first time by JMPR in 2005 (T, R). The compound was listed for additional MRLs by 2010 JMPR at the Forty-first Session of the CCPR.

The manufacturer has submitted supervised crop field trial studies to support additional MRLs for the following commodities: broccoli, cabbage, mustard greens, Swiss chard, tomato (increase MRL), cherry, peach, plum, blueberry, snap bean (common bean), dry bean, and sugar cane. The supervised crop field trials are supplemented by the relevant GAPs, analytical methods, storage stability data, processing studies, and a poultry feeding study.

Methods of analysis

The analytical methods used in the supervised trials are based on the two methods previously included in the JMPR Evaluation in 2005: GC/ECD or HPLC with UV detection. A variation of the GC method uses a mass selective detector (MSD). A variation of the HPLC method uses LC/MS/MS. Adequate method validation at 0.05 mg/kg was reported with each crop field trial study. Average method and concurrent recoveries were all within the range of 70–120%, with relative standard deviations (RSD) at or below 20%.

Stability of residues in stored analytical samples

From the JMPR Report (2005) it can be concluded that minimum storage stability intervals of 12 months for high water content samples, 5 months for high oil content samples, 8 months for acidic commodities, and 12 months for high starch commodities are indicated. Additionally, in some of the crop field trial studies reported a control sample was fortified and stored frozen with the treated field samples. The fortified control was analysed at the time of analysis of the field samples. The percentages remaining were in the 71–118% range. All crop field trial samples were analysed within periods of demonstrated frozen storage stability.

Results of supervised trials on crops

Stone fruits

In all trials, determinations were made on the fruit without pit and no data on pit weights were available to express results on a fruit with pit basis. The absence of pit would be anticipated to yield slightly exaggerated residue values.

Peaches

A report on peach supervised field trials from the US was available. The US GAP is 3 applications at 0.36 kg ai/ha of an EC formulation with an 8 day PHI. The ranked order of residues on peaches (without pit) (n = 15) at the maximum GAP were: 0.20, 0.25, 0.41, 0.42 (2), 0.49, 0.58 (2), 0.66, 0.70, 0.90, 0.92, 1.0 (2), 2.1 mg/kg

Plums

A report on plum supervised field trials form the US was available. The US GAP is 3 applications at 0.36 kg ai/ha with an EC formulation with an 8 day PHI. The ranked order of residues on plums (without pits) (n = 10) at the maximum GAP were: 0.08, 0.16, 0.26, 0.33, 0.35, 0.47, 0.48, 0.62, 0.79, 0.80 mg/kg.

Cherries

A report on cherry supervised field trials form the US was available. The US GAP is 3 applications at 0.36 kg ai/ha with an EC formulation with an 8 day PHI. The ranked order of residues on cherries (without pits) (n = 7) at the maximum GAP were: 0.76, 0.97, 2.0, 2.2, 3.0, 3.9, 4.1 mg/kg.

The Meeting noted that the GAPs are identical for cherry, peach, and nectarine and that the US label specifies use on stone fruit. The Meeting decided to use the cherry supervised field trial data to estimate a maximum residue level of 7 mg/kg for stone fruit and an STMR of 2.2 mg/kg.

The value derived from use of the NAFTA calculator was 10 mg/kg based on a maximum residue level estimate for cherries (Lognormal 95/99 rule, 99th). However, small data sets may not produce reliable estimates via statistical procedures.

Berries and other small fruits

Blueberries

A report on blueberry supervised field trials in the US was received, where the GAP is 3 applications of an EC formulation at a maximum rate of 0.22 kg ai/ha/application and a PHI of 8 days. Nine trials complied with GAP, and the results in ranked order are: 0.99, 1.0, 1.1, 2.0, 2.1, 2.3, 3.5, 3.6, 3.8 mg/kg.

The Meeting estimated an STMR and maximum residue level of 2.1 and 7 mg/kg, respectively.

Use of the NAFTA statistical procedure yielded a maximum residue level estimate of 8, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations was 6 mg/kg. The statistical calculation has limited utility with small data sets (n = 9).

Strawberry

A report on strawberry supervised field trials in the US and Canada was received, where the GAP 3 applications of an EC formulation with a maximum application rate of 0.087 kg ai/ha/application and a PHI of 1 day. Using the GAP of the US for both Canadian and US trials, 10 trials complied with GAP, and the results in ranked order are: 0.07, 0.11 (3), 0.12, 0.18 (2), 0.22, 0.26, 0.29 mg/kg. The Meeting estimated an STMR and maximum residue level of 0.l5 and 0.5 mg/kg, respectively.

Use of the NAFTA statistical procedure yielded a maximum residue level estimate of 0.45 mg/kg (0.5 mg/kg rounded up), based on the 99th percentile of a log normal distribution. The mean plus three standard deviations is 0.4 mg/kg.

Brassica vegetables

Broccoli

A report on supervised field trials on broccoli in the US was received. The US GAP is for a maximum of 3 applications of an EC formulation at 0.044–0.087 kg ai/ha/application with a seasonal rate maximum of 0.17 kg ai/ha and a PHI of 7 days. The trials were conducted as 3 applications at 0.056 kg ai/ha, which matches the seasonal maximum rate but is only 64% of the single application rate, i.e., 0.087 mg/kg. The retreatment interval was 5 to 8 days. The broccoli residue decline study indicates a slow loss of residue with a half-life of about 14 days. Therefore, an accumulation effect from the 3 applications can be anticipated and, as the trials match the seasonal maximum application rate, they may be considered as complying with maximum GAP. Six trials complied with GAP, and the residues in ranked order are: < 0.05 (2), 0.10, 0.11, 0.14, 0.38 mg/kg.

Cabbage

A report on supervised field trials on cabbage in the US was received. The US GAP is 3 applications of an EC formulation at 0.087 kg ai/ha/application and a PHI of 7 days. The trials were conducted as

3 applications at 0.056 kg ai/ha, which matches the seasonal maximum rate but is only 64% of the single application rate, i.e., 0.087 mg/kg. The retreatment interval was 5 to 8 days. The cabbage residue decline study indicates residues < LOQ at all time intervals. Based on the broccoli decline study, a slow loss of residue with a half-life of about 14 days might be expected. Therefore, an accumulation effect from the 3 applications can be anticipated and, as the trials match the seasonal maximum application rate, they may be considered as complying with maximum GAP. Six trials complied with GAP, and the residues in ranked order are: < 0.05 (3), 0.08, 0.19, 0.48 mg/kg.

The Meeting used the broccoli and cabbage data as mutual support for a brassica vegetable maximum residue estimate of 0.7 mg/kg (broccoli or cabbage) and an STMR estimate of 0.105 mg/kg (broccoli).

The NAFTA statistical procedure produced for broccoli a maximum residue level estimate of 0.6 mg/kg, based on the 99th percentile of a log normal distribution. The NAFTA statistical procedure produced for cabbage a maximum residue level estimate of 0.6 mg/kg, based on the UCL median 95th. Statistical procedures have limited utility with very small data sets (n = 6 each).

Fruiting vegetables, Cucurbits

Cucumber

A report on supervised field trials on cucumbers in the US was received, where the GAP for all cucurbits is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Six trials complied with GAP, and the results in ranked order are: < 0.05 (6) mg/kg.

Melons

A report on supervised field trials on cantaloupe melons in the US was received, where the GAP for all cucurbits is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Eight trials complied with GAP, and the results in ranked order are: < 0.05 (4), 0.05, 0.07, 0.08, 0.09 mg/kg.

Summer squash (zucchini)

A report on supervised field trials on summer squash in the US was received, where the GAP for all cucurbits is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Seven trials complied with GAP, and the results in ranked order are: < 0.05 (6), 0.07 mg/kg.

The Meeting noted that residue levels from the same GAP are similar on cucumber, cantaloupe, and summer squash and decided to estimate an STMR of 0.05 and a maximum residue level of 0.2 mg/kg, respectively, for fruiting vegetables cucurbits.

The NAFTA statistical calculation procedure is not reliable for highly censored data sets. Using the data set with the lowest percentage of censored data (melons), a maximum residue level estimate of 0.11 mg/kg based on the mean plus 3×SD is suggested.

Fruiting vegetables, other than Cucurbits

Peppers

A report on supervised field trials on peppers in Canada and the US was received. The US GAP for all fruiting vegetables (non-cucurbit) is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Twelve bell pepper trials and 4 non-bell pepper trials complied with the US GAP. The non-bell (< 0.05 (2), 0.20, 0.36 mg/kg) results were not from a different population than the bell pepper results, and the combined results (n = 16) in ranked order are: < 0.05 (5), 0.05 (2), 0.07 (2), 0.14, 0.20, 0.22, 0.28, 0.36, 0.37, 0.38 mg/kg.

Tomato

A report on supervised field trials on tomatoes in Canada and the US was received. The US GAP for all fruiting vegetables (non-cucurbit) is 3 applications of an EC formulation at 0.087 kg ai/ha with a

PHI of 1 day. The use for fruiting vegetables non-cucurbit is for fields (outside) only except tomato, where glasshouse use is also specified.

Four glasshouse trials complied with GAP, and the trial results in ranked order are: < 0.05, 0.06, 0.20, 0.47 mg/kg. Fourteen field trials in Canada and the US complied with the US GAP, and the trial results in ranked order are: < 0.05 (3), 0.06 (2), 0.08 (2), 0.10 (2), 0.13 (2), 0.23, 0.26, 0.28 mg/kg.

The glasshouse and field trial results do not appear to be from different populations and may be combined (n = 18) to yield in ranked order: < 0.05 (4), 0.06 (3), 0.08 (2), 0.10 (2), 0.13 (2), 0.20, 0.23, 0.26, 0.28, 0.47 mg/kg.

The Meeting noted that the GAP is identical for pepper and tomato and that the tomato and pepper residue data sets are not from different populations. The Meeting used the data sets for mutual support and based upon the tomato data set (with the highest residue) estimated an STMR of 0.10 and a maximum residue level of 0.7 mg/kg for fruiting vegetables other than cucurbits to replace the existing Codex MRL of 0.02 (*) mg/kg for tomato.

The NAFTA statistical procedure estimated a maximum residue level of 0.6 mg/kg for pepper based on the mean plus 3 standard deviations and a maximum residue level of 0.6 mg/kg for tomato, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations was 0.6 mg/kg for pepper and 0.5 mg/kg for tomato. The Meeting considered 0.7 mg/kg a better estimate, given a highest residue of 0.48 mg/kg in a set of 18 values.

Leafy vegetables (including Brassica leafy)

Mustard greens

A report on supervised field trials on mustard greens in Canada and the US was received. The US GAP for all Brassica leafy vegetables is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 7 days. Eleven trials complied with the US GAP, and the results in ranked order are: 2.0, 2.1, 2.6, 3.0, 3.2, 3.6, 4.4, 5.0, 5.2, 10, 19 mg/kg. The Meeting estimates an STMR of 3.6 and a maximum residue level of 25 mg/kg, respectively.

The NAFTA statistical procedure yielded a maximum residue level estimate of 25 mg/kg, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations is also 25 mg/kg.

Swiss chard

A report on supervised field trials on Swiss chard in the US was received. The US GAP for Swiss chard is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Three trials complied with the US GAP, and residues in ranked order are: 2.3, 4.0, and 6.6 mg/kg.

The Meeting estimated an STMR of 4 and a maximum residue level of 15 mg/kg for Swiss chard. The Meeting noted that the number of trials was marginally acceptable, given that Swiss chard is not generally a major crop in production or in consumption.

The NAFTA statistical procedure yields a maximum residue estimate of 14 mg/kg, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations is 11 mg/kg. Statistical procedures have no utility for very small data sets.

Legume vegetables

Common bean

A report on supervised field trials on snap beans (common bean, green bean) in Canada and the US was received. The US GAP for common bean is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Fourteen trials complied with the US GAP, and the results in ranked order are: < 0.05, 0.10, 0.12 (2), 0.14, 0.16 (2), 0.17, 0.18 (3), 0.32, 0.40, 0.46 mg/kg.

The Meeting estimated an STMR of 0.165 and a maximum residue level of 0.7 kg/mg, respectively.

The NAFTA statistical procedure estimated a maximum residue level of 0.7 mg/kg, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations is 0.60 mg/kg.

Pulses

Bean (dry)

A report on supervised field trials on dry beans in the US was received. The US GAP for dry bean is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Thirteen trials complied with the US GAP, and the results in ranked order are: < 0.05 (10), 0.06, 0.08 (2) mg/kg.

The Meeting estimated an STMR and maximum residue level of 0.05 and 0.1 mg/kg, respectively.

Use of the NAFTA statistical procedure yielded a maximum residue level estimate of 0.15 mg/kg, based on the 99th percentile of a log normal distribution. MLE was used to fill-in the < LOQ values. The mean plus 3 standard deviations is also 0.15 mg/kg. Statistical procedures are not reliable for highly censored data sets, and attributing log normal behaviour to the LOQ data may not be appropriate.

Grasses for sugar

Sugar cane

A report on supervised field trials on sugar cane in the US was received. The US GAP for sugar cane is 5 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 14 days. Seven trials comply with the US GAP, and the results in ranked order are: < 0.05, 0.07 (2), 0.08, 0.10, 0.29, 0.31 mg/kg.

The Meeting estimated an STMR of 0.08 and a maximum residue level of 0.5 mg/kg.

The NAFTA statistical procedure yielded a maximum residue level estimate of 0.6 mg/kg, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations is 0.5 mg/kg. Statistical procedures are unreliable for small data sets.

Animal feed commodities

Bean forage (green)

A report on supervised field trials on snap beans (common bean, green bean) in Canada and the US was received. The US GAP for common bean is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Two types of vine samples were collected at different locations, vine only and vine plus residual pods. Fourteen trials comply with the US GAP, and residue results in ranked order are: 3.1, 5.3, 5.8 (2), 6.6, 6.8, 7.4, 7.8, 8.6, 8.8, 10 (2), 13, 18 mg/kg.

The Meeting estimated an STMR of 8.2 and a highest residue of 18 mg/kg.

Processing studies

Processing studies were provided for plum, tomato, and sugar cane. However, no residues were found in either the sugar cane or processed commodities. The processing factors (transfer factors) and related STMR-Ps are summarized as follows:

Commodity	Number of Studies (n)	Median Novaluron Transfer Factors	Novaluron RAC-STMR (mg/kg)	Novaluron STMR-P (mg/kg)
Plum - dried	2	3.1	0.41	1.27
Tomato - puree	1	< 0.73	0.10	0.073
Tomato - paste	1	1.1	0.10	0.11

The Meeting calculated a maximum residue level of 7 mg/kg for dried plums based on a highest residue of 2.2 mg/kg for stone fruit and a processing factor of 3.1 for plums (2.2 mg/kg × 3.1 = 6.8 mg/kg). This estimate is not needed as the mrl estimate for stone fruit is 7 mg/kg, and 7 mg/kg is equal to or greater than the dried plum estimate.

Farm animal feeding studies

The 2005 JMPR evaluated a ruminant feeding study and derived maximum residue estimates for livestock commodities based on the feeding study, a poultry metabolism study, and the livestock feeding tables then in use. New livestock feeding tables have been adopted, based on the OECD work.

The new uses under consideration by the present JMPR have several livestock feed items: bean vines (green), sugarcane molasses and bagasse, bean seed, and cabbage heads.

The Meeting estimated the dietary burden of novaluron in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual (2009 Edition). Calculation from highest residues, STMR (some bulk blended commodities), and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is assumed to be 100% when the highest residue levels and STMRs are expressed on a dry weight basis.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, chicken broilers, and laying poultry are provided in Annex 6 of the 2010 JMPR Report. The calculations were made according to the animal diets from the US/CAN, EU, and Australia in Appendix IX of the FAO Manual (2009 Edition). Bean forage makes a considerable contribution to the diet of cattle in Australia and to a lesser extent in Europe. Preliminary IEDI calculations with bean forage included in the diets of Australian and European cattle indicate that the ADI may be exceeded in at least one region. Therefore a tiered approach was adopted, and bean forage (green) was not included in the livestock diet for Australia or the European Union because novaluron is not registered for use on beans in Australia or in European Union member states, and forages are not generally in international trade (JMPR Report 2009, General Consideration 2.2). Thus, no residue of novaluron is anticipated on bean forage in Australia or in European Union member states.

Commodity	Level	Animal Dietary Burden, Novaluron, ppm of dry matter diet.			
		US/CAN	EU	Australia	Japan
Beef cattle	Max	1.54	3.03 [a]	2.44	0.0
	Mean	0.44	2.53 [c]	2.44	0.0
Dairy cattle	Max	1.20	1.86 [b]	1.27	0.0
	Mean	1.20	1.36 [d]	1.27	0.0
Poultry – broiler	Max	0.0092	0.174 [e]	0.044	0.0
	Mean	0.0092	0.049 [f]	0.044	0.0
Poultry – layer	Max	0.0092	0.014	0.044 [g]	0.0
	Mean	0.0092	0.014	0.044 [h]	0.0

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian tissues

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

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

[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 tissues.

[f] Highest mean poultry dietary burden suitable for STMR estimates for poultry tissues.

[g] Highest maximum poultry dietary burden suitable for MRL estimates for poultry eggs.

[h] Highest mean poultry dietary burden suitable for STMR estimates for poultry eggs.

A cow feeding study was reviewed by the 2005 JMPR. 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.

Cattle Dietary Burden (ppm)						
Feeding Level [ppm]	Cream	Milk	Muscle	Liver	Kidney	Fat
MAXIMUM RESIDUE LEVEL	Mean	Mean	Highest	Highest	Highest	Highest
MAXIMUM RESIDUE LEVEL beef cattle (3.03) [2.6]			0.10 [0.09]	0.16 [0.14]	0.16 [0.14]	2.6 [2.25]
MAXIMUM RESIDUE LEVEL dairy cattle (1.86) [2.6]	2.0 [2.8]	0.093 [0.13]	0.064 [0.09]	0.10 [0.14]	0.10 [0.14]	1.6 [2.25]
STMR	Mean	Mean	Mean	Mean	Mean	Mean
STMR beef cattle (2.53) [2.6]			0.078 [0.08]	0.13 [0.13]	0.13 [0.13]	1.7 [1.73]
STMR dairy Cattle (1.36) [0.35/2.6]	2.6 [0.68/2.80]	0.13 [0.04/0.13]	0.08 [0.04/0.08]	0.13 [0.05/0.13]	0.13 [0.04/0.13]	1.7 [0.45/1.73]

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

The Meeting estimated the following STMR values: milk 0.13; cream, 2.6 mg/kg; muscle 0.08; edible offal 0.13; fat 1.7 mg/kg. These levels replace previous estimates.

The Meeting estimated the following maximum residue levels for mammalian commodities (except marine): milk 0.2 mg/kg; milk fat 5 mg/kg; meat (fat) 3 mg/kg; edible offal 0.2 mg/kg. The milk fat estimate assumes that cream contains 50% milk fat. However, as these estimates are lower than previous recommendations, which are now CXLs, the Meeting confirmed the previous recommendations: milk 0.4 mg/kg; milk fat 7 mg/kg; meat (fat) 10 mg/kg; edible offal 0.7 mg/kg. The Meeting noted that the decrease in estimates results from the new OECD animal dietary burden diets adopted by the JMPR. For example consumption of cotton gin trash has dropped from 20% to 5%, and consumption of wet apple pomace has dropped from 40% to 20%.

A poultry feeding study was made available to the Meeting. Groups of laying hens were orally dosed with novaluron at levels of 0, 0.12, 0.36, and 1.2 mg/kg for 56 days. Maximum residues at the 0.12 ppm feeding level were 0.080 mg/kg in eggs (day 47), 0.014 mg/kg in muscle, 0.034 mg/kg in liver, 0.039 mg/kg in kidney, and 0.323 mg/kg in fat (abdominal). Average residues were 0.070 mg/kg in eggs (day 47), 0.012 mg/kg in muscle, 0.033 mg/kg in liver, 0.036 mg/kg in kidney,

and 0.307 mg/kg in fat (abdominal). At the 0.36 ppm feeding level, the maximum and average residues in egg were 0.18 mg/kg and 0.174 mg/kg (day 47), respectively.

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.

Poultry Dietary Burden (ppm)					
Feeding Level [ppm]	Egg	Muscle	Liver	Kidney	Fat
MAXIMUM RESIDUE LEVEL	Mean	Highest	Highest		Highest
MAXIMUM RESIDUE LEVEL Broiler (0.044) [0.12]		0.0044 [0.012]	0.012 [0.033]	0.013 [0.036]	0.11 [0.307]
MAXIMUM RESIDUE LEVEL Laying (0.174) [0.12]	0.10 [0.0703]	0.021 [0.014]	0.049 [0.034]	0.056 [0.039]	0.47 [0.323]
STMR	Mean	Mean	Mean		Mean
STMR Broiler (0.044) [0.12]		0.0044 [0.012]	0.012 [0.033]	0.013 [0.036]	0.11 [0.307]
STMR Laying (0.049) [0.12]	0.029 [0.0703]	0.0048 [0.012]	0.013 [0.033]	0.015 [0.036]	0.13 [0.307]

The data from the laying hen feeding study were used to support poultry egg and meat maximum residue levels.

The Meeting estimated the following STMR values: eggs, 0.029 mg/kg; fat, 0.13 mg/kg; muscle, 0.005 mg/kg ; edible offal, 0.015 mg/kg . These replace previous STMR estimates.

The Meeting estimated the following maximum residue levels for poultry commodities: eggs, 0.1 mg/kg; meat (fat), 0.5 mg/kg; edible offal, 0.1 mg/kg. These estimates replace previous recommendations: eggs 0.01 (*) mg/kg; poultry meat (fat) 0.01 (*) mg/kg; poultry, edible offal of 0.01 (*) mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of novaluron were calculated for the 13 GEMS/Food Consumption Cluster Diets using STMRs and STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.01mg/kg bw and the calculated IEDIs were 7–50% of the maximum ADI. The Meeting concluded that the long-term intake of residues of novaluron resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term intake

The2005 JMPR decided that an ARfD was unnecessary. The Meeting therefore concluded that the short-term intake of novaluron residues is unlikely to present a public health concern.

5.20 SPICES (R)

RESIDUE AND ANALYTICAL ASPECTS

Thailand submitted residue data obtained from 407 spice samples collected within a targeted monitoring programme carried out during 2005–2008.

Methods of analysis

The samples were analysed in two accredited laboratories applying either multi-residue methods based on acetone/dichloromethane/sodium chloride water solution extraction and partition and GC-ECD, GC FPD or HPLC detection after post-column derivatization, or using the QUECHER method with HPLC-UV or HPLC-MSD detection. The recoveries reported were comparable, but the LOQ values were substantially higher in 2007–2008 than the earlier years.

No information was provided on the storage conditions and duration between sampling and analyses.

The residues and metabolites analysed are in accord with the residue definitions recommended by the JMPR.

Results of monitoring programmes

The monitoring programme included root or rhizome spices (ginger, turmeric root, kra-chai root and galangal rhizomes), fruit or berry spices (pepper - black and white) and 38 pesticides which were commonly used and where residues were occasionally found in fruits, vegetables, herbs and spice commodities in Thailand. The LOQ values obtained during method validation were often higher than the residue concentrations determined in the samples.

None of the samples contained detectable residues of the following pesticides which had been evaluated by the JMPR: aldicarb, bifenthrin, carbendazim, carbosulfan, cyfluthrin, cyhalothrin, dichlorvos, diazinon, dimethoate, fenitrothion, fenvalerate, malathion, methidathion, methiocarb, omethoate, oxamyl, permethrin, phosalone, pirimiphos-methyl, profenofos and triazophos.

Dicrotophos, fenobucarb, isoprocarb, pirimiphos-ethyl, promecarb and prothiofos residues were also looked for but the samples analysed did not contain detectable residues. As these compounds have not been evaluated by the JMPR, maximum residue levels ccould not be estimated.

Detectable residues were found in the following commodity pesticide combinations:

- Kra-chai root – captan: < 0.05 (43) and 0.29 mg/kg;
- Galangal root – deltamethrin: < 0.05 (71), 0.18, 0.33 mg/kg
- Turmeric root – methomyl: < 0.1 (42), 0.69, 0.94 and 1.47 mg/kg
- Pepper, black and white – carbaryl: 0.09, < 0.1 (120), 0.14, 0.17, 0.35, 0.52, and 0.78 mg/kg
- Pepper, black and white – carbendazim: < 0.1 (122), 0.01, 0.01, 0.01 and 0.02 mg/kg
- Pepper, black and white – chlorpyrifos: 0.02, 0.02, 0.04, < 0.07 (121), 0.08, and 0.55 mg/kg
- Pepper, black and white – cypermethrin: 0.03, < 0.03 (117), 0.04, 0.05 (3), 0.07, 0.17, 0.13, and 0.43 mg/kg
- Pepper, black – ethion: < 0.02 (63) and 0.05 mg/kg

The Meeting noted that the number of samples analysed for captan in kra-chai and for methomyl in turmeric root did not meet the minimum sample size requirement of 58 (JMPR Manual

2nd ed. Section 6.11.1 page 107), therefore no recommendation could be made for these combinations.

Taking into account the number of residue data enabled the estimation of maximum residue levels covering the 95 – < 98% of the potentially present residues only, the Meeting included also the highest residue value in the estimated maximum residue level.

For fruit or berry and root and rhizome subgroups there are CXLs indicated in brackets, respectively, for chorpyrifos (1; 1 mg/kg), cypermethrin (0.1; 0.2 mg/kg), dichlorfos (0.1; 0.1 mg/kg), diazinon (0.1; 0.5 mg/kg), dimethoate (0.5; 0.1 mg/kg), ethion (5; 0.3 mg/kg), fenitrothion (1; 0.1 mg/kg), malathion (1; 0.5 mg/kg), permethrin (0.05*; 0.05* mg/kg), phosalone (2; 3 mg/kg) and pirimophos-methyl (-; 0.5 mg/kg) which cover the residues found in the Thai monitoring programme. These CXLs were confirmed by the present Meeting

For cypermethrin the Meeting estimated, for the fruit and berry subgroup a maximum residue level, median residue and HR of 0.5 mg/kg, 0.05 mg/kg and 0.43 mg/kg, respectively, and withdrew its previous recommendation of 0.1 mg/kg for the maximum residue level.

