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

4.1 ACEPHATE (095)

RESIDUE AND ANALYTICAL ASPECTS

Acephate was last evaluated by the JMPR in 2005 and 2003 when an ADI of 0-0.03 mg/kg bw per day, an ARfD of 0.1 mg/kg bw per day were established and a number of maximum residue levels were estimated. The residue for compliance with MRLs was defined as acephate, but for dietary intake estimation it was decided that methamidophos residues should also be taken into consideration.

Results of supervised trials carried out on cranberry according the US registered uses were submitted for evaluation.

Results of supervised residue trials

The compound can be applied either as broadcast treatment at a rate of 1.12 kg ai/ha with a 90 day PHI, or as two chemigation (applied in irrigation) treatments at a rate of 1.68 kg ai/ha with a PHI of 60 days.

During the 1976 to 1981 growing seasons 39 field trials were conducted on cranberries in three geographical regions of USA. For each test, single or multiple broadcast foliar applications of acephate were made with individual application rates of 0.56–3.36 kg ai/ha resulting in total application rates of 1.12 to 13.4 kg ai/ha/season. Cranberry fruit samples were taken between 6 and 131 days following the last application.

Exact storage intervals were not reported for each sample in these studies. Samples were stored frozen from harvest to analysis for up to 16 months. Storage stability tests for various intervals were reported by the 2003 JMPR for several crops. The results suggest that the decrease in residues during storage was not significant.

The cranberry samples were extracted with ethyl acetate, cleaned up on GPC column and detected with NPD. The stated limits of quantification were 0.02 mg/kg for acephate and 0.01 mg/kg for methamidophos. Average of concurrent recoveries of acephate and methamidophos from mature berries fortified at 0.25 mg/kg and 0.1 mg/kg were 84.8% and 80.6%, respectively.

Three trials were performed at approximate US GAP. The average acephate residues in replicate samples were 0.06, 0.18 and 0.2 mg/kg (methamidophos residue was not detectable).

The Meeting estimated a maximum residue level of 0.5, HR of 0.2 and STMR of 0.18.

The Methamidophos residues in cranberry fruits should be below 0.01 mg/kg.

In seventrials, performed with 3 to 5 applications of 0.84–3.36 kg ai/ha at each timing, cranberry cocktail (cranberry juice) was prepared from the fruits harvested between 14–46 days after the last application. The total residues (sum of acephate and methamidophos) in fruit and cocktail (juice) were:

	Total residues mg/kg						
Fruit	0.425	0.745	1.15	1.15	1.15	1.95	2.25
Cocktail	0.15	0.26	0.26	0.13	0.62	0.59	0.71
Fp	0.35	0.35	0.23	0.11	0.32	0.26	0.28
Estimated processing factor			median:	0.28	average:	0.27	

DIETARY RISK ASSESSMENT

Long-term intake

The GEMS/Food regional diets specify the following long-term cranberry consumption (g/day per person) for various cluster diets: A (0.1); D (0.3); F (0.6); M (2.5). The consumption of cranberry in other regions is nil.

The highest IEDI in the 13 GEMS/Food regional diets, based on estimated STMR, was 0.03% of the maximum ADI (0.03 mg/kg bw).

The Meeting concluded that the long-term intake of residues of acephate from use on cranberry will not practically increase the intake of residues from other uses considered earlier by the JMPR.

Short-term intake

The GEMS/Food regional diet specifies the large portion sizes of cranberry of 3.53 g/kg bw for adults and 6.78 g/kg bw for children (both are from the USA).

The IESTIs of acephate calculated on the basis of the large portion size and the estimated HR of 0.2 mg/kg are 0.71% and 1.4% of the ARfD for adults and children, respectively.

The Meeting concluded that the short-term intake of residues resulting from the use of acephate on cranberry that have been considered by the JMPR is unlikely to present a public health concern.

4.2 ALDICARB (117)

RESIDUE AND ANALYTICAL ASPECTS

Aldicarb residues were last evaluated by the JMPR in 2001 and 2002. In 2001 residues in individual units of banana and potato and a processing study on potato were evaluated. The Meeting recommended a maximum residue level of 0.2 mg/kg for banana and confirmed a previous recommendation of 0.5 mg/kg for potato.

The IESTI calculated for banana, potato and microwaved potato exceed the ARfD for aldicarb (0.003 mg/kg bw) for both the general population (excluding women of child-bearing age) (140–160% above the ARfD) and children (330–560% above the ARfD). A variability factor of 5 was used in the calculation of the intake for banana. In 2002, based on additional residue data provided from individual banana fingers and composite samples, the Meeting recommended the application of a variability factor of 3 for the calculation of the IESTI of aldicarb in banana. The refined IESTI represented 40% ARfD for the general population and 110% ARfD for children.

For potato, a highest residue from individual unit data of 1.2 mg/kg was used in the first term of the equation for case 2a, with no variability factor (see Chapter 3 of 2003 JMPR Report). The HR from a composite sample (0.45 mg/kg) was used in the second part of the equation.

At its 35th, 36th, 37th and 38th Sessions, the CCPR returned the draft MRL for banana and potato to Step 6 due to acute intake concerns. The Committee requested that the JMPR consider using alternative GAPs to estimate lower MRLs (see General Considerations 2.3). The present Meeting received GAP information for potato from the government of The Netherlands.

The residue definition of aldicarb is the sum of aldicarb, aldicarb sulfone and aldicarb sulfoxide, expressed as aldicarb.

Results of supervised residue trials

Banana

Based on twenty four trials conducted in France (Guadalupe and Martinique) and Côte d'Ivoire submitted to the 2001 JMPR with bagged and unbagged banana according to GAP, the Meeting recommended a HR of 0.10 mg/kg in banana pulp and a maximum residue level of 0.2 for aldicarb in banana. No additional residues trials or GAP information were provided.

The Meeting concluded that none of the residue data relating to available GAP suggests a lower maximum residue level to replace the current proposal of 0.2 mg/kg for aldicarb in banana.

Potato

Forty five trials conducted in Europe and USA with aldicarb in potatoes according to GAP were evaluated by the 2001 JMPR. Twenty trials were conducted according to GAP of the Netherlands (furrow application at 12.8 g/100m, corresponding to 1.7 kg ai/ha or broadcast application of 3.36 kg ai/ha), giving a highest residue of 0.36 mg/kg. Nine trials conducted according to GAP in Greece, Italy and Spain (furrow at 2.5 kg ai/ha) gave a highest residue of 0.45 mg/kg. In Europe, the PHI is 90 days. Sixteen trials conducted in the USA (GAP of 3.36 kg ai/ha with a PHI of 150 days, positive displacement) gave a highest residue of 0.20 mg/kg.

New GAP information in the Netherlands indicates a furrow application of 0.75 kg ai/ha and broadcast application of 3 kg ai/ha with no specified PHI. Ten furrow trials (at 13 g/100m) previously evaluated against the Netherlands GAP do not match the new GAP.

The residues derived from the 35 trials, according to the current GAP, in ranked order were: < 0.02, < 0.03 (3), 0.02 (2), 0.03 (6), 0.04 (6), 0.05, 0.06 (4), 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.18, 0.20 (2), 0.27 (2), 0.36 and 0.45 mg/kg.

The Meeting concluded that none of the residue data relating to available GAP suggests a lower maximum residue level to replace the current proposal of 0.5 mg/kg for aldicarb in potato.

4.3 AMINOPYRALID (220)

TOXICOLOGY

Aminopyralid is the ISO approved name for 4-amino-3,6-dichloropyridine-2-carboxylic acid (CAS No. 150114-71-9). It is a postemergence auxin-type herbicide used for the control of a wide variety of broadleaf weed species.

Aminopyralid has not been evaluated previously by the JMPR and was scheduled for evaluation at the request of the CCPR.

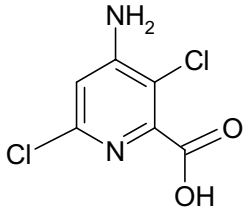
During the preparation of the toxicological working paper and before the present meeting, it became apparent at a late stage that, in addition to the free acid, the substance on which toxicological data had been submitted, the triisopropanolamonium (TIPA) salt and the potassium salt were also used as active ingredients in some parts of the world. From publicly available information from several toxicological studies, there was evidence that the TIPA salt is appreciably more potent than the free acid. However, these studies had not been submitted to the JMPR. In response to a question from the Meeting, the sponsor explained that this effect was most likely to be due to differences in absorption kinetics as a consequence of the respective physicochemical properties of the compounds, and the different vehicles used to administer the compounds. This conclusion was based on a number of studies not evaluated by the Meeting. In the absence of a full evaluation of these studies, the Meeting was not confident that it could dismiss the relevance of the findings with the TIPA salt.

The Meeting therefore had to defer completion of its evaluation of aminopyralid until all the data had been submitted and evaluated. The Meeting emphasized the importance of complete submission of data to enable state-of-knowledge risk assessments to be performed.

RESIDUE AND ANALYTICAL ASPECTS

Aminopyralid is a new herbicide that is used for the control of broadleaf weeds in pastures and cereal crops. It was advanced to the 2006 JMPR schedule of new compounds by the 37th session of the CCPR. The manufacturer submitted studies on metabolism in plants and animals, analytical methods, storage stability, environmental fate and degradation, supervised field trials, processing and farm animal (livestock) feeding.

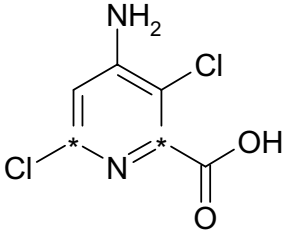
Chemical name and structure:



4-amino-3, 6-dichloropyridine-2-carboxylic acid

Animal metabolism

The meeting received metabolism studies in lactating goats and laying hens. In both studies, aminopyralid was labelled in the 2- and 6-positions of the pyridine ring, as shown below.



A single lactating goat was orally dosed for 6 days with [^{14}C] aminopyralid at the equivalent of 14 ppm in the feed (0.26 mg/kg bw per day). Total radioactivity was measured in samples of milk,

urine, faeces, cage wash and tissues. A large proportion of the administered dose was eliminated via urine and faeces, with each accounting for approximately 46% of the total administered dose; the total eliminated was 92% of the administered dose. Approximately 3% of the administered dose was present in cage wash and < 0.1% was present in milk and tissues.

The radioactivity in milk was found to plateau within 24 to 48 hours after dosing had commenced. The total radioactivity in milk was approximately 0.05% of the total administered dose, with concentrations ranging 0.003–0.008 mg/kg aminopyralid equivalents.

TRR in tissues were 0.008 mg/kg equivalents in liver, 0.071 mg/kg equivalents in kidneys, 0.001 mg/kg equivalents in composite fat and non-detectable in composite muscle.

Methanol extraction of milk followed by partitioning with ether and hexane resulted in recovery of 71% TRR. Methanol extraction of liver and kidney samples followed by partitioning with hexane resulted in release of 58% and 80% TRR, respectively. Further characterisation was not conducted in milk or liver due to very low levels of radioactivity being present.

One radiolabelled component representing approximately 80% ^{14}C in kidney was identified by HPLC analysis of kidney extracts; this was parent aminopyralid present at 0.057 mg/kg. In summary, aminopyralid was rapidly excreted from the goat, with detectable residues of 0.06 mg/kg present in kidneys only.

Ten laying hens of 45 weeks age were orally dosed for 7 days with ^{14}C aminopyralid at the equivalent of 10.5 ppm in the feed. TRR in excreta collected daily ranged from 55% to 87% of the nominal daily dose over 1 to 6 days of the study. All eggs contained low levels of radioactivity that gradually increased to a plateau level of 0.004 mg/kg aminopyralid equivalents within 5 to 7 days of the study. TRR in all eggs collected over the study period accounted for < 0.01% of the total administered dose.

TRR in tissues were < 0.01% of the total administered dose. TRR in muscle and fat were comparable, corresponding to 0.0018 and 0.0017 mg/kg aminopyralid equivalents, respectively. TRR in skin (with fat) and liver were 0.0029 and 0.0024 mg/kg aminopyralid equivalents, respectively. The levels of radioactivity in eggs and tissues were low and were not further characterized.

Residues in excreta were readily extracted into CH_3CN:H_2O with approximately 96% TRR being recovered. HPLC analysis of the excreta extracts indicated that 93% of the radioactivity was composed of unchanged aminopyralid.

In summary, aminopyralid is readily excreted by hens following oral dosing for 7 days at 10 ppm in the feed. TRR in eggs on days 6 and 7 of the study were 0.004 mg/kg aminopyralid equivalents. TRR in muscle and fat were non-detectable (< 0.002 mg/kg aminopyralid equivalents), while TRR in liver and skin/fat were 0.002–0.003 mg/kg aminopyralid equivalents.

The Meeting concluded that aminopyralid is readily eliminated by lactating goats and laying hens following oral dosing, and that it does not undergo any significant metabolism. Most of the eliminated radioactivity was recovered as unchanged aminopyralid.

Plant metabolism

Metabolism studies for aminopyralid applying to wheat and grass/pastures were submitted to the Meeting. In both studies, aminopyralid was labelled in the 2- and 6-positions of the pyridine ring, as shown above.

^{14}C aminopyralid was applied to spring wheat at rates of 40 and 80 g ai/ha. The wheat was at growth stages BBCH 26 – 28 (6 to 8 tillers detectable) at the time of application. Samples of plant material (forage) were taken at 0 and 14 days after application; hay was sampled at 35 days after application and grain and straw at 86 days after application. Homogenised samples were extracted with CH_3CN:H_2O followed by partitioning with CH_3CN/CH_2Cl_2 prior to HPLC analysis. In forage and hay 88–96% of the extracted radioactivity was composed of free and/or conjugated forms of

aminopyralid. Similarly in straw and grain 89 and 69%, respectively, of the extracted radioactivity was composed of free and conjugated aminopyralid. Acid/base treatment of the extracted solids and aqueous phase extracts released another 4% and 7% of the TRR in straw and grain, respectively.

Three types of pasture grasses (perennial ryegrass, big bluestem and *Panicum maximum*) were treated with a single application of ^{14}C aminopyralid at a rate of 360 g ai/ha. Samples of grass were collected for analysis at 0, 7, 14, 21 and 42 days after application.

During the first 7 days after application, aminopyralid comprised approximately 49–97% of the TRR. After 7 days, the amount of extracted aminopyralid decreased and large proportions of other metabolites formed, ranging 18–60% of the TRR at 7 to 42 days after application in grass forage. Acid/base hydrolysis of the metabolites released radioactivity that was subsequently identified by HPLC analysis as aminopyralid. The metabolites were glucose conjugates of aminopyralid that were easily released by base and/or acid hydrolysis. Overall, 87–96% of the TRR in grass forage and hay was identified as aminopyralid and conjugates of aminopyralid.

In summary, the two plant metabolism studies demonstrated that aminopyralid forms the major proportion of the radioactivity when applied to wheat and pasture grasses. With time, the plant converts aminopyralid to glucose conjugates that are easily released by base and/or acid hydrolysis to parent compound.

Environmental fate

The meeting received information on the environmental fate of aminopyralid in soil, including studies on photodegradation on soil, aerobic soil degradation and crop rotation studies (confined and field). ^{14}C aminopyralid was labelled in the 2- and 6-positions of the pyridine ring in all soil studies.

In a photodegradation study on soil, aminopyralid degraded into non-extracted ^{14}C and CO_2. The half-life (DT_{50}) for photodegradation of aminopyralid was 61 days and DT_{90} was 203 days.

Aerobic soil degradation of ^{14}C aminopyralid was investigated in a range of European and US soils. As found in the soil photodegradation study, aminopyralid degrades to CO_2 and non-extracted residues under aerobic conditions; no other residues were identified. Reported DT_{50} values ranged from 18 – 343 days and DT_{90} values ranged 45 – 1141 days.

Data were reported from field dissipation studies that were conducted in Europe, US and Canada. The reported DT_{50} values from the field studies ranged from 8 to 54 days with the majority of values approximating 30 to 35 days. DT_{90} values ranged 26 to 430 days.

Crop rotation studies were conducted in a leafy vegetable (lettuce), a root crop (turnip) and a cereal crop (sorghum). The crops were grown in soil treated with ^{14}C aminopyralid either 90 or 120 days prior to sowing. The results from the different crops were similar, with radioactivity ranging 0.002 – 0.007 mg/kg equivalents in lettuce, turnip roots and tops and sorghum grain and 'late forage'. The highest levels of radioactivity were present in 'early forage' of sorghum at 0.03 mg/kg equivalents from sorghum sown at 90 days after application. Extraction of the radioactivity led to results similar to those in the wheat and grass metabolism studies, i.e. the radioactivity was composed of aminopyralid and conjugates that were easily released by base hydrolysis of extracted phases and non-extracted solids.

Methods of analysis

The Meeting received details of analytical methods for the determination of residues of aminopyralid in agricultural commodities (namely grass pastures, cereal grains, cereal forage and straw), bovine tissues and milk and soil.

Methods for the quantitative determination of aminopyralid residues in barley, sorghum, wheat and grass pasture were provided to the Meeting (method GRM 02.31). Residues are determined using LC/MS/MS. The validated LOQ for all matrices is reported as 0.01 mg/kg. Residues of

aminopyralid and its conjugates are extracted from the sample matrices by homogenisation with mild base, followed by acidification and purification on an SPE column. Aminopyralid in the purified extract is derivatized to its butyl ester form and quantified using LC/MS/MS.

In the method validation component of the study, untreated control samples of barley, sorghum and wheat grain; barley, sorghum and wheat forage; barley straw, sorghum stover and wheat straw; pasture grass forage and hay were fortified with aminopyralid at concentrations ranging 0.01–0.5 mg/kg for grain, 0.01–5 mg/kg for forage and straw and 0.01–20 mg/kg for grass forage and hay. Mean recoveries in all samples ranged 92–109% over all concentrations tested. Independent laboratory validation confirmed the LOQ of 0.01 mg/kg, and mean recoveries ranged 93–120% over all matrices tested.

The extraction efficiency of aminopyralid was determined by extracting wheat grain, forage, straw, hay and pasture grass samples from the metabolism studies in accordance with method GRM 02.31. The extraction efficiencies of the pasture grass samples ranged 88 – 114% and of the wheat matrices ranged 72–101% when calculated based on the total radioactivity.

A GC/MS method for the determination of aminopyralid, fluroxypyr and 2,4-D residues in pastures was provided, which was a modified version of the method described above and has a validated LOQ of 1 mg/kg. Recoveries were validated over a range of concentrations (1–100 mg/kg) and ranged 78–115% with a mean recovery of 95%. The reported LOD was 0.2 mg/kg in grass pasture samples.

Aminopyralid residues in animal tissues and milk are also determined by LC/MS/MS with a validated limit of quantitation of 0.01 mg/kg (method GRM 03.18). Residues are extracted with MeOH/$NaHCO_3$ solution, purified using a SPE plate and derivatized to form the 1-butyl ester. The method was validated over the concentration range of 0.01–2.5 mg/kg in kidney and 0.01–1 mg/kg for all other tissues and milk. The mean recoveries in bovine fat, muscle, liver and kidney ranged 79–96% and in whole milk, skim milk and cream ranged 73–89%. In an independent laboratory validation, the LOQ of 0.01 mg/kg was confirmed for aminopyralid in bovine milk and kidneys using LC/MS/MS. The mean recoveries in bovine milk and kidney were 83% and 87%, respectively.

Methods were provided for the determination of aminopyralid residues in soil (Method GRM 02.34). The soil method was validated with recoveries being conducted in four soil types at concentrations ranging 0.0015–0.1 mg/kg with a mean recovery of 88%; the validated LOQ was 0.0015 mg/kg.

Stability of pesticide residues in stored analytical samples

The storage stability of aminopyralid in pasture grass and hay and wheat grain and straw was investigated. Samples of hay, forage (grass), wheat grain and wheat straw were fortified with aminopyralid at a concentration of 0.1 mg/kg and placed in frozen storage at –20 °C. Aminopyralid residues are stable under conditions of frozen storage for up to 489 days in grass hay and forage, and up to 469 days in wheat grain and straw, with 86% and 88% aminopyralid remaining in fortified grass hay and forage, respectively and 91% and 87% remaining in wheat grain and straw, respectively

Storage stability in animal tissues and milk was not conducted as samples from the metabolism and livestock feeding study were analysed within 3 months of sample collection.

Residue definition

The results of the plant metabolism studies on wheat and pasture grasses indicate that aminopyralid is not significantly metabolised and is transformed to glucose conjugates. Greater than 90% extracted TRR is identified as aminopyralid and conjugates with no metabolites formed to any extent.

In goats and hens, administered aminopyralid is readily eliminated following oral dosing, and it does not undergo any significant metabolism. Greater than 93% of the eliminated radioactivity was

recovered as unchanged aminopyralid. Detected radioactivity in goat kidney was identified as aminopyralid.

Analytical methods for plant and animal matrices and soil determine aminopyralid and any conjugates that are hydrolysed by acid/base as the butyl ester derivative of aminopyralid.

On the basis of the metabolism in plants and animals and the analytical methodology submitted, the Meeting recommended a residue definition for aminopyralid for plants and animals.

Definition of the residue (for compliance with the MRL for all commodities and for estimation of dietary intake for plant and animal commodities): aminopyralid and its conjugates that can be hydrolysed, expressed as aminopyralid.

The residue is not fat-soluble.

Results of supervised trials on crops

In all supervised field trials, commercial formulations containing either the potassium salt or triisopropanolammonium (TIPA) salt were used. In several trials both salt forms were used and in addition many formulations included combinations of the aminopyralid salts with other herbicides such as 2,4-D, fluroxypyr and triclopyr. The aminopyralid TIPA salt dissociates rapidly in water to the aminopyralid acid at pH values greater than 2.56.

Supervised trials for the foliar application of aminopyralid on cereals, namely barley, oats and wheat, and pasture grasses were provided to the Meeting.

Cereal grains

Barley

Data for barley was received from trials conducted in Australia. The registered use in Australia allows a single application between 3-leaf to 1st node (BBCH 13-31) at a rate of 5–7.5 g ai/ha with a nil PHI for harvest and a non-grazing interval of 7 days after application.

The residues in barley grain from four trials in Australia are in rank order: 0.03, 0.04, 0.06, 0.06, and 0.07 (2) mg/kg.

Data for barley was received from two trials conducted in Spain, however there is no GAP for barley in Spain.

The Meeting considered that there were insufficient trials to estimate a maximum residue level for barley.

Oats

Data for oats were received from trials conducted in Australia where two different formulations were used. The registered use in Australia allows a single application between 3-leaf to 1st node (BBCH 13-31) at a rate of 5–7.5 g ai/ha with a nil PHI and grazing at 7 days after application.

The residues in oat grain from four trials in Australia are in rank order: < 0.01, 0.01, 0.02 and 0.03 (4) mg/kg.

The Meeting considered that there were insufficient trials to estimate a maximum residue level for oats.

Wheat

Trials on wheat were conducted in Argentina, Australia, Canada, Hungary, Italy, Poland, Spain and the USA. GAP in Argentina is a single application at rates of 3.75–5 g ai/ha from 3rd leaf to end of

tillering, with a nil PHI for harvest. Residues in wheat grain from trials in Argentina were: < 0.01 (6) mg/kg.

GAP for wheat in Australia is the same as that for barley and oats; a single application between 3-leaf to 1st node (BBCH 13-31) at a rate of 5–7.5 g ai/ha with a nil PHI and grazing at 7 days after application. Residues in wheat grain from the Australian trials are in rank order were: < 0.01 (7), 0.01 (3), 0.02 (2), 0.03 and 0.07 mg/kg.

In the US, GAP allows a single application from 3-leaf to early jointing (BBCH 13 to 30–31) at rates of 7.6–10 g ai/ha, with a PHI of 50 days for harvest and 14 days for grazing/cutting. GAP in Canada is a single application from 2 to 6-leaf stage at a rate of 10 g ai/ha with a PHI of 50 days for harvest and no restrictions for grazing. The Meeting considered that as the GAP in both Canada and USA is specified as an application timing as well as PHI, the stage of crop growth at which the spray is applied is the important determinant compared to the PHI in relation to the final residues in grain. Therefore, trials where the application timings were within the specified GAP for Canada and USA were considered relevant, even though the actual PHIs may have been longer than 50 days.

Residues in wheat grain from the Canadian and US trials are in rank order: < 0.01 (8), 0.01 (14) and 0.02 (5) mg/kg.

Although there are no registered uses of aminopyralid on wheat in Europe, the Meeting considered that the data from the European trials may be included in the estimation of the maximum residue level for wheat as the application rates and application timings are similar to those registered uses in Argentina, Australia, Canada and the USA. The Meeting made reference to the outcomes of the OECD/FAO Zoning project and considered that cropping practices and herbicide use in broadacre crops such as wheat are similar in many regions and therefore the European trials may be considered as being supportive of GAP in other regions, in this case specifically Argentina, Australia, Canada and USA. The residues from the European trials are in rank order: < 0.01 (7) and 0.01 (3) mg/kg.

The Meeting agreed that the data sets for wheat from trials in Argentina, Australia, Canada, Europe and the USA could be combined, therefore the residues in wheat grain in ranked order were: < 0.01 (23), 0.01 (10), 0.011 (3), 0.12, 0.013, (4), 0.014(2), 0.02 (2), 0.021, 0.022, 0.023, 0.025(2), 0.03 and 0.07 mg/kg.

The Meeting also agreed that the data set for wheat could support the data sets for barley and oats, thereby allowing maximum residue levels to be estimated for barley and oats. In addition, registered uses in Australia apply to the minor crop triticale, therefore the combined data set for barley, oats and wheat may also be applied to triticale by crop extrapolation.

Residues for the combined data sets for barley, oats and wheat in ranked order were: < 0.01 (24), 0.01 (11), 0.011 (3), 0.012, 0.013 (4), 0.014 (2), 0.02 (3), 0.021, 0.022, 0.025, 0.025, 0.023, 0.03 (6), 0.04, 0.06 (2), and 0.07 (3)

The Meeting recommended a maximum residue level of 0.1 mg/kg for aminopyralid in barley, oats, triticale and wheat, with an STMR of 0.01 mg/kg.

Livestock feed commodities

In trials conducted in Australia and New Zealand, residues in livestock feed commodities were reported on a ‘dry weight’ basis with associated moisture contents reported for samples at harvest and therefore require no correction for the estimation of MRLs. However the data from trials conducted in all other regions are reported on an ‘as received’ basis and require correction for moisture content by using default factors that are presented in the FAO Manual 2002. The default factors used are indicated and the ‘as received’ figures are adjusted for moisture content in the relevant sections below.

Cereal Straw

The registered use of aminopyralid on barley and oats in Australia allows a single application between 3-leaf to 1st node (BBCH 13-31) at a rate of 5–7.5 g ai/ha with a nil PHI and grazing at 7 days after application.

The data from the Australian trials are reported on a dry weight basis and therefore require no correction for moisture content. Residues in barley straw from trials that correspond to Australian GAP in ranked order were: 0.03 (3), 0.04, 0.07 and 0.08 mg/kg.

Residues in oat straw from trials that correspond to Australian GAP in ranked order were: 0.02, 0.03, 0.04 (3), 0.05 and 0.11 mg/kg.

Data for barley were received from two trials in Spain; these trials corresponded to Australian GAP. Residues when corrected for moisture content (88%) were 0.01 and 0.07 mg/kg.

Wheat straw

The registered use of aminopyralid on wheat in Australia allows a single application between 3-leaf to 1st node (BBCH 13–31) at a rate of 5–7.5 g ai/ha with a nil PHI and grazing at 7 days after application.

The data from the Australian trials are reported on a 'dry weight' basis and therefore require no correction for moisture content. Residues in wheat straw from trials that correspond to Australian GAP in ranked order were: 0.02 (2), 0.04 (2), 0.05, 0.06 (2), 0.07 (2), 0.08, 0.09, 0.1, 0.12 and 0.13 mg/kg.

In the US, GAP allows a single application from 3-leaf to early jointing (BBCH 13-30) at rates of 7.6–10 g ai/ha, with a PHI of 50 days for harvest and 14 days for grazing/cutting. GAP in Canada is a single application from 2 to 6-leaf stage at a rate of 10 g ai/ha with a PHI of 50 days for harvest and a nil PHI for grazing. The Meeting considered that as the GAP in both Canada and USA is specified as application timing as well as PHI, the stage of crop growth at which the spray is applied is the important determinant when compared to the PHI in relation to the final residues in grain. Therefore, trials where the application timings were within the specified GAP for Canada and USA were considered relevant, even though the actual PHIs may have been longer than 50 days. Residues in wheat straw on an 'as received' basis from the Canadian and US trials in ranked order were: 0.02, 0.03, 0.04 (6), 0.05, 0.06 (4), 0.07 (7), 0.08, 0.1 (2), 0.12, 0.13 (2) and 0.14 mg/kg. When corrected for moisture content (12%), residues in wheat straw in ranked order were: 0.02, 0.03, 0.04 (6), 0.06, 0.07 (4), 0.08 (7), 0.09, 0.11 (3), 0.15 (2) and 0.16 mg/kg.

As with the wheat grain, there are no registered uses of aminopyralid on wheat straw in Europe, however the data from the European trials may be included in the estimation of the maximum residue level for wheat as the application rates and application timings are similar to those for registered uses in Argentina, Australia, Canada and USA. In addition, cropping practices and herbicide use in broadacre crops such as wheat are similar in many regions and therefore the European trials may be considered as being supportive of GAP in Argentina, Australia, Canada and USA. Residues in wheat straw from the European trials were reported on an 'as received' basis and in ranked order were: 0.03 (2), 0.04 (2), 0.06, 0.07, 0.08, 0.09, 0.13 and 0.16 mg/kg. When corrected for moisture content (12%), residues in wheat straw in ranked order were: 0.03 (2), 0.04 (2), 0.07, 0.08, 0.09, 0.1, 0.15 and 0.21 mg/kg.

The Meeting agreed that the data sets for wheat straw from trials in Argentina, Australia Canada, Europe and the US were from a single population and could be combined, therefore the residues in ranked order were: 0.02 (3), 0.03 (3), 0.04 (10), 0.05, 0.06 (3), 0.07 (7), 0.08 (9), 0.09 (3), 0.1 (5), 0.12, 0.13, 0.15 (3), 0.16 and 0.21 mg/kg.

The Meeting also agreed that the data set for wheat straw could support the data sets for barley and oat straw. In addition, registered uses in Australia apply to the minor crop triticale;

therefore the combined data set for barley, oats and wheat may also be applied to triticale straw by crop extrapolation.

Residues from the combined data sets for barley, oat and wheat straw in rank order were: 0.01, 0.02 (4), 0.03 (7), 0.04 (14), 0.05 (2), 0.06 (3), 0.07 (9), 0.08 (10), 0.09 (3), 0.1 (6), 0.12, 0.13, 0.15 (3), 0.16 and 0.21 mg/kg. The Meeting recommended a maximum residue level of 0.3 mg/kg for aminopyralid in straw of barley, oats, triticale and wheat, with a highest residue of 0.21 mg/kg and an STMR of 0.07 mg/kg.

Cereal forage

GAP in Australia for barley and oats allows grazing of forage at 7 days after an application between 3-leaf to 1st node (BBCH 13–31) at a rate of 5–7.5 g ai/ha. Residues in barley forage (as reported on a dry weight basis) from trials that correspond to GAP were 0.54 and 0.71 mg/kg. Residues in oat forage were 0.34, 0.4 and 0.79 mg/kg.

The Meeting considered that the trials for barley and oat forage could be combined with the data set for wheat forage for the purposes of estimating the livestock dietary burden.

GAP in Australia for wheat allows application between 3-leaf to 1st node (BBCH 13–31) at a rate of 5–7.5 g ai/ha, with grazing of forage at 7 days after application. Residues in wheat forage (as reported on a dry weight basis) from trials that corresponded to GAP were 0.16, 0.45, 0.48, 0.71, 0.77, 1.02 mg/kg.

In the US, GAP allows a single application from 3-leaf to early jointing (BBCH 30-31) at rates of 7.6–10 g ai/ha, with an interval of 14 days after application for grazing or cutting. Residues in wheat forage that correspond to US GAP (as reported on an 'as received' basis) in ranked order were: 0.07, 0.1 (2), 0.16 and 0.19 mg/kg. When corrected for moisture content (75%), residues in wheat forage were: 0.28, 0.4 (2), 0.64 and 0.76 mg/kg.

GAP in Canada is a single application from 2 to 6-leaf stage at a rate of 10 g ai/ha with no restrictions on grazing. Residues in wheat forage (on an 'as received' basis) from trials that corresponded to Canadian GAP were: 0.11, 0.42, 0.49, 0.53, 0.72 and 0.85 mg/kg. An additional 25 US trials corresponded to GAP in Canada and residues in ranked order were: 0.16 (2), 0.19, 0.21, 0.26, 0.29, 0.3 (2), 0.32, 0.36, 0.37 (2), 0.38, 0.4, 0.41 (2), 0.42, 0.45, 0.49, 0.52, 0.53, 0.54, 0.63 (2) and 0.67 mg/kg. When corrected for moisture content (75%), residues were: 0.64 (2), 0.76, 0.84, 1.04, 1.16, 1.2 (2), 1.28, 1.44, 1.48 (2), 1.52, 1.6, 1.64 (2), 1.68, 1.8, 1.96, 2.08, 2.12, 2.16, 2.52 (2), and 2.68 mg/kg.

The Meeting considered that the trials corresponding to GAP in Australia, Canada and the US were from the same population and decided to combine the data for the purposes of estimating the livestock dietary burden. The residues in barley, oat and wheat forage in ranked order were: 0.16, 0.28, 0.34, 0.4 (2), 0.4, 0.45, 0.48, 0.54, 0.64 (3), 0.71, 0.71, 0.76 (2), 0.77, 0.79, 0.84, 1.02, 1.04, 1.16, 1.2 (2), 1.28, 1.44, 1.48 (2), 1.52, 1.6, 1.64 (2), 1.68, 1.8, 1.96, 2.08, 2.12, 2.16, 2.52 (2) and 2.68 mg/kg. The highest residue is 2.7 mg/kg and the STMR is 1.03 mg/kg.

Wheat hay

Residues in wheat hay were reported from trials conducted in the US and Canada. The GAP for wheat in the US is single application from 3-leaf to early jointing (BBCH 13–30) at rates of 7.6–10 g ai/ha, with a PHI of 50 days for harvest and 14 days after application for grazing or cutting. The GAP for wheat in Canada is a single application from 2 to 6-leaf stage at a rate of 10 g ai/ha with a PHI of 50 days for harvest and no restrictions for grazing.

Residues in wheat hay from US trials that correspond to US GAP (as reported on an 'as received' basis) were: 0.21, 0.25, 0.26, 0.34 and 0.61 mg/kg. When corrected for moisture content (88%), residues on a dry weight basis were: 0.24, 0.28, 0.29, 0.39 and 0.69 mg/kg.

Residues from Canadian trials that correspond to Canadian GAP were: 0.37, 1.28, 1.46, 1.48, 2.32 and 2.36 mg/kg. When corrected for moisture content (12%), residues on a dry weight basis were: 0.42, 1.45, 1.66, 1.68, 2.64, 2.68 mg/kg.

An additional 25 US trials corresponded to Canadian GAP and residues on an 'as received' basis were: 0.34, 0.38, 0.43, 0.45, 0.54 (2), 0.69 (2), 0.71, 0.76 (2), 0.83, 0.87, 0.98 (2), 1.02, 1.23, 1.24, 1.31, 1.32, 1.33, 1.37, 1.46, 1.67 and 1.88 mg/kg. When corrected for moisture content (12%), residues on a dry weight basis were: 0.38, 0.43, 0.49, 0.51, 0.61 (2), 0.78, 0.81, 0.86 (2), 0.94, 0.99, 1.1 (2), 1.16, 1.39, 1.41, 1.49, 1.5 (2), 1.56, 1.66, 1.89, 2.14 mg/kg.

The Meeting agreed to combine the data sets from Canada and the USA and residues in wheat hay on a dry weight basis were: 0.24, 0.28, 0.29, 0.38, 0.39, 0.42, 0.43, 0.49, 0.51, 0.61 (2), 0.69, 0.78, 0.81, 0.86 (2), 0.94, 0.99, 1.1 (2), 1.16, 1.39, 1.41, 1.45, 1.49, 1.5 (2), 1.56, 1.66 (2), 1.68, 1.89, 2.14, 2.64 and 2.68 mg/kg. The Meeting recommended a maximum residue level of 3 mg/kg in wheat hay (n = 36), with a highest residue of 2.7 mg/kg and an STMR of 1 mg/kg.

The Meeting decided that wheat forage (when expressed on a dry weight basis) is similar to wheat hay for the purposes of estimating the livestock dietary burden. Therefore only one of the two commodities is considered necessary for inclusion in the livestock dietary burden tables. The highest residue in cereal forage/hay is 2.7 mg/kg and the STMR is 1 mg/kg.

Grass Pastures: forage and hay

The meeting received data for grass pastures (forage) and hay from trials conducted in Australia, Brazil, Canada, France, Germany, Italy, New Zealand, Spain, the UK and USA.

GAP in Brazil allows a single application at rates of 40–100 g ae/ha with no specified interval to harvest or for grazing. Forage residue data, calculated as the average of replicate measurements that correspond to Brazilian GAP expressed on an 'as received' basis were: 1.3, 1.4, 3.6, 6.3 and 11.6 mg/kg. When corrected for moisture content (75%) residues were: 5.2, 5.6, 14.4, and 46.4 mg/kg.

Trials from Europe were evaluated against UK GAP, which allows a single application at 60 g ae/ha with a 7 days interval for grazing/cutting. Forage data from trials in France, Germany, Italy, Spain and the UK that correspond to UK GAP expressed on an as received basis were: 0.8, 1, 1.3, 1.5, 1.8, 2.0, 2.2, and 3 mg/kg. Correcting for moisture content (75%), residues in forage on a dry weight basis were: 3.2, 4, 5.2, 6, 7.2, 7.6, 8.8 and 12 mg/kg. The sampling intervals for hay did not correspond to the PHI of 7 days.

GAP in Canada allows application at 60–120 g ae/ha with no restrictions for grazing/cutting. Residues in forage as expressed on an as received basis were: 9.1, 10.7, 12.2, 12.7, 12.8, 13.2, 13.7, 13.8 and 14.6 mg/kg. Correcting for moisture content (75%), residues on a dry weight basis were: 36.4, 42.8, 48.8, 50.8, 52.1, 52.8, 54.8, 55.2 and 58.4 mg/kg. Residues in hay that correspond to GAP are on an as received basis were: 15.1, 15.9, 16.8, 21.6, 22.2, 25.1, 26.2, 30, and 55 mg/kg. When corrected for moisture content (12%), residues were: 17.1, 18.1, 19.1, 24.5, 25.2, 29.8, 34.1 and 62.5 mg/kg.

GAP in the US allows application at 50–120 g ae/ha with no restrictions for grazing/cutting of forage and hay. Residues in forage as expressed on an as received basis were: 4.6, 4.8 (2), 5, 6.1, 6.5, 6.9, 8.7, 9.4, 10, 10.1, 11.1, 11.2, 12.5, and 16 mg/kg. Correcting for moisture content (75%), residues on a dry weight basis were: 18.4, 19.2 (2), 20, 24.4, 26, 27.6, 34.8, 37.6, 40 (2), 44 92), 50 and 64 mg/kg.

Residues in hay on an 'as received' basis were: 10.6, 10.9, 12.4, 15.7, 15.9, 16, 17.9, 18.1, 18.2 (2), 18.6, 20.3, 25.8, 26.3 and 32.2 mg/kg. Correcting for moisture content (12%), residues on a dry weight basis were: 12, 12.4, 14.1, 17.8, 18.1, 18.2, 20.3, 20.5, 20.7, 21.1, 23.1, 29.3, 29.9 and 36.6 mg/kg.

GAP in New Zealand is application at 60 g ae/ha with a nil PHI for gazing/cutting. Forage data from trials that correspond to GAP expressed on a dry weight basis were: 6.2, 7.3, 11.3, 38.8, 42.4, and 48 mg/kg.

GAP in Australia is application at rates ranging 150–210 g ae/ha with a nil PHI for grazing/cutting. Forage data from trials that correspond to GAP were (as expressed on a 'dry weight' basis): 9, 12 (3), 19, 37.1, 52.5, and 103 mg/kg.

The Meeting agreed that for the purposes of estimating livestock dietary burden, the GAP from Australia led to the highest residues in grass pasture. However the data from the US and Canadian trials also fall within the spread of the values from the limited Australian trials. The Meeting therefore agreed to combine the data sets from Australia, Canada and the US; residues in forage on a dry weight basis were: 18.4, 19.2 (2), 20, 24.4, 26, 27.6, 34.8, 36.4, 37.1, 37.6, 40 (2), 42.8, 44 (2), 48.8, 50, 50.8, 52.1, 52.5, 52.8, 54.8, 55.2, 58.4, 64 and 103 mg/kg. The Meeting recommended a highest residue of 103 mg/kg for the purposes of estimating the livestock dietary burden, with an STMR of 41 mg/kg.

Residues in hay from trials conducted in Canada and the US can also be combined on the basis of application rate and nil PHI. Residues are in rank order and on a dry weight basis: 12, 12.4, 14.1, 17.1, 17.8, 18.1 (2), 18.2, 19.1, 20.3, 20.5, 20.7, 21.2, 23.1, 24.5, 25.2, 29.3, 29.8, 29.9, 34.1, 36.6 and 62.5 mg/kg. The Meeting recommended a maximum residue level of 70 mg/kg for grass hay, with a highest residue of 63 mg/kg and an STMR of 21 mg/kg for the purposes of estimating livestock dietary burden.

Fate of residues during processing

A processing study for wheat was provided to the Meeting. A summary of the processing factors and the resulting STMR-P values is provided.

Raw Agricultural Commodity				*Processed Commodity*			
Commodity	*MRL (mg/kg)*	*STMR (mg/kg)*	*HR (mg/kg)*	*Commodity*	*PF*	*MRL (mg/kg)*	*STMR-P (mg/kg)*
Wheat	*0.1*	*0.01*	*0.07*	*Wheat bran*	*2.4*	*0.3*	*0.024*
				Flour	*0.2*	–	*0.002*
				Germ	*0.36*	–	*0.0036*
				Aspirated grain fraction	*6.1*	–	*0.06*

Data from the processing study indicate that there is concentration of aminopyralid residues in wheat bran and aspirated grain fractions, with processing factors of 2.4 and 6.1, respectively. The Meeting agreed to recommend a maximum residue level of 0.3 mg/kg for wheat bran. An HR-P of 0.17 mg/kg is estimated for wheat bran (wheat milled by-products) and 0.43 mg/kg is estimated for aspirated grain fractions for inclusion in the livestock dietary burden. The corresponding STMR-P values for livestock burden are 0.024 mg/kg for wheat bran (wheat milled by-products) and 0.06 mg/kg for aspirated grain fractions.

Farm animal feeding studies

Groups of lactating dairy cows received the equivalent of 0, 32.8, 64.5, 181.5 and 644.7 ppm in the feed for 28 days. Following the dosing period, there was an additional depuration phase of 14 days, with slaughter intervals of 3, 7 and 14 days after withdrawal from dosing.

Residues were determined in liver, kidney, muscle, fat, whole milk, skim milk and cream.

Residues in whole milk following dosing at 32.8 ppm in the feed were < 0.01 mg/kg over the 28 days period. Residues reached plateau within 2 to 3 days of dosing. Residues in milk ranged < 0.01–0.024 mg/kg and 0.011–0.028 mg/kg following dosing at 64.5 and 181.5 ppm, respectively. Aminopyralid residues ranged 0.023–0.127 mg/kg following dosing at 644.7 ppm. Residues had declined to < 0.01 mg/kg within 2 days of withdrawal from dosing at the highest level of 644.7 ppm.

The highest aminopyralid residues in tissues following dosing at 32.8 ppm level were: muscle < 0.01 mg/kg, fat 0.01 mg/kg, liver < 0.01 mg/kg, and kidney 0.1 mg/kg. Following dosing at 64.5 ppm, aminopyralid residues were < 0.01 mg/kg in muscle, 0.01 mg/kg in fat and liver and 0.2 mg/kg in kidney.

The highest aminopyralid residues in tissues following dosing at 181.5 ppm level were 0.05 mg/kg in muscle and liver, 0.09 mg/kg in fat, and 1.5 mg/kg in kidney. The highest aminopyralid residues in tissues following dosing at 644.7 ppm level were 0.03 mg/kg in muscle, 0.04 mg/kg in fat, 0.06 mg/kg in liver, and 2.5 mg/kg in kidney.

As there is no hen or poultry feeding study, the hen metabolism study is used to recommend appropriate maximum residue levels in hen tissues and eggs. The dose level in the hen metabolism study was 10.5 ppm in the feed and hens were dosed daily for 7 days. TRR in muscle, skin/fat, fat, liver and eggs were < 0.01 mg/kg which is the limit of quantitation in the method used to determine aminopyralid residues in animal tissues and milk. Although the method was not validated for eggs, the Meeting considered that as aminopyralid is not fat-soluble and that the method had been validated for bovine tissues and milk, it would also be applicable to eggs.

Farm animal dietary burden

The Meeting estimated the dietary burden of aminopyralid residues in livestock (farm animals) on the basis of the livestock diets listed in the FAO Manual 2002.

The maximum dietary burden calculations include the highest residues (HR) and STMR-P values which are used for the estimation of maximum residue levels in animal commodities such as milk, eggs, meat and offal. The STMR dietary burden calculations for livestock allow an estimate of the median residues in milk, eggs, meat and offal that can be used in the chronic dietary assessments and there STMR and STMR-P values for feeds are used.

The percentage dry matter is taken as 100% when highest residues and STMR values are already expressed on a dry weight basis.

Estimated maximum dietary burden of farm animals

Commodity	Group	Residue (mg/kg)	HR/STMR	*Diet content (%)*			Residue Contribution (mg/kg)		
				Beef cattle	*Dairy cattle*	*Poultry*	Beef cattle	Dairy cattle	Poultry
Cereal forage	AF	2.7	HR	*100*	*60*	*10*	2.7	1.62	0.27
Cereal straw	AS	0.21	HR	*80*	*20*	*10*	0.17	0.04	0.02
Grass forage	AF	103	HR	***100***	***100***	***10***	**103**	**103**	**10.3**
Grass hay	AS	63	HR	*100*	*60*	*10*	63	37.8	6.3
Cereal grain	GC	0.01	HR	*80*	*40*	***40***	0.06	0.03	**0.03**
Wheat milled by-products	CF	0.02	STMR-P	*40*	*40*	***50***	0.07	0.07	**0.08**
AGF*	–	0.06	STMR-P	*5*	–		0.003		
Total				***100***	***100***	***100***	**103**	**103**	**10.4**

* Aspirated grain fractions

The calculated highest dietary burdens for beef cattle, dairy cattle and poultry are 103, 103, and 10.4 ppm, respectively.

Estimated STMR dietary burden of farm animals

Commodity	Group	Residue (mg/kg)	STMR/ STMR-P	*Diet content (%)*			Residue Contribution (mg/kg)		
				Beef cattle	*Dairy cattle*	*Poultry*	Beef cattle	Dairy cattle	Poultry
Cereal forage	AF	1	STMR	*100*	*60*	*10*	1	0.6	0.1
Cereal straw	AS	0.07	STMR	*80*	*20*	*10*	0.06	0.01	0.01
Grass forage	AF	37	STMR	***100***	***100***	***10***	**37**	**37**	**3.7**
Grass hay	AS	21	STMR	*100*	*60*	*10*	21	12.6	2.1
Cereal grain	GC	0.01	STMR	*80*	*40*	***40***	< 0.01	< 0.01	**< 0.01**
Wheat milled by-products	CF	0.02	STMR-P	*40*	*40*	***50***	0.01	0.01	**0.01**
AGF*	–	0.06	STMR-P	*5*	–	–	0.003	–	–
Total				***100***	***100***	***100***	**37**	**37**	**3.7**

** Aspirated grain fractions*

The STMR dietary burdens for beef cattle, dairy cattle and poultry are 37, 37 and 3.7 mg/kg, respectively.

Animal commodity maximum residue levels

The livestock dietary burdens used for the estimation of the maximum residue levels for animal commodities were 103 ppm for beef and dairy cattle and 10.4 ppm for poultry. The livestock dietary burdens used for the STMR estimation for dietary risk assessment were 37 ppm for beef and dairy cattle and 3.7 ppm for poultry.

For poultry, the maximum dietary burden of 10.3 ppm is very similar to the dose level of 10.5 ppm in the hen metabolism study. Residues in hen tissues and eggs were < 0.01 mg/kg following dosing for 7 consecutive days. On the basis of the hen metabolism study, the Meeting recommended maximum residue levels of *0.01 mg/kg poultry meat, poultry offal and eggs. These values of *0.01 mg/kg were also used in the dietary risk assessment.

For cattle, the maximum dietary burden of 103 ppm is between the dose levels of 64.5 ppm and 181.5 ppm. The residues in kidney are the highest of all tissues and range 0.45–2.5 mg/kg between these two feed levels. On the basis of interpolation between the two feed levels, the Meeting recommended a maximum residue level of 1 mg/kg for mammalian kidney. For liver and other offal, the Meeting recommended a maximum residue level of 0.05 mg/kg. For milk, the meeting recommended a maximum residue level of 0.02 mg/kg. For meat, the Meeting recommended a maximum residue level of 0.1 mg/kg on the basis of higher levels being present in fat compared to muscle at the same dose levels.

Dietary burden (ppm)			Residues (mg/kg)					
Feed level [ppm]	Milk		Meat (fat)		Liver		Kidney	
	Highest	Mean	Highest	Mean	Highest	Mean	Highest	Mean
MRL estimate (beef and dairy cattle)								
(103 ppm)		0.016	0.026, (0.054)		0.031		0.87	

[64.5/181.5]	[0.024, 0.028]	[< 0.01, 0.046]	[0.014, 0.054]	[0.202, 1.537]
STMR estimate (beef and cattle)				
(37 ppm) [32.8 ppm]	0.01	0.01	0.01	0.1

For the purposes of the dietary risk assessment, the STMR estimate for the livestock dietary burden is 37 ppm for beef and dairy cattle and 3.7 ppm for poultry. Based on the poultry metabolism study, the STMR values for poultry and eggs are 0.01 mg/kg. In the lactating cattle study, the feed level of 32.8 is close to the STMR level of 37 ppm. The STMR values for milk, meat (fat) and liver are 0.01 mg/kg and 0.1 mg/kg for kidney.

Conclusions

On the basis of the data from supervised trials and farm animal feeding studies, the Meeting provisionally estimated maximum residue levels, but these are not recommended for use as maximum residue limits (MRLs) because of the deferred toxicological evaluation.

DIETARY RISK ASSESSMENT

Long-term intake and short-term intake

As the Meeting received an incomplete toxicology data submission, the dietary risk assessment for aminopyralid could not be finalised.

4.4 BIFENAZATE (219)

TOXICOLOGY

Bifenazate is the ISO approved name for *N*'-(4-methoxy-biphenyl-3-yl) hydrazine carboxylic acid isopropyl ester (IUPAC). Bifenazate, a carbazate compound, is a new acaricide with a unique mode of action that is very selective for spider mites. It is intended for use on apples, pears, nectarines, peaches, plums, prunes, strawberries, grapes, hops, and ornamentals.

Bifenazate was evaluated by the JMPR at the request of the Thirty-eighth Session of the CCPR. The JMPR has not previously evaluated bifenazate.

All pivotal studies with bifenazate were certified as complying with GLP.

Biochemical aspects

In toxicokinetic studies, rats were given a single dose of radiolabelled bifenazate (10 or 1000 mg/kg bw) or were pretreated with unlabelled bifenazate (10 mg/kg bw per day for 14 days) then given a dose of radiolabelled bifenazate administered by gavage. On the basis of urinary and biliary excretion, about 79–85% and 22–29% of the orally administered dose was absorbed within 72 hours at 10 and 1000 mg/kg bw. A peak in plasma concentrations of radioactivity was observed 5–6 hours and 18–24 hours after dosing at 10 and 1000 mg/kg bw, respectively. The elimination half-life at 10 and 1000 mg/kg bw was between 11.5 and 15.6 hours. Approximately 90% of the administered dose was eliminated in excreta within 48 hours and 96 hours at 10 and 1000 mg/kg bw, respectively. Faeces were the major route of excretion (66–82% of the administered dose), with 8–24% of the administered

dose being recovered in the urine. Approximately 68–73% of the administered dose was excreted in the bile within 72 hours at 10 mg/kg bw and 21–26% of the administered dose at 1000 mg/kg bw. Approximately 0.5% of the administered dose was detected in the tissues and residual carcass at 168 h, with highest concentrations of radioactivity in the liver, kidney and blood. Systemically absorbed bifenazate was extensively metabolized. The major metabolites of bifenazate in the faeces and urine resulted from hydrazine oxidation, demethylation, ring hydroxylation, removal of the hydrazinecarboxylic acid side-chain, and conjugation of the biphenyl ring moiety with glucuronic acid and sulfate. A total of eight metabolites and bifenazate were identified in the faeces and three metabolites were identified in the urine. The primary metabolite(s) in the urine were sulfate and glucuronide conjugates. Unchanged bifenazate was isolated in the faeces of males and females (5–7% and 48–61% of the faecal radioactivity at 10 and 1000 mg/kg bw, respectively). In faeces, metabolite D3598 (a product of oxidation of hydrazine moiety) was detected (4–5% and 1–2% of the faecal radioactivity at 10 and 1000 mg/kg bw). Excretion, distribution and metabolite profiles were essentially independent of pretreatment and sex.

Toxicological data

Bifenazate has low toxicity when administered orally, dermally or by inhalation. The median lethal dose (LD_{50}) after oral administration was > 5000 mg/kg bw in mice and rats. The LD_{50} in rats treated dermally was > 5000 mg/kg bw. The median lethal concentration (LC_{50}) in rats treated by inhalation (nose only) was > 4.4 mg/L (dust). Bifenazate was slightly irritating to the eyes and skin of rabbits. Bifenazate was not a skin sensitizer in guinea-pigs (Buehler test), but gave a positive response (mild sensitizer) in a Magnusson & Kligmann (maximization) test in guinea-pigs.