On the basis of the monitoring data, the Meeting concluded that the residue concentrations listed below were suitable for establishing MRLs and for assessing IEDIs and IESTIs.

Maximum, HR and STMR residue values recommended for fruit or berry and root and rhizome spices.

Codex Number	Commodity	Pesticide	Maximum residue level (mg/kg)		Median residue mg/kg	HR mg/kg
			New	Previous		
028B	Fruit or berry	Carbaryl	0.8		0.1	0.78
		Carbendazim	0.1		0.1	0.1
		Cypermethrin	0.5	0.1	0.03	0.43
0.28D	Root and rhizome	Deltamethrin	0.5		0.05	0.33

Taking into account that sufficient number of random samples were analysed and no detectable residue was found in any of the samples, the Meeting estimated maximum residue median and high levels in root and rhizome and fruit or berry spice groups at the reported highest LOQ values shown in the table below:

Maximum, median and high residue values [mg/kg] based on LOQ of pesticides

	028D Root and rhizome spices	028B Fruit and berry
Aldicarb	0.02	0.07
Bifenthrin	0.05	0.03
Captan	0.05	-
Carbaryl	0.1	
Carbendazim	0.1	
Carbosulfan	0.1	0.07
Cyfluthrin	0.05	0.03
Cyhalothrin	0.05	0.03
Deltamethrin		0.03
Fenvalerate	0.05	0.03
Methidathion	0.05	0.02
Methiocarb	0.1	0.07
Methomyl		0.07
Omethoate	0.05	0.02
Oxamyl	0.05	0.07
Profenofos	0.05	0.07
Triazophos	0.1	0.07

DIETARY RISK ASSESSMENT

The Meeting concluded that, it is unlikely that the dietary intake estimated by previous meetings would be markedly affected by the consumption of food containing spices considered by the present Meeting.

5.21 TEBUCONAZOLE (189)

TOXICOLOGY

Tebuconazole is the International Organization for Standardization (ISO)–approved name for (*RS*)-1-*p*-chlorophenyl-4,4-dimethyl-3-(1H-1,2,4-triazol-1-ylmethyl)pentan-3-ol (International Union of Pure and Applied Chemistry [IUPAC]), for which the Chemical Abstracts Service (CAS) No. is 107534-96-3. Tebuconazole is a triazole fungicide that acts by inhibiting sterol biosynthesis in fungi (demethylation inhibitor).

The toxicity of tebuconazole was first evaluated by the 1994 Joint FAO/WHO Meeting on Pesticide Residues (JMPR). That Meeting established an acceptable daily intake (ADI) of 0–0.03 mg/kg body weight (bw) on the basis of a no-observed-adverse-effect level (NOAEL) of 2.9 mg/kg bw per day for histopathological alterations in the adrenal glands seen at 4.4 mg/kg bw per day and above in two 52-week toxicity studies in dogs and using a safety factor of 100.

Tebuconazole was re-evaluated by the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR). Three new studies (acute neurotoxicity study, subacute neurotoxicity study and a developmental neurotoxicity study) since the last review by the JMPR were made available. All pivotal studies with tebuconazole were certified as complying with good laboratory practice (GLP) unless otherwise stated.

Biochemical aspects

In a toxicokinetic study, groups of male and female rats were given tebuconazole uniformly labelled with ^{14}C in either the phenyl ring or the 3,5-triazole ring as a single dose at 2 or 20 mg/kg bw or as 14 repeated doses of 2 mg/kg bw per day, followed by a single oral dose of radioactive tebuconazole at 2 mg/kg bw. Tebuconazole was rapidly absorbed from the gastrointestinal tract of rats and rapidly excreted from the body. Between 86% and 98% of the dose was excreted in the urine and faeces in 72 h; most excretion occurred in the first 48 h. Faecal excretion within 72 h after administration was about 80% of the applied dose in males and about 65% in females; urinary excretion amounted to about 16% of the applied dose in males and about 33% in females. No significant differences in the absorption, distribution and excretion occurred following administration of single oral low dose or high dose or repeated doses. Male rats with biliary fistulae excreted 90.7% of the dose with the bile, 7.4% in the urine and 1.5% in faeces within 48 h, suggesting complete absorption of tebuconazole in intact rats. Only 0.3% of the radioactivity was detected in exhaled air within 72 h following oral administration of tebuconazole. After 72 h, less than 1% of the administered dose could be detected in the organs, tissues and the remaining carcass, indicating no potential for bioaccumulation. Highest residues were found in the liver and kidney. Tebuconazole was rapidly distributed (within 1 h) in the body, as determined by whole-body radioautography. The peak concentration of radioactivity in plasma was found at 0.33–1.7 h. The terminal half-life of radiolabel was 32.0–52.5 h. Tebuconazole was extensively metabolized in the body following oral administration. Less than 0.7% of parent tebuconazole was detected in the excreta at 72 h after administration. The metabolic pathway in rats also demonstrated sex-related differences. The main metabolites of tebuconazole in male rats were the oxidation products of one of the methyl groups of the tertiary butyl moiety (i.e., the alcohol and the carboxylic acid). Metabolism in female animals resulted preferentially in simple oxidation products (e.g., hydroxy and carboxy metabolites) and then conjugation to the glucuronide and sulfate, with only minor cleavage of the triazole moiety. In male animals, the primary oxidation products were further oxidized to triol and keto acid derivatives; in addition, cleavage of the triazole ring occurred, as indicated in trials with triazole-labelled compound. The free triazole accounted for about 5% of the administered dose in the urine of the males and 1.5% in that of females.

Toxicological data

Tebuconazole has low to moderate acute toxicity in mice and rats via the oral route. The oral median lethal dose (LD_{50}) of tebuconazole was 1700 and 4000 mg/kg bw in fasted female and male rats, respectively. The oral LD_{50} of tebuconazole in mice was 3025 and 1615 mg/kg bw in fasted female and male mice, respectively. The LD_{50} in rats treated dermally was greater than 2000 mg/kg bw. The median lethal concentration (LC_{50}) in rats treated by inhalation (nose only) was greater than 0.82 mg/L. Tebuconazole was non-irritating to the eyes and skin of rabbits. Tebuconazole was not a skin sensitizer in guinea-pigs, as determined by the Magnusson and Kligman (maximization) test and the Buehler test.

In a non-GLP 28-day gavage study of toxicity in rats, decreases in haemoglobin concentration and haematocrit values were observed at 100 and 300 mg/kg bw per day. At 100 and 300 mg/kg bw per day, the weights of the liver and spleen were increased in both sexes, and the weight of the kidney was increased in females. A reduced iron content was observed in the spleen of females at 100 mg/kg bw per day. The NOAEL in the 28-day gavage study in rats was 30 mg/kg bw per day, on the basis of changes in haematological and clinical chemical parameters and organ weights at 100 mg/kg bw per day. In a 90-day dietary toxicity study in rats, reduced body weight gain was observed at 400 ppm in females during the first 6 weeks. Histopathological examination revealed an increased incidence of intraplasmatic vacuoles in the cells of the zona fasciculata of the adrenals (probably lipid accumulation) in some females at 400 ppm and in all females at 1600 ppm. The NOAEL was 100 ppm (equal to 10.8 mg/kg bw per day), based on a reduction in body weights in females at 400 ppm (equal to 46.5 mg/kg bw per day).

The NOAEL in a 90-day dietary study of toxicity in dogs was 200 ppm (equal to 8.5 mg/kg bw per day), based on decreased body weight gain and food consumption at 1000 ppm (equal to 41 mg/kg bw per day). Two 1-year dietary studies of toxicity were conducted in dogs with tebuconazole. The overall NOAEL was 100 ppm (equal to 2.9 mg/kg bw per day), based on intracytoplasmic vacuoles in cells of the zona fasciculata of the adrenals and slight hypertrophy accompanied by an increased incidence of large fatty vacuoles seen at 150 ppm (equal to 4.4 mg/kg bw per day) and above.

The carcinogenic potential of tebuconazole was studied in mice and rats. Two carcinogenicity studies were conducted in mice. In the first study, the NOAEL was 20 ppm (equal to 5.9 mg/kg bw per day), based on the increased incidence of centrilobular fine vacuolization in the liver of males at 60 ppm (equal to 18 mg/kg bw per day). There was no evidence of any carcinogenic potential, but the effects on the liver at the lowest-observed-adverse-effect level (LOAEL) and above were not very marked in intensity, posing a question as to whether a maximum tolerated dose (MTD) had been reached in this study. Therefore, a second carcinogenicity study was conducted at higher doses. In the second study, no NOAEL was identified. The LOAEL was 500 ppm (equal to 85 mg/kg bw per day), based on liver toxicity. The incidence of liver tumours in male and female mice was significantly elevated at 1500 ppm (equal to 279 mg/kg bw per day) and was markedly above the range of spontaneous incidences observed in this mouse strain.

In the carcinogenicity study in rats, the NOAEL was 300 ppm (equal to 15.9 mg/kg bw per day), based on body weight depression in both sexes and an increased incidence of pigment deposits in the Kupffer cells in the liver of females at 1000 ppm (equal to 55 mg/kg bw per day). No treatment-related tumours were observed.

Tebuconazole was not genotoxic in an adequate range of in vitro and in vivo genotoxicity tests.

The Meeting concluded that tebuconazole is unlikely to be genotoxic.

In view of the absence of genotoxic potential, the absence of carcinogenicity in rats and no carcinogenicity in mice relevant to human dietary exposure levels, the Meeting concluded that tebuconazole is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, the reproductive parameters were not affected at doses up to 1000 ppm (equal to 72.3 mg/kg bw per day), the highest dose tested. The NOAEL for parental systemic toxicity and offspring toxicity was 300 ppm (equal to 21.6 mg/kg bw per day), based on reduced food consumption and decreased body weights in parental animals and pups seen at 1000 ppm (equal to 72.3 mg/kg bw per day).

Several developmental toxicity studies in mice, rats and rabbits using gavage administration were submitted. The overall NOAEL for maternal toxicity in the oral gavage studies in mice, rats and rabbits was 30 mg/kg bw per day, mainly based on decreases in body weights and body weight gains (during the early treatment period) at 100 mg/kg bw per day. Marginal effects in studies in mice (haematological effects) and rats (reduced body weight gains) were not considered as adverse. Selected liver parameters (enzymes, weights and clinical chemistry) were evaluated in developmental toxicity studies in mice and rats. Changes in the liver parameters in these studies were considered an adaptive response and not considered as adverse. In one study in mice, there was an increase in the number of small fetuses (runts) at doses of 30 mg/kg bw per day and above. These small fetuses, defined on the basis of low body weights, were considered unlikely to be due to a single exposure or a small number of exposures. The NOAEL for developmental toxicity in mice was 10 mg/kg bw per day. In other studies in mice, rats and rabbits, developmental effects included increased resorptions, a decreased number of live fetuses, decreased fetal weights, incomplete ossification and visceral and skeletal anomalies. In addition, post-implantation loss was observed in mice. These developmental effects were observed consistently at doses above 30 mg/kg bw per day and in the presence of maternal toxicity in all studies. The overall NOAEL for developmental toxicity was 30 mg/kg bw per day in rats and rabbits.

The Meeting concluded that tebuconazole caused developmental toxicity and teratogenic effects at doses that were maternally toxic in rats and rabbits.

In a study of acute neurotoxicity in rats with tebuconazole, the NOAEL was 50 mg/kg bw based on increased motor activity in male and female rats and decreased footsplay in female rats at 100 mg/kg bw. In a 90-day study of neurotoxicity in rats, no systemic or neurotoxic effects were seen at doses up to 1600 ppm (equal to 107 mg/kg bw per day), the highest dose tested. In a developmental neurotoxicity study in rats with dietary administration, the maternal NOAEL was 300 ppm (equal to 22 mg/kg bw per day), based on decreased body weights, body weight gains and food consumption, prolonged gestation with mortality, and an increased number of dead fetuses at 1000 ppm (equal to 65 mg/kg bw per day). The offspring toxicity NOAEL was 300 ppm (equal to 22 mg/kg bw per day), based on decreased pup viability, decreases in body weights and absolute brain weights, brain measurements and evidence of developmental delays seen at 1000 ppm (equal to 65 mg/kg bw per day), the highest dose tested. Tebuconazole did not produce neurobehavioural or neuropathological changes.

Workers did not report any adverse effects while handling tebuconazole in a production facility. The workers were monitored by routine physical examination and clinical chemistry measurements.

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

Toxicological evaluation

The Meeting reaffirmed the ADI of 0–0.03 mg/kg bw on the basis of an overall NOAEL of 2.9 mg/kg bw per day in two 1-year dietary toxicity studies in dogs, based on histopathological alterations in the adrenals seen at the LOAEL of 4.4 mg/kg bw per day, and using a safety factor of 100.

The Meeting established an acute reference dose (ARfD) of 0.3 mg/kg bw on the basis of a maternal and developmental toxicity NOAEL of 30 mg/kg bw per day in studies of developmental toxicity in rats and rabbits based on maternal toxicity manifested as decreases in body weight gains in the early treatment period and visceral and skeletal anomalies seen at higher doses. The increased

incidence of the number of small fetuses, defined on the basis of low body weights, was considered unlikely to be due to a single exposure or a small number of exposures. The ARfD is supported by the NOAEL of 30 mg/kg bw per day observed in a 28-day oral (gavage) toxicity study in rats based on changes in haematological parameters seen at the LOAEL of 100 mg/kg bw per day, which might be produced by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Twenty-one-month study of toxicity and carcinogenicity[a,b]	Toxicity	20 ppm, equal to 5.9 mg/kg bw per day	60 ppm, equal to 18 mg/kg bw per day
		Carcinogenicity	180 ppm, equal to 53 mg/kg bw per day	500 ppm, equal to 85 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	10 mg/kg bw per day	30 mg/kg bw per day
Rat	Twenty-eight-day study of toxicity[c]	Toxicity	30 mg/kg bw per day	100 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity[b]	Toxicity	300 ppm, equal to 15.9 mg/kg bw per day	1000 ppm, equal to 55 mg/kg bw per day
		Carcinogenicity	1000 ppm, equal to 55 mg/kg bw per day[d]	—
	Two-generation study of reproductive toxicity[a]	Parental toxicity	300 ppm, equal to 21.6 mg/kg bw per day	1000 ppm, equal to 72.3 mg/kg bw per day[d]
		Offspring toxicity	300 ppm, equal to 21.6 mg/kg bw per day	1000 ppm, equal to 72.3 mg/kg bw per day[d]
		Reproductive toxicity	1000 ppm, equal to 72.3 mg/kg bw per day[d]	—
	Developmental toxicity[c]	Maternal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
Rabbit	Developmental toxicity[c]	Maternal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
Dog	Two 1-year studies of toxicity[a,b]	Toxicity	100 ppm, equal to 2.9 mg/kg bw per day	150 ppm, equal to 4.4 mg/kg bw per day

[a] Dietary administration.

[b] Two or more studies combined.

[c] Gavage administration.

[d] Highest dose tested.

Estimate of acceptable daily intake for humans

0–0.03 mg/kg bw

Estimate of acute reference dose

0.3 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Complete and rapid
Dermal absorption	Not available
Distribution	Extensive
Potential for accumulation	None
Rate and extent of excretion	Rapid and extensive
Metabolism in animals	Extensive; metabolic pathways include hydrolysis, oxidation and conjugation
Toxicologically significant compounds in animals, plants and the environment	Tebuconazole and 1,2,4-triazole
Acute toxicity	
Rat, LD_{50}, oral	1700 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 0.82 mg/L, dust (4 h exposure, nose only)
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Non-irritating
Guinea-pig, dermal sensitization	Not a sensitizer (Magnusson and Kligman and Buehler tests)
Short-term studies of toxicity	
Target/critical effect	Adrenals/hypertrophy of zona fasciculata cells (dogs)
	Liver, blood system and adrenals (rats)
Lowest relevant oral NOAEL	2.9 mg/kg bw per day (overall from two 1-year toxicity studies in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rats)
Lowest relevant inhalation NOAEC	0.5 mg/L
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver toxicity (mice and rats)
Lowest relevant NOAEL	5.9 mg/kg bw per day (carcinogenicity study in mice)
Carcinogenicity	Not carcinogenic in rats, but hepatocarcinogenic in mice; unlikely to pose a carcinogenic risk at human dietary exposure levels
Genotoxicity	
	Not genotoxic

Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects
Lowest relevant reproductive NOAEL	1000 ppm, equal to 72.3 mg/kg bw per day, highest dose tested (rats)
Developmental target/critical effect	Developmental toxicity, including teratogenicity, only at maternally toxic doses in rats and rabbits
Lowest relevant developmental NOAEL	30 mg/kg bw per day (rats, rabbits); 10 mg/kg bw per day (mice; runts)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	Increased motor activity in rats
Subchronic neurotoxicity	No neurotoxicity in rats
Developmental neurotoxicity	No neurodevelopmental toxicity in rats
Other toxicological studies	
	None
Medical data	
	No adverse effects reported

Summary

	Value	Study	Safety factor
ADI	0–0.03 mg/kg bw	Two 1-year toxicity studies in dogs	100
ARfD	0.3 mg/kg bw	Developmental toxicity studies in rats and rabbits, supported by a 28-day study of toxicity in rats (gavage)	100

5.22 THIAMETHOXAM (245)

TOXICOLOGY

Thiamethoxam is the International Organization for Standardization (ISO)–approved name for (*EZ*)-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine (International Union of Pure and Applied Chemistry [IUPAC]), with Chemical Abstracts Service (CAS) No. 153719-23-4. It is a neonicotinoid insecticide active against a broad range of commercially important sucking and chewing pests. The biological effects of this chemical class in target species are mediated primarily by an interaction with nicotinic acetylcholine receptor sites.

Thiamethoxam is being reviewed 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). Non-GLP studies were identified as such.

Biochemical aspects

In rats given [^{14}C]thiamethoxam labelled in either the thiazole or oxadiazine rings as a single oral dose of 0.5 or 100 mg/kg body weight (bw), the radiolabel was rapidly and completely absorbed, based on the recoveries in excreta. The time to reach maximum concentrations in plasma was 1–4 h. Distribution to the tissues was generally non-selective, but resulted in higher concentrations in liver and blood. Tissue residues in rats amounted to 0.3% of the total applied dose after 7 days.

The depletion from the tissues followed first-order kinetics, with half-lives in all tissues in the range of 2–6 h, independent of the dose level, the site of the label and the sex of the rats. Seven days after oral administration of 0.5 mg/kg bw, the tissue residues were very low. The absorbed material was rapidly excreted from rats, predominantly in the urine. The routes of elimination and the urinary pattern of the rapidly excreted thiamethoxam and its metabolites were complex and independent of the route of administration, the dose level, pretreatment with non-radio-labelled thiamethoxam, the site of label and the sex of the animals.

In rats, about 20–30% of the dose was biotransformed, whereas 70–80% was eliminated as unchanged thiamethoxam. Within 24 h, about 90% of the dose was excreted via kidneys with recovery in urine, and about 4% via the bile with recovery in the faeces; total faecal recovery was about 5%. In mice, 30–60% of the dose was biotransformed and eliminated mainly in urine, but faecal elimination accounted for about 19%.

Twenty-two metabolites were isolated from the excreta of rats and identified. The quantitatively most important metabolite was CGA 322704 (clothianidin), which accounted for about 10% of the dose. The individual contributions of all the other metabolites did not exceed 1% of the dose. Plasma concentrations of two of these minor metabolites, CGA 330050 and CGA 265307, were 15 to 140-fold higher in mouse than in rat. The major reaction involved in the biotransformation of thiamethoxam is cleavage of the oxadiazine ring to the corresponding nitroguanidine compound. Minor pathways are reduction of the nitroguanidine group, yielding a hydrazine, followed by either acylation or further reduction to a guanidine derivative, hydrolysis of the guanidine group to the corresponding urea, demethylation of the guanidine group and substitution of the chlorine of the thiazole ring by glutathione. Cleavage between the thiazole and oxadiazine ring occurs to a small extent and is mediated by either glutathione or oxidative dealkylation. The glutathione derivatives are prone to further degradation. Both the thiazole and oxadiazine moieties are susceptible to oxidative attack. These minor pathways proceed to small molecules and ultimately, probably, to carbon dioxide. The small molecules generated may enter the general metabolism. Metabolic degradation of thiamethoxam in mice proceeded via the same pathway as in rats. All major and almost all minor metabolites found in rat excreta were also detected in mouse excreta.

In vitro comparisons of thiamethoxam metabolism in mouse, rat and human liver microsomal preparations clearly support the significantly higher generation of CGA 330050 and CGA 265307 in mice compared with rats and additionally, demonstrates that human liver microsomes metabolize thiamethoxam in a manner quantitatively similar to and not exceeding that of rats.

Toxicological data

The acute toxicity of thiamethoxam is low, the oral median lethal dose (LD_{50}) being 1563 mg/kg bw in rats and 871 mg/kg bw in mice. Signs of toxicity at high doses included tonic or clonic convulsions, ptosis and reduced locomotor activity. The acute dermal LD_{50} of thiamethoxam in rats was greater than 2000 mg/kg bw. The 4 h acute inhalation median lethal concentration (LC_{50}) of thiamethoxam in rats was greater than 3.72 mg/L (the mean achieved concentration). Thiamethoxam was not irritating to rabbit skin or rabbit eyes. Thiamethoxam was not a skin sensitizer in the Magnusson and Kligman maximization test in guinea-pigs.

The short-term oral toxicity of thiamethoxam administered via the diet was evaluated in mice, rats and dogs. These consisted of 4-week range-finding studies in rats followed by 13-week toxicity studies in rats and dogs and a 52-week toxicity study in dogs. A 13-week range-finding study was also conducted in mice.

The liver was identified as a target organ in mice and rats. Treatment for 13 weeks induced liver hypertrophy, inflammatory cell infiltration and pigmentation of hepatocytes and Kupffer cells in both rodent species. In mice, single-cell necrosis and apoptosis occurred in parallel with these alterations.

The kidney was identified as a target organ in rats, but not in mice or dogs. Both sexes were affected, but there was a difference between the sexes in both morphology and sensitivity. In males, nephrotoxicity was characterized by tubular epithelial hyaline droplet accumulation, acute and chronic tubule lesions, basophilic proliferation and cast formation. The pattern of effects in male rat kidneys resembled α_{2u}-globulin nephropathy, which is generally accepted to be a phenomenon exclusively found in males of some strains of rats. Immunohistochemical studies on kidneys from male rats exposed to thiamethoxam for 28 days or 3, 12 or 24 months with a specific anti-α_{2u}-globulin antibody identified treatment-related increases in renal α_{2u}-globulin accumulation, particularly after 28 days and 3 months of treatment. It was concluded that the renal changes observed in male rats treated with thiamethoxam represent a mild α_{2u}-globulin nephropathy, which is male rat specific and has no human relevance. Renal lesions in females were confined to an increased incidence of chronic tubular lesions and an increase in the severity of nephrocalcinosis. Other observations, particularly basophilic proliferation, tended to be increased in all groups of females at 28 days and may represent the beginnings of chronic progressive nephropathy. However, such observations were not repeated after 3 (or 12) months of exposure. Therefore, the no-observed-adverse-effect levels (NOAELs) of human relevance in rats were derived on the basis of effects in organs other than male kidney in the repeated-dose toxicity studies after 28 days and 3 months of treatment as well as in the 2-year study.

Other target organs and changes in rats were fatty changes in the adrenal cortex, enhanced haemosiderosis or extramedullary haematopoiesis in the spleen and follicular epithelial hypertrophy in the thyroid gland. Thymic and splenic atrophy in dogs and alterations suggestive of delayed maturation of the gonads in dogs and female mice occurred at doses causing substantial growth retardation.

The NOAELs derived from short-term studies, in which thiamethoxam was administered orally, were as follows:

- The NOAEL in the 90-day dietary study in mice with thiamethoxam was 100 ppm (equal to 14.3 mg/kg bw per day), based on raised platelet counts at 1250 ppm (equal to 176 mg/kg bw per day in females). Minimal lymphocytic infiltration and hepatocyte hypertrophy were observed in males at 100 ppm and 1250 ppm; in the absence of any other hepatic changes, these were considered an adaptive response or an early sign of mouse-specific hepatotoxicity.

- The NOAEL in the 28-day dietary study in rats was 100 ppm (equal to 8.0 mg/kg bw per day), based on increased plasma cholesterol concentrations at a dose level of 1000 ppm (equal to 81.7 mg/kg bw per day). The male rat–specific kidney effects have no human relevance, and therefore they are not considered for the NOAEL.
- The NOAEL in the 90-day dietary study in rats was 250 ppm (equal to 17.6 mg/kg bw per day in males), based on reduced body weight gain and histological findings in the adrenals at 1250 ppm (equal to 84.9 mg/kg bw per day). Observation of hyaline droplet accumulation in the kidneys of male rats was considered indicative of α_{2u}-globulin involvement, which is male rat specific and has no human significance.
- The NOAEL in the 90-day oral toxicity study in dogs was 250 ppm (equal to 8.23 mg/kg bw per day), based on prolonged thromboplastin times in both sexes at 1000 ppm (equal to 32 mg/kg bw per day).
- The NOAEL in the 52-week oral toxicity study in dogs was 750 ppm (equal to 21 mg/kg bw per day), based on prolonged thromboplastin times and reductions in testis weights at 1500 ppm (equal to 42 mg/kg bw per day).

Long-term toxicity and carcinogenicity studies were performed in mice and rats. The main target organs were the liver in mice and female rats and the kidneys in male rats. In rats, the principal findings were increased incidences of renal tubule regenerative lesions, which were considered to represent the sequelae of the rat-specific nephropathies observed in short-term studies. Minor and morphologically different changes occurred in the spleen of both rats and mice.

The NOAEL in the 78-week dietary study in mice was 20 ppm (equal to 2.63 mg/kg bw per day), based on hepatotoxic effects (i.e., increased liver weights, hepatocellular hypertrophy, pigment deposition, inflammatory cell infiltration and single-cell necrosis) at 500 ppm (equal to 63.8 mg/kg bw per day). Thiamethoxam was tumorigenic in mice and induced hepatocellular adenomas in male and female mice at a dose level of 500 ppm and hepatocellular adenocarcinomas in male mice at 2500 ppm (equal to 354 mg/kg bw per day).