In the absence of any specific studies addressing effects after single doses, attention was paid to effects after one or several doses in short-term studies with repeated doses. In a 28-day feeding study in mice, there were no deaths at 200 ppm (equivalent to 34 mg/kg bw per day). Deaths were observed starting on day 3 at 1000 ppm and above. At a dose of 2500 or 5000 ppm, all treated animals died. Antemortem findings (hunched posture, hypoactive behaviour, pale appearance, urine staining, tremors, dyspnoea, thinness and/or partial eye closure) were not reported before days 6–8 in 5 out of 20 animals at approximately 275 mg/kg bw per day, or before days 7–8 in 2 out of 10 males at approximately 550 mg/kg bw per day. In a 28-day feeding study in rats, there were no deaths before dosing day 14 in animals given bifenazate at a dose of up to 10000 ppm (equal to 410 mg/kg bw per day) and there were no clinical signs before week 2 of dosing at up to 10000 ppm. Toxicologically significant reduction in erythrocyte counts, haemoglobin and erythrocyte volume fraction were observed at 10000 ppm at termination.

In short-term and long-term studies in mice, rats and dogs, the primary effects of bifenazate were on the haematopoietic system and the liver.

In a 90-day dietary study of toxicity in mice, an increase in the incidence of haemosiderin pigment and/or severity of this effect was seen in the spleen at 100 ppm (equal to 16.2 mg/kg bw per day) and above, although no significant changes in blood parameters were seen. The NOAEL was 50 ppm (equal to 8.0 mg/kg bw per day).

In a 90-day dietary study of toxicity in rats, decreased body-weight gains (females), decreases in erythrocytes and haemoglobin (females), increases in relative spleen and kidney weights (females), hepatocellular necrosis (males), increased pigment in the spleen (both sexes) extramedullary haematopoiesis in the spleen (females), vacuolation of the zona fasciculata of the adrenal cortex (males) and hepatocellular hypertrophy were seen at 200 ppm (equal to 13.3 mg/kg bw per day). The NOAEL was 40 ppm (equal to 8.0 mg/kg bw per day).

In a 90-day study of toxicity in dogs, alterations in haematological and related parameters (decreases in erythrocytes, haemoglobin and erythrocyte volume fraction, increases in reticulocytes, mean corpuscle volume (MCV), mean corpuscular haemoglobin (MCH), anisocytosis and platelets, a decrease in protein peak 4 (females only), brown-coloured urine (males only), brown pigment in

Kupffer cells) and increases in absolute and relative liver weights, hepatocellular hypertrophy (females only) were seen at 400 ppm (equal to 10.4 mg/kg bw per day). The NOAEL was 40 ppm (equal to 0.9 mg/kg bw per day). In a 52-week study of toxicity in dogs, haematological changes (decreases in values for erythrocyte counts, haemoglobin and erythrocyte volume fraction; increases in reticulocyte counts and MCV), changes in clinical chemistry and urine analysis parameters (increased concentration of serum total bilirubin, urinary bilirubin, and brown coloration of the urine), and histopathological changes (mild to moderate hyperplasia of the bone marrow of the rib, femur and sternum and brown pigment in liver and kidney) were seen at the LOAEL of 400 ppm (equal to 8.9 mg/kg bw per day). The NOAEL was 40 ppm (equal to 1.01 mg/kg bw per day).

When administered dermally, bifenazate displayed toxic effects that were qualitatively similar to those seen after oral administration. In a 21-day study of dermal toxicity in rats, the NOAEL was 80 mg/kg bw per day based on haematological effects seen at 400 mg/kg bw per day and above.

Bifenazate gave negative results in an adequate range of studies of genotoxicity in vitro and in vivo.

The Meeting concluded that bifenazate is unlikely to be genotoxic.

In long-term studies of toxicity and carcinogenicity in mice and rats, there was no treatment-related neoplasticity. Survival was not affected by treatment with bifenazate in mice and rats. At 100 ppm (equal to 19.7 mg/kg bw per day), decreases in counts for leukocytes and lymphocytes were observed in male mice. In female mice, decreases in body-weight gains were observed at 175 ppm (equal to 35.7 mg/kg bw per day). The NOAEL was 10 ppm (1.5 mg/kg bw per day) in males and 100 ppm (equal to 19.7 mg/kg bw per day) in females. In rats, decreases in body-weight gain, food consumption and haematological parameters were seen at the LOAEL of 200 ppm (equal to 9.7 mg/kg bw per day). The NOAEL for systemic toxicity was 80 ppm (equal to 3.9 mg/kg bw per day). Bifenazate was not carcinogenic in mice or rats.

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

In a two-generation study of reproduction in rats, offspring toxicity or reproductive parameters were not affected at the highest dose tested (200 ppm, equal to 15.3 mg/kg bw per day). The NOAEL for parental systemic toxicity was 20 ppm (equal to 1.5 mg/kg bw per day) on the basis of decreases in body-weight gains. Bifenazate was not embryotoxic, fetotoxic or teratogenic at doses of 500 (the highest dose tested) or 200 mg/kg bw per day (the highest dose tested) in rats and rabbits, respectively.

The Meeting concluded that bifenazate is not teratogenic nor a reproductive toxicant.

No treatment-related clinical signs of neurotoxicity were observed in the studies that were provided. Therefore, no specific studies of neurotoxicity were necessary.

No studies of toxicity with metabolites of bifenazate were submitted. Parent bifenazate and bifenazate-diazene (D 3593) readily undergo chemical interconversion, so the Meeting considered that these compounds were assessed in the studies with bifenazate. Since other major metabolites of bifenazate are polar glucuronide or sulfate conjugates that are rapidly excreted, the Meeting concluded that these metabolites are likely to be less toxic than bifenazate.

No significant adverse effects were reported in personnel of production plants.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.01 mg/kg bw based on a NOAEL of 40 ppm (equal to 1.0 mg/kg bw per day) for compensatory haematopoiesis, alteration in urine analysis parameters and liver

toxicity seen at 400 ppm (equal to 9.0 mg/kg bw per day) and above in a 52-week study in dogs fed bifenazate, and using a 100-fold safety factor.

The Meeting concluded that it was not necessary to establish an ARfD for bifenazate on the basis of its low acute toxicity, lack of haemolytic effects in a 28-day study of toxicity in mice, the absence of developmental toxicity in rats and rabbits, the lack of clinical signs of neurotoxicity in the database, and the absence of any other toxicological end-point that would be likely to be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	79-week study of toxicity and carcinogenicity[a]	Toxicity	10 ppm, equal to 1.5 mg/kg bw per day	100 ppm, equal to 15.4 mg/kg bw per day
		Carcinogenicity	175 ppm, equal to 35.7 mg/kg bw per day[c]	
Rat	2-year study of toxicity and carcinogenicity[a]	Toxicity	80 ppm, equal to 3.9 mg/kg bw per day	160 ppm, equal to 9.7 mg/kg bw per day
		Carcinogenicity	160 ppm, equal to 9.7 mg/kg bw per day[c]	—
	Multigeneration study of reproductive toxicity[a]	Parental toxicity	20 ppm, equal to 1.5 mg/kg bw per day	80 ppm, equal to 6.1 mg/kg bw per day
		Offspring toxicity	200 ppm equal to 15.3 mg/kg bw per day	
	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	100 mg/kg bw per day
		Embryo/fetotoxicity	500 mg/kg bw per day[c]	—
Rabbit	Developmental toxicity[b]	Maternal toxicity	200 mg/kg bw per day[c]	—
		Embryo-fetotoxicity	200 mg/kg bw per day	—
Dog	90-day study of toxicity[a]	Toxicity	40 ppm, equal to 0.9 mg/kg bw per day	400 ppm, equal to 10.4 mg/kg bw per day
	1-year study of toxicity[a]	Toxicity	40 ppm, equal to 1.0 mg/kg bw per day	400 ppm, equal to 8.9 mg/kg bw per day

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

Unnecessary

Information that would be useful for 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 bifenazate

Absorption, distribution, excretion, and metabolism in mammals	
Rate and extent of oral absorption	Moderate and incomplete; maximum blood concentration reached by 5–6 h; later at higher doses. About 79–85% and 22–29% absorbed within 72 hours at 10 and 1000 mg/kg bw, respectively
Distribution	Widely distributed in tissues
Potential for accumulation	No evidence of significant accumulation
Rate and extent of excretion	Approximately 90% (27% in urine and 63% in faeces) within 48 hours at 10 mg/kg bw per day.
Metabolism in animals	Extensive; metabolic pathways include hydrazine oxidation, demethylation, ring hydroxylation, cleavage of the hydrazine-carboxylic acid portion of the molecule and conjugation with glucuronic acid and sulfate
Toxicologically significant compounds	Bifenazate and bifenazate-diazene (compounds readily interconvert)
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rat, LD_{50}, dermal	> 5000 mg/kg bw
Rat, LC_{50}, inhalation	> 4.4 mg/L dust (4-h exposure, nose only)
Rabbit, skin irritation	Minimal irritation
Rabbit, eye irritation	Minimal irritation
Guinea-pig, skin sensitization	Not a sensitizer (Buehler test)
	Mild sensitizer (maximization)
Short-term studies of toxicity	
Target/critical effect	Haematopoietic system
Lowest relevant oral NOAEL	1.0 mg/kg bw per day (90-day and 1-year study in dogs)
Lowest relevant dermal NOAEL	80 mg/kg bw per day (21-day study in rats)
Lowest relevant inhalation NOAEL	No data
Genotoxicity	
	No genotoxic potential
Long-term studies of toxicity and carcinogenicity	

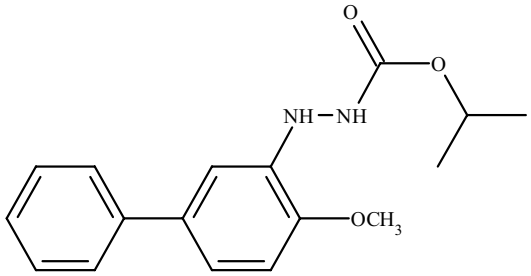
Target/critical effect	Haematopoietic system
Lowest relevant NOAEL	1.5 mg/kg bw per day (78-week study in mice)
Carcinogenicity	Not carcinogenic in mice and rats
Reproductive toxicity	
Reproduction target/critical effect	No toxicologically relevant effects
Lowest relevant reproductive NOAEL	15.3 mg/kg bw per day (rats, highest dose tested)
Developmental target/critical effect	No developmental toxicity in rats and rabbits at highest dose tested
Lowest relevant developmental NOAEL	200 mg/kg bw per day (rabbits; highest dose tested)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	No clinical signs observed in available toxicological studies
Medical data	
	No significant adverse health effects reported

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.01 mg/kg bw	Dog, 1-year study of toxicity	100
ARfD	Unnecessary	—	—

RESIDUE AND ANALYTICAL ASPECTS

Bifenazate was considered for the first time by the present meeting. It is a selective acaricide which controls the motile stage of mites either by direct contact or through contact with foliar residues.



IUPAC: Isopropyl 2-(4-methoxybiphenyl-3-yl)hydrazinoformate

CAS: 1-methylethyl 2-(4-methoxy[1,1'-biphenyl]-3-yl)hydrazinecarboxylate

The Meeting received information on bifenazate metabolism and environmental fate, methods of residue analysis, freezer storage stability, national registered use patterns, supervised residue trials, fate of residues in processing and national MRLs. Australia and Japan submitted GAP information and labels to support MRLs for bifenazate.

Animal metabolism

The Meeting received animal metabolism studies with bifenazate in rats, lactating goats and laying hens. Bifenazate ^{14}C labelled in the substituted phenyl ring was used in all of the metabolism studies.

Bifenazate is readily converted to bifenazate-diazene (isopropyl 2-(4-methoxybiphenyl-3-yl)diazenoformate) by mild oxidation. Primary metabolites are readily produced by removal of the side chain and by hydroxylation of the biphenyl rings. Glucuronide and sulfate conjugates are also produced.

When rats were orally dosed with labelled bifenazate it was readily absorbed followed by extensive metabolism and excretion. Parent bifenazate and the following metabolites were identified in excreta: bifenazate glucuronide, bifenazate-diazene, 4-hydroxy bifenazate, 4-hydroxy bifenazate-diazene, 4-hydroxybiphenyl and its sulfate conjugate, 4,4'-dihydroxybiphenyl and its glucuronate and sulfate conjugates, 4-methoxybiphenyl and 4-hydroxy-4'-methoxybiphenyl and its conjugates. (See the toxicology report for more details of laboratory animal metabolism)

When a lactating goat was orally dosed with labelled bifenazate for 4 consecutive days at 21 mg/animal per day, equivalent to 10 ppm in the feed, most of the administered ^{14}C was excreted in the faeces (47%) and urine (19.5%). ^{14}C recovery was borderline at 68%. Residues in milk and tissues plus blood accounted for 0.22% and 2.0% of the dose respectively.

Metabolite 4-hydroxybiphenyl sulfate was the major identified component of the residue in milk (41% of TRR), while bifenazate and bifenazate-diazene comprised 9%. In muscle, residue levels were low with 4-hydroxybiphenyl the major identified component. In the fat, bifenazate was the major component at 53–58% of TRR. Residue levels and patterns in omental and perirenal fats were quite similar.

In goat liver, only 10% of the TRR was extractable. Bifenazate + bifenazate-diazene and 4-hydroxybiphenyl glucuronide were the main identified components, each comprising about 1% of TRR. In goat kidney, 4-hydroxybiphenyl glucuronide and sulfate accounted for approximately 14% of TRR. Bifenazate + bifenazate-diazene comprised less than 2% of TRR. In both liver and kidney, some of the unextractable TRR was apparently bound to protein.

The concentration of parent compound + bifenazate-diazene was substantially higher in the fat than in the other tissues suggesting that bifenazate (+ bifenazate-diazene) is a fat-soluble compound. No information was available on the residue distribution into the fat of goat milk.

When laying hens were orally dosed with labelled bifenazate for 4 consecutive days at 1.3 mg/bird per day, equivalent to 10 ppm in the feed, most of the administered ^{14}C was excreted in the faeces (84%). ^{14}C recovery was approximately 85%. Residues in eggs and tissues accounted for 0.1% and 1.4% of the dose respectively. Residues were not detectable (< 0.005 mg/kg) in breast muscle and egg white.

The major identified residues in liver, skin + fat and egg yolk were 4-hydroxybiphenyl (0.013 mg/kg, 2% TRR), bifenazate-diazene (0.008 mg/kg, 17% TRR) and bifenazate (0.005 mg/kg, 20% TRR), respectively. The distribution of bifenazate and bifenazate-diazene in the tissues and egg yolk suggests fat solubility.

The metabolic pathways in goats and poultry were generally similar, but additional conjugates were identified in the goat.

Plant metabolism

The Meeting received plant metabolism studies with bifenazate on oranges, apples, grapes, radish and cotton.

In plants, most of the resultant residue from the use of bifenazate was a surface residue. Parent bifenazate was the major component of the residue at shorter intervals and the major identified

component at longer intervals after treatment. Bifenazate-diazene was usually also present, but at much lower levels than parent bifenazate. Very little of the residue was translocated to the roots from treated radish foliage.

When Valencia orange trees were treated with a single application of WP formulated [^{14}C]bifenazate (0.42 and 2.2 kg ai/ha), approximately 80% of the residue was on the fruit surface 43 days after treatment, with bifenazate + bifenazate-diazene constituting 83% of TRR in and on the fruit. Bifenazate-diazene oxide, 4-methoxybiphenyl and 3-hydroxy-4-methoxybiphenyl were identified as minor components. After the rinsed oranges were separated into peel and the peeled fruits were homogenized to pulp and juice, the TRR distribution was mostly into the peel (approx 19% of TRR in whole fruit) with 0.9% in the pulp and 1% in the juice. Bifenazate was the only identified component in the juice at 0.003 and 0.001 mg/kg from the 0.42 and 2.2 kg ai/ha treatments respectively.

The TRR in oranges declined substantially at longer harvest intervals of 184, 274 and 442 days. Bifenazate and bifenazate-diazene were identified as components of the residue even at the longer intervals.

When Granny Smith apple trees were treated with a single application of WP formulated [^{14}C]bifenazate (0.42 and 2.2 kg ai/ha), approximately 60% of the residue was on the fruit surface 101 days after treatment, with bifenazate + bifenazate-diazene constituting 38% of TRR in and on the fruit. Bifenazate-diazene oxide and 4-methoxybiphenyl were identified as minor components. After the rinsed apples were homogenized and centrifuged to produce pomace and juice, the TRR distribution was mostly into the pomace (approx 30% of TRR in whole fruit) with approx 10% into the juice. Parent bifenazate and identified metabolites were not detected (< 0.001 mg/kg) in the juice.

Grape vines (variety Thompson Seedless) were treated with a single foliar application of WP formulated [^{14}C]bifenazate at 0.56 and 1.1 kg ai/ha and grapes were harvested 30 days later at maturity. Approximately 97% of the residue was surface residue. Bifenazate + bifenazate-diazene accounted for 98% and 95% of the TRR for the 0.56 and 1.1 kg ai/ha treatments respectively.

Radish plants (variety French Breakfast) were sprayed with a single foliar application of WS formulated [^{14}C]bifenazate at 1.1 and 2.2 kg ai/ha and harvested 7 days later for analysis. Most of the ^{14}C remained on the foliage (TRR 13 and 21 mg/kg) with little reaching the roots (0.0023 and 0.0043 mg/kg). The majority of the residue (60% and 80% TRR) remained on the surface. Bifenazate + bifenazate-diazene accounted for 57% and 71% of the TRR in and on the radish tops. A ring-hydroxylated bifenazate-diazene was identified as constituting approximately 1.3% of the TRR in radish tops.

After cotton plants (variety Maxxa), at late bloom to early boll set, were sprayed with a single foliar application of WP formulated [^{14}C]bifenazate (0.56 and 2.2 kg ai/ha), bifenazate and identifiable metabolites were present at very low levels (each < 0.001 mg/kg) in the cotton seed harvested 112 days after treatment. A high proportion (77–82%) of the cotton gin trash residue was extractable, with bifenazate approximately 50% of the extractable residue and bifenazate-diazene, bifenazate-diazene oxide and 4-methoxybiphenyl identified as minor residue components.

Environmental fate in soil

The Meeting received information on crop rotational studies for bifenazate. Information on soil metabolism and field dissipation was not required because no bifenazate uses as seed treatments or on root crops were provided for evaluation.

In a confined rotational crop study in USA a loamy sand soil was treated directly with ^{14}C labelled bifenazate at a rate equivalent to 0.56 kg ai/ha and allowed to age under greenhouse conditions prior to the sowing of the rotational crops. Crops of carrots, lettuce and wheat were sown into the treated soil in pots at intervals of 30, 125 and 360 days after treatment.

Immature lettuce were sampled at the 4-5 leaf stage. Immature carrot plants were sampled when carrots were approximately 6 mm in diameter. Wheat forage samples were taken approximately 5 weeks after sowing. The remainder of the crops were grown to maturity and subsequently harvested and analysed for ^{14}C (TRR) content. Samples were extracted and, where extractable residues exceeded 0.01 mg/kg, they were analysed by HPLC. No parent compound or reference metabolite was observed (LOQ 0.01 mg/kg). The unextractable residual solids from the wheat straw and fractions from the wheat forage were subjected to acid, base and enzyme hydrolysis, but no parent bifenazate or recognizable metabolite was released.

Methods of residue analysis

The Meeting received descriptions and validation data for analytical methods for residues of bifenazate in raw agricultural commodities, processed commodities, feed commodities, animal tissues, milk and eggs.

Because bifenazate and bifenazate-diazene are readily interconverted by mild oxidation and reduction conditions, the measured residue includes both compounds. The analytical methods use a mild reduction with ascorbic acid to convert the bifenazate-diazene residue to bifenazate before the measurement step. Residues are typically extracted with acetonitrile and water acidified with acetic acid. After a partition cleanup and reduction with ascorbic acid, the residue is analysed by HPLC with coulometric detection. The oxidative coulometric detection system is quite selective. Substituted hydrazines such as bifenazate are oxidized at 200 mV, but most sample matrix components are not.

LC-MS/MS has also been used in place of coulometric detection. The $[M+H]^+$ ion is used as the precursor ion for bifenazate. Transitions 301.1/198.1 (for quantification) and 301.1/170.1 are observed.

Numerous recovery data on a wide range of crop and animal commodity substrates and processed commodities were provided from validation testing of the methods, which showed that the methods were valid over the relevant concentration ranges. The validated LOQ was typically 0.01 mg/kg.

None of the tested multiresidue methods was suitable for the analysis of bifenazate and bifenazate-diazene.

Samples of apples and oranges from [^{14}C]bifenazate crop metabolism studies were extracted with acetonitrile + acetic acid and analysed by the HPLC-coulometer method and an HPLC-radiometric method. The HPLC-coulometer results were approximately 60% of those from the radiometric method.

Samples of fat and liver from a goat dosed orally for 4 consecutive days with [^{14}C]bifenazate at the equivalent of 20 ppm in the feed as in a goat metabolism study were analysed by the HPLC-coulometer method and by radiolabel measurement for bifenazate + bifenazate-diazene residues. Agreement was good for the fat tissue (0.043 and 0.045 mg/kg, radiolabel and enforcement respectively) while for the liver the level was too low for the enforcement method (0.0082 and < 0.01 mg/kg). Samples of milk and liver were hydrolysed with hydrochloric acid for 2 hours to convert the sulfate conjugate of 4-hydroxybiphenyl to the free metabolite for analysis. The analytical results for 4-hydroxybiphenyl, by a suggested enforcement method, were in good agreement with the radiolabel measurement for liver and in reasonable agreement for milk.

Stability of residues in stored analytical samples

The Meeting received information on the freezer storage stability of residues of bifenazate and bifenazate-diazene in apples, apricots, cantaloupe, cherries, cotton seed, cotton seed hulls, cotton seed meal, cotton seed refined oil, egg yolk, fat, gin trash, grape juice, grapes, kidney, liver, milk, mint, muscle, oranges, peaches, peppers, plums, potatoes, poultry liver, poultry muscle, poultry skin + fat, prunes, tomato, tomato paste and tomato puree.

Bifenazate residues (measured as bifenazate + bifenazate-diazene) are not particularly stable in some substrates. Stability is improved where the commodity is stored unchopped and in processed commodities presumably where enzymes are denatured. Bifenazate residues are stable in fat and milk, but are particularly unstable in kidney. Bifenazate residues are unstable in potato tuber matrix to the extent that disappearance from spiked samples causes difficulty with analytical recovery testing.

In a number of substrates some losses appeared to occur at spiking or soon after, but these losses may not be relevant when assessing the stability of incurred residues.

Residues of bifenazate or bifenazate-diazene measured as the sum of bifenazate and bifenazate-diazene did not decline by more than 30% when spiked into the following substrates and stored in a freezer at temperatures below -18°C for the interval tested: homogenized tomato 6 months; homogenized peppers 6 months; homogenized mint tops 102 days; sliced plums 4 weeks; tomato paste 4 weeks; tomato puree 4 weeks; cottonseed refined oil 28 days; apples skin surface 224 days; grapes surface 224 days; peaches skin surface 223 days; homogenized oranges 186 days; grape juice 186 days; homogenized prunes 182 days; milk 202 days; fat 95 days.

Estimates were made of the time interval for a 30% decline of residues of bifenazate or bifenazate-diazene measured as the sum of bifenazate and bifenazate-diazene when spiked into the following substrates and stored in a freezer at temperatures below -18°C: homogenized cherries 2.6 months; homogenized cantaloupe 3.9 months; homogenized apples 106 days; homogenized grapes 22 days; homogenized peaches 92 days; muscle 10 days.

In some matrices, e.g. cotton seed, the stability data were variable and difficult to interpret precisely.

When bifenazate was spiked into control samples of egg yolk, hen skin + fat, thigh muscle and liver and stored for 6 months below -10 °C, residues were stable in egg yolk and liver. In thigh muscle, 45% of the bifenazate disappeared, with 14% and 11% appearing as 4-hydroxybiphenyl and bifenazate-diazene respectively. In skin + fat, 97% of the bifenazate disappeared with 4%, 4% and 59% appearing as 4-hydroxybiphenyl, 4-methoxybiphenyl and bifenazate-diazene respectively.

Samples from the laying hen metabolism study were analysed by HPLC before and after freezer storage of 121–171 days to test the stability of incurred residues. The qualitative appearance of the initial and final chromatograms were reasonably similar for egg yolk, skin-with-fat and liver. Substantial changes were apparent for thigh muscle, but total residues in thigh muscle were very low (0.006 mg/kg).

Definition of the residue

The composition of the residue in the metabolism studies, the available residue data in the supervised trials, the toxicological significance of metabolites, the capabilities of enforcement analytical methods and the national residue definitions already operating all influence the decision on residue definition.

Parent compound and metabolite bifenazate-diazene are readily interconverted, so both should be included in the residue definition.

In crop residue situations, parent compound comprised a substantial part of the residue for commodities that were directly sprayed, so bifenazate and bifenazate-diazene should constitute the residue definition for crops.

In goat fat, poultry fats and egg yolks, the sum of bifenazate and bifenazate-diazene was the major identifiable residue.

In goat muscle, liver, kidney and milk, 4-hydroxybiphenyl and its conjugates constituted the main identifiable residue. However, 4-hydroxybiphenyl may arise from sources other than bifenazate

uses. It is a mammalian[33] and fungal[34] metabolite of biphenyl, a post-harvest fungicide used on citrus. It is also an industrial chemical used in the rubber industry[35]. Origins of 4-hydroxybiphenyl other than bifenazate mean that it would not be useful as part of an enforcement residue definition.

In the animal metabolism studies, the concentration of bifenazate + bifenazate-diazene was higher in the fat than in other tissues. In the dairy cow feeding study, the residue of bifenazate + bifenazate-diazene partitioned into the butter fat at the highest dosing level. The octanol-water partition coefficient of bifenazate (log P_{OW} = 3.5) also suggests that fat-solubility for the parent compound.

The Meeting recommended a residue definition for bifenazate for plants and animals.

Definition of the residue (for compliance with the MRL and for estimation of dietary intake): sum of bifenazate and bifenazate-diazene (diazenecarboxylic acid, 2-(4-methoxy-[1,1'-biphenyl-3-yl] 1-methylethyl ester), expressed as bifenazate. The residue is fat soluble.

Results of supervised trials on crops

The Meeting received supervised trials data for bifenazate uses on citrus fruits (mandarin, natsudaidai, lime), pome fruits (apple, pear), stone fruits (apricot, peach, plum, cherry), berry fruits (grapes, strawberry), figs, cucurbit fruiting vegetables (cantaloupe, watermelon, cucumber, summer squash), fruiting vegetables (tomato, peppers, egg plant), tree nuts (almond, pecan), cotton and herbs (mint, hops, tea).

Trials from Japan were available only in summary form and could not be evaluated.

All other trials were from the USA. In most trials, duplicate field samples from an unreplicated plot were taken at each sampling time and were analysed separately. For the purposes of the evaluation, the mean of the two results was taken as the best estimate of the residue from the plot.

Labels (or translations of labels) were available from Australia, Japan describing the registered uses of bifenazate.

Pome fruits

Bifenazate is registered in USA for use on pome fruit trees at 0.42–0.56 kg ai/ha with a PHI of 7 days.

In 14 US trials on apples in 1998 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.049, 0.058, 0.16, 0.16, 0.17, 0.18, 0.18, 0.19, 0.20, 0.22, 0.23, 0.37, 0.38 and 0.58 mg/kg.

In eight trials on pears in USA in 1998 with conditions matching the registered use, residues of bifenazate + bifenazate-diazene were: 0.094, 0.097, 0.10, 0.13, 0.14, 0.16, 0.24 and 0.29 mg/kg. The Meeting noted that the pear samples had spent 15–16 months in frozen storage, which exceeded the proven frozen storage interval for apples (7–8 months) representing pome fruits. However, the residue levels appeared to be stable on the fruit surface for the interval tested and the residue trials were accepted as valid.

The Meeting decided to combine the apple data and pear data for a pome fruits group estimation (populations not significantly different – Mann-Whitney test). The combined pome fruit data (22 values), in rank order were: 0.049, 0.058, 0.094, 0.097, 0.10, 0.13, 0.14, 0.16, 0.16, 0.16, 0.17, 0.18, 0.18, 0.19, 0.2, 0.22, 0.23, 0.24, 0.29, 0.37, 0.38 and 0.58 mg/kg.

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[33] Wiebkin P, Fry JR, Jones CA, Lowing RK and Bridges JW. 1978. Biphenyl metabolism in isolated rat hepatocytes: effect of induction and nature of the conjugates. *Biochemical Pharmacology* 27:1899-1907.
[34] Schwartz RD, Williams AL and Hutchinson. 1980. Microbial production 4,4'-dihydroxybiphenyl: biphenyl hydroxylation by fungi. *Appl. Environ. Microbiol.* 39:702-708.
[35] Merck Index. 1996. 12th Edition. 7459 *p*-phenylphenol.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in pome fruits, of 0.7 and 0.175 mg/kg respectively.

Stone fruits

Bifenazate is registered in USA for use on stone fruit trees at 0.42–0.56 kg ai/ha with a PHI of 3 days.

In five US trials on apricots in 2002 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.23, 0.30, 0.44, 0.59 and 0.73 mg/kg.

In 12 US trials on peaches in 1998 and 2002 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.13, 0.16, 0.17, 0.22, 0.23, 0.23, 0.26, 0.40, 0.44, 0.45, 0.55 and 1.2 mg/kg.

In eight US trials on plums in 1998 and 2002 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.01, 0.03, 0.034, 0.04, 0.04, 0.04, 0.07 and 0.13 mg/kg.

In 14 US trials on cherries in 2001 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.29, 0.23, 1.6, 0.11, 0.48, 0.20, 0.42, 0.89, 0.71, 1.2, 0.81, 0.18, 0.27 and 0.34 mg/kg. The data were on pitted cherries, but the Meeting accepted the data as valid for MRL setting.

The residue data from peaches, apricots and cherries appeared to be from similar populations and were combined for a stone fruits group MRL. Residues on plums appeared to be much lower (significantly different from peach and cherry residues – Mann-Whitney test) than on the other stone fruits and were not included in the data set for STMR estimation.

Residue data on stone fruits in rank order (median underlined) were: 0.11, 0.13, 0.16, 0.17, 0.18, 0.20, 0.22, 0.23, 0.23, 0.23, 0.23, 0.26, 0.27, 0.29, 0.30, 0.34, 0.40, 0.42, 0.44, 0.44, 0.45, 0.48, 0.55, 0.59, 0.71, 0.73, 0.81, 0.89, 1.2, 1.2 and 1.6 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in stone fruits of 2 and 0.34 mg/kg respectively.

Grapes

Bifenazate is registered in USA for use on grape vines at 0.42–0.56 kg ai/ha with a PHI of 14 days.

In 12 US trials on grapes in 1998 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.05, 0.07, 0.10, 0.11, 0.17, 0.17, 0.20, 0.21, 0.29, 0.31, 0.33 and 0.55 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in grapes, of 0.7 and 0.185 mg/kg respectively.

Strawberries

Bifenazate is registered in USA for use on strawberries with two treatments at 0.42–0.56 kg ai/ha and a PHI of 1 day.

In seven US trials on strawberries in 1999 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.29, 0.49, 0.53, 0.63, 0.68, 0.93 and 1.0 mg/kg.

One strawberry trial had produced values of 3.4 and 2.9 mg/kg for its 3 day sample and 0.44 as the mean of the 1 day samples. The authors of the report discounted the high values as being due to analytical error, but found no specific cause. The trial was not included in this appraisal because of doubts about its validity.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in strawberries, of 2 and 0.63 mg/kg respectively.

Fruiting vegetables, cucurbits

Bifenazate is registered in USA for use on cucurbit vegetables at 0.42–0.56 kg ai/ha with a PHI of 3 days.

In eight US trials on cantaloupes in 2000 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.03, 0.04, 0.04, 0.04, 0.05, 0.08, 0.10 and 0.16 mg/kg.

In eight US trials on cucumbers in 2000 matching GAP, residues of bifenazate + bifenazate-diazene were: < 0.01, < 0.01, 0.03, 0.04, 0.05, 0.07, 0.08 and 0.22 mg/kg.

In seven US trials on summer squash in 2000 matching GAP, residues of bifenazate + bifenazate-diazene were: < 0.01, 0.01, 0.02, 0.04, 0.06, 0.12 and 0.34 mg/kg.

The Meeting decided to combine the data from cantaloupes, cucumbers and summer squash to support a cucurbit fruiting vegetables group MRL (populations not significantly different – Mann-Whitney test).

Residue data from 23 trials on cucurbit fruiting vegetables in rank order (median underlined) were: < 0.01, < 0.01, < 0.01, 0.01, 0.02, 0.03, 0.03, 0.04, 0.04, 0.04, 0.04, <u>0.04</u>, 0.05, 0.05, 0.06, 0.07, 0.08, 0.08, 0.10, 0.12, 0.16, 0.22 and 0.34 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in cucurbit fruiting vegetables of 0.5 and 0.04 mg/kg respectively.

Fruiting vegetables, other than cucurbits

Bifenazate is registered in USA for use on fruiting vegetables at 0.42–0.56 kg ai/ha with a PHI of 3 days.

In 12 US trials on tomatoes in 2000 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.03, 0.03, 0.04, 0.04, 0.07, 0.09, 0.10, 0.11, 0.13, 0.14, 0.19 and 0.29 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in tomatoes of 0.5 and 0.095 mg/kg respectively.

In eight US trials on bell peppers in 2000 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.13, 0.15, 0.15, 0.23, 0.24, 0.32, 0.52 and 1.1 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in sweet peppers of 2 and 0.235 mg/kg respectively.

In three US trials on non-bell peppers in 2000 matching GAP, residues of bifenazate + bifenazate-diazene were: 0.54, 1.1 and 1.6 mg/kg.

The Meeting noted that the residue data for non-bell peppers, a minor crop, were rather limited, but also noted that two values were equivalent to the high end of the bell pepper data with one slightly higher as expected.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in chili peppers of 3 and 1.1 mg/kg respectively.

The Meeting noted that the registered use of bifenazate referred to the fruiting vegetables group but was unable to recommend a group MRL because the residue levels on the three crops were too different.

Tree nuts

Bifenazate is registered in the USA for use on almonds and other tree nuts (including beech nut, Brazil nut, butternut, cashew, chestnut, hickory nut and Macadamia nut) at 0.42–0.56 kg ai/ha with a PHI of 7 days and on filberts, pecans, pistachios and walnuts with a PHI of 14 days.

In five trials on almonds in USA in 2001, the application rate was 0.84 kg ai/ha, 50% higher than the GAP rate, but acceptable for trials on tree nuts. In five US trials on almonds in 2001

harvested 7 days after treatment, residues of bifenazate + bifenazate-diazene in almond kernels were: 0.01, 0.02, 0.03, 0.05 and 0.10 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in almonds of 0.2 and 0.03 mg/kg respectively.

In five US trials on pecans in 2001 where the application rate (0.85 kg ai/ha) was 50% higher than the GAP rate and a PHI of 14 days, residues of bifenazate + bifenazate-diazene in pecan kernels were: < 0.01 (3), 0.013 and 0.014 mg/kg. The Meeting noted that the application rate was higher than GAP, but the residues were close to the LOQ and could be used for evaluation.

The Meeting agreed to extrapolate the almond data to the tree nuts group and recommended a maximum residue level and an STMR value for bifenazate in tree nuts of 0.2 and 0.03 mg/kg respectively.

Cotton seed

Bifenazate is registered in USA for use on cotton at 0.4–0.8 kg ai/ha with a PHI of 60 days.

In 19 US trials on cotton in 1999 and 2000 matching GAP, residues of bifenazate + bifenazate-diazene in cotton seed were: < 0.01 (10), 0.01, 0.02, 0.03, 0.03, 0.04, 0.04, 0.06, 0.06 and 0.28 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in cotton seed of 0.3 and 0.01 mg/kg respectively.

Mint

Bifenazate is registered in USA for use on mint at 0.42–0.84 kg ai/ha with a PHI of 7 days.

In five US trials on mint in 2000 matching GAP, residues of bifenazate + bifenazate-diazene in mint tops were: 6.4, 6.6, 12.9, 15.4 and 18.1 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in mint of 40 and 12.9 mg/kg respectively.

Hops

Bifenazate is registered in USA for use on hops at 0.42–0.84 kg ai/ha with a PHI of 14 days.

In three US trials on hops in 1999 matching GAP, residues of bifenazate + bifenazate-diazene in mint tops were: 7.1, 7.8 and 9.3 mg/kg.

The Meeting recognized that the database for hops was very limited. However, hops are a minor crop and the Meeting estimated a maximum residue level and an STMR value for bifenazate in hops of 20 and 7.8 mg/kg respectively.

Cotton gin trash

Bifenazate is registered in USA for use on cotton at 0.4–-0.8 kg ai/ha with a PHI of 60 days.

Residues were measured on cotton gin trash in 9 of the previously mentioned cotton trials where the application rates and PHIs matched label rates. Residues of bifenazate + bifenazate-diazene in cotton gin trash were: 0.07, 0.39, 0.69, 0.88, 1.3, 2.5, 3.8, 4.0 and 18 mg/kg. No maximum residue level was estimated for dry cotton fodder (cotton gin trash) because it is not traded internationally.

Almond hulls

In five trials on almonds in USA in 2001, the application rate was 0.84 kg ai/ha, 50% higher than the GAP rate, but acceptable for trials on tree nuts. In five US trials on almonds in 2001, harvested 7 days after treatment, residues of bifenazate + bifenazate-diazene in almond hulls were: 1.8, 2.8, 5.0, 5.1 and 6.9 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in almond hulls of 10 and 5.0 mg/kg respectively. The highest residue was 6.9 mg/kg.

Fate of residues during processing

The Meeting received information on the fate of bifenazate residues during the juicing of apples, the drying of prunes, the production of grape juice and raisins, the production of tomato paste and puree, the production of cotton seed oil and the processing of mint tops.

Apples from bifenazate field trials at exaggerated (5×) rates were ground in a hammer mill and the mash was collected in cloths sacks and pressed in a hydraulic press to produce the wet pomace and juice.

Plums were harvested 3 days after a bifenazate treatment, placed in mesh bags and dried in a drying tunnel for 18 to 27 hours at 71–88°C simulating a commercial process.

Fresh field-treated grapes were fed into a crusher/stemmer to produce a grape pulp that was heated in a steam kettle and then pressed to separate juice and wet pomace. Grapes for raisins were placed on trays or paper to dry with turning after 7 days. After 14 days the stems were removed to produce the raisins.

Approximately 11 kg of fresh mint tops were subject to steam distillation in a cooker to produce 33–43 mL of oil. The oil samples were then filtered and refrigerated.

Cotton seed was cracked and dried at 55–71°C to a kernel moisture level of 12%. After further heating, the kernel material was flaked, steam treated and extracted with hexane to produce meal and crude oil. Sodium hydroxide treatment of the crude oil produced the refined cotton seed oil.

Tomatoes were first cleaned and then soaked for 3 minutes in a dilute sodium hydroxide solution, then thoroughly rinsed. Tomatoes were then chopped and rapidly heated to about 80°C and skin and seeds were separated from juice. Juice was evaporated to produce a puree. Further concentration and addition of salt produced a paste that was heated to approximately 85°C and canned.

Calculated processing factors and the mean or best estimate are summarized in the following table.

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors (PF).	Median or best estimate PF
Apple	wet pomace	1.8, 1.7	1.8
Apples	apple juice	0.23, 0.10	0.17
Cotton seed	hulls	0.105, 0.35	0.23
Cotton seed	cotton seed meal	< 0.0095, < 0.0038	< 0.0038
Cotton seed	cotton seed refined oil	< 0.0095, < 0.0038	< 0.0038
Grapes	grape juice	0.054, 0.17	0.11
Grapes	raisins	0.36, 3.2	3.2
Plums	dried prunes	0.5, < 0.3	0.5
Tomato	tomato paste	1.26	1.3
Tomato	tomato puree	5.6	5.6

The processing factors for wet apple pomace (1.8) and apple juice (0.17) were applied to the estimated STMR for pome fruits (0.175 mg/kg) to produce STMR-P values for wet apple pomace (0.32 mg/kg) and apple juice (0.030 mg/kg).

The processing factor for dried prunes (0.5) was applied to the median residue for plums (0.04 mg/kg) to produce an STMR-P value for dried prunes (0.02 mg/kg).

The processing factors for raisins (3.2) and grape juice (0.11) were applied to the estimated STMR for grapes (0.185 mg/kg) to produce STMR-P values for raisins (0.59 mg/kg) and grape juice (0.020 mg/kg). The processing factor for raisins (3.2) was applied to the grape residue data (highest value 0.55 mg/kg) to produce an estimated highest value for dried grapes (1.76 mg/kg).

The Meeting estimated a maximum residue level for bifenazate in dried grapes (= currants, raisins, sultanas) of 2 mg/kg.

The processing factors for tomato puree (5.6) and tomato paste (1.3) were applied to the estimated STMR for tomatoes (0.095 mg/kg) to produce STMR-P values for tomato puree (0.53 mg/kg) and tomato paste (0.13 mg/kg).

The processing factors for cotton seed hulls (0.23), cotton seed meal (< 0.0038) and cotton seed refined oil (< 0.0038) were applied to the estimated STMR for cotton seed (0.01 mg/kg) to produce STMR-P values for cotton seed hulls (0.0023 mg/kg), cotton seed meal (0.00004 mg/kg) and cotton seed refined oil (0.00004 mg/kg).

Residues in animal commodities

Farm animal feeding

The meeting received a lactating dairy cow feeding study, which provided information on likely residues resulting in animal tissues and milk from residues in the animal diet.

Lactating Holstein cows were dosed with bifenazate at the equivalent of 1 (1×), 3 (3×) and 10 (10×) ppm in the dry-weight diet for 28 consecutive days. Milk was collected throughout and tissues were collected for residue analysis of bifenazate + bifenazate-diazene and metabolite 4-hydroxybiphenyl and its sulfate conjugate from animals slaughtered on day 29.

Residues of bifenazate + bifenazate-diazene did not exceed the LOQ (0.01 mg/kg) in loin muscle, round muscle, liver, milk or skim milk at the highest dosing level 10 ppm. Residues were detected in the kidney of one animal at 0.01 mg/kg.

Residues of 4-hydroxybiphenyl and its sulfate conjugate did not exceed the LOQ (0.01 mg/kg) in any sample of tissue, milk or butterfat.

Residues were present in omental and perirenal fat in the 3 ppm feeding group (0.01–0.03 mg/kg) and the 10 ppm feeding group (0.03–0.10 mg/kg), but not in the 1 ppm feeding group. Residues were also present in butterfat from the 10 ppm group (0.01–0.03 mg/kg) but not from the 3 ppm group.

The dairy cow feeding study confirms the fat-solubility of the residue, bifenazate + bifenazate-diazene and that fat is the target tissue.

Farm animal dietary burden

The Meeting estimated the dietary burden of bifenazate in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual. Calculation from highest residue 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 dietary burden of farm animals

Commodity	CC	Residue mg/kg	Basis	DM %	Residue dw mg/kg	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cattle*	*Poultry*	Beef cattle	Dairy cattle	Poultry
Almond hulls	AM	6.9	highest residue	90	7.7						
Apple pomace, wet	AB	0.32	STMR-P	40	0.800	*40*	*20*		0.32	0.16	
Cotton fodder, dry	AM	18	highest residue	90	20.000	*20*	*20*		4.00	4.00	
Cotton seed	SO	0.28	highest residue	88	0.318	*25*	*25*		0.08	0.08	
Cotton seed hulls	AM	0.0023	STMR-P	90	0.003						
Cotton seed meal		0.00004	STMR-P	89	0.000			*20*			0.00
Total						*85*	*65*	*20*	4.40	4.24	0.00

Estimated mean dietary burden of farm animals

Commodity	CC	Residue mg/kg	Basis	DM %	Residue dw mg/kg	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cattle*	*Poultry*	Beef cattle	Dairy cattle	Poultry
Almond hulls	AM	5.0	STMR	90	5.6	*10*	*10*		0.56	0.56	
Apple pomace, wet	AB	0.32	STMR-P	40	0.800	*40*	*20*		0.32	0.16	
Cotton fodder, dry	AM	1.3	median residue	90	1.444	*10*	*10*		0.14	0.14	
Cotton seed	SO	0.01	STMR	88	0.011	*25*	*25*		0.00	0.00	
Cotton seed hulls	AM	0.0023	STMR-P	90	0.003						
Cotton seed meal		0.00004	STMR-P	89	0.000			*20*			0.00
Total						*85*	*65*	*20*	1.02	0.86	0.00

Animal commodities, MRL estimation

For MRL estimation, the high residues in the tissues were calculated by interpolating the maximum dietary burden between the relevant feeding levels from the dairy cow feeding study and using the highest tissue concentrations from individual animals within those feeding groups. The high residues for butterfat were calculated similarly except that the mean butterfat concentrations from the relevant groups were used instead of the highest individual values.

Cattle

The STMR values for the tissues, milk and butterfat were calculated by interpolating the STMR dietary burdens between the relevant feeding levels from the dairy cow feeding study and using the mean tissue and 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) Feeding level [ppm]	Milk	Butterfat	Muscle	Liver	Kidney	Fat
MRL						
	mean	mean	highest	highest	highest	highest
MRL beef cattle (4.4) [3, 10]			< 0.01 [< 0.01, < 0.01]	< 0.01 [< 0.01, < 0.01]	< 0.01 [< 0.01, 0.01]	0.044 [0.03, 0.10]
MRL dairy cattle (4.24) [3, 10]	< 0.01 [< 0.01, < 0.01]	0.013 [< 0.01, 0.03]				
STMR						
	mean	mean	mean	mean	mean	mean
STMR beef cattle (1.02) [0, 1]			< 0.01 [0, < 0.01]	< 0.01 [0, < 0.01]	< 0.01 [0, < 0.01]	< 0.01 [0, < 0.01]
STMR dairy cattle (0.86) [0, 1]	< 0.01 [0, < 0.01]	< 0.01 [0, < 0.01]				

The Meeting estimated dietary burdens for bifenazate in dairy cows to be 4.24 and 0.86 ppm (maximum and mean) and for beef cattle to be 4.4 and 1.02 ppm (maximum and mean), which are all less than feeding levels that produced residues below LOQ (< 0.01 mg/kg) in the milk, muscle and liver.

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

For kidney, there was one residue detection from three animals at the 10 ppm feeding level, so for a dietary burden of 4.4 ppm, the residue in kidney should not exceed 0.01 mg/kg. The kidney and liver residues were used to support an edible offal MRL recommendation.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in mammalian edible offal of 0.01* and 0.01 mg/kg, respectively.

By interpolation, the highest residue in fat was estimated as 0.044 mg/kg, while the STMR value was below the LOQ (0.01 mg/kg).

The Meeting estimated a maximum residue level for bifenazate in mammalian meat of 0.05 (fat) mg/kg. The associated STMR values for muscle and fat were 0.01 and 0.01 mg/kg.

By interpolation, the highest residue in butterfat was estimated as 0.013 mg/kg, while the STMR value was below the LOQ (0.01 mg/kg). The Meeting noted that, in this experiment, the yield of butterfat averaged 13% of the milk sample, suggesting that this "butterfat" may have contained only about 33% lipid (if the milk contained 4% lipid). This would mean that the highest residue would be approximately 0.039 mg/kg, expressed on the lipid content.

The Meeting estimated a maximum residue level and an STMR value for bifenazate in milk fats of 0.05 and 0.01 mg/kg, respectively.

Poultry

The dietary burden for poultry, currently based only on cotton seed meal is very low and is essentially zero. According to the poultry metabolism study, residues in poultry tissues and eggs were very low even for a 10 ppm dietary burden. Bifenazate residues, with current uses, are therefore not anticipated to occur in poultry tissues and eggs.

The Meeting estimated maximum residue levels of 0.01* (fat), 0.01* and 0.01* for bifenazate in poultry meat, poultry offal and eggs, respectively. The Meeting also estimated STMR values of 0 mg/kg for bifenazate residues in poultry meat (muscle 0 mg/kg; fat 0 mg/kg), poultry edible offal and eggs.

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 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 1–20% of the ADI (0-0.01 mg/kg bw). The Meeting concluded that the long-term intake of residues of bifenazate from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The Meeting decided that it was unnecessary to establish an ARfD. The Meeting concluded that the short-term intake of bifenazate residues is unlikely to present a public health concern.

4.5 BOSCALID (221)

TOXICOLOGY

Boscalid is the provisionally approved ISO name for 2-chloro-*N*-(4'-chlorobiphenyl-2-yl)nicotinamide (IUPAC) or 2-chloro-*N*-(4'-chloro[1,1'-biphenyl]-2-yl)-3-pyridinecarboxamide (CAS). It is an anilide fungicide that inhibits mitochondrial respiration, thereby inhibiting spore germination, germ-tube elongation, mycelial growth, and sporulation of pathogenic fungi on the leaf surface, and is used against a broad spectrum of diseases in a wide range of crops. Boscalid is being reviewed for the first time by the present Meeting at the request of the CCPR. All critical studies complied with GLP.

Biochemical aspects

In rats given [^{14}C]boscalid as a single oral dose at 50 or 500 mg/kg bw, the radiolabel was rapidly but incompletely absorbed from the gastrointestinal tract, widely distributed, and rapidly eliminated from the body. The excretion balance of boscalid demonstrates that at doses of 50 and 500 mg/kg bw approximately 16% and 3%, respectively, of the applied radioactivity is excreted via the urine. Excretion via the faeces accounted for 80% (lowest dose) to 95% (highest dose) of the dose; however, 40% of the lowest dose and 12% of the highest dose was eliminated from the body via the bile. Bioavailability decreased with increasing dose, and was estimated to be about 50% at the lowest dose, but only about 15% at the highest dose. The plasma concentration–time curve showed two maxima. The initial half-life was approximately 7–8 hours and the terminal half-life was approximately 20–40 hours. Tissue distribution determination showed that the largest amounts of radioactivity were in the gastrointestinal tract, liver and adipose tissues. There is no evidence for a cumulative potential of boscalid.

The dermal absorption of boscalid in rats in vivo is approximately 8% or less, depending on the duration of exposure and concentration applied. The initial rate of penetration through rat epidermal membranes was at least 7.7-fold greater than through human epidermal membranes. When the amount of radioactivity remaining associated with the skin was also taken into account, it was

concluded that there is no notable difference between rats and humans in the bioavailability of boscalid applied to the skin.

After oral administration to male and female rats, the systemically available portion of boscalid was rapidly and extensively metabolized to a large number of biotransformation products. The hydroxylation of the diphenyl moiety was the quantitatively most important pathway. The second important pathway was the substitution of the chlorine of 2-chloropyridine by conjugation with glutathione. Partial cleavage of the glutathione moiety afforded the cysteine conjugate and finally the sulfhydryl compound that was subsequently methylated or oxidized. In addition, the introduction of glutathione and a second hydroxyl group into the diphenyl moiety was observed. Combinations of these reactions and the conjugation of the hydroxyl groups with glucuronic acid or sulfate, and the conjugation of the sulfhydryl group with glucuronic acid led to the large number of metabolites that have been identified. Cleavage of the amide bond appeared to be negligible because 2-chloronicotinic acid was detected only in trace amounts. No major differences were observed with regard to label, sex or dose.

Toxicological data

In male and female rats, the toxicity of boscalid was low, with values for the oral LD_{50} of > 5000 mg/kg bw, dermal LD_{50} of > 2000 mg/kg bw and inhalation LC_{50} of > 6.7 mg/L. Furthermore, boscalid is not irritating to the skin or the eyes of rabbits. In a guinea-pig maximization test for sensitizing potential, about one fifth of the animals developed a reaction upon challenge.

Overall, in short-term studies with boscalid, the signs of toxicity observed in mice, rats and dogs were similar, with reduced body-weight gain, changes in clinical chemistry, and liver enlargement being common features. The results of the short-term studies suggest that the increased liver weights were indicative of an adaptive response to exposure. Histopathology confirmed the liver as a target organ with observation of hypertrophy of hepatocytes, although this too is indicative of an adaptive response. Hypertrophy was accompanied by proliferation of smooth endoplasmic reticulum and the induction of cytochrome P450 protein (although no increased activities of specific CYP isoenzymes were identified) and several microsomal enzymes involved in conjugation reactions. The rat was the only species investigated for these particular effects. There were also increases in blood GGT activity at higher doses. Furthermore, in mice and rats given diets containing high concentrations of boscalid there was increased lipid accumulation in the liver. Absolute thyroid weights were increased in male and female rats of some high-dose groups, but not in dogs in which there were, however, some increases in relative weight of the thyroid. In male rats there was an increased incidence of thyroid follicular cell hyperplasia at doses of 2000 ppm, equal to 139 mg/kg bw, and higher, but this did not occur in female rats or in dogs of either sex. There is evidence that this effect is due to excessive perturbation of the pituitary–hypothalamus–thyroid-axis homeostatic mechanism, consisting of increases in the activity of hepatic glucuronyltransferase enzymes, some of which are involved in the metabolism of thyroid hormones, and in decreases in the concentrations of circulating thyroid hormones.

The NOAELs for the short-term dietary studies were: 90-day study in rats, 500 ppm (equal to 34 mg/kg bw per day); 90-day dietary study in mice, 150 ppm (equal to 29 mg/kg bw per day); 90-day study in dogs, 250 ppm (equal to 7.6 mg/kg bw per day); 12-month study in dogs, 800 ppm (equal to 22 mg/kg bw per day). In a 4-week study of dermal toxicity with boscalid in rats, no substance-related systemic findings were detected at 1000 mg/kg bw per day, the highest dose tested.