Special studies on thiamethoxam (the *EZ*-isomer mixture as used in all toxicity studies) were performed to investigate the etiology of adenoma and adenocarcinoma formation in mouse liver during an 18-month oncogenicity study. The hypothesis investigated was that the mouse specificity in this response is due to a very large species difference in metabolism of thiamethoxam, as demonstrated by 15-fold and 140-fold higher plasma concentrations of CGA 330050 and CGA 265307, respectively, in mice than in rats following 10 weeks of dosing with thiamethoxam. This large difference is supported by in vitro comparison of thiamethoxam metabolism by microsomal preparations from mouse, rat and human liver. Although these metabolites also occur with rat microsomes, their concentrations are very much lower than in mice. The data also suggested that humans were likely to be even less susceptible than rats to the hepatic effects of thiamethoxam. The mode of action proposed for development of these tumours is based on the hepatotoxicity of the metabolite CGA 330050 in particular, with CGA 265307 exacerbating its effect, and the subsequent sustained cell proliferation of mouse hepatocytes, leading to the development of a higher incidence of hepatocellular tumours. Not all elements for a mode of action have been identified, but the available data support the contention of a low risk to humans with regard to both hepatotoxicity and carcinogenicity and the absence of any genotoxic involvement. An alternative metabolic pathway to CGA 265307 in both mice and rats is via CGA 322704. The *E*-isomer of CGA 322704 was evaluated at the present Meeting, and it was concluded that it is not carcinogenic in mice or rats.

The NOAEL in this 78-week dietary study in mice for non-hepatic effects is 1250 ppm (equal to 162 mg/kg bw per day), based on reductions in body weight and effects on spleen and stomach at 2500 ppm (equal to 354 mg/kg bw per day).

The NOAEL in the 104-week dietary study in rats was 1000 ppm (equal to 50.3 mg/kg bw per day in females), based on foci of cellular alteration in the liver and increased severity of splenic haemosiderosis at 3000 ppm (equal to 155 mg/kg bw per day). Increased incidences of renal chronic

tubular lesions and basophilic proliferation were observed exclusively in male rats at 500 ppm (equal to 21.0 mg/kg bw per day). These renal lesions were considered to represent the outcome of α_{2u}-globulin-mediated nephropathy, which is widely acknowledged as male rat specific and not relevant in human risk assessment, and therefore they were not used to identify the NOAEL.

Thiamethoxam was tested for genotoxicity and mutagenicity in an adequate range of assays, both in vitro and in vivo. In none of these assays was there any evidence of genotoxic or mutagenic potential.

The Meeting concluded that thiamethoxam is unlikely to be genotoxic.

On the basis of the absence of genotoxicity in vivo, the absence of carcinogenicity in rats and the mode of action by which liver tumours arise in mice, the Meeting concluded that thiamethoxam is unlikely to pose a carcinogenic risk at human dietary exposure levels.

Hyaline change and casts in renal tubules were observed in male rats in the multigeneration studies at 1000 ppm (equal to 45.6 mg/kg bw per day). This observation has no human relevance. Therefore, the relevant NOAEL for parental toxicity is 1000 ppm (equal to 45.6 mg/kg bw per day), based on significantly reduced body weight gain at 2500 ppm (equal to 117.6 mg/kg bw per day in F_0 generation males). The overall NOAEL for reproductive toxicity in the multigeneration studies in rats was 1000 ppm (equal to 74.8 mg/kg bw per day for F_1 males), based on minimal testicular germ cell loss or disorganization, with or without Sertoli cell vacuolization (and unaccompanied by any reduction in epididymal sperm numbers), at 2500 ppm (equal to 191.5 mg/kg bw per day). These effects were not observed in the first study, a difference that could be attributed to a refinement of the methods used for sperm observations between the first and second studies. The overall NOAEL for offspring was 30 ppm (equal to 1.4 mg/kg bw per day for the males), based on marginal reductions in body weight gains of F_{2a} and F_{2b} pups during lactation at 1000 ppm (equal to 45.6 mg/kg bw per day for males) in the first of the two studies.

The NOAEL for maternal toxicity in the developmental toxicity study in rats was 30 mg/kg bw per day, based on slightly decreased body weight gain in dams, providing a lowest-observed-adverse-effect level (LOAEL) of 200 mg/kg bw per day. The NOAEL for fetotoxicity was 200 mg/kg bw per day, based on mild reduction in mean fetal body weight at 750 mg/kg bw per day. Further evidence of fetotoxicity at this dose was increased incidences of skeletal anomalies (irregular or absent ossification of the occipital bone) and skeletal variants (poor ossification of sternebra 5, shortened 13th rib and non-ossification of metatarsal 1).

The NOAEL for maternal toxicity in the developmental toxicity study in rabbits was 15 mg/kg bw per day, based on reduction in body weight gain and food consumption during the treatment period in dams at 50 mg/kg bw per day. The NOAEL for fetotoxicity in rabbits was 50 mg/kg bw per day, based on increased post-implantation loss and reduction in fetal body weights at 150 mg/kg bw per day. Further evidence of fetotoxicity at this dose was increased incidence of delayed and absent ossification as well as an increased incidence of fused sternebrae in fetuses.

The Meeting concluded that thiamethoxam can cause fetotoxicity and skeletal anomalies (malformations and variants), but only at maternally toxic doses.

An acute neurotoxicity study, a 13-week neurotoxicity study and a developmental neurotoxicity study were conducted in rats. A comprehensive set of neurotoxicity end-points was investigated in these studies, including an evaluation of potential to induce neurobehavioural or neuromorphological changes. The studies did not show any specific neurotoxicity after repeated exposure of adult rats or any specific developmental neurotoxicity in the offspring, including at doses causing maternal toxicity. Acute administration of thiamethoxam at dose levels approaching the LD_{50} produces a range of transient neurobehavioural effects, including tonic or clonic convulsions, ptosis and reduced locomotor activity. The NOAEL in the single-dose neurotoxicity study in rats was 100 mg/kg bw, based on transient behavioural changes at 500 mg/kg bw. The NOAEL for systemic toxicity in the 13-week neurotoxicity study was 1500 ppm (equal to 95.4 mg/kg bw per day in males), and the NOAEL for neurotoxicity was 3000 ppm (equal to 216.4 mg/kg bw per day in females), the

highest dose tested, based on the absence of treatment-related effects at these doses. The NOAEL for systemic toxicity in a study of developmental neurotoxicity was 400 ppm (equal to 34.5 mg/kg bw per day), based on decreased body weight gain and food consumption in dams throughout gestation and postpartum, as well as reduced birth weight, reduced pup body weight gain, some evidence of delayed preputial separation and small changes in brain morphometry, but without any quantitative histological or behavioural changes, at 4000 ppm (equal to 298.7 mg/kg bw per day). The NOAEL for developmental neurotoxicity was 4000 ppm (equal to 298.7 mg/kg bw per day), the highest dose tested.

The Meeting concluded that thiamethoxam is not a neurotoxin in mammals at the tested dose levels, although it is a member of the neonicotinoid chemical class, the biological effects of which in target species are mediated primarily by an interaction with nicotinic acetylcholine receptor sites.

No information on medical surveillance or poisoning incidents was available.

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.08 mg/kg bw on the basis of a NOAEL of 250 ppm (equal to 8.23 mg/kg bw per day) in a 90-day study of toxicity in dogs, based on prolonged thromboplastin time. A safety factor of 100 was applied. This ADI is protective of the hepatotoxic and hepatocarcinogenic effects observed in mice, which were not observed in rats because of a marked species difference in metabolism. It is also protective of the marginally toxic effects observed in a multigeneration study in rats at 46 mg/kg bw per day.

A number of blood chemistry and haematology parameters in dogs were considered as a basis for the ADI, but the only consistently altered parameter was measures of blood coagulation. Other end-points that received consideration included food consumption reduction in a gavage study of developmental toxicity in rabbits. Renal changes observed in rats arose by processes not relevant for risk assessment at human dietary exposure levels.

An acute reference dose (ARfD) of 1 mg/kg bw was established on the basis of a NOAEL of 100 mg/kg bw in a single-dose study of neurotoxicity in rats. A safety factor of 100 was applied. The transient functional changes in rats appeared to be mild signs of overt toxicity rather than neurotoxicity. The neurotoxicity study was supported by a single-dose study of toxicity in mice, in which clinical signs of toxicity were observed at 500 mg/kg bw, the lowest dose tested.

The metabolite of thiamethoxam, CGA322704 (clothianidin), was evaluated separately by the present Meeting.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Ninety-day range-finding study of toxicity	Toxicity	100 ppm, equal to 14.3 mg/kg bw per day	1250 ppm, equal to 176 mg/kg bw per day
	Eighteen-month study of toxicity and carcinogenicity	Toxicity[a]	20 ppm, equal to 2.63 mg/kg bw per day	500 ppm, equal to 63.8 mg/kg bw per day
		Carcinogenicity[b]	20 ppm, equal to 2.63 mg/kg bw per day	500 ppm, equal to 63.8 mg/kg bw per day
Rat	Single-dose test of neurotoxicity	Toxicity	100 mg/kg bw	500 mg/kg bw

Species	Study	Effect	NOAEL	LOAEL
	Ninety-day study of toxicity	Toxicity[c]	250 ppm, equal to 17.6 mg/kg bw per day	1250 ppm, equal to 84.9 mg/kg bw per day
	Twenty-four-month studies of toxicity and carcinogenicity	Toxicity[c]	1000 ppm, equal to 50.3 mg/kg bw per day	3000 ppm, equal to 155 mg/kg bw per day
		Carcinogenicity	3000 ppm, equal to 155 mg/kg bw per day[d]	—
	Two-generation study of reproductive toxicity (1)	Reproductive toxicity	2500 ppm, equal to 117.6 mg/kg bw per day[d]	—
		Parental toxicity[c]	1000 ppm, equal to 45.6 mg/kg bw per day	2500 ppm, equal to 117.6 mg/kg bw per day
		Offspring toxicity	30 ppm, equal to 1.4 mg/kg bw per day	1000 ppm, equal to 45.6 mg/kg bw per day[e]
	Two-generation study of reproductive toxicity (2)	Reproductive toxicity	1000 ppm, equal to 74.8 mg/kg bw per day	2500 ppm, equal to 191.5 mg/kg bw per day
		Parental toxicity[c]	1000 ppm, equal to 61.7 mg/kg bw per day	2500 ppm, equal to 155.6 mg/kg bw per day
		Offspring toxicity	1000 ppm, equal to 74.8 mg/kg bw per day	2500 ppm, equal to 191.5 mg/kg bw per day
	Developmental toxicity study	Maternal toxicity	30 mg/kg bw per day	200 mg/kg bw per day
		Embryo and fetal toxicity	200 mg/kg bw per day	750 mg/kg bw per day
Rabbit	Developmental toxicity study	Maternal toxicity	15 mg/kg bw per day	50 mg/kg bw per day
		Embryo and fetal toxicity	50 mg/kg bw per day	150 mg/kg bw per day
Dog	Ninety-day study of toxicity	Toxicity	250 ppm, equal to 8.23 mg/kg bw per day	1000 ppm, equal to 32 mg/kg bw per day

[a] Mouse particularly susceptible to hepatotoxicity, based on the mode of action of thiamethoxam.

[b] No carcinogenicity relevant to humans based on mode of action considerations of tumorigenic effects in mice.

[c] Toxicity relevant to humans, not including nephrotoxicity specific for male rats.

[d] Highest dose tested.

[e] Marginal LOAEL.

Estimate of acceptable daily intake for humans

0–0.08 mg/kg bw

Estimate of acute reference dose

1 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and extensive, > 90%
Distribution	Distributed throughout the body; higher concentrations in liver and blood
Potential for accumulation	None
Rate and extent of excretion	High, > 90% within 24 h
Metabolism in animals	22 metabolites identified in rats
Toxicologically significant compounds (animals, plants and environment)	Parent; CGA330050; CGA322704 (clothianidin)
Acute toxicity	
Rat, LD_{50}, oral	1563 mg/kg bw
Mouse, LD_{50}, oral	871 mg/kg bw
Rat, LC_{50}, inhalation	> 3.7 mg/L (4 h)
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman test)
Short-term studies of toxicity	
Target/critical effect	Coagulation in dogs
Lowest relevant oral NOAEL	8.23 mg/kg bw per day (3-month study in dogs)
Lowest relevant dermal NOAEL	60 mg/kg bw per day (liver, 4-week study in rats)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver, spleen, stomach (mice)
Lowest relevant NOAEL	2.63 mg/kg bw per day (18-month study in mice)
Carcinogenicity	Carcinogenic in mice, but unlikely to pose a risk at human dietary exposure levels, based on the proposed mode of action
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Reproductive target/critical effect	Preweaning weight gain
Lowest relevant reproductive NOAEL	74.8 mg/kg bw per day (rat)
Developmental target/critical effect	Rat: Not teratogenic; reduced live birth weight, delayed ossifications
	Rabbit: Reduced pup body weight, delayed ossifications and increased incidences of skeletal abnormalities
Lowest relevant developmental NOAEL	50 mg/kg bw per day (rabbit)
Neurotoxicity/delayed neurotoxicity	

	No signs of neurotoxicity
Other toxicological studies	
	Mechanistic studies relevant to hepatotoxicity and hepatocarcinogenicity in mice and renal toxicity in rats
Medical data	
	No reports of toxicity in workers exposed during manufacture or use

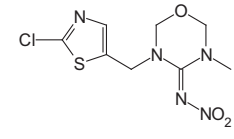
Summary

	Value	Study	Safety factor
ADI	0–0.08 mg/kg bw	Ninety-day study of toxicity in dogs	100
ARfD	1 mg/kg bw	Neurotoxicity study in rats supported by a single-dose toxicity study in mice	100

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of thiamethoxam were considered for the first time by the present meeting.

Thiamethoxam (ISO common name), a nicotinoid compound, has broad spectrum activity against sucking and chewing insects in vegetables, ornamentals, field crops, deciduous fruits, citrus, cotton and rice. It possesses contact and stomach activity. Its activity against foliar feeding insects following seed treatment, application to the soil, distribution via irrigation systems, or when applied to the trunks of trees, results from its systemic properties. It is also registered for direct foliar application.



The IUPAC name for thiamethoxam is (EZ)-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine and the CA name is 3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-4*H*-1,3,5-oxadiazin-4-imine.

Thiamethoxam labelled either in the 2-position of the thiazole moiety or on the carbon of the guanidine moiety (4-oxadiazine label) was used in the metabolism and environmental fate studies.

Animal metabolism

Information was available on metabolism of thiamethoxam in laboratory animals, lactating goats and laying hens.

When rats were orally dosed with labelled thiamethoxam, 70–80% of the dose was eliminated in the urine as parent thiamethoxam. The main metabolite in urine was CGA 322704 (*N*-(2-chlorothiazol-5-ylmethyl)-*N*'-methyl-*N*''-nitroguanidine) accounting for approximately 10% of the dose. Numerous low-level metabolites were identified. Metabolism in laboratory animals was summarized and evaluated by the WHO panel of the JMPR in 2010.

When lactating goats were orally dosed with labelled thiamethoxam, approximately 1% of the dose appeared in the milk and 3–4% in the tissues.

Metabolite CGA 322704 was the major component (44% and 45%) of the residue in milk, while parent thiamethoxam was the major component in goat fat (36% and 52%), muscle (51% and 54%) and kidneys (21% and 22%).

Products of further metabolism occurred in the goat liver. NOA 421276 (N-(2-chlorothiazol-5-ylmethyl)-guanidine), NOA 421275 (N-(2-chlorothiazol-5-ylmethyl)-N'-methyl-guanidine), L14 (2-

oxopropionic acid [3-(2-chloro-thiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidene]-hydrazide) and NOA 407475 (3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidineamine) were metabolites found at levels exceeding 10% TRR in the liver. Parent thiamethoxam and CGA 322704 were present in liver tissue at approximately 1% and 6–7% of TRR respectively.

When laying hens were dosed with labelled thiamethoxam, most of the dose was excreted in the droppings. Eggs accounted for approximately 0.1% of the administered dose and tissues approximately 1–1.5%.

Parent thiamethoxam was not the major component of the residue in any hen tissue or eggs, but did constitute approximately 21% TRR in lean meat, 5–15% in fat + skin, 2–5% in egg white and 11% in egg yolks.

Metabolite CGA 265307 (N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine) was the major residue component in the eggs, both whites (45% and 47%) and yolks (69% and 54%), and also in fat + skin (54% and 57%). Metabolite CGA 322704 was the major residue component in hen liver (34% and 39%) while metabolite MU3 (amino-([(2-chlorothiazol-5-ylmethyl)-amino]-methylene)-hydrazide) was the major component of the lean meat residue (39% and 28%).

Other metabolites present at more than 10% TRR were: NOA 421275 (N-(2-chlorothiazol-5-ylmethyl)-N'-methyl-guanidine) in lean meat, MU3 in hen liver, CGA 322704 and NOA 404617 (1-(2-chloro-thiazol-5-ylmethyl)-3-nitrourea) in egg white and CGA 322704 in egg yolk.

Animal metabolism summary

When animals were orally dosed with labelled thiamethoxam, the ^{14}C was readily excreted in urine and faeces and an array of metabolites was produced.

In lactating goats, metabolite CGA 322704 was the major component of the residue in milk, while parent thiamethoxam was the major component in muscle, fat and kidney. Further degraded metabolites occurred in the liver. Metabolite NOA 421276 was the major identified component of the residue in goat liver.

In laying hens, parent thiamethoxam was not the major component of the residue in any tissue or eggs, but did constitute approximately 21% of the ^{14}C in lean meat. Metabolite CGA 265307 was the major residue component in the eggs and in fat + skin. Metabolite CGA 322704 was the major residue component in liver while metabolite MU3 was the major component of the lean meat residue.

Plant metabolism

Information was available on the metabolism of thiamethoxam in maize, rice, pears, cucumbers, lettuce and potatoes.

When maize seeds treated with [^{14}C-oxadiazin]thiamethoxam were sown and grown through to maturity, ^{14}C residues were detected in whole tops (day 33 after sowing), forage (day 124) and grain and fodder (maturity, day 166). The TRR level of 18 mg/kg in the whole tops with 40% TRR identified as thiamethoxam demonstrated that thiamethoxam is readily taken up and translocated. Parent thiamethoxam was the major identified component of the residues in whole tops and maize grain. Metabolite NOA 421275 (*N*-(2-chlorothiazol-5-ylmethyl)-*N′*-methyl-guanidine) was the major identified component of the forage and fodder. Metabolite CGA 322704 constituted approximately 10% TRR in forage and grain.

In the companion maize seed metabolism study, maize seeds treated with [^{14}C-thiazolyl]thiamethoxam were sown and grown through to maturity. ^{14}C residues were detected in tops (day 33 after sowing), forage (day 124) and grain and fodder (maturity, day 166). Parent thiamethoxam was the major component of residues in the tops (47% TRR). Metabolites appearing as

10% or more of TRR were: NOA 407475 (3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidineamine) in tops, CGA 322704 and NOA 421275 in forage and NOA 421275 in fodder. In the grain, 65% of TRR was unextracted; thiamethoxam and CGA 322704 were the only identified residue components.

In a soil treatment maize experiment, [^{14}C-oxadiazin]thiamethoxam was applied to the soil around maize plants at the 2 leaf stage. Parent thiamethoxam and CGA 322704 were the major identified components of the residues in 89 days forage and grain. Metabolite 1-methyl-3-nitroguanidine at approximately 10% TRR was the major identified component of the fodder.

The companion soil treatment study with [^{14}C-thiazolyl]thiamethoxam again found that thiamethoxam and CGA 322704 were the major identified components in the forage and grain. NOA 421275 at approximately 10% TRR was the major component of the fodder.

In a rice metabolism study, [^{14}C-oxadiazin]thiamethoxam was formulated as granules and applied to the seedling box 24 hours before planting out. A parallel experiment was run with [^{14}C-thiazolyl]thiamethoxam. Release of ^{14}C into the paddy water was rapid and the radiolabel was readily translocated to all parts of the plant. Thiamethoxam was the major component of the residues in the early stages. At maturity, parent thiamethoxam was not identified in the grain, when 88% TRR was unextracted. Metabolites CGA 322704 and *N*-methylurea were the major identified components of the rice grain residues but at only 1–2% TRR. Parent thiamethoxam and CGA 355190 (3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-one) were the main components of the straw residues while thiamethoxam and CGA 322704 were the main components in the husks.

In a separate rice metabolism study, [^{14}C-oxadiazin]thiamethoxam formulated as a WP was applied twice as foliar treatments at booting stage and 50 days later. A parallel experiment was run with [^{14}C-thiazolyl]thiamethoxam. Parent thiamethoxam was the major identified component in grain (13% and 4.5%), husks (65% and71%) and straw (53% and 14.5%) with CGA 322704 the second largest identified component. The non-extracted component in the grain accounted for 63% and 91% of the TRR.

The non-extracted ^{14}C in grains, husk and straw was found to be incorporated into starch, cellulose, hemicellulose or proteins.

Pears were subject to foliar sprays with [^{14}C-oxadiazin]thiamethoxam and [^{14}C-thiazolyl]thiamethoxam formulated as a WP—two cover sprays, 13 days apart with the final spray 15 days before harvest. For each treatment and application rate, thiamethoxam and CGA 322704 were the major identified components of the residues in fruit, together accounting for approximately 50% of the TRR. None of the other metabolites exceeded 10% TRR.

Cucumber plots were subject to foliar sprays with [^{14}C-oxadiazin]thiamethoxam and [^{14}C-thiazolyl]thiamethoxam formulated as a WP—first spray at full flowering and the second 10 days later, 14 days prior to mature harvest. NOA 407475 (3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidineamine) and thiamethoxam were the major identified components of the residues in cucumbers, together accounting for approximately 30–40% the TRR. CGA 322704 and other metabolites were minor components, each accounting for less than 1–2% TRR.

Field grown lettuce were subject to foliar sprays with [^{14}C-oxadiazin]thiamethoxam and [^{14}C-thiazolyl]thiamethoxam formulated as a WG—three times at weekly intervals. Parent thiamethoxam was the major component of the residues accounting for approximately 40% of the residues 14 days after the final treatment. Numerous metabolites were identified, but at day 14 none exceeded 8% of the TRR. The non-extracted residue fraction accounting for 13% and 19% of TRR was subjected to vigorous treatment and extraction, which released ^{14}C material of a very polar nature believed to be derived from natural plant components.

In a potato metabolism study, potato seed-pieces treated with [^{14}C-thiazol]thiamethoxam and [^{14}C-oxadiazin]thiamethoxam were sown and the potatoes were grown to new potato size (84 days after sowing) and maturity (106 days).

Parent thiamethoxam was the major identified residue in the harvested potatoes at 10–27% of TRR. Metabolite CGA 322704 was present at 6–13% of TRR. Metabolite CGA 282149 (3,6-dihydro-3-methyl-*N*-nitro-2H-1,3,5-oxadiazin-4-amine) constituted approximately 6–10% TRR while CGA 349208 (2-chloro-5-thiazolemethanol) and its conjugate also accounted for approximately 6–10% TRR. A number of other metabolites were identified, but none exceeded 10% TRR.

Plant metabolism summary

Thiamethoxam was readily taken up from treated seed, treated soil or sprayed foliage and translocated within the plant and it produced many metabolites. Parent thiamethoxam was usually an important component of the residues.

Metabolic degradation pathways were similar in the various plants tested: maize, rice, pears, cucumbers, lettuce and potatoes.

Parent thiamethoxam and metabolite CGA 322704 appeared in plant metabolism profiles above 10% TRR more often than other metabolites. Other metabolites to appear above 10% TRR at least once were: 1-methylguanidine, CGA 282149, CGA 355190, NOA 407475 and NOA 421275.

N-nitroguanidine was the only plant metabolite (identified in lettuce at 0.3–1.5% TRR) that did not also appear as an animal metabolite. *N*-nitroguanidine may occur from other sources—it is an industrial chemical with uses in the explosives industry and as a chemical intermediate in the manufacture of pharmaceuticals.

Environmental fate in soil

Information was available on aerobic soil metabolism for thiamethoxam, CGA 322704, CGA 355190 (3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-one) and NOA 407475 (3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidineamine). Studies on rice paddy metabolism, soil surface photolysis and rotational crops were also provided.

Soil metabolism and photolysis

When labelled thiamethoxam was incubated in soils under aerobic conditions at 20 °C and 40% max water capacity, its half-life ranged from 80 to 300 days. Higher temperatures or higher moisture levels increased the rate of disappearance. CGA 322704 and CGA 355190 were usually the main identified soil metabolites. After 180 days, approximately 12–20% of the dose had been mineralized and 7–16% was unextracted.

When labelled CGA 322704 was incubated in soils under aerobic conditions at 20 °C and 40% max water capacity, its half-life was approximately 100–300 days. The half-life for labelled CGA 355190 under these same conditions was 15–30 days.

When [^{14}C-thiazol]thiamethoxam was exposed to a paddy soil system at 25 °C, thiamethoxam disappeared with a half-life of approximately 50–70 days. The main metabolite was NOA 407475, produced under the reducing conditions of the paddy soil.

NOA 407475 was quite persistent at 20 °C and 40% max water capacity in soils under aerobic conditions, with 77% and 86% of the dose remaining after a test of 180 days (estimated half-life exceeding 300 days).

In a 30 days study with the soil photolysis of labelled thiamethoxam at 25 °C and 75% field moisture capacity, the amount remaining after photolysis was 66% and 59% compared with the dark controls 83% and 83%. CGA 322704 and CGA 355190 were the main products identified.

Soil metabolism summary

When labelled thiamethoxam was incubated in soils under aerobic conditions at 20 °C, its half-life varied from 80 to 300 days. In 6 months of incubation, the percentage of dose mineralized was approximately 12 to 20% and the percentage that was unextracted was approximately 7 to 16%.

The main soil metabolites identified were: CGA 322704 (N-(2-chlorothiazol-5-ylmethyl)-N'-methyl-N''-nitroguanidine) and CGA 355190 (3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-one). Metabolite NOA 407475 (3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylidineamine) was identified under rice paddy conditions. The disappearance of thiamethoxam under soil photolysis conditions was faster than in the dark controls but the main products were CGA 322704 and CGA 355190, the same as for soil metabolism.