Long-term feeding studies with boscalid in rats and mice confirmed that the primary target organ was the liver. There was no evidence for a carcinogenic potential in mice, and a higher incidence of thyroid follicular cell tumours in rats was due to benign neoplasms, the incidence of these tumours being not statistically significantly different from that in the control group. Since no clear increase in the incidence of thyroid follicular cell tumours was observed, it was not considered necessary to investigate modes of action in a formal or detailed manner. In addition, the 10% benchmark-dose lower 95% confidence level ($BMDL_{10}$) for thyroid adenomas in male rats, according

to a number of statistical models, was 76 mg/kg bw per day. This demonstration, that very high doses are required to produce proliferative responses, even in rats, reinforces the conclusion drawn from the mechanistic studies, i.e. that this is exclusively a phenomenon that occurs at high doses and is not relevant for human exposure. The NOAEL identified in long-term studies in rats was 100 ppm, equal to 4.4 mg/kg bw per day, on the basis of increased GGT activity and hepatic centrilobular hypertrophy and eosinophilic foci in males and increased concentration of cholesterol and reduced prothrombin times in females at 500 ppm, which may be considered as an LOAEL. In long-term studies in mice, the NOAEL was 80 ppm (equal to 13 mg/kg bw per day) on the basis of decreased body-weight gain in males.

Boscalid was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence for genotoxicity was observed in any test. The Meeting concluded that boscalid is unlikely to be genotoxic.

In the absence of genotoxicity and any evidence of relevant carcinogenicity in rodents, the Meeting concluded that boscalid is unlikely to pose a carcinogenic risk to humans.

The reproductive toxicity of boscalid was investigated in a two-generation study of reproduction in rats and in studies of developmental toxicity in rats and rabbits.

Reproductive function was not affected in rats in the two-generation study with boscalid and the NOAEL for reproductive function was 10000 ppm, equal to 1034 mg/kg bw per day, the highest dose tested. The NOAEL for systemic toxicity in the parental animals in the two-generation study was 100 ppm, equal to 10 mg/kg bw per day on the basis of reduced body-weight gain, liver-weight increases, spleen-weight decreases and increased incidences of hepatic centrilobular hypertrophy at 1000 ppm, equal to 101 mg/kg bw per day. In pups, decreased body-weight gain and reduced spleen weights at 1000 ppm were the effects that defined the NOAEL for offspring toxicity at 100 ppm, equal to 10 mg/kg bw per day. In the two-generation study of toxicity in rats, there were reductions in spleen and thymus weight in the pups, but these were not consistent with regard to sex and generation and therefore not considered to be toxicologically significant.

In a study of developmental toxicity, rats were given boscalid at doses of up to 1000 mg/kg bw per day. No maternal toxicity was observed. There was an increased incidence of delayed ossifications (of thoracic centra), which was statistically significantly increased at 1000 mg/kg bw and exceeded the range for historical controls. The NOAEL for maternal toxicity was 1000 mg/kg bw per day, the highest dose tested, and the NOAEL for developmental toxicity was 300 mg/kg bw on the basis of reduced ossification of thoracic centra.

In a study of developmental toxicity in rabbits given boscalid at doses of up to 1000 mg/kg bw per day, significant maternal toxicity, consisting of reduced feed consumption and body-weight gain, was observed at the highest dose. There was an increased incidence of delayed ossifications (of thoracic centra) at 1000 mg/kg bw per day. Both the observed litter incidence of delayed ossifications and the number of affected fetuses per litter were statistically significantly increased above control levels and clearly exceeded the range for historical controls. The increase in fetal incidence was dose-related and exceeded the range for historical controls in all groups, including the controls. The NOAEL for maternal toxicity was 300 mg/kg bw per day and the NOAEL for developmental toxicity was 300 mg/kg bw per day on the basis of reduced ossification of thoracic centra.

No signs of neurotoxicity were noted in any studies, including in specific studies for neurotoxicity.

There was no evidence of immunotoxicity in a study for immunotoxicity in adult rats exposed to boscalid at dietary concentrations of up to 10000 ppm, equal to 736.2 mg/kg bw per day for 4 weeks.

The Meeting concluded that the existing data were adequate to characterize the potential hazard to fetuses, infants and children.

Toxicological evaluation

An ADI of 0–0.04 mg/kg bw was established for boscalid based on the NOAEL of 4.4 mg/kg bw per day, identified on the basis of increased GGT activity and increased incidences of hepatic eosinophilic foci in male rats in a 24-month long-term dietary study of toxicity and carcinogenicity and a safety factor of 100.

The Meeting concluded that it was not necessary to establish an ARfD for boscalid in view of the well-demonstrated lack of toxicity in studies of acute toxicity, the absence of relevant developmental toxicity that could have occurred as a consequence of a single exposure, the absence of any indication of neurotoxicity and the absence of any other adverse effects that would be likely to be induced after a single or a small number of exposures in repeat-dose studies.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	18-month study of toxicity and carcinogenicity	Toxicity	80 ppm, equal to 13 mg/kg bw per day	400 ppm, equal to 65 mg/kg bw per day
		Carcinogenicity	8000 ppm[a], equal to 1345 mg/kg bw per day	—
Rat	24-month studies of toxicity and carcinogenicity	Toxicity	100 ppm, equal to 4.4 mg/kg bw per day	500ppm, equal to 23 mg/kg bw per day
		Carcinogenicity	2500 ppm[a], equal to 116 mg/kg bw per day	—
	Two-generation study of reproductive toxicity[b]	Reproductive toxicity	10000 ppm[a] equal to 1034 mg/kg bw per day	—
		Parental toxicity	100 ppm, equal to 10 mg/kg bw per day	1000 ppm, equal to 101 mg/kg bw per day
		Offspring toxicity	100 ppm, equal to 10 mg/kg bw per day	1000 ppm, equivalent to 101 mg/kg bw per day
	Developmental toxicity [c]	Maternal toxicity	1000 mg/kg bw per day [a]	—
		Embryo and fetal toxicity	300 mg/kg bw[a] per day	1000 mg/kg bw per day
Rabbit	Developmental toxicity[c]	Maternal toxicity	300 mg/kg bw per day	1000 mg/kg bw per day
		Embryo and fetal toxicity	300 mg/kg bw per day	1000 mg/kg bw per day
Dog	1-year study of toxicity	Toxicity	800 ppm, equal to 22 mg/kg bw per day	2000 ppm, equal to 57 mg/kg bw per day

[a] Highest dose tested

[b] Measurements of intake of the compound are the mean of the premating phases for F_0 and F_1 females

[c] Gavage administration

Estimate of acceptable daily intake for humans

0–0.04 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 boscalid

Absorption, distribution, excretion and metabolism	
Rate and extent of oral absorption	High, inverse dose-dependent bioavailability of 50–15%; two plasma T_{max} values, 1 hours and 8h (rat)
Dermal absorption	Approximately 8% (rat)
Distribution	Distributed throughout the body; higher concentrations in liver and gastrointestinal tract
Potential for accumulation	No evidence
Rate and extent of excretion	High (but determined by the low rate of absorption); essentially 100% excretion in bile and urine within 168 h,
Metabolism in animals	Extensive, about 40 metabolites, little parent compound remaining
Toxicologically significant compounds (animals, plants and environment)	Parent
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rat, LC_{50}, inhalation	> 6.7 mg/L air (4 h)
Rabbit, LD_{50}, dermal	> 2000 mg/kg bw
Rabbit, skin irritation	Not irritating
Rabbit, eye irritation	Not irritating
Guinea-pig, skin sensitization	Not sensitizing
Short-term studies of toxicity	
Target/critical effect	Liver, thyroid; body weight
Lowest relevant oral NOAEL	22 mg/kg bw per day (12-month study in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (4-week study in rats)
Lowest relevant inhalation NOAEC	No data
Genotoxicity	Not genotoxic in vivo or in vitro

Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver, thyroid; body weight
Lowest relevant NOAEL	4.4 mg/kg bw per day (24-month study in rats)
Carcinogenicity	Boscalid induced a low incidence of benign thyroid tumours in rats
Reproductive toxicity	
Reproductive target/critical effect	None
Lowest relevant reproductive NOAEL	1034 mg/kg bw[a,b] per day
Developmental target/critical effect	Not teratogenic; reduced fetal body weight, delayed ossifications
Lowest relevant developmental NOAEL	300 mg/kg bw[a] per day (rat, rabbit)
Neurotoxicity/delayed neurotoxicity	
	No signs of neurotoxicity
Other toxicological studies	
	Liver xenobiotic metabolizing enzyme induction.
Medical data	
	No reports of toxicity in workers exposed during manufacture or use

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.04 mg/kg bw	Rat, 2-year study of toxicity and carcinogenicity	100
ARfD	Unnecessary	—	—

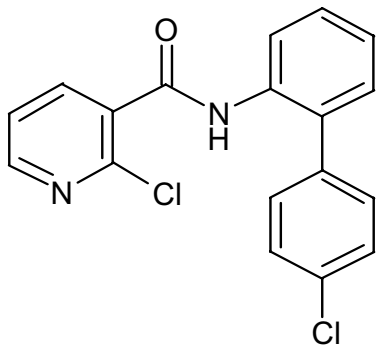
[a] Highest dose tested

[b] Measurements of intake of the compound are the mean of the pre-mating phases for P and F_1 females

RESIDUE AND ANALYTICAL ASPECTS

Boscalid was considered for the first time by the present Meeting. It is an anilide fungicide that inhibits mitochondrial respiration, thereby inhibiting spore germination, germ tube elongation, mycelial growth, and sporulation of pathogenic fungi on the leaf surface, and is used against a broad spectrum of diseases in a wide range of crops.

2-Chloro-N-(4'-chlorobiphenyl-2-yl) nicotinamide



Animal metabolism

The Meeting received animal metabolism studies for boscalid in lactating goats and laying hens.

When lactating goats were orally dosed with [diphenyl-U-^{14}C] labelled boscalid for 5 consecutive days at about 65 mg/animal per day, equivalent to 35 ppm in the feed, most of the administered ^{14}C was excreted in the faeces (46% and 64%) and urine (23% and 44%). ^{14}C recovery amounted to 94–95% of the total radioactivity. Milk and tissues accounted for 0.06%–0.15% and 0.46%–0.66% of the administered ^{14}C respectively.

The major residues in muscle were boscalid, the hydroxylated compound M510F01 (2-chloro-N-(4'-chloro-5-hydroxybiphenyl- 2-yl)nicotinamide) and the glucuronic acid conjugate M510F02 (4'-chloro-6-{[(2-chloro-3-pyridinyl)carbonyl] amino}biphenyl-3- yl glycopyranosiduronic acid). These three metabolites were also detected in kidney. The main residues in fat were identified as boscalid and M510F01. The main residues in milk extracts were boscalid, M510F01, M510F02, and 4-chloro-2'-(acetylamino)-biphenyl (M510F53). Further characterisation of boscalid residues in liver demonstrated that the parent compound, M510F01, and M510F53 were the major residues. M510F53 originated from bound residues of parent compound during extraction with microwave treatment. Parent compound and its hydroxylated metabolite M510F01, including the conjugate M510F02 were the major residues in milk and each of the tissues.

When laying hens were orally dosed with [diphenyl-U-^{14}C] labelled boscalid for 10 consecutive days with 1.6 mg/bird per day, equivalent to 12.5 ppm in the feed, most of the administered ^{14}C was excreted in the excreta (97.7%). Recovery of ^{14}C amounted to 98.3% of the total radioactivity. Eggs and tissues accounted for 0.115% and 0.046% of the dose respectively.

The parent compound and its hydroxylated metabolite M510F01 were the main residues in eggs. Muscle had a very low residue levels and therefore was not further investigated. The main residue in fat was the parent compound.

Although there were similarities in the metabolic pathways in lactating goats and in poultry, there were also some differences, e.g., M510F53 in liver and milk was not identified in poultry tissues and eggs. The major residues in animal tissues are parent compound and M510F01 and M510F02. M510F54 was identified in chicken as a minor metabolite. M510F54 was found in liver and milk of lactating goats, but was not identified.

No metabolism study was performed in pigs since the metabolic patterns in rodents (rats) and ruminants (goats) did not differ significantly (See the toxicology report for more details of laboratory animal metabolism).

Plant metabolism

The Meeting received plant metabolism studies with boscalid on grapes, lettuce and beans.

In each crop tested, parent compound generally represented more than 90% of the total ^{14}C residue and showed almost no further metabolism to carbohydrates, proteins or other natural products.

When grapes plants were treated three times with ^{14}C-boscalid (diphenyl- and pyridine-label), parent compound represented more than 90% of the total ^{14}C residue in the samples taken at the maturity of grapes. An HPLC analysis of the methanol and the water extracts of all matrices showed that in grapes 92.7% of the TRR were represented by the unchanged parent compound for the diphenyl label and 92.2% for the pyridine label.

When lettuce plants were treated 3 times with ^{14}C-boscalid (diphenyl- and pyridine-label), parent compound represented more than 90% of the total ^{14}C residue in the samples taken 18 days after the last application.

When green beans were treated with 3 foliar applications, approximately 8–10 days apart, of ^{14}C-boscalid (diphenyl- and pyridine-label), the majority of the residue associated with the fruit sampled 14/15 and 53/51 (diphenyl/pyridine label) days after the final application was mainly boscalid, accounting for about 90% of the residue.

Environmental fate in soil

The Meeting received information on the environmental fate of boscalid in soil, including studies on aerobic soil metabolism, field dissipation and crop rotational studies.

When [^{14}C]-boscalid labelled in the diphenyl ring or the pyridine ring was incubated with four different soils under aerobic conditions in the dark at different temperatures and soil moistures, it degraded slowly and identifiable metabolites were a minor part of the residue and almost degraded at the same rate. The pyridine-label test compound was mineralized to $^{14}CO_2$ more quickly than the diphenyl-label test compound. No volatiles other than $^{14}CO_2$ were found. The soil metabolism and degradation studies described so far showed that boscalid is finally degraded in soil to CO_2 and bound residues.

Boscalid did not show a tendency to move into deeper layers of soil and was primarily detected in the top 10 cm soil layer during field dissipation trials (four different soils) of duration up to 12-18 months. Boscalid concentrations declined to half of their initial values in 28 days to 208 days. In all trials a DT_{90} could not be reached within one year after application to bare soil.

In a confined rotational crop study in Germany, soil was treated directly with [^{14}C]-boscalid labelled in the diphenyl ring or the pyridine ring. Crops of lettuce, radish and wheat were sown into the treated soil at intervals of 30, 120, 270 and 365 days after treatment and were grown to maturity and harvested for analysis. The residues in the edible parts of succeeding crops destined for human consumption were low for lettuce and radish root, and slightly higher for wheat grain after all four plant back intervals. The major part of the residues was identified as parent. The concentration of boscalid in lettuce leaf ranged from 55.6–94.1% TRR, in radish leaf from 69.4–90.2% TRR, in radish root from 52.6–92.8% TRR and in wheat straw from 50.0–87.5% TRR. In wheat grain the concentration of parent was lower (1.9–35.4% TRR, $\leq$ 0.028 mg/kg).

Field trials on rotational crop studies weren't submitted prior to this Meeting and couldn't be used for evaluation.

Methods of residue analysis

The Meeting received description and validation data for analytical methods for residues of boscalid in raw agricultural commodities, processed commodities, feed commodities as well as animal tissues, milk and eggs.

The methods rely on HPLC-UV, HPLC-MS/MS, GC-ECD and GC-MSD for analysis of boscalid in the various matrices. A multi-residue method with GC-ECD and GC-MSD suitable for

enforcement for plant and animal commodities (LOQ values 0.0025–0.02 mg/kg) was adapted from an existing method (DFSG S19).

Numerous recovery data on a wide range of substrates were provided with validation testing of methods which showed that they were valid over the relevant concentration ranges.

Stability of residues in stored analytical samples

The Meeting received information on the freezer storage stability of residues of boscalid in wheat (green plant without roots, grain and straw), oilseed rape, sugar beet (roots), white cabbage (head), peach (fruit), peas, tomato paste, liver, milk, muscle.

Residues were stable (less than 30% disappearance) in various plant matrices over a period of 2 years and longer. Storage data were available for some animal commodities for at least 5 months, and were suitable for showing stability of the residues in samples from these studies.

Definition of the residue

The composition of the residue in the metabolism studies, the available residue data in the supervised trials, the toxicological significance of metabolites, the capabilities of enforcement analytical methods and the national residue definitions already operating all influence the decision for an appropriate residue definition.

The metabolism of boscalid was investigated in grapes, lettuce and beans. Unchanged parent compound formed the major part of the residue in these studies. The cleavage products M510F62 (chlorophenylaminobenzene) and M510F47 (chloronicotinic acid) and in addition hydroxy-parent and sugar conjugates were also identified in beans. However, all metabolites were of minor importance. Therefore only parent is included in the residue definition.

Metabolism studies performed on goats and hens show that residues in products of animal origin derive from the parent compound as well as from the hydroxylated metabolite M510F01 including its conjugates. M510F54 in chicken eggs was not found in lactating goats' tissues and milk, and M510F53 in liver and milk was not found in poultry tissues and eggs.

Ruminant feeding studies show that boscalid preferentially accumulates in cream as opposed to whole milk (concentration ratio is 9:1). The boscalid ratio between fat and muscle was about 5:1. In the metabolism studies of lactating goats, the ratio between fat and muscle was about 6:1. The log octanol-water partition coefficient was approximately 3 and also suggests that boscalid is likely to be a fat-soluble compound, although it does not accumulate in animal tissues, milk and eggs.

Based on the available comparative animal and plant metabolism studies, the Meeting recommended a residue definition for boscalid for plants and animals:

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

Definition of the residue (for estimation of dietary intake for animal commodities): sum of boscalid, 2-chloro-N-(4'-chloro-5-hydroxybiphenyl-2-yl)nicotinamide including its conjugate, expressed as boscalid.

The residue is fat soluble.

Results of supervised trials on crops

The Meeting received supervised trial data for boscalid uses on apple, peach, plum, cherry, raspberries, blueberries, strawberry, grapes, banana, onion, leek, broccoli, cabbages, cauliflowers, Brussels sprouts, cucumbers, cantaloupe, summer squash, melons, tomatoes, peppers, mustard greens, lettuce, curly kale, beans, peas, soybeans, carrot, radish, potato, cereal grain (barley, wheat), almond, pecan nut, pistachio, canola, sunflower, peanuts and coffee.

Field studies on residues in follow-up and rotational crops were provided only at a late stage of the Meeting. In view of the wide range of crops in which boscalid residues may be present above the LOQ, the evaluation of residues deriving from direct application and through uptake from soil has to be assessed together, which was not possible due to late submission of the reports. Consequently, the Meeting could not make recommendations for residue levels in annual crops (onion, leek, broccoli, cabbages, cauliflower, Brussels sprouts, cucumbers, cantaloupe, summer squash, melons, strawberry, tomatoes, peppers, mustard greens, lettuce, curly kale, beans, peas, soybeans, carrot, radish, potato, canola, sunflower and peanuts). The supervised residue trials with direct application and field trials on rotational crops will be evaluated together at a future meeting when all results will become available.

Processing trials with boscalid were considered valid because the processing factors should not be influenced by higher residues than that achieved by GAP. It is common practice to apply a pesticide at an exaggerated rate in processing trials to achieve measurable levels in processed commodities.

Trials from Japan were available only in summary form and could not be evaluated.

Apples

Boscalid has approval for use on apple in the UK for up to four applications at 0.202 kg ai/ha with a 7 day PHI. Supervised trials were conducted on apple trees conforming to UK GAP in Belgium (1), Germany (6), France (11), Italy (7), and the Netherlands (1) in 2000, 2001 and 2003. The residues in ranked order were: 0.14, 0.15, 0.19, 0.20, 0.24, 0.24, 0.29, 0.29, 0.30, 0.32, 0.32, 0.34, 0.36, 0.37, 0.39, 0.39, 0.42, 0.42, 0.43, 0.49, 0.51, 0.53, 0.55, 0.65, 0.86, 1.24 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for boscalid in apples of 2 and 0.365 mg/kg respectively.

Stone fruit

Supervised trials were conducted on stone fruits in the USA (GAP: five applications at 0.256 kg ai/kg with a 0 day PHI) in 1999 and 2004. Twenty two trials were conducted on peach conforming to US GAP. The residues in ranked were: 0.16, 0.19, 0.19, 0.32, 0.32, 0.33, 0.40, 0.40, 0.42, 0.48, 0.48, 0.49, 0.49, 0.49, 0.52, 0.62, 0.64, 0.66, 0.73, 0.75, 0.79, 1.19 mg/kg.

Sixteen trials were conducted on plums conforming to US GAP in 2001 and 2004. The residues in ranked order, median underlined, were: 0.08, 0.09, 0.1, 0.11, 0.14, 0.15, 0.17, 0.17, 0.24, 0.25, 0.32, 0.34, 0.46, 0.55, 0.57, 0.70 mg/kg.

Thirteen trials were conducted on cherries conforming to US GAP in 2001 and 2004. The residues of boscalid in ranked order, median underlined, were: 0.64, 0.74, 0.76, 0.91, 1.0, 1.09, 1.21, 1.31, 1.42, 1.49, 1.5, 1.51, 1.64 mg/kg.

The data for peach was significantly different from those for plums. The data for peach and plums were also significantly different from those for cherry, and so could not be combined. The Meeting agreed to use the data from cherry and estimated a maximum residue level and an STMR value for boscalid in stone fruit of 3 and 1.21 mg/kg respectively.

Berries and other small fruits

Six supervised trials were conducted on raspberries in USA and Canada conforming to the GAP of the USA in 1999 and 2004 (GAP: four applications at 0.406 kg ai/kg with a 0 day PHI). The residues of boscalid in ranked order were: 1.49, 2.00, 2.44, 2.69, 3.45, 3.73 mg/kg.

Twelve supervised trials were conducted on blueberries in USA and Canada conforming to US GAP (0.406 kg ai/ha, four applications, 0 day PHI) in 1999 and 2004. The residues found in ranked order were: 0.84, 1.16, 1.26, 1.27, 1.46, 2.34, 2.62, 2.65, 3.79, 4.35, 6.78, 6.83 mg/kg.

The Meeting agreed that data populations for raspberries and blueberries could be combined, therefore, the residues of boscalid in ranked order, median underlined, were: 0.84, 1.16, 1.26, 1.27, 1.46, 1.49, 2.00, 2.34, 2.44, 2.62, 2.65, 2.69, 3.45, 3.73, 3.79, 4.35, 6.78, 6.83 mg/kg. The Meeting estimated a maximum residue level and STMR values for boscalid in berries and other small fruits except strawberry and grapes of 10 and 2.53 mg/kg respectively.

Boscalid is approved for use in strawberries in the UK at 0.481 kg ai/kg, a maximum of two applications with a 3 day PHI. Supervised trials conforming to UK GAP were conducted on strawberry in Demark, France, Germany, Greece, Italy, Spain, Sweden and the Netherlands in 2003 and 2004. At the GAP of the UK, residue values from outdoor trials in France were 0.20, 0.41, 0.42, 0.45, 0.89, 1.74 mg/kg; in Denmark 0.38 mg/kg; in Germany 0.19, 0.35 mg/kg; in Greece 1.87 mg/kg; in Italy 0.47, 0.68, 0.69 mg/kg; in Sweden 0.15 mg/kg; in the Netherlands 0.46 mg/kg; and those in the UK were 0.27, 0.55 mg/kg. In summary, residues of boscalid in strawberry from the 17 European trials in ranked order were: 0.15, 0.19, 0.20, 0.27, 0.35, 0.38, 0.41, 0.42, 0.45, 0.46, 0.47, 0.55, 0.68, 0.69, 0.89, 1.74, 1.87 mg/kg.

At UK GAP, the residue values from indoor trials in France were 0.28, 0.57, 0.68 mg/kg; in Italy were 0.31, 0.46 mg/kg; and in Spain were 0.23, 0.27, 0.34, 0.49 mg/kg. The ranked order of residue values were: 0.23, 0.27, 0.28, 0.31, 0.34, 0.46, 0.49, 0.57, 0.68 mg/kg.

The outdoor and indoor residue data appeared to be similar populations and were combined. The residues in ranked order were: 0.15, 0.19, 0.20, 0.23, 0.27 (2), 0.28, 0.31, 0.34, 0.35, 0.38, 0.41, 0.42, 0.45, 0.46 (2), 0.47, 0.49, 0.55, 0.57, 0.68 (2), 0.69, 0.89, 1.74 and 1.87 mg/kg.

No recommendation can be made for strawberries until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Sixteen supervised trials were conducted on grapes in USA (GAP: 0.392 kg ai/ha, three applications with a 14 day PHI) in 1999. The residues in ranked order were: 0.33, 0.34 (2), 0.36, 0.50, 0.65 (2), 0.92, 1.26, 1.38, 1.50, 1.83, 2.08, 2.28, 2.97, 3.13 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for boscalid in grapes of 5 and 1.09 mg/kg respectively.

Banana

Twelve supervised trials conforming to the GAP of the USA (0.150 kg ai/ha, four applications with a 0 day PHI) were conducted on banana in Costa Rica, Panama, Guatemala, Honduras, Ecuador and Colombia in 2004. The residues in ranked order for bagged bananas were: < 0.05 (12) mg/kg. The residues in ranked order for unbagged bananas were: < 0.05 (5), 0.07, 0.07, 0.09, 0.10, 0.10, 0.11, 0.18 mg/kg. The ranked order of concentrations on banana pulp was: < 0.05 (12) mg/kg.

The unbagged and bagged residue data populations for whole fruit of banana were significantly different and couldn't be combined. The Meeting estimated a maximum residue level, based on unbagged bananas, and an STMR value, based on banana pulp, for boscalid in banana of 0.2 and 0.05 mg/kg respectively.

Bulb vegetables

Data from five supervised trials on green onions was received from the USA (GAP: 0.326 kg ai/ha, six applications, 7 day PHI) in 1999. The residues in ranked order on green onions were: 1.13, 2.01, 2.20, 2.39, 2.73 mg/kg.

Ten supervised trials were conducted on bulb onions in the USA (maximum GAP: 0.326 kg ai/ha, six applications, 7 day PHI) in 1999. The residues in ranked order on bulb onions were: < 0.05, 0.05, 0.1, 0.11, 0.13, 0.22, 0.78, 0.92, 0.93, 2.61 mg/kg.

Eleven supervised trials were conducted on leek in Belgium in 1999 and 2000 (maximum GAP of two applications at 0.400 kg ai/ha with a 14 day PHI), France (no national GAP, that of the Netherlands used) in 2003, Germany in 1999 and 2000 (no national GAP, that of the Netherlands used), the Netherlands in 1999 and 2000 (three 3 applications at 0.410 kg ai/ha with a 14 day PHI), UK in 2000 (no national GAP, that of the Netherlands used). In summary, residues of boscalid in leek from the 11 European trials in ranked order were: 0.58, 0.62, 0.8, 0.9, 0.93, 1.02, 1.16, 1.31 (2), 1.90, 2.30 mg/kg.

No recommendation can be made for bulb vegetables until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Brassica

Six supervised trials were conducted on broccoli in the USA in 2001 (GAP: two applications at 0.441 kg ai/ha with a 0 day PHI). The residues on broccoli in ranked order were: 0.81, 0.98, 1.45, 1.59, 1.70 and 2.70 mg/kg.

Three supervised trials were conducted on broccoli one from Germany (no national GAP, the GAP for cauliflower from the UK used: three applications at 0.267 kg ai/ha with a 14 day PHI) and two trials from France (no national GAP, that of UK cauliflower used). The residues on broccoli in ranked order were: < 0.05, < 0.05 and 0.20 mg/kg.