Rotational crops

When lettuce, radish and wheat were grown in a rotational crop situation 29, 119 and 362 days after treatment of bare ground with labelled thiamethoxam at 0.2 kg ai/ha, TRR levels were generally low: 0.035 mg/kg and below for lettuce; 0.12 mg/kg and below for radish tops; 0.007 mg/kg and below for radish roots and 0.15 mg/kg and below for wheat grain. Higher TRR levels were found in wheat straw: 0.05–0.75 mg/kg.

Parent thiamethoxam was the most commonly detected component of the residue and was present at higher concentrations (up to 0.023 mg/kg) than other components in lettuce and radish. In wheat straw and grain, parent thiamethoxam (up to 0.038 mg/kg in straw and 0.0002 mg/kg in grain) and metabolite CGA 322704 (up to 0.044 mg/kg in straw and 0.001 mg/kg in grain) were the most commonly detected. However, in some cases other metabolites were present at higher levels: CGA 265307 (N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine) in wheat grain and 1-methylguanidine (CGA 382191), NOA 405217 (N-nitro-N'-methylguanidine), NOA 421275 (N-(2-chlorothiazol-5-ylmethyl)-N'-methyl-guanidine) and CGA 265307 (N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine) in wheat straw.

Residues of parent thiamethoxam and some metabolites could occur in rotational crops, but generally at very low levels. Detections would be unlikely except for residues in commodities such as wheat straw, which will be covered by MRLs in any case because of approved direct uses. Additional information relevant to CGA 322704 fate and behaviour is available in the clothianidin rotational crop studies.

Methods of analysis

Analytical methods and validation data for residues of thiamethoxam and CGA 322704 in animal and plant matrices were made available to the Meeting. Methods had been subjected to independent laboratory validation. Analytical recovery data for thiamethoxam and CGA 322704 at residue concentrations on numerous substrates were available to the Meeting.

Residues of parent thiamethoxam and metabolite CGA 322704 in plant and animal matrices may be analysed by HPLC-MS or HPLC-UV with an LOQ of 0.01 mg/kg after a series of cleanup steps.

In method AG-675, which relies on acetonitrile-water for sample extraction, a microwave extraction procedure is necessary for good extraction of residues from some animal commodities, especially liver. Analysis of residues in liver was not possible with the HPLC-UV finish because of too many interfering peaks, but was successful with the LC-MS/MS finish.

Samples with incurred residues from the metabolism studies were analysed by method AG-675, but interpretation was difficult because of uncertainties in the data (some concentrations below 0.05 mg/kg). For pears and cucumbers, the analytical method concentration of thiamethoxam was approximately 40–90% of the metabolism value. For thiamethoxam in goat meat, the analytical

method result was 56–79% of the metabolism result. The thiamethoxam concentration in goats' milk, measured by method AG-675 was only about 20% of the value from the metabolism study. In each of these tests, the results for CGA 322704 were similar to those for thiamethoxam. However, the data were from different laboratories on samples with different storage histories, making interpretation difficult.

Supporting information relevant to the efficient extraction of CGA 322704 from milk and other matrices by acetonitrile-water is provided in the clothianidin studies on samples with incurred residues from clothianidin metabolism studies. This information on efficient extraction of CGA 322704 residues would also support the efficient extraction of thiamethoxam residues, which had behaved similarly but erratically, in the thiamethoxam studies.

Method REM-179 versions were used for analysis of plant commodities. Samples are homogenized and extracted with water + methanol. Cleanup is affected by solvent partition and cartridge columns.

Pears from the metabolism study were extracted and analysed by method REM 179.3 for comparison with the ^{14}C measurements. Measured concentrations of thiamethoxam in the pear were 0.196, 0.143 and 0.130 mg/kg for the original metabolism study, by radiolabel analysis on the LC fraction and by HPLC-UV respectively. Similarly, measured concentrations of CGA 322704 (expressed as thiamethoxam) were 0.134, 0.0875 and 0.0775 mg/kg for the same three situations.

Thiamethoxam, CGA 322704 and CGA 265307 (N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine) were not suitable analytes for the multiresidue methods tested (DFG Method S 19 and FDA multiresidue methods). In the FDA methods, thiamethoxam was not recovered from the cleanup columns.

Stability of residues in stored analytical samples

The meeting received information on the freezer storage stability of thiamethoxam and metabolite CGA 322704 at residue concentrations in apples, tomatoes, potato tubers, rape seed, maize grain, cranberries, hops, barley grain, barley hay, barley straw, pearled barley and barley flour. For the animal commodities, (beef, liver, milk and eggs), freezer storage stability data were available for thiamethoxam and two metabolites CGA 322704 and CGA 265307.

Thiamethoxam, CGA 322704 and CGA 265307 were apparently stable at residue concentrations in the various substrates tested at the freezer temperatures and test durations. The durations of test were mostly 1–2 years, but some were less. Test temperatures were mostly approximately –18 °C to –20 °C, but other storage temperatures were used in some storage stability tests, e.g., between –26 °C and –4 °C.

Definition of the residue

In animal commodities, parent thiamethoxam was a major component of the residues in goat muscle, fat and kidney, while CGA 322704 was the main component in milk, but thiamethoxam was also a substantial residue component in milk. Thiamethoxam constituted only approximately 1% of the residues in goat liver with CGA 322704 about 6–7%. Some other metabolites were present at higher levels.

In laying hens, parent thiamethoxam was not the major component of the residues in any tissue or eggs, but did constitute approximately 21% TRR in lean meat, 5–15% in fat + skin and 11% in egg yolk. Thiamethoxam was a very minor part of the residues in poultry liver, whereas CGA 322704 constituted 34% and 39% of the liver TRR (8.2 and 9.2 mg/kg) in the poultry metabolism study with ^{14}C labels in the thiazol and oxadiazine positions, respectively. Metabolite CGA 265307 was the major residue component in the eggs, both whites (45% and 47%) and yolks (69% and 54%), and also in fat + skin (54% and 57%). Metabolite MU3 was the major residue component in lean hen meat.

The complexity of the metabolite mixture makes it difficult to select an ideal residue definition for risk assessment in poultry.

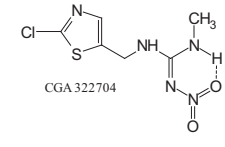
The Meeting decided to include CGA 265307 and MU3 with thiamethoxam in the intake assessment of residues in poultry. Metabolite CGA 322704 will be included in the clothianidin risk assessment.

Because the dietary burden was low and no feeding study was available for poultry, data from the poultry metabolism studies were used in the risk assessment.

For most purposes, thiamethoxam and CGA 322704 are adequate for monitoring residues in animal commodities.

In plant metabolism, parent thiamethoxam is usually an important component of the residues. Metabolite CGA 322704 occurs in plant metabolism profiles above 10% TRR more commonly than do other plant metabolites. For plant commodities thiamethoxam and CGA 322704 are the most important residues.

Thiamethoxam is described as an EZ mixture. It is generally believed that the activation energy for the E↔Z interconversion for the C = N bond is low and that an equilibrium mixture is rapidly established at ambient temperature. The situation is likely to be similar for metabolite CGA 322704. In this case the E form is likely to be favoured in the equilibrium mixture because of possible formation of a hydrogen bond from the secondary amine to the nitro group. The E form of CGA 322704 is equivalent to the compound clothianidin and with E↔Z interconversion, CGA 322704 will appear the same as clothianidin in the analytical methods.



CGA 322704

Clothianidin residues may arise from the use of clothianidin or from the use of thiamethoxam. Separate residue definitions are needed:

- for thiamethoxam
- for clothianidin (from uses of clothianidin) and CGA 322704 (from uses of thiamethoxam), appearing as clothianidin.

The Meeting recommended the following residue definition for thiamethoxam.

Definition of the residue for animal and plant commodities (for compliance with the MRL): *thiamethoxam*.

Definition of the residue for plants and animals (except poultry), (for estimation of dietary intake): *thiamethoxam;* and

CGA 322704 (CGA 322704 to be included with clothianidin and considered separately from thiamethoxam). See also clothianidin.

Definition of the residue for poultry (for estimation of dietary intake): *sum of thiamethoxam, CGA 265307 and MU3, expressed as thiamethoxam;* and

CGA 322704 (CGA 322704 to be included with clothianidin and considered separately from thiamethoxam). See also clothianidin.

The residue is not fat-soluble.

Note that thiamethoxam metabolite CGA 322704 (N-(2-chlorothiazol-5-ylmethyl)-N'-methyl-N"-nitroguanidine) will appear as clothianidin in the analytical method and residues of CGA 322704 occurring in food are included in the clothianidin MRLs.

Metabolite CGA 265307: N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine.

Metabolite MU3: amino-([(2-chlorothiazol-5-ylmethyl)-amino]-methylene)-hydrazide.

Results from supervised trials on crops

The Meeting received supervised field trials data for thiamethoxam uses on citrus, pome fruits, plums, peaches, cherries, strawberries, cranberries, blueberries, caneberries, grapes, bananas, mangoes, papaya, pineapples, broccoli, cabbage, mustard greens, cucumbers, melons, cantaloupes, summer squash, sweet corn, tomatoes, bell peppers, chilli peppers, egg plants, sweet peppers, lettuce, spinach, snap beans, lima beans, succulent peas, dry beans, peas (green pods), peas (dry seed), soya beans, carrots, radishes, potatoes, sugar beets, artichokes, celery, maize, barley, wheat, rice, pecan, sunflower, cotton, oilseed rape, cacao beans, coffee, pea forage and fodder, maize forage and fodder, barley straw and fodder, wheat straw and fodder, rice straw, beet leaves and tops, oilseed rape fodder and forage, hops and tea.

For a specific crop, sets of trials were often available with different methods of application, e.g., foliar, soil treatment and seed treatment, and from different regions. The set of trials with an adequate number of trials and producing the highest residues was selected for maximum residue level estimation. The set of trials selected for thiamethoxam maximum residue level estimation was not necessarily the same set selected for metabolite CGA 322704.

The estimated maximum residue levels for CGA 322704 are transferred to the clothianidin report for integration with the estimates for clothianidin.

Citrus fruits

Supervised trials data for citrus were available from Spain, Indonesia and the USA.

Thiamethoxam may be used in Spain as a single foliar treatment of citrus with a WG formulation at a spray concentration of 0.0075 kg ai/hL and harvest of fruit 28 days later.

In seven thiamethoxam trials on oranges in Spain in accord with Spanish GAP, thiamethoxam residue concentrations in whole oranges in rank order were: < 0.02, 0.02, 0.03, 0.05, 0.05, 0.06 and 0.06 mg/kg. Thiamethoxam residues in orange flesh were: < 0.02 (6) and 0.02 mg/kg. In one Spanish orange trial residues were at measurable levels in both flesh (0.02 mg/kg) and fruit (0.05 mg/kg) providing a factor of 0.4 to estimate thiamethoxam residues in edible portion from residues in whole fruit from foliar treatment. In the same seven orange trials from Spain, residues of CGA 322704 in whole oranges as a metabolite of thiamethoxam were: < 0.02 (5), 0.02 and 0.03 mg/kg. CGA 322704 residues in orange flesh were: < 0.02 (7) mg/kg.

In six thiamethoxam trials on lemons in Spain in accord with Spanish GAP, thiamethoxam residue concentrations in whole lemons in rank order were: 0.02, 0.04, 0.07, 0.07, 0.08 and 0.08 mg/kg. Thiamethoxam residues in lemon flesh were: < 0.02 (5) and 0.02 mg/kg. In the same six lemon trials from Spain, residues of CGA 322704 in whole lemons were: < 0.02, 0.02, 0.02, 0.02, 0.03 and 0.04 mg/kg. CGA 322704 residues in lemon flesh were: < 0.02 (6) mg/kg.

In eight thiamethoxam trials on mandarins in Spain in accord with Spanish GAP, thiamethoxam residue concentrations in whole mandarins in rank order were: < 0.02 (2), 0.02, 0.02, 0.03, 0.04, 0.07 and 0.10 mg/kg. Thiamethoxam residues in mandarin flesh in nine trials were: < 0.02 (7), 0.02 and 0.02 mg/kg. In the same eight mandarin trials from Spain, residues of CGA 322704 in whole mandarins in rank order were: < 0.02 (3), 0.02, 0.02, 0.02, 0.03 and 0.05 mg/kg (NAFTA calculator: 0.057. OECD calculator Mean + 4SD: 0.068). CGA 322704 residues in mandarin flesh in nine trials were: < 0.02 (8) and 0.02 mg/kg. This CGA 322704 data set was selected for maximum residue level estimation.

In Indonesia, thiamethoxam may be applied twice as foliar sprays on citrus with a ZC formulation at 0.085 kg ai/ha and harvest 42 days after the final application. In three trials on oranges in Indonesia in accord with Indonesian GAP, residues of thiamethoxam were : < 0.01, 0.03 and 0.05 mg/kg. Residues of CGA 322704 were not detected.

Thiamethoxam may be used in the USA as a single soil treatment with SL formulations (chemigation in the root zone, drench around tree trunk and out to root zone or band each side of row) at 0.19 kg ai/ha. Thiamethoxam may also be used in two foliar applications with WG at 0.096 kg ai/ha during the production of citrus fruits. Fruit may be harvested on the same day as treatment.

In 12 orange trials in the USA matching the soil surface application GAP, residues of thiamethoxam were all < 0.01 mg/kg. In the same trials, residues of CGA 322704 in the oranges were also all < 0.01 mg/kg.

In six grapefruit trials in the USA matching the soil surface application GAP, residues of thiamethoxam were all < 0.01 mg/kg. In the same trials, residues of CGA 322704 in the grapefruits were also all < 0.01 mg/kg.

In five lemon trials in the USA matching the soil surface application GAP, residues of thiamethoxam were all < 0.01 mg/kg. In the same trials, residues of CGA 322704 in the lemons were also all < 0.01 mg/kg.

In 14 orange trials in the USA matching the US GAP for foliar application with a WG formulation, thiamethoxam residues, in rank order, were: 0.03, 0.04, 0.06, 0.06, 0.06, 0.07, 0.07, 0.08, 0.12, 0.13, 0.13, 0.19, 0.21 and 0.26 mg/kg (NAFTA calculator: 0.393. OECD calculator Mean + 4SD: 0.386). This data set was selected for maximum residue level estimation.

In the same 14 orange trials in the USA, residues of CGA 322704 in rank order were: < 0.01 (8), 0.01, 0.02, 0.02, 0.02, 0.02 and 0.03 mg/kg.

In eight grapefruit trials in the USA matching US GAP for foliar application with a WG formulation, thiamethoxam residues, in rank order, were: 0.02, 0.03, 0.04, 0.06, 0.06, 0.08, 0.10 and 0.17 mg/kg. In the same eight trials, residues of CGA 322704 in rank order were: < 0.01 (6), 0.03 and 0.03 mg/kg.

In six lemon trials in the USA matching US GAP for foliar application with a WG formulation, thiamethoxam residues, in rank order, were: 0.05, 0.06, 0.11, 0.12, 0.14 and 0.17 mg/kg. In the same six trials, residues of CGA 322704 in rank order were: < 0.01, 0.01, 0.01, 0.02, 0.02 and 0.02 mg/kg.

Summary—Citrus fruits

Residue data with suitable GAP were available for oranges, lemons, mandarins and grapefruit. The Meeting noted that thiamethoxam residues were highest in orange trials from the USA and that CGA 322704 residues were highest in mandarin trials from Spain and decided to estimate citrus group maximum residue levels based on these data sets.

On the basis of the foliar applications on oranges in the USA, the Meeting estimated a maximum residue level of 0.5 mg/kg for thiamethoxam on citrus fruits.

The STMR and HR for thiamethoxam in citrus were derived from the median and high residue of the US orange trials and a factor (residues in edible portion ÷ residues in whole fruit = 0.4) from the Spanish trials. The Meeting estimated STMR and HR values of 0.028 and 0.104 mg/kg respectively for thiamethoxam residues in citrus fruits.

On the basis of the CGA 322704 data on mandarins from eight trials with foliar application of thiamethoxam in Spain, the Meeting estimated a maximum residue level of 0.07 mg/kg for CGA 322704 on citrus fruits.

On the basis of the CGA 322704 data on mandarin flesh from nine trials in Spain, the Meeting estimated STMR and HR values of 0.02 and 0.02 mg/kg respectively for CGA 322704 residues in citrus fruits.

Pome fruits

Supervised trials data for pome fruits were available from the USA.

US GAP for pome fruit allows the use of thiamethoxam for foliar application at 0.096 kg ai/ha with a 35 days PHI and 0.048 kg ai/ha with a 14 days PHI.

In 15 apple trials in the USA matching GAP for foliar application and the final rate suitable for a 14 days PHI, thiamethoxam residues in rank order were: 0.03, 0.04, 0.04, 0.05, 0.06, 0.06, 0.06, 0.07, 0.08, 0.08, 0.09, 0.09, 0.10, 0.12 and 0.15 mg/kg (NAFTA calculator: 0.189. OECD calculator 3×Mean: 0.224). In the same 15 trials, residues of CGA 322704 in apples in rank order were: < 0.01 (13), 0.01 and 0.02 mg/kg.

In six pear trials in the USA matching GAP for foliar application and the final rate suitable for a 14 days PHI, thiamethoxam residues in rank order were: 0.03, 0.03, 0.04, 0.05, 0.05 and 0.08 mg/kg. In the same six trials, residues of CGA 322704 in pears in rank order were: 0.01, 0.02, 0.02, 0.03, 0.03 and 0.04 mg/kg (NAFTA calculator: 0.071. OECD calculator 3×Mean: 0.075).

Summary—Pome fruits

Residue data with suitable GAP were available for apples and pears from the USA. The Meeting noted that thiamethoxam residues were higher in the apple trials and that CGA 322704 residues were higher in pears. The Meeting decided to estimate pome fruit group maximum residue levels based on these data sets.

On the basis of the foliar applications on apples in the USA, the Meeting estimated a maximum residue level of 0.3 mg/kg for thiamethoxam on pome fruits. On the basis of the CGA 322704 data on pears from the US trials, the Meeting estimated a maximum residue level of 0.1 mg/kg for CGA 322704 on pome fruits.

The STMR and HR for thiamethoxam in pome fruits were derived from the median and high residues of the US apple trials. The Meeting estimated STMR and HR values of 0.07 and 0.15 mg/kg respectively for thiamethoxam residues in pome fruits. The STMR and HR for CGA 322704 in pome fruits were derived from the median and high residues of the US thiamethoxam pear trials. The Meeting estimated STMR and HR values of 0.025 and 0.04 mg/kg respectively for CGA 322704 residues in pome fruits.

Stone fruits

Supervised trials data were available for plums, peaches and cherries from the USA and cherries from France, Italy, Spain and Switzerland. No suitable GAP was available to evaluate the Swiss trials.

US GAP for stone fruits allows the use of thiamethoxam for foliar application at 0.096 kg ai/ha with a 14 days PHI.

In eight plum trials in the USA matching stone fruit GAP, thiamethoxam residues in plums in rank order were: < 0.01 (5), 0.01, 0.02 and 0.02 mg/kg. In the same eight trials, residues of CGA 322704 in plums in rank order were: < 0.01 (6), 0.01 and 0.02 mg/kg.

In 11 peach trials in the USA matching stone fruit GAP, thiamethoxam residues in peaches in rank order were: 0.01, 0.02, 0.02, 0.02, 0.03, 0.04, 0.04, 0.05, 0.05, 0.06 and 0.19 mg/kg.

In the same 11 peach trials, residues of CGA 322704 in peaches in rank order were: 0.01, 0.02, 0.02, 0.02, 0.02, 0.04, 0.04, 0.04, 0.04, 0.05 and 0.12 mg/kg (NAFTA calculator: 0.144. OECD calculator Mean + 4SD: 0.158). This data set was selected for maximum residue level estimation.

In 10 cherry trials in the USA matching stone fruit GAP, thiamethoxam residues in cherries in rank order were: 0.13, 0.17, 0.19, 0.19, 0.20, 0.21, 0.22, 0.22, 0.24 and 0.28 mg/kg. In the same 10 trials, residues of CGA 322704 in cherries in rank order were: < 0.01, < 0.01, 0.01, 0.01, 0.01, 0.02, 0.02, 0.03, 0.03 and 0.03 mg/kg.

Spanish GAP for cherries allows the use of thiamethoxam for two foliar applications with a spray concentration of 0.0075 kg ai/hL followed by a 7 days PHI.

In 12 cherry trials in France (seven), Italy (three) and Spain (two) matching the Spanish GAP, thiamethoxam residues in cherries in rank order were: 0.13, 0.15, 0.16, 0.16, 0.17, 0.19, 0.20, 0.26, 0.31, 0.49, 0.50 and 0.60 mg/kg (NAFTA calculator: 0.827. OECD calculator Mean + 4SD: 0.927). This data set was selected for maximum residue level estimation.

In the same 12 cherry trials, residues of CGA 322704 in cherries in rank order were: < 0.02 (7), 0.02, 0.02, 0.03, 0.04 and 0.06 mg/kg.

Summary—Stone fruits

Residue data with suitable GAP were available for plums, peaches and cherries. The Meeting noted that thiamethoxam residues were highest in cherry trials from Europe and that CGA 322704 residues were highest in peach trials from the USA and decided to estimate stone fruits group maximum residue levels based on these two data sets.

On the basis of the foliar applications on cherries in 12 trials in France, Italy and Spain, the Meeting estimated a maximum residue level of 1 mg/kg for thiamethoxam on stone fruits. The Meeting estimated STMR and HR values of 0.195 and 0.60 mg/kg respectively for thiamethoxam residues in stone fruits.

On the basis of the CGA 322704 data on peaches from 11 trials in the USA, the Meeting estimated a maximum residue level of 0.2 mg/kg for CGA 322704 on stone fruits. The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.04 and 0.12 mg/kg respectively for CGA 322704 residues in stone fruits.

Berries and other small fruits

Supervised trials data were available for strawberries, cranberries, blueberries, caneberries and grapes.

Cranberry

Supervised trials data were available for cranberries from the USA.

During the production of cranberries in the USA, thiamethoxam as a WG formulation may be used for foliar sprays at 0.070 kg ai/ha with observation of a 30 days PHI.

In six cranberry trials in the USA with a WG formulation and matching the conditions of the foliar treatment GAP, thiamethoxam residues in cranberries were all below LOQ (0.01 mg/kg). In the same six trials, residues of CGA 322704 in cranberries were also all below LOQ (0.01 mg/kg).

Blueberries

Supervised trials data were available for blueberries from the USA.

Thiamethoxam may be used as foliar applications (WG formulation) or a soil-applied surface band (SL formulation) during the production of blueberries in the USA. The application rate is 0.070 kg ai/ha in the foliar use (PHI 3 days) or, for bushberries (includes blueberries), 0.20 kg ai/ha for the band application followed by a PHI of 75 days.

In seven blueberry trials in the USA with an SL formulation and matching the conditions of the soil-applied surface band treatment GAP, thiamethoxam residues in blueberries were all below LOQ (0.01 mg/kg). In the same seven trials, residues of CGA 322704 in blueberries were also all below LOQ (0.01 mg/kg).

In nine blueberry trials in the USA with a WG formulation and matching the conditions of the foliar treatment GAP, thiamethoxam residues in blueberries in rank order were: < 0.01, 0.05, 0.06, 0.06, 0.07, 0.07, 0.07, 0.07 and 0.11 mg/kg. In the same nine trials, residues of CGA 322704 in

blueberries in rank order were: < 0.01 (4), 0.01, 0.01, 0.02, 0.03 and 0.05 mg/kg. This CGA 322704 data set was used as part of the data for maximum residue level estimation for the berry fruits group.

Blackberries, raspberries and boysenberries

Supervised trials data were available from the USA for caneberries: raspberries (four trials), blackberries (one trial) and boysenberries (one trial).

Thiamethoxam may be used as foliar applications (WG formulation) during the production of caneberries in the USA. The application rate is 0.053 kg ai/ha and the crop may be harvested 3 days after an application.

In six caneberry trials in the USA matching the conditions of the foliar treatment GAP, thiamethoxam residues in blackberries, raspberries and boysenberries in rank order were: 0.01, 0.06, 0.10, 0.12, 0.19 and 0.20 mg/kg. In the same six trials, residues of CGA 322704 in blackberries, raspberries and boysenberries in rank order were: < 0.01 (2), 0.01, 0.02, 0.02 and 0.04 mg/kg. This CGA 322704 data set was used as part of the data for maximum residue level estimation for the berry fruits group.

For CGA 322704, the data from nine blueberry trials and six caneberry trials were combined to represent the group: < 0.01 (6), 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, 0.03, 0.04 and 0.05 mg/kg (NAFTA calculator: 0.056. OECD calculator Mean + 4SD: 0.069).

Grapes

Supervised trials data were available for grapes from France, Italy, Spain and Switzerland.

In Spain and Italy, thiamethoxam formulated as WG is approved for foliar application to grapes at 0.050 kg ai/ha, with harvest permitted 21 days later. The trials from France, Italy and Spain were evaluated using the GAP from Spain and Italy. No suitable GAP was available for evaluation of the Swiss trials.

In 11 grape trials in Europe (seven French, one Italian and three Spanish) matching the conditions of the Spanish and Italian GAP, thiamethoxam residues in grapes in rank order were: < 0.02 (2), 0.02, 0.02, 0.02, 0.04, 0.04, 0.07, 0.13, 0.17 and 0.21 mg/kg (NAFTA calculator: 0.276. OECD calculator Mean + 4SD: 0.345). In the same 11 trials, residues of CGA 322704 in grapes were: < 0.02 (10) and 0.02 mg/kg.

On the basis of the foliar applications on grapes in 11 European trials, the Meeting estimated a maximum residue level of 0.4 mg/kg for thiamethoxam in grapes. On the basis of the CGA 322704 data on grapes from the same 11 trials, the Meeting estimated a maximum residue level of 0.05 mg/kg for CGA 322704 on grapes. The residue levels of thiamethoxam and CGA 322704 occurring in grapes allow grapes to be included in the berry fruit group MRLs.

Strawberry

Supervised trials data were available for strawberries from the USA.

During the production of strawberries in the USA, thiamethoxam may be used as a single soil drench treatment (0.20 kg ai/ha) with an SL formulation at the base of the plants followed by harvest 65 days later. Alternatively, a WG formulation may be used for foliar sprays at 0.070 kg ai/ha with observation of a 3 days PHI.

In eight strawberry trials in the USA with an SL formulation and matching the conditions of the drench treatment GAP, but with some flexibility in the PHI, thiamethoxam residues in strawberries in rank order were: < 0.01, < 0.01, 0.01, 0.01, 0.02, 0.02, 0.03 and 0.03 mg/kg. In the same eight trials, residues of CGA 322704 in strawberries were all below LOQ (0.01 mg/kg).

In eight strawberry trials in the USA with a WG formulation and matching the conditions of the foliar treatment GAP, thiamethoxam residues in strawberries in rank order were: 0.02, 0.02, 0.05, 0.05, 0.06, 0.14, 0.22 and 0.26 mg/kg (NAFTA calculator: 0.378. OECD calculator Mean + 4SD:

0.476). This thiamethoxam data set was selected for maximum residue level estimation for the berry fruits group. In the same eight trials, residues of CGA 322704 in strawberries were all below LOQ (0.01 mg/kg).

Summary—Berries and other small fruits

Residue data with suitable GAP were available for strawberries, cranberries, blueberries, caneberries and grapes. The Meeting noted that thiamethoxam residues were highest in strawberries and that CGA 322704 residues were highest in blueberries and caneberries and decided to estimate berry fruit group maximum residue levels based on these two data sets.

Grapes are often evaluated separately because the crop is rarely included in a berries crop group GAP and specific grape data are needed for its important processed commodities. However, the estimated maximum residue level for grapes closely agrees with that estimated for the other berry fruits, so the Meeting agreed to include the grapes with the berry fruits proposals.

On the basis of the foliar applications on strawberries in eight US trials, the Meeting estimated a maximum residue level of 0.5 mg/kg for thiamethoxam in berries and other small fruits.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.055 and 0.26 mg/kg respectively for thiamethoxam residues in berries and other small fruits.

On the basis of the nine blueberry trials and six caneberry trials from the USA, the Meeting estimated a maximum residue level of 0.07 mg/kg for CGA 322704 in berries and other small fruits.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.01 and 0.05 mg/kg respectively for CGA 322704 residues in berries and other small fruits.

Assorted tropical and sub-tropical fruits—inedible peel

Supervised trials data were available for bananas, mangoes, papaya and pineapples.

Banana

Supervised trials data were available for bananas from Cameroon.

In Cameroon, thiamethoxam WG is approved for use as a drench to the banana stem at a concentration of 0.20 kg ai/hL and application volume 100 mL per plant, equivalent to 0.2 g ai per plant, with harvest permitted on the same day.

In three banana trials with thiamethoxam in Cameroon at the approved application rate and one at double rate and with bananas harvested 7–60 days after treatment, thiamethoxam residues in bananas were all below LOQ (0.02 mg/kg). In a further trial at the label rate, banana pulp was analysed but again thiamethoxam residues were below LOQ (0.02 mg/kg). In all these samples, CGA 322704 residues also were all below LOQ (0.02 mg/kg).

The Meeting estimated a maximum residue level of 0.02* mg/kg for thiamethoxam in bananas. On the basis of the CGA 322704 data on bananas from the same 12 trials, the Meeting estimated a maximum residue level of 0.02* mg/kg for CGA 322704 on bananas.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.02 and 0.02 mg/kg for thiamethoxam residues in bananas. The Meeting also estimated STMR and HR values of 0.02 and 0.02 mg/kg for CGA 322704 residues in bananas.

Mango

Supervised trials data were available for mangoes from South Africa.

In South Africa, thiamethoxam is approved for application to mango trees as a drench around the trees or by drip irrigation at a dose of 1.4 g ai per tree. The timing of the application is set by a seasonal instruction: apply from last week in July to mid August. The harvesting season for mangoes would follow in early to mid-summer.

One of the trials was compromised of residues of thiamethoxam (0.02 mg/kg) and CGA 322704 (0.02 mg/kg) appearing in samples from the control plot at similar levels to those from treated plots.

Three of the mango trials followed the label rate for application: 1.4 g ai per tree, resulting in thiamethoxam residues in mangoes, 0.04, 0.10 and 0.11 mg/kg. The same three trials produced CGA 322704 residues in mangoes of < 0.02, 0.02 and 0.02 mg/kg.

Three trials for mangoes are insufficient to support a maximum residue level.

Papaya

Supervised trials data were available for papaya from Brazil and Côte d'Ivoire. No GAP was available to evaluate the Côte d'Ivoire trials.

In Brazil, thiamethoxam is approved as a soil drench application for papaya at a rate equivalent to 0.20 kg ai/ha. A PHI of 14 days is specified.

Four of the papaya trials in Brazil followed the label rate of application, 0.2 kg ai/ha with thiamethoxam residues in papaya fruits all below LOQ (0.01 mg/kg). The same four trials produced CGA 322704 residues in papaya fruits also all below LOQ (0.01 mg/kg).

Four of the papaya trials in Brazil followed a double rate of application, 0.4 kg ai/ha with the same results as the label rate, thiamethoxam residues in papaya fruits all below LOQ (0.01 mg/kg). The same four trials produced CGA 322704 residues in papaya fruits also all below LOQ (0.01 mg/kg).

The Meeting estimated a maximum residue level of 0.01* mg/kg for thiamethoxam in papaya. On the basis of the CGA 322704 data on papaya from the same trials, the Meeting estimated a maximum residue level of 0.01* mg/kg for CGA 322704 on papaya.

The Meeting estimated STMR and HR values of 0 and 0 mg/kg for thiamethoxam residues in papayas. The Meeting also estimated STMR and HR values of 0 and 0 mg/kg for CGA 322704 residues in papayas.

Pineapple

Supervised trials data were available for pineapples from Brazil.

In Brazil, thiamethoxam is approved for pineapples as a pre-seedling transplant immersion in a solution concentration 0.075 kg ai/hL, and as a soil drench at the plant base 45–60 days after transplant at an application rate of 0.20 kg ai/ha.

In the Brazilian trials, this seedling treatment and soil drench usage GAP was followed, but another thiamethoxam soil drench was added 0–60 days before harvest. In the four trials, thiamethoxam residues in pineapples were all below LOQ (0.01 mg/kg). Residues of CGA 322704 were also all below LOQ (0.01 mg/kg).

The Meeting estimated a maximum residue level of 0.01* mg/kg for thiamethoxam in pineapples. On the basis of the CGA 322704 data on pineapples from the same trials, the Meeting estimated a maximum residue level of 0.01* mg/kg for CGA 322704 on pineapples.

The Meeting estimated STMR and HR values of 0 and 0 mg/kg for thiamethoxam residues in pineapples. The Meeting also estimated STMR and HR values of 0 and 0 mg/kg for CGA 322704 residues in pineapples.

Brassica vegetables

Supervised trials data were available for cabbages and broccoli.

Cabbages

Supervised trials data on cabbage were available from the USA.

In the USA, foliar applications of thiamethoxam may be made to head and stem Brassica vegetables (includes cabbage) at 0.096 kg ai/ha, with harvest on the same day.

Soil drench applications of thiamethoxam to Brassica vegetables at 0.19 kg ai/ha with a 30 days PHI are also registered. The soil drench rate in the cabbage trials was 0.14 kg ai/ha and the data were not evaluated.

In eight cabbage trials in the USA matching the foliar GAP conditions, thiamethoxam residues in cabbages (with wrapper leaves) in rank order were: 0.57, 0.59, 0.62, 0.69, 0.78, 0.91, 1.1 and 3.0 mg/kg. In the same eight trials, residues of CGA 322704 in cabbages (with wrapper leaves) in rank order were: 0.02, 0.02, 0.03, 0.03, 0.04, 0.05, 0.06 and 0.08 mg/kg.

In the same eight cabbage trials, residues were also measured on cabbage heads only, i.e., with wrapper leaves removed. Thiamethoxam residues in cabbage heads in rank order were: 0.01, 0.02, 0.03, 0.05, 0.05, 0.09, 0.11 and 0.14 mg/kg. In the same eight trials, residues of CGA 322704 in cabbage heads were: < 0.01 (7) and 0.01 mg/kg.

Two of the cabbage trials matching the foliar GAP conditions were side-by-side trials providing bridging data for the use of WG and SL formulations. Thiamethoxam residues in the head + wrapper leaves were 0.15 and 0.57 mg/kg for SL and 0.69 and 0.58 mg/kg for WG, and for head only the residues were < 0.01 and 0.01 mg/kg for SL and 0.05 and 0.02 mg/kg for WG. CGA 322704 residues in the head + wrapper leaves were < 0.01 and 0.04 mg/kg for SL and 0.04 and 0.05 mg/kg for WG. The results suggest equivalence, so only one of the bridging trials should be included in the dataset for STMR and maximum residue level estimation.

The cabbage datasets become:

Thiamethoxam—head + wrapper leaves (n = 7): 0.59, 0.62, 0.69, 0.78, 0.91, 1.1 and 3.0 mg/kg. (NAFTA calculator: 3.67. OECD calculator Mean + 4SD:4.53)

CGA 322704—head + wrapper leaves (n = 7): 0.02, 0.02, 0.03, 0.03, 0.05, 0.06 and 0.08 mg/kg. (NAFTA calculator: 0.129. OECD calculator Mean + 4SD: 0.132)

Thiamethoxam—head only (n = 7): 0.02, 0.03, 0.05, 0.05, 0.09, 0.11 and 0.14 mg/kg

CGA 322704—head only (n = 7): < 0.01 (6) and 0.01 mg/kg.

Broccoli

Supervised trials data on broccoli were available from the USA.

In the USA, foliar applications of thiamethoxam may be made to head and stem Brassica vegetables (includes broccoli) at 0.096 kg ai/ha, with harvest on the same day.

In 10 broccoli trials in the USA matching the GAP conditions, thiamethoxam residues in broccoli in rank order were: 0.30, 0.30, 0.34, 0.37, 0.41, 0.49, 0.57, 0.66, 1.1 and 1.1 mg/kg. In the same 10 trials, residues of CGA 322704 in broccoli in rank order were: < 0.01 (4), 0.01, 0.02, 0.03, 0.04, 0.04 and 0.04 mg/kg.

Four of the broccoli trials matching the foliar GAP conditions were side-by-side trials providing bridging data for the use of WG and SL formulations. In one pair of trials, from California, thiamethoxam residues in the head + stem were 0.34 and 0.37 g/kg for SL and 0.49 and 0.44 mg/kg for WG. CGA 322704 residues were 0.01 and 0.01 mg/kg for SL and 0.02 and 0.02 mg/kg for WG. In the second pair of trials, from Texas, thiamethoxam residues in the head + stem were 0.38 and 0.41 g/kg for SL and 0.32 and 0.34 mg/kg for WG. CGA 322704 residues were 0.02 and 0.04 mg/kg

for SL and 0.03 and 0.02 mg/kg for WG. The results suggest equivalence, so only one from each pair of the bridging trials should be included in the dataset for STMR and maximum residue level estimation.

The broccoli datasets (n = 8) become:

Thiamethoxam 0.30, 0.30, 0.41, 0.49, 0.57, 0.66, 1.1 and 1.1 mg/kg

CGA 322704 < 0.01 (4), 0.02, 0.04, 0.04 and 0.04 mg/kg.

These data sets were selected for the STMR and HR estimation for the Brassica group.

Summary—Brassica vegetables group

Residue data with suitable GAP were available for broccoli and cabbages. The Meeting noted that residues in cabbage with wrapper leaves had higher residues than the broccoli and decided to use the cabbage data to support Brassica group MRLs.

On the basis of the foliar applications on cabbages in the US trials, the Meeting estimated a maximum residue level of 5 mg/kg for thiamethoxam on Brassica vegetables. On the basis of the CGA 322704 data on cabbages from the same trials, the Meeting estimated a maximum residue level of 0.2 mg/kg for CGA 322704 on Brassica vegetables.

The Meeting noted that residues in broccoli had higher residues than the cabbages (heads only) and decided to use the broccoli data to support Brassica group STMRs and HRs.

On the basis of the foliar applications on broccoli in the eight US trials, the Meeting estimated an STMR and an HR value of 0.53 and 1.1 mg/kg respectively for thiamethoxam on Brassica vegetables. On the basis of the CGA 322704 data on broccoli from the same trials, the Meeting estimated an STMR and an HR value of 0.015 and 0.04 mg/kg respectively for CGA 322704 on Brassica vegetables.

For livestock dietary burden, it is more appropriate to include the cabbage wrapper leaves in the STMR and high residue estimates. In this case the STMR and high residue values for thiamethoxam on cabbages are 0.78 and 3.0 mg/kg respectively. For CGA 322704, the STMR and high residue values on cabbage are 0.03 and 0.08 mg/kg respectively.

Fruiting vegetables, Cucurbits

Supervised trials data were available for cucumbers, melons and cantaloupes and summer squash.

Cucumber

Supervised trials data on cucumbers were available from France, Netherlands, Spain and the USA.

In the USA, foliar applications of thiamethoxam may be made to cucurbit vegetables (includes cucumbers) at 0.096 kg ai/ha, with harvest on the same day.

In-furrow spray or soil surface band applications of thiamethoxam to cucurbit vegetables at 0.19 kg ai/ha with a 30 days PHI are also registered in the USA. The in-furrow and surface band treatment rate in the cucumber trials was 0.14 kg ai/ha and the data could not be evaluated.

In eight cucumber trials in the USA matching the foliar GAP conditions, thiamethoxam residues in cucumbers in rank order were: 0.02, 0.04, 0.05, 0.07, 0.07, 0.08, 0.09 and 0.11 mg/kg. In the same eight trials, residues of CGA 322704 in cucumbers were all below LOQ < 0.01 mg/kg).

In Italy, thiamethoxam may be applied to cucumbers by drip or drench at 0.2 kg ai/ha, with harvest permitted 3 days later. Drip refers to application to the base of each plant through the drip application system. Drench is application by watering soil around plants.

The protected cucumber trials in France, Netherlands and Spain relied on drip, drench and syringe applications. A syringe may be used in an experimental situation to simulate drip application.

In six cucumber trials in France, Netherlands and Spain following Italian GAP, thiamethoxam residues in cucumbers in rank order were: 0.06, 0.06, 0.09, 0.12, 0.14 and 0.29 mg/kg (NAFTA calculator: 0.432. OECD calculator Mean + 4SD: 0.471). The Meeting noted that application at 0.1 kg ai/ha (½ label rate) produced residues of 0.17 and 0.12 mg/kg. In the same six trials, residues of CGA 322704 in cucumbers were all below LOQ < 0.02 mg/kg). These data sets for both thiamethoxam and CGA 322704 were selected for estimation of maximum residue levels for cucurbit fruiting vegetables.

Melons and cantaloupes

Supervised trials data on melons and cantaloupes were available from Italy, Spain and the USA.

Thiamethoxam is approved for use on melons in Spain as a drip irrigation method of application: 0.20 kg ai/ha for indoor production and 0.10 kg ai/ha for outdoor production. A PHI of 3 days is specified.

The two trials from Italy could not be evaluated because no suitable GAP was available.

In four melon trials in Spain matching the drip irrigation GAP conditions (but with allowances on the PHI), thiamethoxam residues in cucumbers in rank order were: < 0.02, 0.02, 0.02 and 0.03 mg/kg. In the same four trials, residues of CGA 322704 in melons were all below LOQ < 0.02 mg/kg).

In the USA, foliar applications of thiamethoxam may be made to cucurbit vegetables (includes cantaloupes) at 0.096 kg ai/ha, with harvest on the same day.

In-furrow spray applications of thiamethoxam to cucurbit vegetables at 0.19 kg ai/ha with a 30 days PHI are also registered in the USA. The in-furrow treatment rate in the cantaloupe trials was 0.14 kg ai/ha and the data could not be evaluated.

In six cantaloupe trials in the USA matching the foliar application GAP conditions, thiamethoxam residues in cantaloupes in rank order were: 0.03, 0.03, 0.04, 0.07, 0.13 and 0.16 mg/kg. In the same six trials, residues of CGA 322704 in cantaloupes were all below LOQ (0.01 mg/kg).

Summer squash

Supervised trials data for thiamethoxam use on summer squash were available from the USA.

In the USA, foliar applications of thiamethoxam as a WG may be made to cucurbit vegetables (includes summer squash) at 0.096 kg ai/ha, with harvest on the same day.

In five summer squash trials in the USA matching the foliar application GAP conditions, thiamethoxam residues in summer squash in rank order were: 0.02, 0.05, 0.06, 0.07 and 0.16 mg/kg. In the same five trials, residues of CGA 322704 in summer squash in rank order were all below LOQ (0.01 mg/kg).

Summary—Fruiting vegetables, Cucurbits

Residue data with suitable GAP were available for cucumbers, melons and cantaloupes and summer squash. The Meeting noted that thiamethoxam residues were highest in cucumbers and that CGA 322704 residues were below LOQ in cucurbit fruiting vegetables. The Meeting decided to estimate cucurbit fruiting vegetables group maximum residue levels based on the cucumber data sets.

On the basis of the drip, drench and syringe applications on cucumbers in six European trials, the Meeting estimated a maximum residue level of 0.5 mg/kg for thiamethoxam on cucurbit fruiting vegetables. On the basis of the CGA 322704 data on cucumbers from the same six trials, the Meeting estimated a maximum residue level of 0.02* mg/kg for CGA 322704 on cucurbit fruiting vegetables.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.105 and 0.29 mg/kg respectively for thiamethoxam residues in cucurbit fruiting

vegetables. The Meeting estimated STMR and HR values of 0.02 and 0.02 mg/kg for CGA 322704 residues in cucurbit fruiting vegetables.

Fruiting vegetables, other than Cucurbits

Supervised trials data were available for sweet corn, tomatoes, peppers, egg plants and okra.

Egg plant

Supervised trials data for thiamethoxam use on egg plants were available from Switzerland and the UK.

Thiamethoxam is approved in Italy for foliar application on egg plants at 0.10 kg ai/ha, two applications at an interval of 7 days, with harvest 3 days after application.

In one greenhouse egg plant trial in the UK matching Italian GAP, thiamethoxam residues in egg plant were 0.12 mg/kg with CGA 322704 residues < 0.02 mg/kg.

Sweet corn

Supervised trials data for thiamethoxam use on sweet corn were available from the USA.

In the USA, thiamethoxam is formulated as an FS seed treatment that may be used on sweet corn at 1.25 mg ai per kernel. This is equivalent to approx 4.5 g ai/kg seed for a single kernel weight of 0.28 g.

In 12 sweet corn trials in the USA where the seed had been treated with thiamethoxam FS at 4.5 g ai/kg seed, thiamethoxam residues and CGA 322704 residues in the harvested sweet corn ears were all below LOQ (0.01 mg/kg).

The Meeting estimated a maximum residue level and STMR and HR values, all at 0.01 mg/kg for thiamethoxam in sweet corn (corn-on-the-cob).

The Meeting estimated a maximum residue level and STMR and HR values, all at 0.01 mg/kg for CGA 322704 in sweet corn (corn-on-the-cob).

Peppers

Supervised trials data for thiamethoxam use on bell peppers and chilli peppers were available from the USA and on sweet peppers from France, Italy, Spain, Switzerland and the UK. No suitable GAP was available to evaluate the data from Switzerland and the UK.

Thiamethoxam is approved in Italy for foliar application on peppers at 0.10 kg ai/ha, with harvest 3 days after application.

In eight sweet pepper field trials in Italy and Spain matching the Italian GAP conditions for peppers, thiamethoxam residues in sweet peppers in rank order were: 0.03, 0.03, 0.06, 0.08, 0.08, 0.09, 0.13 and 0.24 mg/kg. In the same eight trials, residues of CGA 322704 in sweet peppers were all below LOQ (0.02 mg/kg).

In 11 sweet pepper greenhouse trials in France, Italy, Spain, Switzerland and the UK matching the Italian GAP conditions for peppers, thiamethoxam residues in sweet peppers in rank order were: 0.07, 0.07, 0.08, 0.08, 0.08, 0.08, 0.10, 0.12, 0.16, 0.26 and 0.47 mg/kg (NAFTA calculator: 0.510. OECD calculator Mean + 4SD: 0.632). In the same 11 trials, residues of CGA 322704 in sweet peppers were: < 0.02 (9), 0.02 and 0.03 mg/kg. These data sets were selected for maximum residue level estimations for the fruiting vegetables group, except sweet corn.

In the USA, foliar applications of thiamethoxam as a WG may be made to fruiting vegetables (includes peppers) at 0.096 kg ai/ha, with harvest on the same day.

In six bell pepper trials in the USA matching the foliar GAP conditions for fruiting vegetables, thiamethoxam residues in sweet peppers in rank order were: 0.03, 0.06, 0.08, 0.10, 0.13

and 0.18 mg/kg. In the same six trials, residues of CGA 322704 in sweet peppers were: < 0.01 (5) and 0.01 mg/kg.

In three chilli pepper trials in the USA matching the foliar GAP conditions for fruiting vegetables, thiamethoxam residues in chilli peppers in rank order were: 0.06, 0.11 and 0.22 mg/kg. In the same three trials, residues of CGA 322704 in chilli peppers were: < 0.01 (2) and 0.06 mg/kg.

Okra

Supervised trials data for thiamethoxam use on okra were available from Côte d'Ivoire.

In Kenya, foliar applications of thiamethoxam as a WG may be made to okra at 0.10 kg ai/ha, with harvest 3 days later. The Meeting agreed to evaluate the data from Côte d'Ivoire with the Kenyan GAP, allowing that the 2 days PHI in the trials was sufficiently close to the 3 days PHI specified in the Kenyan GAP.

In four okra trials in Côte d'Ivoire at an application rate of 0.10 kg ai/ha and a PHI of 3 days, reported thiamethoxam residues in okra in rank order were: 0.03, 0.07, 0.07 and 0.24 mg/kg. The analytical method used for thiamethoxam residue analysis was an imidacloprid residue analytical method, presumably adapted to thiamethoxam. No validation data were available, but procedural recoveries of 78% and 70% were recorded. Metabolite CGA 322704 residues were not included in the analyses and the reported residues of thiamethoxam include only parent thiamethoxam.

Tomato

Supervised trials data for thiamethoxam use on tomatoes were available from France, Italy, Spain, Switzerland and the USA. No suitable GAP was available to evaluate the Swiss trials.

Thiamethoxam is approved for foliar application on tomatoes in Italy at 0.10 kg ai/ha, with harvest 3 days after application.

In 17 tomato field trials in France, Italy and Spain in accord with the GAP conditions of Italy, thiamethoxam residues in tomatoes in rank order were: < 0.02 (7), 0.02, 0.02, 0.02, 0.02, 0.02, 0.03, 0.03, 0.03, 0.04 and 0.04 mg/kg. In the same 17 trials, residues of CGA 322704 in tomatoes were: < 0.02 (16) and 0.03 mg/kg.

In 10 tomato greenhouse trials in France, Italy, Spain and Switzerland in accord with the GAP conditions of Italy, thiamethoxam residues in tomatoes in rank order were: 0.02, 0.02, 0.02, 0.03, 0.03, 0.03, 0.03, 0.06, 0.07 and 0.12 mg/kg. In the same 10 trials, residues of CGA 322704 in tomatoes were all below LOQ (0.02 mg/kg).

In the USA, foliar applications of thiamethoxam as a WG may be made to fruiting vegetables (includes tomatoes) at 0.096 kg ai/ha, with harvest on the same day.

In 20 tomato trials in the USA matching the foliar GAP conditions, thiamethoxam residues in tomatoes in rank order were: 0.02, 0.03, 0.03, 0.04, 0.04, 0.05, 0.05, 0.06, 0.06, 0.06, 0.06, 0.07, 0.07, 0.07, 0.08, 0.10, 0.10, 0.12, 0.14 and 0.15 mg/kg. In the same 20 trials, residues of CGA 322704 in tomatoes in rank order were: < 0.01 (9), 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, 0.02, 0.03, 0.03, 0.04 and 0.05 mg/kg.

Four of the tomato trials matching the foliar GAP conditions were side-by-side trials providing bridging data for the use of WG and SL formulations. In one pair of trials, from California, thiamethoxam residues in the tomatoes were 0.03 and 0.07 g/kg for SL and 0.06 and 0.02 mg/kg for WG. CGA 322704 residues were < 0.01 and 0.02 mg/kg for SL and < 0.01 and 0.01 mg/kg for WG. In the second pair of trials, from Florida, thiamethoxam residues in the tomatoes were 0.10 and 0.08 g/kg for SL and 0.05 and 0.06 mg/kg for WG. CGA 322704 residues were < 0.01 (2)for both SL and WG. The results suggest equivalence, so only one from each pair of the bridging trials should be included in the dataset for STMR and maximum residue levels estimation.

The tomato datasets become (n = 18): thiamethoxam 0.02, 0.03, 0.03, 0.04, 0.04, 0.05, 0.05, 0.06, 0.06, 0.07, 0.07, 0.07, 0.08, 0.10, 0.10, 0.12, 0.14 and 0.15 mg/kg; CGA 322704 < 0.01 (8), 0.01, 0.01, 0.02, 0.02, 0.02, 0.02, 0.03, 0.03, 0.04 and 0.05 mg/kg.

Summary—Fruiting vegetables, other than Cucurbits

Residue data with suitable GAP were available for sweet corn, tomatoes, peppers, egg plants and okra. The Meeting noted that thiamethoxam residues and CGA 322704 were highest in peppers and decided to estimate fruiting vegetable group maximum residue levels based on the peppers data sets. Residues in sweet corn appeared inconsistent with residues from other members of the commodity group, so the Meeting agreed on separate MRLs for sweet corn. Mushrooms were also excluded from the group MRLs.

On the basis of the foliar applications on sweet peppers in 11 greenhouse trials in France, Italy, Spain, Switzerland and the UK the Meeting estimated a maximum residue level of 0.7 mg/kg for thiamethoxam in fruiting vegetables other than cucurbits, except sweet corn. On the basis of the CGA 322704 data on sweet peppers from the same 11 trials, the Meeting estimated a maximum residue level of 0.05 mg/kg for CGA 322704 in fruiting vegetables other than cucurbits, except sweet corn and mushrooms.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.08 and 0.47 mg/kg respectively for thiamethoxam residues in fruiting vegetables other than cucurbits, except sweet corn and mushrooms. The Meeting estimated STMR and HR values of 0.02 and 0.03 mg/kg for CGA 322704 residues in fruiting vegetables other than cucurbits, except sweet corn and mushrooms.