The data populations for the USA and the EU were deemed significantly different and as such couldn't be combined.

Six supervised trials were conducted on cabbage in USA in 2001 (GAP: two applications at 0.441 kg ai/ha with a 0 day PHI). The residues on cabbage in ranked order were: 0.64, 0.73, 1.06, 1.78, 2.22, 2.33 mg/kg.

Boscalid is approved for use on cauliflower in the UK at 0.267 kg ai/ha, three applications with a 14 day PHI. Seven supervised trials were conducted on cauliflower in Denmark in 2003, France in 2003 and 2004, Germany in 2004, the Netherlands in 2003 and the UK in 2003conforming with UK GAP. The residues on cauliflower in ranked order were: < 0.05 (5), 0.06, 0.55 mg/kg.

Boscalid is approved for use on Brussels sprouts in the UK at 0.267 kg ai/ha, three applications with a 14 day PHI. Nine supervised trials were conducted on Brussels sprouts in Denmark in 2003, France in 2004, Germany in 2003 and 2004, the Netherlands in 2003, Sweden in 2003 and 2004 and the UK in 2003 and 2004 conforming to UK GAP. The residues on Brussels sprouts in ranked order were: < 0.05 (2), 0.06, 0.10, 0.15, 0.16, 0.23, 0.34 and 0.40 mg/kg.

The data for broccoli was significantly different from those for Brussels sprouts (Mann-Whitney test). The data for cauliflower was significantly different from those for Brussels sprouts. The data for cabbage was significantly different from those for Brussels sprouts. The data for cabbage were significantly different from those for cauliflower and so could not be combined. The data populations for broccoli against US GAP and cabbage were not significantly different. In summary, residues of boscalid in broccoli and cabbage from the 12 US trials in rank order were: 0.64, 0.73, 0.81, 0.98, 1.06, 1.45, 1.59, 1.70, 1.78, 2.22, 2.33 and 2.70 mg/kg.

No recommendation can be made for brassica vegetables until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Fruiting vegetables, cucurbits

Ten supervised trials were conducted on cucumber in USA in 2001 and 2004 (GAP: four applications at 0.326 kg ai/ha with a 0 day PHI). The residues on cucumber in ranked order were: 0.05, 0.07 (3), 0.12, 0.13, 0.14 (2), 0.26 and 0.31 mg/kg.

Eight supervised trials were conducted on cantaloupe in USA in 2001 and 2004 (GAP: four applications at 0.326 kg ai/ha with a 0 day PHI). The residues on cantaloupe in ranked order were: 0.14, 0.23, 0.29, 0.39, 0.57, 0.56, 0.71 and 1.27 mg/kg.

Boscalid is approved for use in Germany on melons at 0.1 kg ai/ha, three applications with a 3 day PHI. Eight supervised trials, conforming to German GAP, were conducted on melons in Italy in 2000 and Spain in 1999 and 2000. The residues in ranked order were: < 0.05 (8) mg/kg.

The data populations for cantaloupe and melons were significantly different and could not be combined.

Nine supervised trials were conducted on Summer squash in USA in 2001 and 2004 (GAP: four applications at 0.326 kg ai/ha with a 0 day PHI). The residues in ranked order on summer squash were: 0.11, 0.12, 0.14, 0.16 (2), 0.19, 0.27, 0.31, 0.95 mg/kg.

The data for cucumber and summer squash appeared to be similar populations and could be combined. The data for cucumber was significantly different from those for cantaloupe. The data for cantaloupe was significantly different from those for summer squash.

No recommendation can be made for fruiting vegetables, cucurbits until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Fruiting vegetables other than cucurbits (except fungi, mushroom and sweet corn)

Supervised trials were conducted on tomatoes in USA in 1999 and 2004 (GAP: two applications at 0.613 kg ai/ha with a 0 day PHI). Twelve trials were conducted at GAP. The residues in ranked order were: 0.17, 0.21, 0.22, 0.24, 0.25, 0.27, 0.28, 0.3, 0.59, 0.61, 0.79, 0.92 mg/kg.

Supervised trials were conducted on non-bell and bell peppers in USA in 1999 and 2004 (GAP: six applications at 0.172 kg ai/ha with a 0 day PHI). In six US trials on bell peppers in 1999 matching the maximum GAP, residues of boscalid were: < 0.05, 0.08, 0.09, 0.14, 0.16, 0.3 mg/kg. In three US trials on non-bell peppers in 1999 matching maximum GAP, residues of boscalid were: 0.14, 0.30 and 0.83 mg/kg.

The data populations for non-bell and bell peppers were not significantly different data and were combined. The residues on peppers in ranked order were: < 0.05, 0.08, 0.09, 0.14 (2), 0.16, 0.3 (2), 0.83 mg/kg.

The data populations for peppers and tomatoes were not significantly different and could be combined. The residues in ranked order were: < 0.05, 0.08, 0.09, 0.14 (2), 0.16, 0.17, 0.21, 0.22, 0.24, 0.25, 0.27, 0.28, 0.3 (3), 0.59, 0.61, 0.79, 0.83, 0.92 mg/kg.

No recommendation can be made for Fruiting vegetables other than cucurbits (except fungi, mushroom and sweet corn) until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Leafy vegetables

Eleven supervised trials were conducted on Mustard greens in USA in 2001, 2004 and 2005 (GAP: two applications at 0.441 kg ai/ha with a 14 day PHI). Eight trials were conducted conforming to US GAP, with residues in ranked order of: of 0.45, 0.54, 0.92, 2.80, 3.1, 6.04, 12.9, 14.4 mg/kg.

Eight supervised trials were conducted on head lettuce and leafy lettuce in USA (GAP: two applications at 0.441 kg ai/ha with a 14 day PHI), respectively. The residues on head lettuce in ranked order were: 0.11, 0.98, 1.77, 2.53, 2.68, 2.73, 3.18, 6.15 mg/kg and on leafy lettuce were: 0.74, 1.60, 1.63, 1.91, 4.87, 5.14, 9.36 and 9.55 mg/kg.

The data populations for head lettuce and leaf lettuce were not significantly different and could be combined. The ranked order of concentrations was: 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.

Eighteen supervised trials were conducted on outdoor lettuce in France (6), Germany (5), the Netherlands (2), Spain (5) in 1999 and 2000 conforming to Belgian GAP of two applications at 0.4 kg ai/ha with a 14 day PHI. The residues on outdoor lettuce in ranked order were: < 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.

Eight supervised trials were conducted on indoor lettuce in France (4), Germany (1), the Netherlands (1) and Spain (2) in 2002 conforming to Belgian GAP. The residues on indoor lettuce in ranked order were: 0.37, 0.71, 1.52, 2.31, 2.50, 5.63, 5.96 and 6.11 mg/kg.

The outdoor and indoor residue data population for head lettuce in Europe were significantly different and could not be combined.

The US and European residue (indoor lettuce) data populations for head lettuce were not significantly different and could be combined. The residues on head lettuce in ranked order were: 0.11, 0.37, 0.72, 0.74, 0.98, 1.52, 1.6, 1.63, 1.77, 1.91, 2.32, 2.5, 2.53, 2.68, 2.73, 3.18, 4.87, 5.14, 5.42, 5.63, 5.96, 6.11, 9.36, 9.55 mg/kg.

Data was received from six supervised trials conducted on Curly kale in Denmark in 2000 (1), the Netherlands in 1999 (1), Sweden in 1999 (1) and UK in 1999 and 2000 (3) at 0.4 kg ai/ha (0.133 kg ai/hL). The trials did not conform to UK GAP of three applications at a rate of 0.267 kg ai/ha, i.e., treatments were made at a rate 50% higher than GAP with one extra application. As a result the data on Curly kale could not be evaluated (0.11, 0.50, 0.55, 0.67, 2.80, 3.20 mg/kg).

The combined data populations for lettuce were not significantly different from those for mustard greens and could be combined. The residues in ranked order were: 0.11, 0.37, 0.45, 0.54, 0.72, 0.74, 0.92, 0.98, 1.52, 1.60, 1.63, 1.77, 1.91, 2.32, 2.50, 2.53, 2.68, 2.73, 2.80, 3.10, 3.18, 4.87, 5.14, 5.42, 5.63, 5.96, 6.04, 6.11, 9.36, 9.55, 12.9, 14.4 mg/kg.

No recommendation can be made for leafy vegetables until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Legume vegetables

Boscalid is approved for use in France with a maximum GAP of two applications at a rate of 0.5 kg ai/ha with a 7 day PHI. Eleven supervised trials were conducted on outdoor beans in Denmark 1999 and 2000 (3), France in 2000 (4), Germany in 1999 and 2000 (4) conforming to French GAP. The residues on field grown beans, with pod, were: 0.13, 0.22, 0.26, 0.29, 0.47, 0.50, 0.53, 0.62, 0.67, 0.83, 0.95 mg/kg.

Eight supervised trials were conducted on indoor beans in Spain in 1999 and 2000 conforming to French GAP. The residues on indoor beans, with pod, in ranked order were: 0.06, 0.28, 0.28, 0.29, 0.61, 0.69, 1.65, 1.67 mg/kg.

The outdoor and indoor residue data populations for beans, with pod, were not significantly different and could be combined. The residues on beans with pod in ranked order were: 0.06, 0.13, 0.22, 0.26, 0.28, 0.28, 0.29, 0.29, 0.47, 0.50, 0.53, 0.61, 0.62, 0.67, 0.69, 0.83, 0.95, 1.65, 1.67 mg/kg.

Eleven supervised trials were conducted on peas in USA in 2001 (maximum GAP: two applications at 0.539 kg ai/ha with a 7 day PHI) where peas were shelled in eight of the trials. The residues in ranked order on shelled peas (succulent seeds) were: < 0.05 (2), 0.06, 0.07, 0.15, 0.19, 0.24, 0.37 mg/kg. The residues on peas (pod and succulent seeds) in ranked order were: 0.64, 0.97, 1.39 mg/kg.

The data populations for shelled peas (succulent seeds) in the EU and peas (pods and succulent seed) were significantly different and could not be combined.

Seventeen supervised trials were conducted on soybean in USA in 2002 (maximum GAP: two applications at 0.539 kg ai/ha with a 7 day PHI). The residues on immature soybean in ranked order were: < 0.05 (11), 0.05, 0.06, 0.08, 0.09, 0.2, 1.18 mg/kg.

Ten supervised trials were conducted on snap beans in USA in 2000 (maximum GAP: two applications at 0.5 kg ai/ha with a 7 day PHI). The residues on snap bean (young pods) in ranked order were: 0.13, 0.28, 0.36, 0.41, 0.42, 0.46, 0.52, 0.54, 0.72, 0.97 mg/kg.

Seven supervised trials were conducted on Lima bean in USA in 2000 (maximum GAP: two applications at 0.5 kg ai/ha with a 7 day PHI). The residues on Lima bean (young pods and immature beans) in ranked order were: < 0.05 (2), 0.07 (2), 0.08 (2), 0.47 mg/kg.

The data for beans with pods were significantly different from those for succulent shelled peas. The data for beans with pods were significantly different from those for immature soybean. The data for snap beans were significantly different from those for lima beans and couldn't be combined. The data for snap beans were not significantly different from those for beans with pod. The data populations for peas with pod and beans with pod were not significantly different. In summary, residues of boscalid in beans with pods, peas with pods and snap beans from the 32 US trials in rank order were: 0.06, 0.13 (2), 0.22, 0.26, 0.28 (3), 0.29 (2), 0.36, 0.41, 0.42, 0.46, 0.47, 0.50, 0.52, 0.53, 0.54, 0.61, 0.62, 0.64, 0.67, 0.69, 0.72, 0.83, 0.95, 0.97 (2), 1.39, 1.65, 1.67 mg/kg.

No recommendation can be made for legume vegetables until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Pulses

Ten supervised trials were conducted on beans in USA in 2000 (maximum GAP: two applications at 0.539 kg ai/ha with a 21 day PHI). The residues on dry beans in ranked order were: < 0.05 (4), 0.06, 0.09, 0.12, 0.14, 0.37, 1.92 mg/kg.

Nine supervised trials were conducted on peas in USA in 2000 (maximum GAP: two applications at 0.539 kg ai/ha with a 21 day PHI). The residues on dry peas in ranked order were: 0.05, 0.09, 0.11, 0.12, 0.16, 0.17, 0.23, 0.31, 0.46 mg/kg.

The data populations for dry beans and dry shelled peas were not significantly different and could be combined. In summary, residues of boscalid in dry beans and dry peas from the 19 US trials in rank order were: < 0.05 (4), 0.05, 0.06, 0.09, 0.09, 0.11, 0.12 (2), 0.14, 0.16, 0.17, 0.23, 0.31, 0.37, 0.39, 1.92 mg/kg.

Seventeen supervised trials were conducted on soybean in USA in 2002 (maximum GAP: two applications at 0.54 kg ai/ha with a 21 day PHI). The residues on dry soybean in ranked order were: < 0.05 (17) mg/kg.

No recommendation can be made for pulses until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Carrot

Eight supervised trials were conducted on carrot in USA in 1999 (GAP: six applications at 0.185 kg ai/ha with a 0 day PHI). In two trials in 1999, matching GAP, residues of boscalid were: 0.19, 0.12 mg/kg. In six other trials only three applications were made but the total rate applied was equivalent and residue levels at PHI were similar. The Meeting agreed to combine the data at the same total application rate. The residues on carrot in ranked order were: < 0.05, 0.06, 0.12, 0.17, 0.18, 0.19, 0.28, 0.34 mg/kg.

No recommendation can be made for carrot until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Radish

Five supervised trials were conducted on radish in USA in 1999 (no GAP). As no trials were conducted according to a GAP, the Meeting did not recommend a maximum residue level for radish.

Potato

Sixteen supervised trials were conducted on potato in USA in 2000 (GAP: two applications at 0.49 kg ai/ha with a 30 day PHI). The residues on potato in ranked order were: < 0.05 (16) mg/kg.

No recommendation can be made for potato until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Cereal grains

Boscalid is approved for use on cereal grains in Germany (GAP: two applications at 0.35 kg ai/ha with no specified PHI). Data from six supervised trials were submitted on barley conforming to German GAP from Denmark from 2005 (1), France from 2005 (2), Germany from 2005 (1), the Netherlands from 2003 (1) and the UK from 2003 (1). The residues on barley in ranked order were: < 0.01 (2), 0.02, 0.03, 0.12, 0.19 mg/kg.

Eight supervised trials were submitted on wheat conforming to German GAP from Belgium from 2005 (1), France from 2003 and 2005 (5), Germany from 2003 (1), the UK from 2003 (1). The residues on wheat in ranked order were: < 0.01, 0.01 (3), 0.03, 0.06 (2), 0.27 mg/kg.

The data populations for barley and wheat were not significantly different and could be combined. In summary, residues of boscalid in barley and wheat from the 14 EU trials in ranked order were: < 0.01 (3), 0.01 (3), 0.02, 0.03 (2), 0.06 (2), 0.12, 0.19, 0.27 mg/kg.

Tree nuts

Boscalid is approved in the USA on tree nuts with four applications at 0.256 kg ai/ha with a 25 day PHI. Data was submitted from twenty supervised trials conducted on almond in USA between 1999 and 2003. In ten trials on almond from 2003 matching GAP, residues of boscalid were: < 0.05 (20) mg/kg.

Ten supervised trials were submitted on pecan nut from the USA from 1999 conforming to US GAP, i.e., four applications at 0.256 kg ai/ha with a 25 day PHI. The residues of boscalid in pecan nuts in ranked order were: < 0.05 (10) mg/kg.

Six supervised trials were conducted on pistachio nuts in USA in 1999 (maximum GAP: 0.256 kg ai/ha, four applications, 25 day PHI). In six US trials on pistachio in 1999 matching GAP, residues of boscalid, median residue underlined, were: < 0.05(2), <u>0.19</u>, <u>0.35</u>, 0.45, 0.64 mg/kg.

The data populations for almond and pistachio, and pecan nut and pistachio were significantly different and couldn't be combined.

The Meeting agreed to use the data from almond and pecan, and estimated a maximum residue level and an STMR value for boscalid in tree nuts except pistachio of 0.05 (*) and 0.05 mg/kg respectively.

The Meeting agreed to use the data from pistachio, and estimated a maximum residue level and an STMR value for boscalid in pistachio of 1 and 0.27 mg/kg respectively.

Canola

Trials on canola were conducted in USA in 2000 (GAP: 0.294 kg ai/ha, two applications with a 21 day PHI). In the 16 US trials the application rate (0.45 kg ai/ha) was 50% higher than the GAP rate and at PHI of 20–22 days.

The Meeting noted that the application rate was 50% higher than GAP, and as such the residue values couldn't be used for evaluation.

Sunflower

Eight supervised trials were conducted on sunflower in the USA according to GAP in 2001 (GAP: two applications at 0.44 kg ai/ha with a 21 day PHI). The residues in ranked order were: < 0.05, 0.08, 0.09, 0.13, 0.16, 0.16, 0.23, 0.45 mg/kg.

No recommendation can be made for sunflower until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Peanut

Twelve supervised trials were conducted on peanut in USA according to GAP in 2000 (GAP: three applications at 0.49 kg ai/ha with a 14 day PHI). The residues in peanut in ranked order were: < 0.05 (11), 0.05 mg/kg.

No recommendation can be made for peanut until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Coffee

Seven supervised trials were conducted on coffee in Brazil in 2000 (GAP: one application at 0.075 kg ai/ha with a 45 day PHI). In four of the trials the application rate of 0.15 kg ai/ha was two times that of the maximum GAP. The Meeting noted that while the application rate was higher than GAP, the residues were below the LOQ (0.05 mg/kg) and could be used for evaluation.

The Meeting estimated a maximum residue level and an STMR value for boscalid in coffee of 0.05 (*) and 0.05 mg/kg respectively.

Animal feedstuffs

Almond hull

See previous section on almond for GAP in USA. In ten supervised trials on almond at US GAP, residues of boscalid in almond hull in rank order, with median and highest residue values underlined, were: 2.21, 2.64, 3.30, 3.42, <u>3.45</u>, <u>3.91</u>, 5.41, 6.78, 11.3, <u>11.9</u> mg/kg (fresh weight).

Allowing for the standard 90% dry matter for almond hulls (*FAO Manual*, p. 147), the Meeting estimated a maximum residue level of 15 mg/kg and an STMR of 4.1 mg/kg for almond hulls (dry weight). A highest residue level of 13 mg/kg was estimated for calculating the dietary burden of farm animals.

Straw and fodder (dry) cereal grains

In 10 trials on barley at German GAP, residues of boscalid in barley straw in rank order, median and highest residue underlined, were: 0.51, 2.5, 5.8, 13, 14, 27 mg/kg (fresh weight). See previous section on wheat for GAP in Europe. In eight trials on wheat at German GAP, residues of boscalid in wheat straw in rank order were: 3.0, 3.1, 5.3, 5.8, 7.9, 7.9, 11, 15 mg/kg (fresh weight).

Peanut fodder

See previous section on peanut for GAP in USA in 2000. Residues of boscalid in peanut hay in rank order were: 3.2, 5.8, 6.7, 6.7, 7.8, 9.0, 13, 20, 24, 28, 29 mg/kg.

No recommendation can be made for peanut fodder until the contribution of residues from direct application as well as uptake through the soil can be assessed.

Soybean forage

See previous section on soybean for GAP in USA in 2002. Seventeen supervised were conducted on soybean.

The Meeting noted that the PHIs were double that of the GAP, as such the residues couldn't be used for evaluation.

Soybean fodder

See previous section on soybean for GAP in USA in 2002. In 17 supervised trials on soybean at USA GAP, residues of boscalid in soybean hay in rank order were: 1.3, 1.4, 1.8, 2.0, 2.1, 2.3, 2.8, 3.6, 4.6, 4.8, 5.3, 6.7, 7.1, 7.3, 7.8, 11, 21 mg/kg.

Fate of residues during processing

The Meeting received information on the fate of boscalid residues during aqueous hydrolysis under conditions of pasteurisation, baking, brewing and boiling and sterilisation. Information was also provided on the fate of boscalid residues during the food processing of citrus, apples, plum, cherries, strawberries, grapes, white cabbage, gherkins, tomatoes, head lettuce, peas, soybeans, carrots, sugar beet, barley, winter wheat, corn, peanuts, sunflower, cotton, canola seed, mint and hops.

Boscalid was not degraded during the simulation of pasteurisation (pH 4, 90°C) nor during simulated baking, boiling, brewing (pH 5, 100°C) or during sterilisation (pH 6, 120°C).

The processing factors for wet apple pomace (6.06) and apple juice (0.08) were applied to the estimated STMR for apple (0.365 mg/kg) to produce STMR-P values for wet apple pomace (2.2 mg/kg) and apple juice (0.03 mg/kg).

The processing factors for plum to dried prunes (2.80) and to puree (1.95) were applied to the estimated STMR for plums (0.205 mg/kg) to produce an STMR-P value for prunes (0.57 mg/kg) and puree (0.40 mg/kg).

The processing factors for raisins (2.42), wet pomace (2.50), wine (0.35) and juice (0.42) were applied to the estimated STMR for grapes (1.09 mg/kg) to produce STMR-P values for raisins (2.6 mg/kg), wet pomace (2.7 mg/kg), wine (0.38 mg/kg) and grape juice (0.46 mg/kg). The processing factor for raisins (2.4) was applied to the grape residue data (HR of 3.2 mg/kg) to produce an estimated highest value for dried grapes (7.8 mg/kg).

The Meeting estimated a maximum residue level for boscalid in dried grapes (= currants, raisins, sultanas) of 10 mg/kg.

Residues in animal commodities

Farm animal feeding

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

Lactating Holstein cows were dosed with boscalid at the equivalent of 1.5 (1×), 4.5 (3×) and 18 (12×) ppm in the dry-weight diet for 28 consecutive days. Milk was collected twice daily for analysis. Animals were sacrificed within 23 hours after the final dosing, except for one cow of the 12× group which was sacrificed seven days after the final dose to determine residue levels post dosing.

No residues were detected in milk samples taken from the control and the 1× dose groups. In a few samples from the 3× dose group, residues just above the LOQ of 0.01 mg/kg for boscalid were detected, but no residues of M510F01 or M510F02 were observed. In the group average, residues were below the LOQ. In the 12× dose group, residues of boscalid occurred regularly from day one onward with residues reaching a plateau on day 14 with average residues between 0.04 mg/kg and 0.05 mg/kg. M510F53 was below LOQ (< 0.01 mg/kg) in milk from all three treatment groups.

In the tissues, the mean residues of boscalid at the 3 dosing levels were: muscle (< 0.05, < 0.05, < 0.05 mg/kg); fat (0.06, 0.11, 0.27 mg/kg); liver (< 0.05, 0.06, 0.18 mg/kg); kidney (< 0.05, 0.07, 0.24 mg/kg).

M510F53 was below LOQ (< 0.01 mg/kg) in liver from 1× and 3× dose groups, and up to 0.09 mg/kg from 12× dose group.

Residues depleted quickly from the milk of a high-dose animal after dosing was stopped, falling below LOQ (0.01 mg/kg) after 2 days. Residues fell to below the LOQ (< 0.05 mg/kg) in all tissues. It was shown by samples from the withdrawal animal that no residues in milk was observed two day after dosing had stopped and boscalid were rapidly excreted.

Farm animal dietary burden

The Meeting noted that field trials on rotational crops were provided at a late stage of the Meeting, and decided to estimate maximum residue levels and STMRs on annual crops that may lead to animal feeds at a future JMPR when all the data can be examined together. The Meeting was also informed that a new livestock feeding study is commencing in 2007. The Meeting decided to calculate the livestock dietary burden and estimate maximum residue levels and STMRs for animal commodities at a future JMPR meeting.

DIETARY RISK ASSESSMENT

Long-term intake

The Meeting could not make any recommendation for residue levels in annual crops since field studies on residues in follow-up and rotational crops were provided only at a late stage of the Meeting. In view of the wide range of crops in which boscalid residues may be present above the LOQ, maximum residue levels could not be recommended for a large number of crops. The Meeting decided that the estimation of the long-term intake would not be realistic at this time. Consequently, the long-term intake will be estimated at a future meeting when the residues deriving from both direct application and those taken up from the soil in a rotational crop situation can be evaluated together.

Short-term intake

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

4.6 CHLORPYRIFOS (017)

RESIDUE AND ANALYTICAL ASPECTS

Chlorpyrifos was last evaluated by the JMPR in 2004 when an ADI of 0-0.01 mg/kg bw per day and an ARfD of 0.1 mg/kg bw per day were established, and a number of maximum residue levels were estimated. The 2004 JMPR defined the residue as chlorpyrifos for both compliance with MRLs and estimation of dietary intake.

Results of supervised trials, carried out on cranberry according the US registered uses were submitted for evaluation.

Results of supervised trials on crops

Residues were detected and reported as 3,5,6-trichloro-2-pyridinol (TCP). Residues in chlorpyrifos equivalents were calculated by multiplying the TCP residue values by 1.786. The limit of quantification was reported as 0.02 or 0.03 mg/kg TCP.

Concurrent recoveries of TCP fortified in cranberries at 0.20 or 0.25 mg/kg spike levels were 92–130% (110 ± 13.4, n=6). Control samples from each test site were analyzed. The apparent TCP residues were between < 0.03 and 0.06 mg/kg.

The concurrent and previous stability studies reported by the 2004 JMPR suggest that the decrease of residues during storage was not significant.

Nine field trials on cranberries were carried out in three geographical region of USA. Chlorpyrifos (EC 48%) was applied once at 1.68 or 3.36 kg ai/ha or twice at 0.84, 1.68, or 3.36 kg ai/ha for total seasonal rates of 1.68, 3.36, or 6.72 kg ai/ha. None of the dosage rates corresponds to the maximum registered single dose of 2.24 kg ai/ha. Samples were collected at the registered PHI at one site. In other cases the PHI was much longer. Individual samples collected for analyses contained 20 g of fruit. In order to best represent the expected residues in composite samples, the averages of residues were calculated for each trial.

The residues expressed as chlorpyrifos derived from trials performed with ± 30% maximum rate are in rank order: 0.42, 0.49, and 0.55 mg/kg.

Taking into account the minimum data requirement (three trials) specified for commodities which are insignificant in trade and do not raise any intake concern (2004 JMPR Report, pp. 30-31), the Meeting estimated a maximum residue level of 1 mg/kg, HR of 0.55 mg/kg and an STMR of 0.49 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The GEMS/Food Consumption Cluster Diets specifies the following long-term cranberry consumption (g/day per person) for various diets: A (0.1); D (0.3); F (0.6); M (2.5). The cranberry consumption in the other regions is nil.

The highest IEDI in the 13 GEMS/Food regional diets based on the estimated STMR was 0.2% of the maximum ADI (0.01 mg/kg bw).

The Meeting concluded that the long-term intake of residues of chlorpyrifos use on cranberry will not practically increase the intake of residues from other uses considered earlier by the JMPR.

Short-term intake

The GEMS/Food regional diet specifies the large portion sizes of cranberry of 3.53 g/kg bw for adults and 6.78 g/kg bw for children (both are from the USA).