The JMPR Manual (Section 6.9.2) explains that a generic factor may be used for conversion of residues from fresh peppers to dried chilli peppers. The factor is 10 for the estimation of residue levels of pesticides in dried chilli peppers from the HR values estimated for residues in or on sweet peppers.

The Meeting agreed to apply the default factor of 10 for dried chilli peppers to the STMR (0.08 mg/kg) and HR (0.47 mg/kg) values for thiamethoxam in fruiting vegetables other than cucurbits (based on sweet pepper data) and estimated a maximum residue level, an STMR and an HR for thiamethoxam in dried chilli peppers of 7, 0.8 and 4.7 mg/kg, respectively.

For CGA 322704, the Meeting also agreed to apply the default factor of 10 for dried chilli peppers to the STMR (0.02 mg/kg) and HR (0.03 mg/kg) values based on sweet peppers and estimated a maximum residue level, an STMR and an HR for CGA 322704 in dried chilli peppers of 0.5, 0.2 and 0.3 mg/kg, respectively.

Leafy vegetables

Supervised trials data were available for lettuce, spinach and mustard greens.

Lettuce

Supervised trials data for thiamethoxam use on lettuce were available from the USA.

In the USA, foliar applications of thiamethoxam as a WG may be made to leafy vegetables (includes lettuce) at 0.096 kg ai/ha, with harvest 7 days after treatment.

Thiamethoxam may also be used as a soil treatment at planting (in-furrow spray, surface band or drench) for leafy vegetables at 0.19 kg ai/ha with an expected time to harvest of 65 days. A shanked into root zone after transplanting application at 0.19 kg ai/ha, with a 35 days PHI is also available.

In eight head lettuce trials in the USA matching the foliar GAP conditions, thiamethoxam residues in head lettuces in rank order were: 0.02, 0.04, 0.11, 0.12, 0.20, 0.24, 0.25 and 0.45 mg/kg.

In the same eight trials, residues of CGA 322704 in head lettuces in rank order were: < 0.01 (4), 0.01, 0.01, 0.01 and 0.03 mg/kg.

In 10 leaf lettuce trials in the USA matching the foliar GAP conditions, thiamethoxam residues in leaf lettuces in rank order were: 0.07, 0.13, 0.22, 0.25, 0.53, 0.55, 0.86, 0.88, 1.14 and 1.9 mg/kg (NAFTA calculator: 3.442. OECD calculator Mean + 4SD: 2.914). This data set was selected for a thiamethoxam maximum residue level estimation for the leafy vegetables commodity group.

In the same 10 trials, residues of CGA 322704 in leaf lettuces in rank order were: < 0.01, 0.01, 0.01, 0.01, 0.03, 0.03, 0.04, 0.04, 0.04 and 0.07 mg/kg.

In six leaf lettuce trials in the USA matching the soil treatment GAP conditions, thiamethoxam residues in leaf lettuces in rank order were: 0.03, 0.05, 0.12, 0.36, 0.55 and 0.85 mg/kg.

In the same six trials, residues of CGA 322704 in leaf lettuces in rank order were: < 0.01 (2), 0.03, 0.03, 0.05 and 0.14 mg/kg.

Spinach

Supervised trials data for thiamethoxam use on spinach were available from the USA.

In the USA, foliar applications of thiamethoxam as a WG may be made to leafy vegetables (includes spinach) at 0.096 kg ai/ha, with harvest 7 days after treatment.

In 10 spinach trials in the USA matching the foliar GAP conditions for leafy vegetables, thiamethoxam residues in spinach in rank order were: 0.02, 0.02, 0.05, 0.07, 0.22, 0.28, 0.28, 0.28, 0.62 and 0.66 mg/kg.

In the same 10 trials, residues of CGA 322704 in spinach in rank order were: 0.10, 0.13, 0.21, 0.39, 0.49, 0.54, 0.61, 0.62, 0.77 and 0.80 mg/kg (NAFTA calculator: 2.157. OECD calculator Mean + 4SD: 1.475). This data set was selected for a CGA 322704 maximum residue level estimation for the leafy vegetables commodity group.

Mustard greens

Supervised trials data on mustard greens were available from the USA.

In the USA, foliar applications of thiamethoxam may be made to leafy greens Brassica vegetables (includes mustard greens) at 0.096 kg ai/ha, with harvest 7 days after an application.

In-furrow spray or soil surface band applications of thiamethoxam to Brassica vegetables at 0.19 kg ai/ha with a 30 days PHI are also registered uses. The in-furrow and surface band treatments rate in the mustard greens trials was 0.14 kg ai/ha and the data could not be evaluated.

In six mustard greens trials in the USA matching the foliar GAP conditions, thiamethoxam residues in mustard greens in rank order were: 0.38, 0.42, 0.42, 0.66, 0.69 and 0.75 mg/kg. In the same six trials, residues of CGA 322704 in mustard greens in rank order were: 0.07, 0.08, 0.12, 0.16, 0.23 and 0.29 mg/kg.

Two of the mustard greens trials matching the foliar GAP conditions were side-by-side trials providing bridging data for the use of WG and SL formulations. Thiamethoxam residues in the leaves were 0.69 and 0.60 mg/kg for SL and 0.69 and 0.75 mg/kg for WG. CGA 322704 residues in the leaves were 0.12 and 0.11 mg/kg for SL and 0.18 and 0.23 mg/kg for WG. The results suggest equivalence, so only one of the bridging trials should be included in the dataset for STMR and maximum residue level estimation.

The mustard green datasets become (n = 5): thiamethoxam 038, 0.42, 0.42, 0.66, and 0.75 mg/kg; CGA 322704 0.07, 0.08, 0.16, 0.23 and 0.29 mg/kg.

Summary—Leafy vegetables

Residue data with suitable GAP were available for leaf lettuce, head lettuce, spinach and mustard greens. The Meeting noted that thiamethoxam residues were highest in leaf lettuce and that CGA 322704 residues were highest in spinach and decided to estimate leafy vegetables group maximum residue levels based on these two data sets.

On the basis of the foliar applications on leaf lettuces in 10 US trials, the Meeting estimated a maximum residue level of 3 mg/kg for thiamethoxam on leafy vegetables. The STMR and HR values were 0.54 and 1.9 mg/kg, respectively.

On the basis of the foliar applications on spinach in 10 US trials, the Meeting estimated a maximum residue level of 2 mg/kg for CGA 322704 on leafy vegetables. The STMR and HR values were 0.52 and 0.80 mg/kg, respectively.

Legume vegetables

Supervised trials data were available for beans and peas.

Beans

Supervised trials data for thiamethoxam seed treatment uses on beans were available from the USA.

In the USA, thiamethoxam is registered for use as an FS formulation on bean seed at 50 g ai per 100 kg seed, i.e., 0.5 g ai/kg seed.

In seven snap bean trials in the US with seeds treated at the label rate (0.5 g ai/kg seed) and in seven trials where seeds were treated at 3 × the label rate, residues of thiamethoxam and CGA 322704 did not exceed the LOQ (0.01 mg/kg) in the harvested snap beans (include succulent seeds and pods).

In six lima bean trials in the US with seeds treated at the label rate (0.5 g ai/kg seed) and in six trials where seeds were treated at 3 × the label rate, residues of thiamethoxam and CGA 322704 did not exceed the LOQ (0.01 mg/kg) in the harvested lima beans (include succulent seeds, pods are discarded).

Peas

Supervised trials data for thiamethoxam seed treatment uses on peas were available from the USA.

In the USA, thiamethoxam is registered for use as an FS formulation on pea seeds at 25 g ai per 100 kg seed, i.e., 0.25 g ai/kg seed.

In seven pea trials in the US with seeds treated at 2 × the label rate (0.5 g ai/kg seed) and in seven trials where seeds were treated at 6 × the label rate, residues of thiamethoxam and CGA 322704 did not exceed the LOQ (0.01 mg/kg) in the harvested succulent shelled peas (include succulent seeds, pods are discarded), except for two trials at 6 × where a thiamethoxam residue of 0.01 mg/kg was recorded.

In three pea trials in the US with seeds treated at the 2 × the label rate (0.5 g ai/kg seed) and in three trials where seeds were treated at 6 × the label rate, residues of thiamethoxam and CGA 322704 did not exceed the LOQ (0.01 mg/kg) in the harvested succulent edible pods (include succulent seeds and pods), except for one trial at 6 × where a thiamethoxam residue of 0.01 mg/kg was recorded.

Summary—Legume vegetables

Residue data with suitable GAP were available for snap beans, lima beans, succulent shelled peas and succulent seeds and pods. Residues were below LOQ. The Meeting decided to estimate legume vegetables group maximum residue levels.

On the basis of the seed treatment trials on peas and beans, the Meeting estimated a maximum residue level of 0.01(*) mg/kg for thiamethoxam on legume vegetables. On the basis of the CGA 322704 data from the same trials, the Meeting also estimated a maximum residue level of 0.01(*) mg/kg for CGA 322704 on legume vegetables.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.01 and 0.01 mg/kg for thiamethoxam residues in legume vegetables. The Meeting also estimated STMR and HR values of 0.01 and 0.01 mg/kg for CGA 322704 residues in legume vegetables.

Pulses

Supervised trials data were available for beans, peas and soya beans.

Beans, dry

Supervised trials data for thiamethoxam seed treatment uses on beans were available from the USA.

In the USA, thiamethoxam is registered for use as an FS formulation on bean seed at 50 g ai per 100 kg seed, i.e., 0.5 g ai/kg seed.

In nine bean trials in the US with seeds treated at the label rate (0.5 g ai/kg seed) and in nine trials where seeds were treated at 3 × the label rate, residues of thiamethoxam and CGA 322704 did not exceed the LOQ (0.01 mg/kg) in the harvested dry beans.

Peas, dry

Supervised trials data for thiamethoxam seed treatment uses on peas producing dry peas were available from the USA, Denmark, France and Germany.

In the USA, thiamethoxam is registered for use as an FS formulation on pea seed at 25 g ai per 100 kg seed, i.e., 0.25 g ai/kg seed.

In five pea trials in the US with seeds treated at 2 × the label rate (0.5 g ai/kg seed), residues of thiamethoxam and CGA 322704 did not exceed the LOQ (0.01 mg/kg) in the harvested dry peas. In five pea trials in the US with seeds treated at 6 × the label rate (1.4 g ai/kg seed), residues of thiamethoxam did not exceed the LOQ (0.01 mg/kg) in the harvested dry peas. CGA 322704 residues were: < 0.01 (3), 0.02 and 0.02 mg/kg.

In the Czech Republic, thiamethoxam is registered for use as an FS formulation on pea seed at 53 g ai per 100 kg seed (0.53 g ai/kg seed).

In 20 pea trials in Europe (Denmark—two, France—14 and Germany—four) with seeds treated with thiamethoxam at 0.5 g ai/kg seed (Czech Republic GAP), residues of thiamethoxam in the harvested dry peas at maturity were: < 0.02 (18), 0.02 and < 0.05 mg/kg. In the same 20 trials, residues of CGA 322704 were all below LOQ (0.02 (19) and < 0.05 mg/kg).

The Meeting recognized that residues of thiamethoxam and metabolite CGA 322704 from seed treatment uses were mostly below LOQ, but could sometimes occur in the dry peas.

Soya beans

Supervised trials data for thiamethoxam seed treatment uses on soya beans were available from the USA.

In the USA, thiamethoxam is registered for use as an FS formulation on soya bean seeds at 50 g ai per 100 kg seed, i.e., 0.5 g ai/kg seed.

In 15 soya bean trials in the US with seeds treated at the label rate (0.5 g ai/kg seed), residues of thiamethoxam and CGA 322704 did not exceed the LOQ (0.01 mg/kg) in the harvested soya bean dry seed.

Summary—Pulses

Residue data with suitable GAP were available for dry beans, dry peas and soya beans. Residues were almost all below LOQ. The Meeting decided to estimate pulse group maximum residue levels.

On the basis of the 20 seed treatment trials on peas in Europe, the Meeting estimated a maximum residue level of 0.04 mg/kg for thiamethoxam on pulses. On the basis of the CGA 322704 data from the same trials, the Meeting estimated a maximum residue level of 0.02 mg/kg for CGA 322704 on pulses.

The same data were used for STMR estimates. The Meeting estimated an STMR value of 0.02 mg/kg for thiamethoxam residues in pulses. The Meeting also estimated an STMR value of 0.02 mg/kg for CGA 322704 residues in pulses.

Root and tuber vegetables

Supervised trials data were available for carrots, potatoes, radishes and sugar beet.

Carrots

Supervised trials data for thiamethoxam uses on carrots were available from the USA.

In the USA, thiamethoxam may be used in foliar applications to root vegetables (includes carrot) at 0.070 kg ai/ha, with harvest permitted 7 days after an application. Thiamethoxam may also be used as a soil surface band with incorporation after sowing or in-furrow spray treatments with an application rate of 0.21 kg ai/ha for root vegetables.

In eight carrot trials in the USA matching the foliar GAP conditions, thiamethoxam residues in carrots did not exceed the LOQ (0.01 mg/kg). In the same eight trials, residues of CGA 322704 in carrots also in did not exceed the LOQ (0.01 mg/kg).

In six carrot trials in the USA matching the soil surface band GAP conditions, thiamethoxam residues in carrots in rank order were: < 0.01 (2), 0.01, 0.02, 0.02 and 0.04 mg/kg. In the same six trials, residues of CGA 322704 in carrots did not exceed the LOQ (0.01 mg/kg).

Potatoes

Supervised trials data for thiamethoxam uses on potatoes were available from France, Germany, Spain, Switzerland, the UK and the USA.

In Spain, foliar applications of thiamethoxam may be made to potatoes at 0.025 kg ai/ha, with harvest 7 days after an application. In Hungary, foliar applications of thiamethoxam may be made to potatoes at 0.020 kg ai/ha, with harvest 7 days after an application. These two use patterns are very similar and were used to evaluate the trials from France, Germany, Spain, Switzerland and the UK.

In 13 potato trials in Europe (France—four, Germany—two, Spain—four, Switzerland—two and the UK—one) with foliar application of thiamethoxam at 0.025 kg ai/ha and harvest of tubers 7 days later, residues of thiamethoxam and CGA 322704 did not exceed the LOQs (< 0.02 mg/kg) in any tuber sample.

In the USA, thiamethoxam is registered for foliar application to tuberous and corm vegetables (includes potato) at 0.053 kg ai/ha, with harvest permitted 14 days after an application. Also, potato seed pieces may be treated with thiamethoxam FS at 4.3–6.2 g ai per 100 kg seed.

In 14 potato trials in the USA with foliar application of thiamethoxam at approx 2 × the label rate (0.099 kg ai/ha) and harvest of tubers 14 days later, residues of thiamethoxam and CGA 322704 did not exceed the LOQs (< 0.01 mg/kg) in any tuber sample.

In 16 potato trials in the USA with potato seed pieces treated with thiamethoxam FS and DS at 8 g ai per 100 kg seed pieces, the residues of thiamethoxam in harvested mature tubers were: < 0.01 (11), 0.02, 0.05, 0.14, 0.18 and 0.20 mg/kg (NAFTA calculator: 0.242. OECD calculator Mean + 4SD: 0.308). In the same 16 trials, residues of CGA 322704 in the harvested tubers were: < 0.01

(12), 0.04, 0.04, 0.06 and 0.15 mg/kg (NAFTA calculator: 0.135. OECD calculator Mean+4SD: 0.172). Note that the nominal 8 g ai per 100 kg seed pieces in these trials is 30% higher than the label maximum rate 6.2 g ai per 100 kg seed. These data sets were selected for maximum residue level estimations on the root and tuber vegetables group.

Radish

Supervised trials data for thiamethoxam uses on radishes were available from the USA.

In the USA, thiamethoxam may be used in a single foliar application to radishes at 0.070 kg ai/ha, with harvest permitted 7 days after the application. Thiamethoxam may also be used as a soil surface band with incorporation after sowing with an application rate of 0.11 kg ai/ha for radishes.

In six radish trials in the USA matching the foliar GAP conditions, thiamethoxam residues in radish roots in rank order were: < 0.01 (4), 0.01 and 0.01 mg/kg. In the same six trials, residues of CGA 322704 in radish roots did not exceed the LOQ (0.01 mg/kg).

In six radish trials in the USA matching the foliar GAP conditions, thiamethoxam residues in radish tops in rank order were: 0.07, 0.10, 0.17, 0.18, 0.30 and 0.64 mg/kg. In the same six trials, residues of CGA 322704 in radish tops in rank order were: 0.02, 0.02, 0.03, 0.04, 0.05 and 0.13 mg/kg. The Meeting noted that both the thiamethoxam and CGA 322704 residue concentrations in radish tops fell within the maximum residue levels estimated for the leafy vegetables group.

In four radish trials in the USA matching the soil surface band application GAP conditions, thiamethoxam residues in radish roots in rank order were: < 0.01 (3) and 0.02 mg/kg. In the same four trials, residues of CGA 322704 in radish roots did not exceed the LOQ (0.01 mg/kg).

In four radish trials in the USA matching the soil surface band application GAP conditions, thiamethoxam residues in radish tops in rank order were: < 0.01, 0.09, 0.09 and 0.38 mg/kg. In the same four trials, residues of CGA 322704 in radish tops in rank order were: < 0.01 (2), 0.03 and 0.10 mg/kg.

Sugar beet

Supervised trials data for thiamethoxam uses on sugar beets were available from France, Germany, Italy, Netherlands, Spain, Switzerland and the UK. No suitable GAP information was available to evaluate the trials from Italy, Spain and Switzerland.

In the UK, thiamethoxam is registered for use as an FS formulation on sugar beet seeds at 60 g ai per 100,000 seeds.

In nine sugar beet trials in Europe (France—three, Germany—three, Netherlands—one, Sweden—one and the UK—one) matching UK seed treatment GAP conditions, thiamethoxam residues in harvested sugar beets did not exceed LOQ (0.02 mg/kg). In the same nine trials, residues of CGA 322704 in sugar beets also did not exceed LOQ (0.02 mg/kg).

Summary—Root and tuber vegetables

Residue data with suitable GAP were available for carrots, radishes, potatoes and sugar beets. Residues were highest in potatoes and the Meeting decided to estimate root and tuber vegetables group maximum residue levels based on the potatoes data.

On the basis of the potato seed piece treatment with thiamethoxam FS and DS in 16 US trials, the Meeting estimated a maximum residue level of 0.3 mg/kg for thiamethoxam on root and tuber vegetables. On the basis of the CGA 322704 data on potatoes from the same 16 trials, the Meeting estimated a maximum residue level of 0.2 mg/kg for CGA 322704 on root and tuber vegetables.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.01 and 0.20 mg/kg respectively for thiamethoxam residues in root and tuber

vegetables. The Meeting estimated STMR and HR values of 0.01 and 0.15 mg/kg respectively for CGA 322704 residues in root and tuber vegetables.

Stalk and stem vegetables

Supervised trials data were available for artichokes and celery.

Artichoke, Globe

Supervised trials data for thiamethoxam uses on globe artichokes were available from the USA.

In the USA, thiamethoxam WG may be used in foliar applications to globe artichokes at 0.053 kg ai/ha, with harvest permitted 4 days after an application.

In three globe artichoke trials in the USA matching foliar GAP conditions, thiamethoxam residues in globe artichokes in rank order were: 0.17, 0.23 and 0.24 mg/kg. In the same three trials, residues of CGA 322704 in globe artichokes in rank order were: 0.023, 0.024 and 0.029 mg/kg.

Globe artichoke is a minor crop and the Meeting agreed to evaluate the data. The Meeting estimated a maximum residue level of 0.5 mg/kg for thiamethoxam on globe artichokes. On the basis of the CGA 322704 data on globe artichokes from the same three trials, the Meeting estimated a maximum residue level of 0.05 mg/kg for CGA 322704 on globe artichokes.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.23 and 0.24 mg/kg respectively for thiamethoxam residues in globe artichokes. The Meeting estimated STMR and HR values of 0.024 and 0.029 mg/kg respectively for CGA 322704 residues in globe artichokes.

Celery

Supervised trials data for thiamethoxam uses on celery were available from the USA.

In the USA, thiamethoxam WG may be used in foliar applications on leafy vegetables (includes celery) at 0.096 kg ai/ha, with harvest permitted 7 days after an application. Thiamethoxam may also be used as a soil drench treatment at sowing or planting of leafy vegetables at 0.19 kg ai/ha. Trials with the drench treatment could not be evaluated because the trial rate did not match the GAP rate.

In six celery trials in the USA matching the foliar GAP conditions, thiamethoxam residues in celery in rank order were: 0.09, 0.10, 0.16, 0.25, 0.38 and 0.43 mg/kg (NAFTA calculator: 0.927. OECD calculator Mean + 4SD: 0.812). In the same six trials, residues of CGA 322704 in celery in rank order were: < 0.01 (4), 0.01 and 0.02 mg/kg.

On the basis of the foliar applications on celery in six US trials, the Meeting estimated a maximum residue level of 1 mg/kg for thiamethoxam on celery. On the basis of the CGA 322704 data on celery from the same six trials, the Meeting estimated a maximum residue level of 0.04 mg/kg for CGA 322704 on celery.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.21 and 0.43 mg/kg respectively for thiamethoxam residues in celery. The Meeting estimated STMR and HR values of 0.01 and 0.02 mg/kg respectively for CGA 322704 residues in celery.

Cereal grains

Supervised trials data were available for barley, maize, popcorn, rice and wheat.

Barley

Supervised trials data were available for barley from France, Germany, the UK and the USA.

In the Czech Republic and Romania, thiamethoxam is formulated as an FS seed treatment that may be used on barley at 53 g ai per 100 kg seed, i.e., 0.53 g ai/kg seed.

In 24 barley seed-treatment trials in Europe (France—19, Germany—two and the UK—three) with conditions (application rates 0.53–0.78 g ai/kg seed) approximately aligned with the GAP of the Czech Republic and Romania, thiamethoxam residues in barley grain from 23 trials did not exceed LOQ (0.02 mg/kg), while 0.02 mg/kg was recorded in grain from one trial. In the same 24 trials, residues of CGA 322704 in barley grain also did not exceed LOQ (0.02 mg/kg).

US GAP for barley allows the use of thiamethoxam WG for foliar applications at 0.070 kg ai/ha with a 21 days PHI.

In nine barley trials in the USA matching the foliar GAP conditions, thiamethoxam residues in barley in rank order were: < 0.01 (3), 0.01, 0.12, 0.14, 0.14, 0.15 and 0.21 mg/kg (NAFTA calculator: .0.325. OECD calculator Mean + 4SD: 0.403). In the same nine trials, residues of CGA 322704 in barley in rank order were: < 0.01 (7), 0.01 and 0.02 mg/kg. These data sets were selected for maximum residue level estimations.

On the basis of the foliar applications on barley in nine US trials, the Meeting estimated a maximum residue level of 0.4 mg/kg for thiamethoxam on barley. On the basis of the CGA 322704 data on barley from the same nine trials, the Meeting estimated a maximum residue level of 0.04 mg/kg for CGA 322704 on barley.

The same data were used for STMR estimates. The Meeting estimated an STMR value of 0.12 mg/kg for thiamethoxam residues in barley. The Meeting estimated an STMR value of 0.01 mg/kg for CGA 322704 residues in barley.

Maize

Supervised trials data for thiamethoxam seed treatment uses on maize were available from France, Germany, Spain and the USA.

In the Czech Republic and Romania, thiamethoxam is formulated as an FS seed treatment that may be used on maize at 315 g ai per 100 kg seed, i.e., 3.15 g ai/kg seed.

The European supervised trials on maize were evaluated with the seed treatment GAP of the Czech Republic and Romania.

In 24 maize seed-treatment trials in Europe (France—15, Germany—six, and Spain—three) with conditions aligned with the GAP of the Czech Republic and Romania, thiamethoxam residues in maize grain from 23 trials did not exceed LOQ (0.02 mg/kg), while 0.04 mg/kg was recorded in grain from one trial. In the same 24 trials, residues of CGA 322704 in maize grain also did not exceed LOQ (0.02 mg/kg).

In the USA, thiamethoxam is formulated as an FS seed treatment that may be used on maize at 1.25 mg ai per kernel. This is equivalent to approx 4.5 g ai/kg seed for a single kernel weight of 0.28 g.

In 21 maize trials in the USA matching the US seed treatment GAP conditions, thiamethoxam residues in maize grain did not exceed LOQ (0.01 mg/kg). In the same 21 trials, residues of CGA 322704 in maize grain also did not exceed LOQ (0.01 mg/kg). In two trials with a seed treatment rate of 13.5 g ai/kg seed (3 × the label rate), residues of thiamethoxam and CGA 322704 also did not exceed LOQ (0.01 mg/kg).

The maize metabolism studies showed that very low concentrations of thiamethoxam and metabolite CGA 322704 could occur in the maize grain from a seed treatment.

On the basis of the seed treatment uses on maize in 24 European trials, the Meeting estimated a maximum residue level of 0.05 mg/kg for thiamethoxam on maize. On the basis of the CGA 322704 data on maize from the same 24 trials, the Meeting estimated a maximum residue level of 0.02 mg/kg for CGA 322704 on maize.

The same data were used for STMR estimates. The Meeting estimated an STMR value of 0.02 mg/kg for thiamethoxam residues in maize. The Meeting also estimated an STMR value of 0.02 mg/kg for CGA 322704 residues in maize.

Popcorn

Supervised trials data for thiamethoxam use on popcorn were available from the USA.

In the USA, thiamethoxam is formulated as an FS seed treatment that may be used on popcorn at 1.25 mg ai per kernel. This is equivalent to approx 4.5 g ai/kg seed for a single kernel weight of 0.28 g.

In three popcorn trials in the USA where the seed had been treated with thiamethoxam FS at 4.5 g ai/kg seed, thiamethoxam residues and CGA 322704 residues in the harvested grain were all below LOQ (0.01 mg/kg).

The Meeting estimated a maximum residue level and an STMR value, both at 0.01 mg/kg for thiamethoxam in popcorn.

The Meeting estimated a maximum residue level and an STMR value, both at 0.01 mg/kg for CGA 322704 in popcorn.

Rice

Supervised trials data were available for rice from Brazil and Japan.

In Japan, thiamethoxam formulated as an SC may be applied to rice as foliar sprays at a concentration of 0.0065 kg ai/hL. A 14 days PHI is observed. Thiamethoxam GR may also be used as a seed-box treatment at 0.8 g ai per litre of soil.

In two reverse-decline rice trials in Japan with seed-box treatment and foliar application aligned with GAP, residues of thiamethoxam in hulled rice grain were: 0.064 and 0.092 mg/kg. It should be noted that higher residues occurred at 28 days PHI than at shorter intervals. In the same two trials, CGA 322704 residues in the hulled rice grain were: 0.068 and 0.088 mg/kg.

Brazil has a registered seed treatment use for thiamethoxam FS on rice at 100 g ai per 100 kg seed, i.e., 1 g ai/kg seed. Thiamethoxam as a WG formulation may also be used in foliar applications on rice at 0.0375 kg ai/ha with observation of a 21 days PHI.

In three rice trials in Brazil with application conditions, seed treatment 1.4 g ai/kg seed, and foliar application at 0.05 kg ai/ha (33% higher than label), thiamethoxam residues in rice grain were: < 0.02, < 0.02 and 0.03 mg/kg. In three other trials with application conditions, seed treatment 1.4 g ai/kg seed, and foliar application at 0.028 kg ai/ha (25% lower than label), thiamethoxam residues in rice grain were: 0.27, 0.22 and 0.32 mg/kg. The data are apparently inconsistent with residues from the 0.028 kg ai/ha application rate approximately 10 times as high as residues from the 0.05 kg ai/ha application rate.

Residues of CGA 322704 in the six trials (approximately label rate) from Brazil were < 0.02, < 0.02, < 0.02, 0.02, 0.07 and 0.08 mg/kg.

Six trials for rice are very minimal for a major crop and the Meeting decided not to estimate a maximum residue level.

Wheat

Supervised trials data were available for wheat from France, Germany, Switzerland and the UK.

In the Czech Republic and Romania, thiamethoxam is formulated as an FS seed treatment that may be used on wheat at 53 g ai per 100 kg seed, i.e., 0.53 g ai/kg seed.

In 34 wheat seed-treatment trials in Europe (France—31, Germany—two and the UK—one) with conditions (application rates 0.56–0.64 g ai/kg seed) approximately aligned with the GAP of the Czech Republic and Romania, thiamethoxam residues in wheat grain from 34 trials did not exceed

LOQ (0.02 mg/kg). In the same 34 trials, residues of CGA 322704 in wheat grain also did not exceed LOQ (0.02 mg/kg).

Hungarian GAP for wheat allows the use of thiamethoxam WG for foliar applications at 0.040 kg ai/ha with a 14 days PHI.

In 22 wheat trials in Europe (France—13, Germany—four, Switzerland—two and the UK—three) with conditions aligned with the GAP of Hungary (but application rate 0.050 kg ai/ha instead of 0.040 kg ai/ha and eight trials also included seed treatments), thiamethoxam residues in wheat grain from 22 trials were: < 0.02 (16), 0.02, 0.02, 0.02, 0.03, 0.03 and 0.04 mg/kg (NAFTA calculator: 0.037. OECD calculator Mean + 4SD: 0.042). In the same 22 trials, residues of CGA 322704 in wheat grain did not exceed LOQ (0.02 mg/kg). These data sets were selected for maximum residue level estimations.

On the basis of the foliar applications on wheat in 22 European trials, the Meeting estimated a maximum residue level of 0.05 mg/kg for thiamethoxam on wheat. On the basis of the CGA 322704 data on wheat from the same 22 trials, the Meeting estimated a maximum residue level of 0.02 mg/kg for CGA 322704 on wheat.

The same data were used for STMR estimates. The Meeting estimated STMR values of 0.02 and 0.02 mg/kg respectively for thiamethoxam residues and CGA 322704 residues in wheat.

Tree nuts

Pecans

Supervised trials data were available for pecans from the USA.

In the USA, a ZC (mixed formulation of CS capsule suspension and SC suspension concentrate) is registered for foliar application to pecans at 0.054 kg ai/ha. A 14 days PHI is to be observed.

Eight pecan trials were carried out at five sites in the USA. At three of the sites, application was made with a low-volume concentrated spray to simulate aerial application in one trial and as a high-volume dilute spray in the parallel trial. The remaining two sites had one trial each, one at high volume and the other at low volume. The trials included a second active ingredient, pymetrozine, as a tank mix.

In eight pecan trials at five sites in the USA with foliar application of a thiamethoxam WG formulation at 0.074 kg ai/ha and pecan harvest at 12 or 14 days after the second application, residues of thiamethoxam in pecan kernels did not exceed the LOQ (0.01 mg/kg). In the same eight trials, residues of CGA 322704 in pecan kernels also did not exceed the LOQ (0.01 mg/kg).

On the basis of the foliar applications on pecans in eight US trials, the Meeting estimated a maximum residue level of 0.01 mg/kg for thiamethoxam on pecans. On the basis of the CGA 322704 data on pecans from the same eight trials, the Meeting estimated a maximum residue level of 0.01 mg/kg for CGA 322704 on pecans.

The same data were used for STMR and HR estimates. The Meeting estimated STMR and HR values of 0.01 and 0.01 mg/kg for thiamethoxam residues in pecans. The Meeting also estimated STMR and HR values of 0.01 and 0.01 mg/kg for CGA 322704 residues in pecans.

Oilseed

Supervised trials data were available for cotton seed, oilseed rape and sunflower.

Cotton

Supervised trials data were available for cotton from Greece, Spain and the USA.

In the USA, a thiamethoxam FS formulation is registered for seed-treatment of cotton seed at 0.30–0.34 mg ai per seed. For a 100 mg cotton seed this would translate to 3.0–3.4 g ai/kg seed. Thiamethoxam is also registered for foliar use on cotton at 0.070 kg ai/ha, with observation of a 21 days PHI.

In the cotton trials from the US, the seed treatment rate was in accord with US GAP, but foliar application rates in the trials (0.032, 0.045, 0.05, 0.15 and 0.25 kg ai/ha) were not in accord with the GAP rate, 0.070 kg ai/ha, so it was not possible to evaluate the cotton trials data.

In Spain, a thiamethoxam WG formulation is registered for foliar applications to cotton at 0.050 kg ai/ha with a PHI of 28 days.

In 13 cotton trials in Europe (Greece—eight and Spain—five) matching the foliar GAP conditions of Spain, thiamethoxam residues in cotton seed did not exceed the LOQ (0.02 mg/kg). In the same 13 trials, residues of CGA 322704 in cotton seed also did not exceed the LOQ (0.02 mg/kg). Some of the trials had also included a thiamethoxam seed treatment at 1.9–2.7 g ai/kg seed, but it is expected that the foliar treatment would produce the higher residues; in this case residue levels did not exceed the LOQ from the combined uses. The residue data were reported for dehulled seed and cotton hulls separately. Residues of thiamethoxam and CGA 322704 in cotton hulls were also below LOQ (0.05 mg/kg) in all samples.

Oilseed rape

Supervised trials data were available for seed treatment uses on oilseed rape from France, Germany, Sweden and the UK.

In Germany and the UK, thiamethoxam FS formulations are registered for use as seed treatments on rapeseed at 420 g ai per 100 kg seed.

In 14 trials in France, nine in Germany, one in Sweden and five in the UK where rapeseed was treated with thiamethoxam in WS or FS formulations, then sown and the crop grown to maturity, residues of thiamethoxam in rapeseed were all below LOQ (0.02 mg/kg). Residues of metabolite CGA 322704 in rapeseed were also all below LOQ (0.02 mg/kg) in the same trials.

Sunflowers

Supervised trials data were available for sunflowers from the USA.

In the USA, a thiamethoxam FS formulation is registered for seed-treatment of sunflower seeds at 0.25 mg ai per seed. For a 60–70 mg sunflower seed this would translate to 3.6–4.2 g ai/kg seed.

In eight sunflower trials in the USA matching the GAP conditions, thiamethoxam residues in sunflower seeds did not exceed the LOQ (0.01 mg/kg). In the same eight trials, residues of CGA 322704 in sunflower seeds also did not exceed the LOQ (0.01 mg/kg).

Residues of thiamethoxam and CGA 322704 also did not exceed LOQ (0.01 mg/kg) in two trials where seed treatment rates were 12.2 and 11.3 g ai/kg seed (3 × the label rate), suggesting a nil residue situation.

Summary—Oilseeds

Residue data with suitable GAP were available for sunflowers, cotton and oilseed rape. The Meeting noted that thiamethoxam and CGA 322704 residues were mostly below LOQ, but were highest in cotton seed and decided to estimate oilseed group maximum residue levels based on the cotton seed data set.

On the basis of the foliar applications on cotton in 13 European trials, the Meeting estimated a maximum residue level of 0.02 mg/kg for thiamethoxam on oilseed. On the basis of the

CGA 322704 data on cotton seed from the same 13 trials, the Meeting estimated a maximum residue level of 0.02 mg/kg for CGA 322704 on oilseed.

The same data were used for STMR estimates. The Meeting estimated STMR values of 0.02 and 0.02 mg/kg respectively for thiamethoxam residues and CGA 322704 residues in oilseed.

Seed for beverages and sweets

Cacao

Supervised trials data were available for foliar application of thiamethoxam in the production of cacao beans in Côte d'Ivoire.

In Cameroon, thiamethoxam WG is registered for foliar application to cacao at 0.025 kg ai/ha. A PHI of 30 days is to be observed.

In four cacao trials in Côte d'Ivoire matching the GAP conditions of Cameroon, thiamethoxam residues in fermented dried cacao beans did not exceed the LOQ (0.02 mg/kg). In the same four trials, residues of CGA 322704 in dried cacao beans also did not exceed the LOQ (0.02 mg/kg).

On the basis of the foliar applications on cacao in four Côte d'Ivoire trials, the Meeting estimated a maximum residue level of 0.02 mg/kg for thiamethoxam on dried cacao beans. On the basis of the CGA 322704 data from the same four trials, the Meeting estimated a maximum residue level of 0.02 mg/kg for CGA 322704 on dried cacao beans.

The same data were used for STMR estimates. The Meeting estimated STMR values of 0.02 and 0.02 mg/kg respectively for thiamethoxam residues and CGA 322704 residues in dried cacao beans.

Coffee

Supervised trials data were available for thiamethoxam uses in the production of coffee beans in Brazil.

In Brazil, thiamethoxam may be used in soil treatments in the production of coffee—GR granules applied to the soil at 0.30 kg ai/ha, max annual dose 0.60 kg ai/ha; PHI 90days;WG drench on soil under coffee tree at 0.50 kg ai/ha, PHI 90 days.

In six coffee trials in Brazil matching the GAP conditions of GR treatment of the soil, thiamethoxam residues in coffee beans in rank order were: 0.02, 0.02, 0.02, 0.02, 0.03 and 0.04 mg/kg. In the same six trials, residues of CGA 322704 in coffee beans in rank order were: < 0.01 (4), 0.02 and 0.02 mg/kg.

In six coffee trials in Brazil matching the GAP conditions of WG drench treatment of the soil, thiamethoxam residues in coffee beans in rank order were: 0.02, 0.03, 0.03, 0.04, 0.04 and 0.06 mg/kg (NAFTA calculator: 0.082. OECD calculator 3×Mean: 0.110). In the same six trials, residues of CGA 322704 in coffee beans in rank order were: < 0.01 (3), 0.02, 0.02 and 0.03 mg/kg (NAFTA calculator: 0.046. OECD calculator Mean + 4SD: 0.049). These data sets were selected for maximum residue level estimations.

The Meeting noted that the trials with granular soil treatments produced residues of the same order as those from the drench treatment and provided support for the six soil drench trials.

On the basis of the six Brazilian trials with soil drench treatments, the Meeting estimated a maximum residue level of 0.2 mg/kg for thiamethoxam on coffee beans. On the basis of the CGA 322704 data on coffee beans from the same six trials, the Meeting estimated a maximum residue level of 0.05 mg/kg for CGA 322704 on coffee beans.

The same data were used for STMR estimates. The Meeting estimated STMR values of 0.035 and 0.015 mg/kg respectively for thiamethoxam residues and CGA 322704 residues in coffee beans.

Legume animal feeds

Pea fodder

Supervised trials data for thiamethoxam seed treatment uses on peas producing dry peas were available from the USA, Denmark, France and Germany. Residue data on pea vines and fodder were also provided.

In the Czech Republic, thiamethoxam is registered for use as an FS formulation for pea seed treatment at 53 g ai per 100 kg seed (0.53 g ai/kg seed).

In 12 pea trials in Europe (Denmark—two, France—six and Germany—four) with seeds treated with thiamethoxam at 0.5 g ai/kg seed (Czech Republic GAP), residues of thiamethoxam in the harvested haulm at maturity, i.e., the pea fodder, in rank order were: 0.02 < 0.04, < 0.05 (6), 0.06, 0.11, 0.18 and 0.21 mg/kg. In the same 12 trials, residues of CGA 322704 in the pea fodder were: 0.02, < 0.04 (2), < 0.05 (6), < 0.1 (2) and 0.09 mg/kg.

On a dry-weight basis (DM = 88%), thiamethoxam residues in pea fodder were (n = 12): 0.02, < 0.04, < 0.05 (6), 0.07, 0.13, 0.20 and 0.24 mg/kg (NAFTA calculator: 0.291. OECD calculator Mean + 4SD: 0.361). Residues of CGA 322704 in the pea fodder, dry weight, were (n = 12): 0.02, < 0.04 (2), < 0.05 (6), < 0.1 (2) and 0.10 mg/kg (NAFTA calculator: 0.139).

The Meeting estimated a maximum residue level of 0.3 mg/kg for thiamethoxam on pea fodder. On the basis of the CGA 322704 data from the same 12 trials, the Meeting estimated a maximum residue level of 0.2 mg/kg for CGA 322704 on pea fodder.

The same data were used for STMR and highest residue estimates. The Meeting estimated STMR and highest residue values of 0.05 and 0.24 mg/kg respectively for thiamethoxam residues in pea fodder. The Meeting estimated STMR and highest residue values of 0.05 and 0.10 mg/kg respectively for CGA 322704 residues in pea fodder.

In 11 of the same pea trials in Europe, residue data were available on whole plant (pea vines) sampled approximately 50–70 days after sowing. Residues of thiamethoxam in the pea whole plant, in rank order were: < 0.05(4), 0.02, 0.04, 0.05, 0.05, 0.07, 0.07 and 0.10 mg/kg. In the same 11 trials, residues of CGA 322704 in the pea whole plant were: < 0.04 (4) and < 0.05 (7) mg/kg.

The Meeting estimated STMR and highest residue values of 0.04 and 0.10 mg/kg respectively for thiamethoxam residues in pea vines. The Meeting estimated STMR and highest residue values of 0.05 and 0.05 mg/kg respectively for CGA 322704 residues in pea vines.

Straw, fodder and forage of cereal grains

Maize forage and fodder

Supervised trials data for thiamethoxam seed treatment uses on maize were available from France, Germany, Spain and the USA.

In the Czech Republic and Romania, thiamethoxam is formulated as an FS seed treatment that may be used on maize at 315 g ai per 100 kg seed, i.e., 3.15 g ai/kg seed. The supervised trials on maize from Europe were evaluated with the seed treatment GAP of the Czech Republic and Romania.

In 22 maize seed-treatment trials in Europe (France—15, Germany—six and Spain—one) with conditions aligned with the GAP of the Czech Republic and Romania, thiamethoxam residues in maize fodder from all trials did not exceed LOQ (0.02 (7), 0.04 (8) and 0.05 mg/kg (7)). In the same 22 trials, residues of CGA 322704 in maize fodder also did not exceed LOQ (same LOQs).

In 10 of these trials (France—five and Germany—five), residues were measured on the whole plant at an earlier stage, i.e., maize forage. Thiamethoxam residues in maize forage in these 10 trials did not exceed LOQ (0.02 (5), 0.04 (2) and 0.05 mg/kg (3)). In the same 10 trials, residues of CGA 322704 in maize forage also did not exceed LOQ (same LOQs).

In the USA, thiamethoxam is formulated as an FS seed treatment that may be used on maize or sweet corn at 1.25 mg ai per kernel. This is equivalent to approx 4.5 g ai/kg seed for a single kernel weight of 0.28 g.

In 35 maize and sweet corn trials in the USA matching the US seed treatment GAP conditions, thiamethoxam residues in maize stover (maize fodder) were: < 0.01 (31), 0.01, 0.01, 0.02 and 0.03 mg/kg. In the same 35 trials, residues of CGA 322704 in maize fodder did not exceed LOQ (0.01 mg/kg). On a dry-weight basis (DM = 83%), thiamethoxam residues in maize fodder were (n = 35): < 0.01 (31), 0.01, 0.01, 0.02 and 0.04 mg/kg. These data sets were selected for maximum residue level estimations.

In 33 maize and sweet corn trials in the USA matching the US seed treatment GAP conditions, thiamethoxam residues in maize forage were: < 0.01 (17), 0.01, 0.01, 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, 0.02, 0.02, 0.04, 0.04, 0.04, 0.04, 0.04 and 0.05 mg/kg. In the same 33 trials, residues of CGA 322704 in maize forage were: < 0.01 (30), 0.01, 0.01 and 0.02 mg/kg. The Meeting estimated STMR and highest residue values of 0.01 and 0.05 mg/kg for thiamethoxam in maize forage. The Meeting also estimated STMR and highest residue values of 0.01 and 0.02 respectively for CGA 322704 in maize forage.

On the basis of the seed treatment uses on maize and sweet corn in 35 US trials, the Meeting estimated a maximum residue level of 0.05 mg/kg for thiamethoxam on maize fodder. On the basis of the CGA 322704 data on maize fodder from the same 35 trials, the Meeting estimated a maximum residue level of 0.01 mg/kg for CGA 322704 on maize fodder.

The same data were used for STMR and highest residue estimates. The Meeting estimated STMR and highest residue values of 0.01 and 0.04 mg/kg respectively for thiamethoxam residues in maize fodder. The Meeting estimated STMR and highest residue values of 0.01 and 0.01 mg/kg for CGA 322704 residues in maize fodder.

Barley straw and fodder

Supervised trials data were available for barley from France, Germany, the UK and the USA.

US GAP for barley allows the use of thiamethoxam WG for foliar applications at 0.070 kg ai/ha with a 21 days PHI.

In eight barley trials in the USA matching the foliar GAP conditions, thiamethoxam residues in barley straw in rank order were: < 0.01 (2), 0.03, 0.03, 0.19, 0.26, 0.27 and 0.33 mg/kg. In the same eight trials, residues of CGA 322704 in barley straw in rank order were: < 0.01 (3), 0.01, 0.02, 0.03, 0.03 and 0.03 mg/kg.

In the same eight barley trials in the USA matching the foliar GAP conditions, thiamethoxam residues in barley hay in rank order were: < 0.01 (2), 0.02, 0.02, 0.20, 0.21, 0.25 and 0.27 mg/kg. In the same eight trials, residues of CGA 322704 in barley hay in rank order were: < 0.01 (3), 0.01, 0.02, 0.02, 0.02 and 0.03 mg/kg.

In the Czech Republic and Romania, thiamethoxam is formulated as an FS seed treatment that may be used on barley at 53 g ai per 100 kg seed, i.e., 0.53 g ai/kg seed.

In 24 barley seed treatment trials in Europe (France—19, Germany—two and the UK—three) with conditions (application rates 0.53–0.78 g ai/kg seed) approximately aligned with the GAP of the Czech Republic and Romania, thiamethoxam residues in barley straw from the 24 trials did not exceed LOQ (0.02–0.05 mg/kg). In the same 24 trials, residues of CGA 322704 in barley straw also did not exceed LOQ (0.02–0.05 mg/kg) in 23 of the trials with a CGA 322704 residue of 0.04 mg/kg recorded in one barley straw.

In 10 of the same barley seed-treatment trials in Europe (France—nine and Germany—one), residues were measured on barley whole plant. Thiamethoxam residues in barley whole plant were: < 0.02, < 0.04 (5), < 0.05, 0.05, 0.05 and 0.11 mg/kg. In the same 10 trials, residues of CGA 322704 in barley whole plant did not exceed LOQ (0.02–0.05 mg/kg).

The Meeting estimated STMR and highest residue values of 0.04 and 0.11 mg/kg respectively for thiamethoxam residues in barley whole plant. The Meeting estimated STMR and highest residue values of 0.04 and 0.05 mg/kg respectively for CGA 322704 residues in barley whole plant.

Wheat straw and fodder

Supervised trials data, including data on wheat straw and fodder, were available for wheat from France, Germany, Switzerland and the UK.

In the Czech Republic and Romania, thiamethoxam is formulated as an FS seed treatment that may be used on wheat at 53 g ai per 100 kg seed, i.e., 0.53 g ai/kg seed.

In 34 wheat seed-treatment trials in Europe (France—31, Germany—two and the UK—one) with conditions (application rates 0.56–0.64 g ai/kg seed) approximately aligned with the GAP of the Czech Republic and Romania, thiamethoxam residues in wheat straw from 34 trials did not exceed LOQ (0.04–0.05 mg/kg). In the same 34 trials, residues of CGA 322704 in wheat straw also did not exceed LOQ (0.04–0.05 mg/kg), except for one trial: CGA 322704 residue = 0.05 mg/kg.

In 12 of the same wheat seed-treatment trials in Europe (France—11 and Germany—one), residues were measured on wheat whole plant. Thiamethoxam residues in wheat whole plant were: < 0.02 (4), < 0.04 (5), 0.02, 0.02 and 0.05 mg/kg. In the same 10 trials, residues of CGA 322704 in wheat were: < 0.02 (3), < 0.04 (5), < 0.05, 0.02, 0.02 and 0.02 mg/kg.

Hungarian GAP for wheat allows the use of thiamethoxam WG for foliar applications at 0.040 kg ai/ha with a 14 days PHI.

In 21 wheat trials in Europe (France—14, Germany—two, Switzerland—two and the UK—three) with conditions aligned with the GAP of Hungary (but application rate 0.050 kg ai/ha instead of 0.040 kg ai/ha and six trials also included a seed treatment), thiamethoxam residues in wheat straw from 21 trials were: < 0.04, 0.05, 0.14, 0.15, 0.17, 0.22, 0.25, 0.28, 0.32, 0.33, 0.34, 0.35, 0.37, 0.42, 0.44, 0.51, 0.51, 0.65, 0.80, 1.4 and 1.5 mg/kg. In the same 21 trials, residues of CGA 322704 in wheat straw were: < 0.04 (8), < 0.05 (5), 0.03, 0.04, 0.06, 0.07, 0.08, 0.10, 0.10 and 0.12 mg/kg.

On a dry-weight basis (DM = 88%), thiamethoxam residues in wheat straw were (n = 21): < 0.04, 0.06, 0.16, 0.17, 0.19, 0.25, 0.28, 0.32, 0.36, 0.38, 0.39, 0.40, 0.42, 0.48, 0.50, 0.58, 0.58, 0.74, 0.91, 1.6 and 1.7 mg/kg. On a dry-weight basis (DM=88%), CGA 322704 residues in wheat straw were (n = 21): < 0.04 (8), < 0.05 (5), 0.03, 0.05, 0.07, 0.08, 0.09, 0.11, 0.11 and 0.14 mg/kg. These datasets were used for MRL estimation.

In 12 of these same wheat trials in Europe (France—10 and Germany—two) with conditions aligned with the GAP of Hungary (but application rate 0.050 kg ai/ha instead of 0.040 kg ai/ha and six trials also included a seed treatment), thiamethoxam residues were measured on wheat whole plants or equivalent: < 0.04, 0.28, 0.38, 0.41, 0.50, 0.51, 0.55, 0.58, 0.61, 0.63, 0.66 and 0.73 mg/kg. In the same 12 trials, residues of CGA 322704 in wheat whole plants were: < 0.04 (5), < 0.05 (3), 0.04, 0.05, 0.05 and 0.06 mg/kg.

The Meeting estimated STMR and highest residue values of 0.53 and 0.73 mg/kg respectively for thiamethoxam residues in wheat whole plants. The Meeting estimated STMR and highest residue values of 0.05 and 0.06 mg/kg respectively for CGA 322704 residues in wheat whole plant.

Rice straw

Data were available for rice straw from two supervised trials, but this was insufficient for an evaluation.

Summary of 'Barley straw and fodder' and 'Wheat straw and fodder'

Barley straw and fodder, and wheat straw and fodder, as commodities of trade, may not always be readily distinguishable from each other. It is therefore preferable for the two commodities to have the same MRLs.

Thiamethoxam residues in wheat straw from 21 trials were: < 0.04, 0.05, 0.14, 0.15, 0.17, 0.22, 0.25, 0.28, 0.32, 0.33, 0.34, 0.35, 0.37, 0.42, 0.44, 0.51, 0.51, 0.65, 0.80, 1.4 and 1.5 mg/kg. Thiamethoxam residues in barley straw from eight trials were: < 0.01 (2), 0.03, 0.03, 0.19, 0.26, 0.27 and 0.33 mg/kg.

Residues of CGA 322704 in wheat straw were: < 0.04 (8), < 0.05 (5), 0.03, 0.04, 0.06, 0.07, 0.08, 0.10, 0.10 and 0.12 mg/kg. Residues of CGA 322704 in barley straw were: < 0.01 (3), 0.01, 0.02, 0.03, 0.03 and 0.03 mg/kg.

In this case, residues in wheat straw were higher than in the barley straw. The Meeting agreed to use the wheat straw data for both the barley straw and fodder MRL, and the wheat straw and fodder MRL.

On a dry-weight basis (DM = 88%), thiamethoxam residues in wheat straw were (n = 21): < 0.04, 0.06, 0.16, 0.17, 0.19, 0.25, 0.28, 0.32, 0.36, 0.38, 0.39, 0.40, 0.42, 0.48, 0.50, 0.58, 0.58, 0.74, 0.91, 1.6 and 1.7 mg/kg (NAFTA calculator: 2.974. OECD calculator Mean + 4SD: 2.246). On a dry-weight basis (DM = 88%), CGA 322704 residues in wheat straw were (n = 21): < 0.04 (8), < 0.05 (5), 0.03, 0.05, 0.07, 0.08, 0.09, 0.11, 0.11 and 0.14 mg/kg (NAFTA calculator: 0.149. OECD calculator Mean + 4SD: 0.178).