The IESTIs of chlorpyrifos calculated on the basis of the large portion size and the estimated HR of 0.55 mg/kg are 1.9% and 3.7% of the ARfD for adults and children, respectively.

The Meeting concluded that the short-term intake of residues resulting from the use of chlorpyrifos on cranberry that have been considered by the JMPR is unlikely to present a public health concern.

4.7 CYFLUTHRIN AND BETA-CYFLUTHRIN (157)

TOXICOLOGY

Cyfluthrin, the ISO approved common name for 3-(2,2-dichloro-vinyl)-2,2-dimethyl-cyclopropane-carboxylic acid cyano-(4-fluoro-3-phenoxy-phenyl)-methyl ester(RS)), is a synthetic cyano-containing pyrethroid insecticide. It was evaluated by the JMPR in 1987, when an ADI of 0–0.02 mg/kg bw was established based on a NOAEL of 50 ppm, equal to 2 mg/kg bw per day, which was identified on the basis of reduced body-weight gains in a 2-year study in rats and using a safety factor of 100. In 1997, JECFA also established an ADI of 0–0.02 mg/kg bw.

Technical-grade cyfluthrin consists of a mixture of four diastereomeric pairs of enantiomers (giving rise to eight optical isomers), consisting of two *cis* and two *trans* isomeric pairs. Beta-cyfluthrin consists of two diastereoisomeric pairs, which are the biologically active isomers of cyfluthrin. They are contained in cyfluthrin at a level of about 40%.

Cyfluthrin was re-evaluated by the present Meeting within the periodic review programme of the CCPR. Beta-cyfluthrin has not been evaluated previously. The Meeting reviewed new data on cyfluthrin and beta-cyfluthrin that had not been considered previously, and relevant data from the previous evaluation.

For cyfluthrin, the specifications were established by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) and published as *WHO specifications and evaluations for public health pesticides*: *cyfluthrin* (2004).[36]

Not all pivotal studies with cyfluthrin were certified as being compliant with GLP. These studies were carried out before the OECD guidelines on GLP were promulgated. However, the quality of these studies was considered to be acceptable.

Biochemical aspects

In rats, cyfluthrin is rapidly absorbed and distributed. Peak concentrations in the blood were reached after 1 or 6 h, depending on the vehicle used. About 98% of the radiolabel was eliminated in the urine and faeces within 48 hours after oral administration, with an initial half-life of about 3 hours. Similar amounts were eliminated after intravenous administration. The ratio of excretion in urine:faeces was higher in males (3:1) than in females (3:2). About one third of the administered dose was excreted in bile. The highest concentrations of radiolabel were found in fat, ovaries, adrenal, liver and spleen. Repeat-dosing experiments yielded similar results. In rats, the major metabolic transformation is ester hydrolysis to a 3-phenoxy-4-fluorobenzyl alcohol intermediate and a permethric acid moiety. After ester hydrolysis, the benzyl alcohol moiety is oxidized to the free 3-phenoxy-4-fluorobenzoic acid metabolite, which can either be conjugated with glycine or oxidized to give 4'-hydroxy-3-phenoxy-4-fluorobenzoic acid.

Toxicological data

The acute oral LD_{50} values of cyfluthrin and beta-cyfluthrin in rats ranged from 11 to > 1000 mg/kg bw, depending on the vehicle used and the feeding status of the animals. The observed clinical signs (increased salivation, uncoordinated movements, increased activity and vocalization, and reduced, laboured breathing, apathy, straddle-legged gait (mostly in the rear legs), and reduced sensitivity to external stimuli) are typical of this class of pyrethroids. In rats, the inhalation LC_{50} values ranged from 0.047 to > 1 mg/L, and the dermal LD_{50} values were > 5000 mg/kg bw. Cyfluthrin is not irritating to the skin, slightly irritating to the eyes and is not a skin sensitizer.

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[36] Available from http://www.who.int/whopes/quality/en/Cyfluthrin_spec_eval_WHO_Nov_2004.pdf

The critical end-points induced by cyfluthrin and beta-cyfluthrin are neurotoxicity and reduction in body weight.

Several short-term studies of oral toxicity with cyfluthrin were available for mice, rats and dogs. In a 4-week study in mice, the NOAEL was 300 ppm (equal to 43.1 mg/kg bw per day) on the basis of histological changes in the liver and the submaxillary gland. In one 4-week dietary study and two 3-month dietary studies, the overall NOAEL was 100 ppm (equal to 8.3 mg/kg bw per day) on the basis of a reduction in blood glucose concentration. In a 4-week gavage study, the NOAEL was 20 mg/kg bw per day on the basis of mortality, reduced body weight, increased liver and adrenal weight and clinical signs. In one 6-month study and two 12-month studies in dogs, the overall NOAEL was 200 ppm (equal to 6.5 mg/kg bw per day) on the basis of clinical signs and reductions in body-weight gain.

The effects of short-term oral exposure to beta-cyfluthrin were assessed in rats and dogs. In a 4-week gavage study in rats, the NOAEL was 1 mg/kg bw per day on the basis of clinical signs (increased motility, grooming and digging movements) at 4 mg/kg bw per day, which had already been observed on the first day of administration. In a 13-week dietary study in rats, the NOAEL was 125 ppm (equal to 9.5 mg/kg bw per day) on the basis of clinical signs, and reductions in body-weight gain, food and water consumption. In a 13-week dietary study in dogs, the NOAEL was 60 ppm (equal to 1.3 mg/kg bw per day) on the basis of clinical signs.

The dermal toxicity of cyfluthrin was assessed in 3-week studies in rats and rabbits. In rats, the NOAEL of 340 mg/kg bw per day was identified on the basis of a reduction in food consumption and clinical signs. In rabbits, no toxicologically relevant effects were observed at doses of up to and including 250 mg/kg bw per day (i.e. the highest dose tested).

In short-term studies of toxicity after inhalation of cyfluthrin and beta-cyfluthrin in rats, duration ranging from 5 days to 13 weeks, the overall NOAEC of 0.09 µg/L (equivalent to an inhalational dose of about 0.02 mg/kg bw per day[37]) was identified on the basis of reduced body-weight gain and behavioural changes. The high toxicity of cyfluthrin administered by inhalation, compared with oral exposure, was considered to be caused by the local effects of cyfluthrin on the respiratory system.

In long-term studies of toxicity and carcinogenicity, mice and rats were treated with cyfluthrin at dietary concentrations of up to 1400 and 450 ppm respectively. Statistically significant reductions in body-weight gain (> 10%), which were not related to reductions in food consumption, were consistently found in all studies. In two studies in mice, an overall NOAEL of 200 ppm, equal to 38.4 mg/kg bw per day was identified on the basis of reductions in body-weight gain in females, and macroscopic (crusty zones of the skin of the ear) and histological changes (acanthosis, chronic active inflammation, ulcer, debris of the skin of the ear) in males. The macroscopic and histological effects in the ear are likely to be due to the scratching of the skin by the animals in reaction to local paraesthesia, which is a characteristic of this class of compounds. In two studies in rats, the overall NOAEL was 150 ppm (equal to 6.2 mg/kg bw per day) on the basis of decreases in body-weight gain. The small reductions in body-weight gain (5–6%) observed at lower doses in both studies were not considered to be biologically significant. No evidence for a tumorigenic effect of cyfluthrin was found.

The Meeting concluded that cyfluthrin is not carcinogenic in rodents.

Cyfluthrin and beta-cyfluthrin gave negative results in an adequate range of tests for genotoxicity in vitro and in vivo. The Meeting concluded that cyfluthrin and beta-cyfluthrin are unlikely to be genotoxic.

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[37] Exposure was 6 hours per day. Twenty-four hour respiratory volume for rats is 0.96 ml/kg bw (Zielhuis RL & Van der Kreek FW (1979). The use of safety factors in setting health based permissible levels for occupational exposure. *Int. Arch. Environ. Health*, 42:191–201.)

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

In three multigeneration dietary studies with cyfluthrin in rats, the overall NOAEL for parental toxicity was 125 ppm (equal to 9 mg/kg bw per day) on the basis of reductions in body-weight gain at 400 ppm (equal to 29 mg/kg bw per day), and a borderline reduction in body-weight gain at 150 ppm (equal to 11.4 mg/kg bw per day). The overall NOAEL for offspring toxicity was 50 ppm (equal to 7 mg/kg bw per day) based on coarse tremors in pups during lactation. The overall NOAEL for reproductive effects was 450 ppm (equal to 34.7 mg/kg bw per day), the highest dose tested.

The effect of oral exposure to cyfluthrin on prenatal development was investigated in rats and rabbits. In two studies of developmental toxicity in rats treated by gavage, the overall NOAEL for maternal toxicity was 3 mg/kg bw per day on the basis of clinical signs. The overall NOAEL for fetal toxicity was 30 mg/kg bw per day, i.e. the highest dose tested. In a study of developmental toxicity in rabbits treated by gavage, the NOAEL for maternal and embryo/fetotoxicity was 15 mg/kg bw per day, on the basis of two abortions and one case of complete resorption in the group of 15 dams treated with cyfluthrin at a dose of 45 mg/kg bw per day. In a second study in rabbits, the NOAEL for maternal toxicity was 20 mg/kg bw per day on the basis of reduced food consumption and body-weight gain. The NOAEL for fetotoxicity was 20 mg/kg bw per day on the basis of increased postimplantation loss.

The increased incidence of malformations observed in a study of developmental toxicity in rats treated with cyfluthrin by inhalation was considered to be secondary to effects on pulmonary function.

In a study of developmental toxicity in rats treated with beta-cyfluthrin by gavage, the NOAEL for maternal toxicity was 9.4 mg/kg bw per day on the basis of a reduction in body-weight gain, clinical signs and mortality. The NOAEL for embryo/fetotoxicity was 9.4 mg/kg bw per day on the basis of reduced fetal weight and retarded ossification.

Cyfluthrin did not cause delayed neurotoxicity in hens. In a study of acute neurotoxicity in rats treated by gavage, the NOAEL was 1 mg/kg bw per day on the basis of mild clinical signs of toxicity (shaking) observed in one and two animals at 2.5 and 3 mg/kg bw, respectively. A range of additional studies of neurotoxicity with repeated high doses of cyfluthrin (30–80 mg/kg bw per day) administered by gavage also demonstrated clinical signs of (neuro-)toxicity, including disturbed gait, salivation, tremor and apathy.

Occasionally, in some of the short-term studies of toxicity and studies of neurotoxicity in rats, marked acute toxicity induced by high doses of cyfluthrin was accompanied by limited swelling and fragmentation of myelin, which was reversed within 1–3 months after cessation of treatment. The Meeting concluded that cyfluthrin does not cause irreversible neurological damage.

The (developmental) neurotoxicity of beta-cyfluthrin was investigated in rats. In a study in which single doses were administered by gavage, the NOAEL was 0.5 mg/kg bw per day on the basis of perianal staining, effects in the functional observational battery (decreased approach response in both sexes, oral staining in males and a decreased activity in females) and decreased motor and locomotor activities in females. In a 13-week dietary study, the NOAEL was 30 ppm (equal to 2.3 mg/kg bw per day) on the basis of reductions in body-weight gain and food consumption in females.

In a study of developmental neurotoxicity in rats, the NOAEL for maternal toxicity was 133 ppm (equal to 11 mg/kg bw per day) on the basis of reduced body weight and food consumption. The NOAEL for offspring toxicity was 133 ppm (equal to 11 mg/kg bw per day) on the basis of reduced body-weight gain during lactation and reduced startle habituation at postnatal day 22.

A number of pharmacological studies with cyfluthrin were considered not to be useful for the purpose of dietary risk assessment.

A limited number of studies of acute toxicity and genotoxicity with some metabolites[38] of cyfluthrin was performed. The acute toxicity of the metabolites studied was lower than that of the parent compound. No evidence of mutagenic potential was found for any of the metabolites investigated.

Cyfluthrin caused a topical skin effect, characterized by a stinging sensation in the affected areas in laboratory workers. The areas most commonly affected were the face and mucosal tissues. Annual medical examinations of factory workers revealed no effects on body weights, haematological and urine analysis parameters, ALT and GGT activities and thoracic organs, as examined by X-rays.

The Meeting concluded that the present database was adequate to characterize the potential hazard of cyfluthrin and beta-cyfluthrin to fetuses, infants and children.

Evaluation of the available data showed that the toxicological profiles of cyfluthrin and beta-cyfluthrin appeared to be qualitatively similar. With respect to neurotoxicity, beta-cyfluthrin, being the biologically active component of cyfluthrin, was more potent than cyfluthrin. The Meeting concluded that the database for cyfluthrin was adequate to apply to beta-cyfluthrin. Therefore no additional studies on beta-cyfluthrin were necessary.

Toxicological evaluation

The Meeting considered establishing a group ADI of 0–0.06 mg/kg bw on the basis of an overall NOAEL of 6.2 mg/kg bw per day for reductions in body-weight gain observed in a 2-year dietary study with cyfluthrin in rats, and using an safety factor of 100. The overall LOAEL for this effect was 9.4 mg/kg bw per day, observed in a 13-week dietary study with beta-cyfluthrin in rats. Since the mode of action for reduction in body-weight gain was unknown, the Meeting considered it appropriate to apply the default 100-fold safety factor for this end-point. This was considered to be adequately protective against the neurotoxic effects of beta-cyfluthrin in dietary studies.

The Meeting established a group ARfD for cyfluthrin and beta-cyfluthrin of 0.04 mg/kg bw based on a NOAEL of 1 mg/kg bw for findings of acute neurotoxicity observed in a-4 week study with beta-cyfluthrin administered by gavage, and using a safety factor of 25. This overall NOAEL was supported by the NOAEL of 0.5 mg/kg bw identified on the basis of slight neurotoxic effects at 2 mg/kg bw in a study of neurotoxicity in rats given single doses of beta-cyfluthrin by gavage, and the NOAEL of 1 mg/kg bw identified on the basis of slight clinical effects at 2.5 mg/kg bw in a study in rats given single doses of cyfluthrin by gavage. Furthermore, this overall NOAEL is in line with the threshold dose of 0.9 mg/kg bw for acute effects of beta-cyfluthrin on motor activity.[39] Since the neurotoxicity induced by (beta-)cyfluthrin is dependent on the C_{max} and is reversible, the Meeting considered it appropriate to apply a chemical-specific adjustment factor of 25 for this end-point.

The Meeting noted that the proposed ADI based on body-weight effects in studies with repeated doses was higher than the ARfD. Therefore, the ADI was established at 0–0.04 mg/kg bw, i.e. the same value as the ARfD.

A toxicological monograph was prepared.

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[38] (1) +,-(*R*,*S*)-α-Carboxy-[3-phenoxy-4-fluoro]benzyl-1-(*R*,*S*)-*trans*-3-(2',2'-dichloroethen-1'-yl)-2,2-dimethylcyclo-propanecarboxylic acid ester
(2) +,-(*R*,*S*)-α-Carboxamido-[3-phenoxy-4-fluoro]benzyl-1-(*R*,*S*)-*trans*-3-(2,2-dichloroethen-1-yl)-2,2-dimethyl-cyclopropanecarboxylic acid ester
(3) *cis*-3-(2',2'-Dichloroethen-1'-yl)-2,2-dimethyl-cyclopropanecarboxylic acid
(4) *trans*-3-(2',2'-Dichloroethen-1'-yl)-2,2-dimethyl-cyclopropanecarboxylic acid

[39] Wolansky MJ, Gennings C, Crofton KM (2006) Relative potencies for acute effects of pyrethroids on motor

Levels relevant for risk assessment

(a) Cyfluthrin

Species	Study	Effect	NOAEL	LOAEL
Rat	2-year study of toxicity and carcinogenicity [a]	Toxicity	150 ppm, equal to 6.2 mg/kg bw per day	450 ppm, equal to 19.2 mg/kg bw per day
		Carcinogenicity	450 ppm, equal to 19.2 mg/kg bw per day[c]	— [c]
	Two-generation study of reproductive toxicity[a]	Parental	50 ppm, equal to 3.8 mg/kg bw per day	150 ppm, equal to 11.4 mg/kg bw per day [d]
		Offspring toxicity	50 ppm, equal to 5.1 mg/kg bw per day	150 ppm, equal to 14.0 mg/kg bw per day
		Reproductive toxicity	450 ppm, equal to 34.7 mg/kg bw per day[c]	— [c]
	Two-generation study of reproductive toxicity[a]	Parental	125 ppm, equal to 9 mg/kg bw per day	400 ppm, equal to 29 mg/kg bw per day
		Offspring toxicity	50 ppm, equal to 7 mg/kg bw per day	150 ppm, equal to 19 mg/kg bw per day
		Reproductive toxicity	400 ppm, equal to 29 mg/kg bw per day[c]	— [c]
	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	— [c]
		Fetotoxicity	10 mg/kg bw per day	— [c]
	Acute neurotoxicity[b]	Neurotoxicity	1 mg/kg bw	2.5 mg/kg bw
Dog	6-month study of toxicity [a]	Toxicity	200 ppm, equal to 6.5 mg/kg bw per day	600 ppm, equal to 19.9 mg/kg bw per day

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

[d] Actual NOAEL is likely higher given that the effects were borderline at the LOAEL

(b) Beta-Cyfluthrin

Species	Study	Effect	NOAEL	LOAEL
Rat	4-week study of toxicity [b]	Toxicity	1 mg/kg bw per day	4 mg/kg bw per day
	Developmental toxicity[b]	Maternal toxicity	9.4 mg/kg bw per day	42 mg/kg bw per day
		Fetotoxicity	9.4 mg/kg bw per day	42 mg/kg bw per day
	Acute neurotoxicity[b]	Neurotoxicity	0.5 mg/kg bw	2 mg/kg bw

function in rats. *Toxicological Science* 89:271–277.

	13-week study of neurotoxicity[a]	Neurotoxicity	30 ppm, equal to 2.3 mg/kg bw per day	125 ppm, equal to 9.4 mg/kg bw per day
	Developmental neurotoxicity[a]	Maternal toxicity	133 ppm, equal to 11 mg/kg bw per day	215 ppm, equal to 17.8 mg/kg bw per day
		Fetotoxicity	133 ppm, equal to 11 mg/kg bw per day	215 ppm, equal to 17.8 mg/kg bw per day
Dog	3-month study of toxicity[a]	Toxicity	60 ppm, equal to 1.3 mg/kg bw per day	360 ppm, equal to 9 mg/kg bw per day

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

Estimate of acceptable daily intake for humans

0–0.04 mg/kg bw

Estimate of acute reference dose

0.04 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 exposures

Critical end-points for setting guidance values for exposure to cyfluthrin/beta-cyfluthrin

Absorption, distribution, excretion and metabolism in animals	
Rate and extent of absorption	Rapid and extensive (rats)
Distribution	Highest concentrations in liver, kidney, adrenals, spleen (rats)
Potential for accumulation	Low
Rate and extent of excretion	Rapid (75–91% in urine within 24 hours in rats)
Metabolism in animals	Major metabolites: 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA), 3-phenoxy-4-fluorobenzoic acid, 4'-hydroxy-3-phenoxy-4-fluorobenzoic acid (rats)
Toxicologically significant compounds	Cyfluthrin, beta-cyfluthrin
Acute toxicity	
Rat, LD_{50}, oral	11 to >1000 mg/kg bw
Rat, LD_{50}, dermal	>5000 mg/kg bw
Rat, LC_{50}, inhalation	0.081 to >1.0 mg/L of air
Rabbit, skin irritation	Not an irritant

Rabbit, eye irritation	Slightly irritating
Guinea-pig, skin sensitization	Not sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	Reduced body weight, clinical signs (rats, dogs)
Lowest relevant oral NOAEL	1 mg/kg bw per day (beta-cyfluthrin, rats)
	60 ppm, equal to 1.3 mg/kg bw per day (beta-cyfluthrin, dogs)
Lowest relevant dermal NOAEL	340 mg/kg bw per day (cyfluthrin, rats)
Lowest relevant inhalatory NOAEC	0.09 µg/l (cyfluthrin, rats)
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Reduced body weight (rats)
Lowest relevant NOAEL	150 ppm, equal to 6.2 mg/kg bw per day (cyfluthrin, rats)
Carcinogenicity	Not carcinogenic (mice, rats)
Genotoxicity	
	Not genotoxic in vitro or in vivo
Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects (rats)
Lowest relevant reproductive NOAEL	450 ppm, equal to 34.7 mg/kg bw per day, i.e. highest dose tested (cyfluthrin, rats)
Developmental target	delayed ossification (rats); increased postimplantation loss (rabbits)
Lowest relevant developmental NOAEL	9.4 mg/kg bw per day (beta-cyfluthrin, rats)
Neurotoxicity/delayed neurotoxicity	
Neurotoxicity	Behavioural effects (increased motility, grooming and digging movements)
Lowest relevant oral NOAEL	1 mg/kg bw (single and repeated dose by gavage, beta- cyfluthrin and cyfluthrin, rats)
Other toxicological studies	
	No data
Medical data	
	Topical skin effect, characterized by a stinging sensation in the affected areas in laboratory workers. Areas most commonly affected were the face, and mucosal tissues.

Summary for cyfluthrin and beta-cyfluthrin

	Value	**Study**	**Safety factor**
Group ADI	0–0.04 mg/kg bw	Based on the ARfD	—
Group ARfD	0.04 mg/kg bw	Rat, acute neurotoxicity, beta cyfluthrin	25

4.8 CYPERMETHRINS (INCLUDING ALPHA- AND ZETA-CYPERMETHRIN) (118)

TOXICOLOGY

Cypermethrin is the ISO approved common name for (*RS*)-α-cyano-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. Cypermethrin is a synthetic pyrethroid insecticide containing three chiral centres, giving a racemic mixture of eight isomers comprising four diasterioisomeric pairs. The cypermethrins are alpha-cyano- or type II pyrethroids. Cypermethrin was first evaluated by the 1979 JMPR, when a temporary ADI was established. New toxicological data were evaluated at the 1981 JMPR and an ADI of 0–0.05 mg/kg bw per day was established. Cypermethrin was reviewed by the present Meeting within the periodic review programme of the CCPR; this review included alpha-cypermethrin and zeta-cypermethrin, which had not previously been considered by the JMPR.

Cypermethrin and alpha-cypermethrin were considered by JECFA in 1996 and in 2002. In 2002, JECFA established a group ADI of 0–0.02 mg/kg bw, and recommended that JMPR should also consider this approach. The studies submitted to JECFA were available for consideration by the JMPR at its present meeting. Several studies on cypermethrin that were reviewed by JMPR in 1979 and 1981 were not available at the present meeting, but were considered in this evaluation on the basis of the JMPR summaries. The 2006 JMPR was made aware of a study of developmental neurotoxicity with zeta-cypermethrin that had not been submitted before the present meeting. This study was submitted during the meeting but was not evaluated in detail; however, based on a brief review, the Meeting concluded that this study was not critical for its final conclusion..

For alpha-cypermethrin, the specifications were established by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) and published as *WHO specifications and evaluations for public health pesticides*: *alpha-cypermethrin* (2006).[40]

Most studies, excluding those described in previous JMPR monographs, were certified as having been performed in compliance with GLP and in accordance with the relevant OECD test guidelines.

Biochemical aspects

The fate of orally administered cypermethrin was studied in mice, rats, dogs, and humans, and alpha-cypermethrin was investigated in rats and humans. When administered orally to rats, cypermethrin and alpha-cypermethrin were partially absorbed, distributed widely in the tissues, and excreted rapidly. After a low single oral dose (2 mg/kg bw) of ^{14}C-labelled cypermethrin or alpha-cypermethrin, approximately 50–75% of the radioactivity was excreted in the urine, with little in the expired air, and the remainder in the faeces. As most of the radiolabelled material in the faeces comprised the unmetabolized parent molecule, the role of biliary excretion appears to be minor, although this was not measured directly, and the amount in the urine represents approximately the amount absorbed. Maximum concentrations in the blood were reached at 3–4 hours after dosing at 2 mg/kg bw.

In rats given a single oral dose of ^{14}C-labelled cypermethrin or alpha-cypermethrin at 2 mg/kg bw, the highest tissue concentrations of radioactivity were found in the fat (< 1% of the administered dose), followed by the skin. In rats and mice, radioactivity in the fat was identified as unchanged cypermethrin, present mainly as the *cis* isomer. Elimination of radiolabel from most tissues was rapid, but the elimination half-life of cypermethrin and alpha-cypermethrin in rodent adipose tissue and skin was prolonged (10–40 days). Repeat-dose studies in rats confirmed that cypermethrin accumulates in

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[40] Available from http://www.who.int/whopes/quality/en/Alphacypermethrin_eval_april_2006.pdf

fat and skin, reaching a plateau after dosing for 4 weeks at 2 mg/kg bw per day. Concomitant increases in radioactivity also occurred in the plasma, liver and kidney, but concentrations were an order of magnitude lower than in fat.

In laboratory animals, cypermethrin was readily hydrolysed at the ester bond, followed by hydroxylation and conjugation of the cyclopropyl and phenoxybenzyl moieties of the molecule. Urinary metabolites consistent with a similar metabolic pathway in humans were recovered from orally dosed volunteers. The animal data indicated that there is little isomeric interconversion during metabolism of cypermethrin or alpha-cypermethrin.

Toxicological data

Cypermethrin has low to moderate acute oral toxicity in rats (LD_{50}, 163 to > 3000 mg/kg bw). This variability was only partly explicable by the vehicle used. The acute oral LD_{50} of *cis*-cypermethrin in rats was 160–300 mg/kg bw, indicating that it is considerably more toxic than *trans*-cypermethrin, for which the LD_{50} was > 2000 mg/kg bw under the same conditions. From these results, it would be predicted that alpha-cypermethrin is approximately twice as acutely toxic as cypermethrin. A wide range of acute oral LD_{50} values in rats was also reported for alpha-cypermethrin (LD_{50}, 64 to > 5000 mg/kg bw). Similar studies with zeta-cypermethrin gave fairly consistent results (LD_{50}, 86–367 mg/kg bw). The dermal toxicity of cypermethrin and alpha-cypermethrin was low in rats (LD_{50}, > 1600 mg/kg bw and > 2000 mg/kg bw per day, respectively), as was the dermal toxicity of zeta-cypermethrin in rabbits ($LD_{50,}$ > 2000 mg/kg bw), and inhalation toxicity was moderate for cypermethrin (LC_{50}, 1.260 mg/L) and alpha-cypermethrin (LC_{50}, 1.590 mg/L). Overall, the three isomeric mixtures displayed qualitatively similar profiles for acute toxicity in rats.

In rabbits, cypermethrin, alpha-cypermethrin and zeta-cypermethrin were slight eye irritants and slight skin irritants. Cypermethrin showed potential for skin sensitization in the maximization test in guinea-pigs, but was not a sensitizer according to the Buehler method, while alpha-cypermethrin was not a sensitizer in the maximization test, but zeta-cypermethrin was a skin sensitizer in the Buehler test. Cypermethrins also produce local paraesthesia (a tingling or burning sensation of the skin not associated with tissue damage) as an acute action that is distinct from irritancy.

Cypermethrin, alpha-cypermethrin and zeta-cypermethrin cause neurotoxicity in mammals and insects by causing a long-lasting prolongation of the normally transient increase in sodium permeability of nerve membrane channels during excitation. Salivation, and tremors that progress to clonic-tonic convulsions (choreoathetosis and salivation syndrome), along with gait abnormalities and ataxia are induced in rodents at high doses (> 100 mg/kg bw) but in dogs at lower doses (> 25 mg/kg bw), as seen in studies of acute toxicity and short-term studies of toxicity.