On the basis of the foliar applications on wheat in 21 European trials, the Meeting estimated a maximum residue level of 2 mg/kg for thiamethoxam on wheat straw and fodder, dry. On the basis of the CGA 322704 data on wheat straw from the same 21 trials, the Meeting estimated a maximum residue level of 0.2 mg/kg for CGA 322704 on wheat straw and fodder, dry.

The same data were used for STMR and highest residue estimates. The Meeting estimated STMR and highest residue values of 0.39 and 1.7 mg/kg respectively for thiamethoxam residues in wheat straw and fodder, dry. The Meeting estimated STMR and highest residue values of 0.05 and 0.14 mg/kg respectively for CGA 322704 residues in wheat straw and fodder, dry.

On the basis of these same wheat data, the Meeting estimated a maximum residue level of 2 mg/kg for thiamethoxam on barley straw and fodder, dry, and a maximum residue level of 0.2 mg/kg for CGA 322704 on barley straw and fodder, dry. The Meeting also estimated STMR and highest residue values of 0.39 and 1.7 mg/kg respectively for thiamethoxam residues in barley straw and fodder, dry, and STMR and highest residue values of 0.05 and 0.14 mg/kg respectively for CGA 322704 residues in barley straw and fodder, dry.

Miscellaneous fodder and forage crops

Sugar beet leaves and tops

Supervised trials data for thiamethoxam uses on sugar beets, including data on leaves and tops, were available from France, Germany, Netherlands, Spain, Switzerland and the UK. No suitable GAP information was available to evaluate the trials from Italy, Spain and Switzerland.

In the UK, thiamethoxam is registered for use as an FS formulation on sugar beet seeds at 60 g ai per 100,000 seeds.

In 10 sugar beet trials in Europe (France—three, Germany—three, Netherlands—one, Spain—one, Sweden—one and the UK—one) matching UK seed treatment GAP conditions (application rate 60 ± 15 g ai per 100,000 seeds), thiamethoxam residues in sugar beet tops or leaves did not exceed LOQ (0.02 mg/kg). CGA 322704 residues in sugar beet tops or leaves also did not exceed LOQ (0.02 mg/kg).

The data were used for STMR and highest residue estimates. The Meeting estimated STMR and highest residue values of 0.02 and 0.02 mg/kg for thiamethoxam residues in sugar beet tops or leaves. The Meeting estimated STMR and highest residue values of 0.02 and 0.02 mg/kg also for CGA 322704 residues in sugar beet tops or leaves.

Rape seed forage and fodder

Supervised trials data were available for seed treatment uses on oilseed rape from France, Germany, Sweden and the UK.

In Germany and the UK, thiamethoxam FS formulations are registered for use as seed treatments on rapeseed at 420 g ai per 100 kg seed.

In four trials in France, seven in Germany, one in Sweden and two in the UK where rapeseed was treated with thiamethoxam at the GAP rate, then sown and the forage sampled 1–7 months later, residues of thiamethoxam in rapeseed plant were all below LOQ (0.05 mg/kg). Residues of metabolite CGA 322704 in rapeseed plant were also all below LOQ (0.05 mg/kg) in the same trials.

In seven trials in Germany and one in Sweden where rapeseed was treated with thiamethoxam at the GAP rate, then sown and the crop grown to maturity, residues of thiamethoxam in rapeseed straw were all below LOQ (0.05 mg/kg). Residues of metabolite CGA 322704 in rapeseed straw were also all below LOQ (0.05 mg/kg) in the same trials.

The data were used for STMR and highest residue estimates. The Meeting estimated STMR and highest residue values of 0.05 and 0.05 mg/kg for thiamethoxam residues in rapeseed forage. The Meeting estimated STMR and highest residue values of 0.05 and 0.05 mg/kg also for CGA 322704 residues in rapeseed forage.

Cotton gin by-products

Supervised trials data were available for seed treatment and foliar uses on cotton from the USA.

In the USA, a thiamethoxam FS formulation is registered for seed-treatment of cotton seed at 0.30–0.34 mg ai per seed. For 100 mg cotton seed this would translate to 3.0–3.4 g ai/kg seed. Thiamethoxam is also registered for foliar use on cotton at 0.070 kg ai/ha, with a 21 day PHI.

In the cotton trials from the US, the seed treatment rate was in accord with US GAP, but foliar application rates in the trials (0.032, 0.045, 0.05, 0.15 and 0.25 kg ai/ha) were not in accord with the GAP rate, 0.070 kg ai/ha, so it was not possible to evaluate the cotton trials residue data on gin trash.

Dried herbs

Hops

Supervised trials data for thiamethoxam use on hops were available from the USA.

Thiamethoxam may be used in the USA as a soil surface band application with incorporation during the production of hops. The application rate is 0.14 kg ai/ha and the PHI is 65 days.

In three hops trials in the USA matching the GAP conditions, thiamethoxam residues in hops dry cones in rank order were: < 0.025, 0.027 and 0.055 mg/kg. In the same three trials, residues of CGA 322704 in hops dry cones in rank order were: < 0.025, 0.025 and 0.028 mg/kg.

The Meeting agreed that three trials are insufficient for maximum residue level estimation on hops.

Teas

Supervised trials data for thiamethoxam use on tea were available from Japan.

In Japan, thiamethoxam SG (soluble granule) formulation is registered for foliar application during the production of tea. The spray concentration is 0.005 kg ai/hL and the PHI is 7 days.

Immediately after harvest in the tea trials in Japan, the leaves were processed with an in-house tea processing machine and then enclosed in aluminium bags for delivery to the laboratory. The processing consisted of drying, breaking the leaves to expose enzymes and tissues to oxidation and allowing a period of oxidation by exposure in the air.

In six tea trials in Japan matching the GAP conditions, thiamethoxam residues in crude processed tea leaves in rank order were: 2.1, 2.3, 2.7, 5.5, 7.1 and 8.6 mg/kg (NAFTA calculator: 16.92. OECD calculator Mean + 4SD: 15.76). In the same six trials, residues of CGA 322704 in crude processed tea leaves in rank order were: 0.06, 0.08, 0.08, 0.16, 0.25 and 0.28 mg/kg (NAFTA calculator: 0.581. OECD calculator Mean + 4SD: 0.531).

The Meeting estimated a maximum residue level of 20 mg/kg for thiamethoxam on tea, green and black. On the basis of the CGA 322704 data on tea from the same six trials, the Meeting estimated a maximum residue level of 0.7 mg/kg for CGA 322704 on tea, green and black.

The same data were used for STMR estimates. The Meeting estimated an STMR value of 4.1 mg/kg for thiamethoxam residues in tea. The Meeting estimated an STMR value of 0.12 mg/kg for CGA 322704 residues in tea.

Fate of residues during processing

The Meeting received information on the fate of thiamethoxam residues during the processing of apples to juice and pomace; barley to pearled barley, barley bran, barley flour, beer, wort and malt; coffee beans to roasted coffee; cotton seed to meal and refined oil; grapes to juice, pomace and wine; maize to grits, flour, oil and starch; oranges to pulp, juice and oil; plums to dried prunes; potato to wet peelings, flakes and chips; tomatoes to juice, pulp, puree and paste; and wheat to semolina, bran, flour and bread.

Also information was provided on hydrolysis studies of thiamethoxam to assist with identification of the nature of the residue during processing.

Thiamethoxam was essentially stable during the hydrolysis conditions simulating food processing conditions.

Processing factors have been calculated for thiamethoxam residues during the following processes: apples processing to juice and wet pomace; barley processing to pearled barley, bran, flour, and beer; coffee beans to roasted coffee; cotton seed to meal and oil; grapes to pomace and wine; oranges to pulp and juice; plums to dried prunes; tomatoes to juice, paste and puree; and wheat to semolina, wheat bran, wheat bread and wheat flour. Processing factors were also calculated for CGA 322704 residues in the following processes: apples to apple juice and wet pomace; coffee beans to roasted coffee; plums to dried prunes; and tomatoes to paste and puree.

Calculated processing factors are summarised in the following table. Factors are indicated with a '<' (less-than) sign when the residue in the processed commodity is below the LOQ of the analytical method. The calculation is then made on the LOQ of the analytical method and the residue concentration of the RAC (raw agricultural commodity). The medians of the observed values or the best estimates of the processing factors are summarized in the final column of the table.

Only those processes are included in the table that lead to STMR-P or HR-P values useful for dietary intake estimations or for livestock dietary burden calculations.

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors.	Median or best estimate
THIAMETHOXAM			
Apple	apple juice	0.20, 0.27, 0.38, 0.92, 0.94, 1.00, < 1.00, 1.04	0.93
Apple	wet pomace	1.08, 1.38, 1.41, 1.50, 1.60, 1.67, 1.91, 2.00	1.55
Barley	barley flour	0.08	0.08
Barley	pearled barley	0.25	0.25
Coffee beans	roasted coffee	< 0.14, < 0.14, < 0.17, < 0.20, < 0.20, < 0.20, < 0.25, < 0.25, < 0.25, < 0.33, < 0.33, < 0.50	< 0.14
Cotton seed	cotton seed meal	0.15, 0.20, 0.27, < 0.3, 0.49	0.27
Cotton seed	cotton seed oil refined	< 0.02, < 0.08, < 0.09, < 0.20, < 0.33	< 0.02
Grapes	dry pomace	3.4, 4.4	3.9
Grapes	wet pomace	1.3, 1.5, 4.3	1.5
Grapes	wine	0.70, 0.73, 0.79, 1.00 , 1.05, 1.33, 1.60, 1.60,	1.0
Orange	dried pulp	2.0, 3.25	2.6
Orange	orange juice	< 0.25, < 0.5	< 0.25
Plum	dried prunes	0.60, 0.83, < 1.0	0.83
Tomato	tomato juice	0.67, 1.0	0.67
Tomato	tomato paste	1.25, 2.00, 2.24, 2.40, 2.94, 2.94, 3.10, 3.86, 3.91, 4.21, 4.33, 6.00	3.0
Tomato	tomato pulp	1.0, 1.0	1.0
Tomato	tomato puree	0.40, 0.50, 0.64, 0.91, 1.06, 1.12, 1.13, 1.50, 1.87, 2.00, 2.21, 2.50	1.1
Wheat	semolina	< 0.7	< 0.7
Wheat	wheat bran	1	1
Wheat	wheat bread	< 0.7	< 0.7
Wheat	wheat flour	< 0.7	< 0.7
CGA 322704			
Apple	apple juice	1.0, 1.0, 1.0	1.0
Apple	wet pomace	1.4, 1,5, 1.5	1.5
Coffee beans	roasted coffee	< 0.33, < 0.33, < 0.33, < 0.33, < 0.33, < 0.50, < 0.50, < 0.50, < 0.50, < 0.50	< 0.3
Plum	dried prunes	1.5, 2.0	1.75
Tomato	tomato paste	2.00, 2.38, 3.33, 3.75, 5.50, 5.78, 6.0, 6.0, 6.5, 6.5, 9.7, 11.3	5.9
Tomato	tomato puree	0.50, 0.67, 1.0, 1.19, 1.33, 1.75, 2.50, 2.75, 3.0, 3.44, 3.54, 6.0,	2.1

Thiamethoxam residues in tea were investigated for percentage infusion and, by inference, percentage consumption.

Tea infusions were prepared by adding boiling water to dried and processed tea leaves from a thiamethoxam supervised residue trial and allowed to stand for 5 minutes. The infusion was filtered and analysed and the % infusion (% of residue extracted into the boiling water) was calculated. For thiamethoxam, the average % infusion was 97%, range 68–130%, n = 12. For CGA 322704, average % infusion was 94%, range 80–100%, n = 10.

The processing factors for thiamethoxam residues for oranges → orange juice (0.25) and oranges → orange dry pulp (2.6) were applied to the citrus fruits STMR, 0.028 mg/kg, to produce an orange juice STMR-P of 0.007 mg/kg and an orange dry pulp STMR-P of 0.073 mg/kg.

The processing factors for thiamethoxam residues for apples → apple juice (0.93) and apples → apple pomace (1.55) were applied to the pome fruit STMR, 0.07 mg/kg, to produce an apple juice STMR-P of 0.065 mg/kg and an apple wet pomace STMR-P of 0.11 mg/kg.

The processing factor for thiamethoxam residues for plums → dried prunes (0.83) was applied to the stone fruits STMR and HR, 0.195 and 0.6 mg/kg, to produce a dried prunes STMR-P of 0.16 mg/kg and an HR-P of 0.50 mg/kg.

The processing factors for thiamethoxam residues for grapes → wine (1) and grapes → dry grape pomace (3.9) were applied to the berry fruits STMR, 0.055 mg/kg, to produce a wine STMR-P of 0.055 mg/kg and a dry grape pomace STMR-P of 0.21 mg/kg.

The processing factors for thiamethoxam residues for tomato → tomato juice (0.67), tomato → tomato paste (3), tomato → tomato pulp (1) and tomato → tomato puree (1.1) were applied to the fruiting vegetables STMR, 0.08 mg/kg, to produce a tomato juice STMR-P of 0.054 mg/kg, a tomato paste STMR-P of 0.24 mg/kg, a tomato pulp STMR-P of 0.08 mg/kg and a tomato puree STMR-P of 0.088 mg/kg.

The processing factors for thiamethoxam residues for barley → barley flour (0.08) and barley → pearled barley (0.25) were applied to the barley STMR, 0.12 mg/kg, to produce a barley flour STMR-P of 0.010 mg/kg and a pearled barley STMR-P of 0.030 mg/kg.

The processing factors for thiamethoxam residues for wheat → semolina (0.7), wheat → wheat bran (1), wheat → wheat bread (0.7) and wheat → wheat flour (0.7) were applied to the wheat STMR, 0.02 mg/kg, to produce a semolina STMR-P of 0.014 mg/kg, a wheat bran STMR-P of 0.020 mg/kg, a wheat bread STMR-P of 0.014 mg/kg and a wheat flour STMR-P of 0.014 mg/kg.

The processing factors for thiamethoxam residues for cotton seed → cotton seed meal (0.27) and cotton seed → refined cotton seed oil (0.02) were applied to the oilseed STMR, 0.02 mg/kg, to produce a cotton seed meal STMR-P of 0.0054 mg/kg and a refined cotton seed oil STMR-P of 0.0004 mg/kg.

The processing factor for thiamethoxam residues for coffee beans → roasted coffee (0.14) was applied to the coffee beans STMR, 0.035 mg/kg, to produce a roasted coffee STMR-P of 0.0049 mg/kg.

The fate of CGA 322704 residues during food processing is dealt with in the clothianidin evaluation.

Residues in animal commodities

The Meeting received a lactating dairy cow feeding study, which provided information on likely residues resulting in animal tissues and milk from thiamethoxam residues in the animal diet.

Lactating Holstein dairy cows were dosed for 29 days once daily via gelatin capsule with thiamethoxam at the equivalent of 2, 6 and 20 ppm in the dry-weight diet.

Parent thiamethoxam did not occur above LOQ (0.01 mg/kg) in liver or fat tissues at the highest test dose. Parent thiamethoxam residues were higher in muscle than in other tissues, but residues did not exceed the LOQ at the 2 ppm dosing level.

Metabolite CGA 322704 did not occur above LOQ (0.01 mg/kg) in any of the tissues except liver.

At 2 ppm dosing, the only residues above LOQ in tissues were: CGA 322704 in liver at 0.028–0.049 mg/kg.

At 6 ppm dosing, residues above LOQ in tissues were: thiamethoxam in muscle at 0.01 mg/kg; CGA 322704 in liver at 0.09–0.14 mg/kg.

Residue levels of parent thiamethoxam and metabolite CGA 322704 reached plateau levels in milk approximately 3–5 days after the commencement of dosing. At 2 and 6 ppm dosing, the approximate plateau levels for thiamethoxam in milk were 0.007–0.008 mg/kg and 0.03–0.05 mg/kg,

respectively. For CGA 322704, the plateau levels in milk at 6 ppm dosing were approximately 0.01–0.02 mg/kg.

Livestock dietary burden

The Meeting estimated the dietary burden of thiamethoxam in livestock on the basis of the diets listed in OECD Feed Table 2009 (available from the FAO website: *http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmpr/jmpr-docs/en/)*.

Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities.

Some processed and forage commodities do not appear in the *Recommendations Table* (because no maximum residue level is needed) but they are used in estimating livestock dietary burdens. Those commodities are listed here. Also, the terminology for commodities in the OECD feed tables is not always identical to descriptions in the original studies or Codex descriptions and some clarification is needed.

Commodity	Thiamethoxam STMR or STMR-P, mg/kg	High residue, mg/kg
Apple wet pomace	0.11	
Barley whole plant = Barley forage	0.04	0.11
Beans (dry) = Bean seed	See Recommendations Table, pulses	
Cabbages (including wrapper leaves)	0.78	3.0
Cotton seed meal = Cotton meal	0.0054	
Dry grape pomace	0.21	
Maize = Field corn grain	See Recommendations Table	
Maize fodder = Field corn, stover	See Recommendations Table	
Maize forage = Field corn, forage/silage	0.01	0.05
Orange dry pulp = Citrus dried pulp	0.073	
Pea hay or Pea fodder (dry) = Pea hay	See Recommendations Table	
Pea vines	0.04	0.10
Peas (dry) = Pea seed	See Recommendations Table, pulses	
Rapeseed forage	0.05	0.05
Soya bean (dry) = Soya bean seed	See Recommendations Table, pulses	
Sugar beet tops or leaves = Beet, sugar tops	0.02	0.02
Wheat whole plant = Wheat forage	0.53	0.73

The data on CGA 322704 residues in feed materials will be needed for dietary burden calculations for clothianidin.

Commodity	CGA 322704 STMR or STMR-P, mg/kg	High residue, mg/kg
Barley whole plant	0.04	0.05
Beans (dry) = Bean seed	See Recommendations Table	
Cabbages (including wrapper leaves)	0.03	0.08
Maize = Field corn grain	See Recommendations Table	
Maize fodder = Field corn, stover	See Recommendations Table	
Maize forage = Field corn, forage/silage	0.01	0.02
Pea hay or Pea fodder (dry) = Pea hay	See Recommendations Table	
Pea vines	0.05	0.05
Peas (dry) = Pea seed	See Recommendations Table	
Rapeseed forage	0.05	0.05
Soya bean (dry) = Soya bean seed	See Recommendations Table	
Sugar beet tops or leaves = Beet, sugar tops	0.02	0.02

Commodity	CGA 322704 STMR or STMR-P, mg/kg	High residue, mg/kg
Wheat whole plant = Wheat forage	0.05	0.06

Estimated maximum and mean dietary burdens of livestock

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the livestock diets from US/CAN, EU, Australia and Japan in the OECD Feed Table 2009.

		Livestock dietary burden, thiamethoxam, ppm of dry matter diet			
		US/CAN	EU	Australia	Japan
Max	beef cattle	0.55	5.21	2.92	0.10
	dairy cattle	0.89	5.23[a,c]	2.01	0.12
	Poultry—broiler	0.11	0.27	0.04	0.03
	Poultry—layer	0.11	1.59[e]	0.04	0.02
Mean	beef cattle	0.13	1.60	2.12[b]	0.10
	dairy cattle	0.56	1.59[d]	1.35	0.07
	Poultry—broiler	0.11	0.11	0.04	0.03
	Poultry—layer	0.11	0.59[f]	0.04	0.02

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL 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 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.

Animal commodities maximum residue level estimation

Cattle

For MRL estimation, the high residues in the tissues were calculated by interpolating the maximum dietary burden (5.23 ppm) between the relevant feeding levels (2 and 6 ppm) from the dairy cow feeding study and using the highest tissue concentrations from individual animals within those feeding groups.

The STMR values for the tissues were calculated by interpolating the STMR dietary burden (2.12 ppm) between the relevant feeding levels (2 and 6 ppm) from the dairy cow feeding study and using the mean tissue concentrations from those feeding groups.

For milk MRL estimation, the high residues in the milk were calculated by interpolating the maximum dietary burden (5.23 ppm) between the relevant feeding levels (2 and 6 ppm) from the dairy cow feeding study and using the mean milk concentrations from those feeding groups.

The STMR value for milk was calculated by interpolating the STMR dietary burden (1.59 ppm) between the relevant feeding levels (0 and 2 ppm) from the dairy cow feeding study and using the mean milk concentrations from those feeding groups.

In the table, 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)	Thiamethoxam residues				
Feeding level [ppm]	Milk	Muscle	Liver	Kidney	Fat
MRL					
	mean	highest	highest	highest	highest
MRL beef cattle (5.23) [2, 6]		0.01 [< 0.01, 0.01]	< 0.01 [< 0.01, < 0.01]	< 0.01 [< 0.01, < 0.01]	< 0.01 [< 0.01, < 0.01]
MRL dairy cattle (5.23) [2, 6]	0.028 [0.007, 0.033]				
STMR					
	mean	mean	mean	mean	mean
STMR beef cattle (2.12) [2, 6]		0.01 [< 0.01, 0.01]	< 0.01 [< 0.01, < 0.01]	< 0.01 [< 0.01, < 0.01]	< 0.01 [< 0.01, < 0.01]
STMR dairy cattle (1.59) [0, 2]	0.006 [0, 0.007]				

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

Residues in milk were estimated as 0.028 and 0.006 mg/kg resulting from the maximum (5.23 ppm) and STMR (1.59 ppm) dietary burdens respectively.

The Meeting estimated a maximum residue level for thiamethoxam in milks of 0.05 mg/kg. The Meeting also estimated an STMR for milk of 0.006 mg/kg.

The Meeting estimated a maximum residue level for thiamethoxam in edible offal of 0.01* mg/kg. The estimation is based on the liver and kidney data. The Meeting estimated an STMR value and an HR value of 0.01 and 0.01 mg/kg for edible offal.

For muscle, the residue arising from a dietary burden of 5.23 ppm was calculated as 0.01 mg/kg. The Meeting estimated a maximum residue level for meat as 0.02 mg/kg. STMR and HR values for muscle and fat were all estimated as 0.01 mg/kg.

Cattle—CGA 322704 residues

The residues of CGA 322704 were evaluated in the same way as described above for thiamethoxam.

In the table, 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, thiamethoxam (ppm) Feeding level [ppm]	CGA 322704 residues Milk	Muscle	Liver	Kidney	Fat
MRL					
	mean	highest	highest	highest	highest
MRL beef cattle (5.23) [2, 6]		< 0.01 [< 0.01, < 0.01]	0.12[a] [0.049, 0.14]	< 0.01 [< 0.01, < 0.01]	< 0.01 [< 0.01, < 0.01 (20 ppm)]
MRL dairy cattle (5.23)	0.011				

Dietary burden, thiamethoxam (ppm)	CGA 322704 residues				
Feeding level [ppm]	Milk	Muscle	Liver	Kidney	Fat
[2, 6]	0.005, 0.013]				
STMR					
	mean	mean	mean	mean	mean
STMR beef cattle (2.12) [2, 6]		< 0.01 [< 0.01, < 0.01]	0.041[b] [0.039, 0.12]	< 0.01 [< 0.01, < 0.01]	< 0.01 [< 0.01, < 0.01 (20 ppm)]
STMR dairy cattle (1.59) [0, 2]	0.004 [0, 0.005]				

[a] Residue 0.12 mg/kg expressed as thiamethoxam is equivalent to 0.10 mg/kg expressed as CGA 322704.

[b] Residue 0.041 mg/kg expressed as thiamethoxam is equivalent to 0.0.035 mg/kg expressed as CGA 322704.

The CGA 322704 data from the thiamethoxam cattle feeding studies were used to support the estimation of maximum residue levels for mammalian meat and milk.

CGA 322704 residues in milk were estimated as 0.011 and 0.004 mg/kg resulting from the maximum (5.23 ppm) and STMR (1.59 ppm) dietary burdens respectively.

The Meeting estimated a maximum residue level for CGA 322704 in milks of 0.02 mg/kg. The Meeting also estimated a CGA 322704 STMR for milk of 0.004 mg/kg.

For liver, the CGA 322704 residues arising from dietary burdens of 5.23 ppm and 1.59 ppm were 0.10 and 0.035 mg/kg, respectively. The Meeting estimated a maximum residue level for CGA 322704 in liver of 0.2 mg/kg. The Meeting estimated an STMR value and an HR value of 0.035 and 0.10 mg/kg, respectively, for CGA 322704 residues in liver.

For kidney, the CGA 322704 residue arising from a dietary burden of 5.23 ppm was calculated as < 0.01 mg/kg. The Meeting agreed to use the kidney data to estimate a maximum residue level for edible offal except liver. The Meeting estimated a maximum residue level for edible offal except liver as 0.01* mg/kg. CGA 322704 STMR and HR values for edible offal except liver were estimated as 0.01 mg/kg.

For muscle, the CGA 322704 residue arising from a dietary burden of 5.23 ppm was calculated as < 0.01 mg/kg. The Meeting estimated a maximum residue level for meat as 0.01* mg/kg. STMR and HR values for muscle and fat were all estimated as 0.01 mg/kg.

Poultry

The thiamethoxam maximum dietary burden for poultry is 1.59 ppm and the mean dietary burden is 0.59 ppm.

No poultry feeding study is available for thiamethoxam, but the metabolism studies suggest that parent thiamethoxam would be unlikely to be present at measurable concentrations in poultry tissues or eggs from a dietary burden of 1.59 ppm.

When laying hens in the metabolism studies were dosed with thiamethoxam at the equivalent of 112 and 98 ppm (^{14}C-thiazolyl and ^{14}C-oxadiazin, respectively) in the feed, parent thiamethoxam was found in lean meat and eggs at concentrations of 0.14–0.19 mg/kg and 0.03 mg/kg respectively. It may be reasonably anticipated that the levels of thiamethoxam in tissues and eggs resulting from a dietary burden of 1.59 mg/kg would be well below the LOQ of the analytical method (0.01 mg/kg).

Thiamethoxam was a very minor part of the residue in poultry liver, whereas CGA 322704 constituted 34% and 39% of the liver TRR (8.2 and 9.2 mg/kg) in the poultry metabolism study with ^{14}C labels in the thiazol and oxadiazine positions, respectively. Metabolite CGA 265307 was the major residue component in the eggs, both whites (45% and 47%) and yolks (69% and 54%), and