The main toxicological findings in repeat-dose studies in rodents were reduced weight gain, reduced food consumption, and at higher doses, signs of neurotoxicity (convulsions, tremors, hypersensitivity to touch and sound). Reduced weight gain and food consumption in rodents was observed with cypermethrin at dietary concentrations of 1000 ppm (equivalent to 50 mg/kg bw per day) and above. For alpha-cypermethrin these effects occurred at 100 ppm (equal to 11 mg/kg bw per day) in mice, while for zeta-cypermethrin the same effects were observed at 400 ppm (equal to 26 mg/kg bw per day) in rats. Dogs appeared to be the most sensitive species, with clinical signs of neurotoxicity being observed in the absence of body-weight loss at dietary concentrations of 600 ppm (equivalent to 15 mg/kg bw per day) and 120 ppm (equivalent to 3 mg/kg bw per day) for cypermethrin and alpha-cypermethrin respectively. Dogs dosed with alpha-cypermethrin for 3 months showed the usual clinical signs of pyrethroid toxicity, namely body tremors and variable incidences of head nodding, lip-licking, subduedness, ataxia, and agitation. The NOAEL for clinical signs in the 3-month study was 90 ppm (equivalent to 2.2 mg/kg bw per day). However, dogs dosed for 12 months showed no systemic toxicity. There was, however, abdominal skin reddening, skin reddening of the tail, including ulceration and necrosis of the tail in one male. The NOAEL for this effect was 60 ppm (equivalent to 1.5 mg/kg bw per day). There were no apparent methodological reasons for the disparity in clinical signs observed in the 3-month study in dogs, but not in the 12-month study in

dogs. Similarly, the local skin irritation effects, possibly secondary to paraesthesia, observed after 3 weeks at 120 ppm (equivalent to 3 mg/kg bw per day) in the 12-month study were not found at higher doses (270 ppm, equivalent to 6.7 mg/kg bw per day) in the 3-month study. It was not possible to discount the possibility that this may have been caused by accidental contact with food containing alpha-cypermethrin. For zeta-cypermethrin, there were no studies in dogs. However, repeat-dose studies of neurotoxicity involving functional observational battery tests in rats given diets containing zeta-cypermethrin indicated reduced landing footsplay and motor activity at 400 ppm (equal to 26 mg/kg bw per day).

There was no evidence of carcinogenicity with cypermethrin at dietary concentrations of up to 1600 ppm (equivalent to 240 mg/kg bw per day) in mice and at up to 1500 ppm (equivalent to 75 mg/kg bw per day) in rats. This was also the case in mice given diets containing alpha-cypermethrin at concentrations of up to 300 ppm (equal to 35 mg/kg bw per day), the highest dose tested.

Cypermethrin, alpha-cypermethrin and zeta-cypermethrin gave negative results in an adequate battery of studies of genotoxicity in vitro and in vivo.

In the absence of any carcinogenic potential in rodents and the lack of genotoxic potential in vitro and in vivo, the Meeting concluded that the cypermethrins are unlikely to pose a carcinogenic risk to humans.

In a three-generation study of reproductive toxicity in rats, adults receiving cypermethrin at a dietary concentration of 150 ppm (equal to 11 mg/kg bw per day) showed reduced body-weight gain and food consumption, and pups had lower body-weight gain during lactation at the higher dose of 750 ppm (equal to 56 mg/kg bw per day). Consistent with this, adult rats at 500 ppm (equivalent to 38 mg/kg bw per day) in a two-generation study of reproductive toxicity, also showed reduced body-weight gain and food consumption, but in this case litter size and litter weight were decreased at the same dose. In a two-generation study of reproductive toxicity with zeta-cypermethrin, decreased maternal body-weight gain and food consumption occurred at 375 ppm (equal to 22 mg/kg bw per day), along with decreased pup body weight. In contrast to the studies of reproductive toxicity with cypermethrin, clinical signs were observed in the dams and pups treated with zeta-cypermethrin at 22 mg/kg bw per day and above, although similar NOAELs were obtained (6 mg/kg bw per day). No effects on reproductive performance were observed with either cypermethrin or zeta-cypermethrin.

In studies of developmental toxicity with cypermethrin and alpha-cypermethrin in rats and rabbits, and with zeta-cypermethrin in rats, teratogenicity was not observed. The only developmental effect noted in any of these studies was a slight but statistically significant reduction in fetal weight in rats treated with alpha-cypermethrin when clinical signs of neurotoxicity, and decreased body-weight gain and food consumption were seen in the dams. The NOAEL for these effects was 9 mg/kg bw per day. There were no developmental effects in rabbits given alpha-cypermethrin at up to 30 mg/kg bw per day or cypermethrin at 700 mg/kg bw per day, the highest doses tested, but alpha-cypermethrin was relatively more maternally toxic than cypermethrin in rabbits, causing a decrease in body-weight gain at 30 mg/kg bw per day, while the dose of cypermethrin at which similar effects were seen was 700 mg/kg bw per day.

Studies of acute neurotoxicity in rats were performed with cypermethrin, alpha-cypermethrin and zeta-cypermethrin. With cypermethrin, reduced activity and gait abnormalities were observed at a dose of 20 mg/kg bw; the NOAEL was 4 mg/kg bw. At doses of 60 mg/kg bw and above, salivation, choreoathetosis, altered righting reflex, splayed limbs and flattened posture were observed; urination, landing foot splay and click response were increased; and arousal, grip strengths, touch response and tail-pinch response were decreased. Alpha-cypermethrin induced death, clinical signs, gait abnormalities, abnormal reactivity in the functional observational battery (FOB), and slight to very slight degeneration of sciatic nerve fibres at doses of 20 mg/kg bw and above, with males being more severely affected than females. The NOAEL was 4 mg/kg bw. With zeta-cypermethrin at a dose of 50 mg/kg bw, clinical signs were observed, with additional findings of FOB abnormalities and one female death at 250 mg/kg bw. The NOAEL was 10 mg/kg bw.

Overall, the limited database for zeta-cypermethrin indicated that its toxicity profile was similar to that for cypermethrin and alpha-cypermethrin.

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

Toxicological evaluation

The Meeting acknowledged that since racemic cypermethrin already includes a substantial proportion of alpha- and zeta-cypermethrin, and that all three cypermethrins are qualitatively similar in their toxicity and metabolism, an ADI established for alpha-cypermethrin could apply for all three substances. Since conventional testing of cypermethrin residues in treated commodities is unable to distinguish between the isomers, a group ADI is appropriate.

The Meeting established a group ADI of 0–0.02 mg/kg bw per day based on a NOAEL of 2.2 mg/kg bw per day for severe clinical signs of neurotoxicity in a 3-month dietary study in dogs treated with alpha-cypermethrin, and using a 100-fold safety factor. This NOAEL is supported by a similar NOAEL of 1.5 mg/kg bw per day for abdominal skin reddening and alopecia in a 12-month dietary study in dogs.

The Meeting established a group ARfD of 0.04 mg/kg bw based on the NOAEL of 4 mg/kg bw, and using a 100-fold safety factor. The NOAEL observed in a study of acute neurotoxicity was based on death, clinical signs, changes in FOB tests and degenerative changes to the sciatic nerve at higher doses. Although the database indicated that dogs were more sensitive than rats to neurotoxic effects, the delayed onset of clinical signs (2 days) after dosing at 6.75 mg/kg bw per day in the 3-month study in dogs suggests that the NOAEL in the study of acute toxicity in rats would also be adequate for the most sensitive species.

A toxicological monograph was prepared.

Levels relevant to risk assessment

(a) Cypermethrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	2-year study of toxicity and carcinogenicity [a]	Toxicity	400 ppm, equivalent to 60 mg/kg bw per day	1600 ppm, equivalent to 240 mg/kg bw per day
		Carcinogenicity	1600 ppm, equivalent to 240 mg/kg bw per day[d]	—
Rat	3-month studies of toxicity[a, b]	Toxicity	400 ppm, equivalent to 40 mg/kg bw per day	1500 ppm, equal to 116 mg/kg bw per day
	2-year studies of toxicity and carcinogenicity [a, b]	Toxicity	150 ppm, equivalent to 7.5 mg/kg bw per day	1000 ppm, equivalent to 50 mg/kg bw per day
		Carcinogenicity	1500 ppm, equivalent to 75 mg/kg bw per day[d]	—
	Multigeneration reproductive toxicity[a, b]	Parental toxicity	50 ppm, equal to 3.8 mg/kg bw per day	150 ppm, equal to 11 mg/kg bw per day
		Offspring toxicity	100 ppm, equivalent to 7.5 mg/kg bw per day	500 ppm, equivalent to 38 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	17.5 mg/kg bw per day	35 mg/kg bw per day
		Embryo/fetotoxicity	70 mg/kg bw per day[d]	—

Species	Study	Effect	NOAEL	LOAEL
	Acute neurotoxicity[c]	Neurotoxicity	4 mg/kg bw	20 mg/kg bw
Rabbit	Developmental toxicity[b, c]	Maternal toxicity	450 mg/kg bw per day	700 mg/kg bw per day
		Embryo/fetotoxicity	700 mg/kg bw per day[d]	—
Dog	3-month studies of toxicity[a, b]	Toxicity	500 ppm, equivalent to 12.5 mg/kg bw per day	800 ppm, equal to 25 mg/kg bw per day
	1-year study of toxicity[a]	Toxicity	200 ppm, equal to 5.7 mg/kg bw per day	600 ppm, equal to 18 mg/kg bw per day
	2-year study of toxicity[a]	Toxicity	300 ppm, equivalent to 7.5 mg/kg bw per day	600 ppm, equivalent to 15 mg/kg bw per day

[a] Dietary administration
[b] Two or more studies combined
[c] Gavage administration
[d] Highest dose tested

(b) Alpha-Cypermethrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	3-month study of toxicity[a]	Toxicity	50 ppm, equal to 6.3 mg/kg bw per day	250 ppm, equal to 33 mg/kg bw per day
	18-month study of toxicity and carcinogenicity[a]	Toxicity	30 ppm, equal to 3 mg/kg bw per day	100 ppm, equal to 10.6 mg/kg bw per day
		Carcinogenicity	300 ppm, equal to 35 mg/kg bw per day[d]	—
Rat	3-month study of toxicity[a]	Toxicity	180 ppm, equivalent to 18 mg/kg bw per day	540 ppm, equivalent to 54 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	9 mg/kg bw per day	18 mg/kg bw per day
		Embryo/fetotoxicity	9 mg/kg bw per day	18 mg/kg bw per day
	Acute neurotoxicity[c]	Neurotoxicity	4 mg/kg bw	20 mg/kg bw
Rabbit	Developmental toxicity[c]	Maternal toxicity	15 mg/kg bw per day	30 mg/kg bw per day
		Embryo/fetotoxicity	30 mg/kg bw per day[d]	—
Dog	3-month study of toxicity[a]	Toxicity	90 ppm, equivalent to 2.2 mg/kg bw per day	270 ppm, equivalent to 6.7 mg/kg bw per day
	1-year study of toxicity[a]	Toxicity	60 ppm, equivalent to 1.5 mg/kg bw per day	120 ppm, equivalent to 3 mg/kg bw per day

[a] Dietary administration
[b] Two or more studies combined
[c] Gavage administration
[d] Highest dose tested

(c) Zeta-cypermethrin

Species	Study	Effect	NOAEL	LOAEL

Rat	3-month study of toxicity[a]	Toxicity	250 ppm, equal to 17 mg/kg bw per day	500 ppm, equal to 34 mg/kg bw per day
	Multigeneration reproductive toxicity[a]	Parental and offspring toxicity	100 ppm, equal to 6 mg/kg bw per day	375 ppm, equal to 22 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	12.5 mg/kg bw per day	25 mg/kg bw per day
		Embryo/fetotoxicity	35 mg/kg bw per day[d]	—
	Acute neurotoxicity[c]	Neurotoxicity	10 mg/kg bw	50 mg/kg bw
	3-month study of neurotoxicity[a]	Neurotoxicity	75 ppm, equal to 5 mg/kg bw per day	400 ppm, equal to 26 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

0–0.02 mg/kg bw

Estimate of acute reference dose

0.04 mg/kg bw

Information that would be useful for continued evaluation of the compound

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

Critical end-points relevant for setting guidance values for exposure to cypermethrins

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	T_{max}~3 h; approximately 50–70% absorbed
Dermal absorption	Approximately 1% in humans
Distribution	Throughout the body; highest levels in fat, present mainly as *cis*-isomers
Potential for accumulation	The elimination half-life in fat was 10–25 days after a single oral dose; radioactivity accumulated in fat and skin after repeated oral dosing
Rate and extent of excretion	Rapid; > 95% excreted in 48 h
Metabolism in animals	Extensive, no unchanged cypermethrin excreted in the urine
Toxicologically significant compounds	Parent

Acute toxicity (cypermethrin)

Rat, LD_{50}, oral	200 to > 3000 mg/kg bw
Rat, LD_{50}, dermal	> 1600 mg/kg bw (xylene vehicle); > 4800 mg/kg bw undiluted
Rat, LC_{50}, inhalation	1.260 mg/L air
Guinea-pigs, skin sensitization (test method used)	Sensitizer (maximization); non-sensitizer (Buehler)
Acute toxicity (alpha-cypermethrin)	
Rat, LD_{50}, oral	64 to > 5000 mg/kg bw, depending on vehicle
Rat, LC_{50}, inhalation	1.590 mg/L air
Acute toxicity (zeta-cypermethrin)	
Rat, LD_{50}, oral	86–367 mg/kg bw (corn oil vehicle)
Short-term studies of toxicity	
Target/critical effect	Clinical signs of neurotoxicity
Lowest relevant oral NOAEL	2.2 mg/kg bw per day (90-day study in dogs)
Lowest relevant dermal NOAEL	20 mg/kg bw per day (21-day study in rabbits)
Lowest relevant inhalation NOAEL	0.050 mg/L (21-day study in rats)
Genotoxicity	
	No genotoxic potential
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Reduced body-weight gain and food consumption
Lowest relevant NOAEL	7.5 mg/kg bw per day (2-year dietary study in rats)
Carcinogenicity	Not carcinogenic in rats and mice
Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects; decreased pup body weight
Lowest relevant reproductive NOAEL	6 mg/kg bw per day (rats)
Developmental target/critical effect	Decreased fetal weights (rats)
Lowest relevant developmental NOAEL	9 mg/kg bw per day
Neurotoxicity	
Target/critical effect	Clinical signs, changes in FOB tests and degenerative changes to the sciatic nerve
Lowest relevant NOAEL	4 mg/kg bw per day (single-dose study in rats)
Delayed neurotoxicity	
Target/critical effect	No delayed effect
Lowest relevant NOAEL	> 1000 mg/kg bw per day (hens)
Medical data	Paraesthesia after dermal exposure

Summary for cypermethrins, including alpha-cypermethrin and zeta-cypermethrin

	Value	**Study**	**Safety factor**
Group ADI	0–0.02 mg/kg bw per day	Dog, 3-month dietary study with alpha-cypermethrin	100

Group ARfD	0.04 mg/kg bw	Rat, study of acute neurotoxicity with alpha-cypermethrin	100

4.9 CYROMAZINE (169)

TOXICOLOGY

Cyromazine, the ISO approved name for *N*-cyclopropyl-[1,3,5] triazine-2,4,6-triamine, is a selective insecticide used on a broad range of vegetable crops. It acts by inhibiting the moulting process, particularly in dipterian insects. Cyromazine was first evaluated by the 1990 JMPR, when an ADI of 0–0.02 mg/kg bw was established on the basis of a NOAEL of 1.8 mg/kg bw per day for body-weight changes in a 2-year dietary study in rats and a NOAEL of 2 mg/kg bw per day in a two-generation study of reproductive toxicity in rats, with a safety factor of 100.

Cyromazine was considered by the present Meeting within the periodic review programme of the CCPR. The Meeting reviewed new data on cyromazine, including studies of toxicokinetics, metabolism, dermal absorption, acute toxicity after inhalation, skin sensitization, a 1-year study of toxicity in dogs and a 3-week study of dermal toxicity in rabbits, as well as data on mutagenesis and toxicity for the metabolite, melamine. Relevant data from the previous evaluation were also considered.

All pivotal studies with cyromazine were certified as complying with GLP.

Biochemical aspects

Toxicokinetic studies in rats given ^{14}C-labelled cyromazine as single and repeated oral doses showed that the active substance is rapidly and almost completely absorbed from the gastrointestinal tract and distributed to all organs and tissues. The substance was rapidly excreted, with an initial rapid phase of 2–12 hours followed by a slower phase. More than 97% of the administered dose was excreted within 24 hours, almost exclusively in the urine.

Cyromazine was incompletely metabolized, essentially by methylation, hydroxylation or *N*-dealkylation. The major component present was cyromazine, which accounted for 71–72% of the radiolabel; a further 7% was attributable to melamine, 8–11% to hydroxy-cyromazine and methyl-cyromazine. Only 6% of [U-^{14}C triazine]-metabolites in the urine and 13% in the faeces remained uncharacterized and comprised minor metabolites.

In monkeys (*Macaca fasicicula*), ^{14}C-labelled cyromazine was also rapidly and extensively absorbed and rapidly excreted, predominantly in the urine. Cyromazine accounted for approximately 95% of urinary radioactivity, with the remainder being attributable to melamine.

Toxicological data

Cyromazine has low acute toxicity in rats when administered orally (LD_{50} = 3387 mg/kg bw), dermally (LD_{50} > 3170 mg/kg bw) or by inhalation (4 hours LC_{50} > 3.6 mg/L, the highest achievable concentration). Signs of intoxication were sedation, dyspnoea, curved position and ruffled fur after oral or dermal administration. Animals recovered from systemic symptoms within 9–12 days. After inhalation, a decrease in activity, piloerection and nasal discharge were observed; these clinical signs were no longer seen on day 2 after exposure. Cyromazine is not an irritant to the skin and eyes of rabbits. In a maximization test in guinea-pigs, cyromazine did not show any sensitizing potential.

The toxicity of cyromazine administered orally was investigated in short-term dietary studies: 90-day studies in rats and dogs and a 1-year study in dogs. The main effects were changes in body weight in rats and dogs, and haematological changes in dogs.

The NOAEL in a 90-day study in rats was 3000 ppm (equal to 232 mg/kg bw per day), the highest dose tested. Small changes in body weight were not considered to be toxicologically relevant.

In a 90-day study in dogs, cyromazine induced some reduction in body-weight gain in both sexes at 3000 ppm and in females at 1000 ppm. Food consumption was decreased at 3000 ppm. Decreased erythrocyte values (total erythrocyte count, haemoglobin concentration and erythrocyte volume fraction) were observed in males and females at 3000 ppm and 300 ppm, respectively. The NOAEL was 300 ppm (equal to 12 mg/kg bw per day).

In a 1-year dietary study in dogs, the NOAEL was 200 ppm (equal to 5.7 mg/kg bw per day) on the basis of haematological effects observed at 800 ppm in males.

A NOAEC of 0.058 mg/L (equivalent to 9.3 mg/kg bw per day) was identified on the basis of clinical signs in a 28-day (4hoours per day) study in rats treated by inhalation. Haematology was reversibly affected in males at 0.706 mg/L. In rabbits, dermal exposure to cyromazine at doses of up to 2000 mg/kg bw per day for 21 days (6 hours per day) produced no systemic adverse effects and no observable skin irritation.

Long-term dietary studies of toxicity and carcinogenicity were carried out in mice and rats. Body-weight changes were the critical effects observed in these studies.

The NOAEL in a 2-year study in mice given diets containing cyromazine was 1000 ppm (equal to 126 mg/kg bw per day) on the basis of changes in body weight in males at 3000 ppm. Small and occasional decreases in body weight and food consumption observed at 1000 ppm were not considered toxicologically relevant.

In rats, dietary administration of cyromazine for 2 years resulted in a decrease in mean body weight, body-weight gain and food consumption in males and females at 3000 ppm. The NOAEL for these effects was 300 ppm (equal to 15 mg/kg bw per day).

Non-statistically significant increases in the incidence of mammary gland tumours were observed in female mice (above the highest value in the range for historical controls) and rats (within the range for historical controls) at 3000 ppm.

Cyromazine gave consistently negative results in a comprehensive range of studies of genotoxicity in vitro and in vivo, with the exception of an inconclusive spot test in mice. The Meeting concluded that cyromazine is unlikely to be genotoxic.

In view of the absence of genotoxicity and the equivocal response at the highest dose in the studies of carcinogenicity in mice and rats, the Meeting concluded that cyromazine is unlikely to pose a carcinogenic risk to humans at exposure levels relevant to residues on food.

The reproductive toxicity of cyromazine was examined in a two-generation study in rats, and in studies of developmental toxicity in rats and rabbits.

Dietary administration of cyromazine to rats for two generations resulted in decreased parental body weights and food consumption at doses of 3000 ppm, and decreased pup body weights at 3000 ppm. Male fertility was reduced in the F_0 generation at 3000 ppm. A decrease in pup viability at birth and in mean litter size was observed in F_2 litters at 3000 ppm. The NOAEL for parental toxicity, reproductive and offspring toxicity was 1000 ppm (equal to 51 mg/kg bw per day).

Cyromazine was not teratogenic to rats when administered at a dose of up to 600 mg/kg bw per day. Signs of maternal toxicity were observed at 300 and 600 mg/kg bw per day and fetal toxicity was observed at the highest dose. The NOAEL for maternal toxicity was 100 mg/kg bw per day on the basis of clinical signs of toxicity and decreased body-weight gain. The NOAEL for developmental toxicity was 300 mg/kg bw per day on the basis of a decrease in body weight and reduced ossification at the next highest dose.

In three studies of development toxicity in rabbits, the administration of cyromazine by gavage at a dose of 25 mg/kg bw per day or greater resulted in deaths, clinical signs of toxicity

(decreased urination and defaecation), decrease in body-weight gain, body-weight loss and decrease in food consumption in the dams. Body-weight loss was usually observed within the first few days after dosing and it was not always possible to determine whether this loss was accompanied by a reduction in food intake. The animals rapidly recovered weight after dosing stopped. The overall NOAEL for maternal toxicity was 10 mg/kg bw per day. Cyromazine did not induce teratogenic or fetotoxic effects in rabbits. Increased numbers of abortions, postimplantation losses, resorptions and vertebral variations as well as decreased numbers of viable fetuses were observed only at maternally toxic doses (60 mg/kg bw per day or greater). The overall NOAEL for developmental toxicity was 30 mg/kg bw per day.

No specific studies of neurotoxicity with cyromazine were available; however, no evidence of neurotoxicity was apparent in the available studies of toxicity.

No adverse effects were reported in personnel involved in the production and formulation of cyromazine, or in the use of this product in the field.

The metabolites found in plants, goats, hens and rats are melamine and 1-methylcyromazine. Neither contains new functional groups or structural alerts. Melamine has been investigated for its toxicological properties and results were reported in the published literature. The main toxic effects of dietary exposure to melamine in rats and mice were calculi formation (constituted by melamine and uric acid), inflammatory reactions and hyperplasia in the urinary bladder. The NOAEL for urinary bladder calculi formation and hyperplasia was 1500 ppm (equivalent to 150 mg/kg bw per day) in a 90-day study in rats. Induction of carcinomas of the urinary bladder occurred in male rats fed diets containing melamine at 4500 ppm (equivalent to 225 mg/kg bw per day) for 103 weeks, but not in female rats or in male or female mice. Melamine is not genotoxic in vitro or in vivo. Although bladder tumours related to calculi formation are not considered to be species-specific, they are related to the administration of high doses.[41] Bladder tumours were related to precipitation of urinary melamine with the formation of melamine/uric acid-containing urinary-tract calculi, producing urothelial toxicity and consequent regeneration of the bladder epithelium and ultimately formation of tumours. The non-DNA-reactive mechanism by which melamine produced urinary bladder tumours in male rats occurred only under conditions in which calculi were produced. The risk of developing bladder cancer from calculi is significantly lower in humans than in rodents, most probably because of the usually short time that calculi are present in humans, owing to anatomic and obstructive issues.[23] These bladder tumours are thus an effect that occurs at high doses, having a threshold that is well above the expected human exposure through residues.

The Meeting concluded that the existing database was adequate to characterize the potential hazard of cyromazine and its metabolites to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.06 mg/kg bw based on a NOAEL of 5.7 mg/kg bw per day for haematological effects detected at 23 mg/kg bw per day in males in a 1-year study of toxicity in dogs, and using a safety factor of 100.

The Meeting established an ARfD of 0.1 mg/kg bw based on a NOAEL of 10 mg/kg bw per day for body-weight loss and decrease in food consumption observed soon after dosing at 25 mg/kg bw per day or greater in dams in studies of developmental toxicity in rabbits treated by gavage, and with a safety factor of 100. The reason for these effects was unknown and there is a rapid recovery on cessation of administration. Therefore, this ARfD may be conservative.

A toxicological monograph was prepared.

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[41] IARC Concensus Report (1999b) In: Capen CC, Dybing E, Rice JM and Wilbourn JD, eds. *Species differences in thyroid, kidney and urinary bladder carcinogenesis*. IARC Scientific Publications No. 147. Lyon, France, pp 1–14.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	2-year studies of toxicity and carcinogenicity[a]	Toxicity	1000 ppm, equal to 126 mg/kg bw per day	3000 ppm, equal to 384 mg/kg bw per day
		Carcinogenicity	1000 ppm, equal to 164 mg/kg bw per day	3000 ppm, equal to 476 mg/kg bw per day
Rat	2-year studies of toxicity and carcinogenicity[a]	Toxicity	300 ppm, equal to 15 mg/kg bw per day	3000 ppm, equal to 156 mg/kg bw per day
		Carcinogenicity	3000 ppm, equal to 156 mg/kg bw per day[c]	—
	Multigeneration reproductive toxicity[a]	Parental	1000 ppm, equal to 51 mg/kg bw per day	3000 ppm, equal to 169 mg/kg bw per day
		Offspring toxicity	1000 ppm, equal to 51 mg/kg bw per day	3000 ppm, equal to 169 mg/kg bw per day
		Reproductive toxicity	1000 ppm, equal to 51 mg/kg bw per day	3000 ppm, equal to 169 mg/kg bw per day
	Developmental toxicity[b]	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
		Developmental toxicity	300 mg/kg bw per day	600 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	25 mg/kg bw per day
		Developmental toxicity	30 mg/kg bw per day	60 mg/kg bw per day
Dog	1-year study of toxicity[a]	Toxicity	200 ppm, equal to 5.7 mg/kg bw per day	800 ppm, equal to 23 mg/kg bw per day

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

Estimate of acceptable daily intake for humans

0–0.06 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 exposures

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, 94–97% based on urinary excretion
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Rapid and extensive (> 97% within 24 h, mainly via urine)
Metabolism in animals	Incomplete metabolism, essentially by methylation, hydroxylation or *N*-dealkylation
Toxicologically significant compounds	Parent compound and melamine
Acute toxicity	
Rat, LD_{50}, oral	3387 mg/kg bw
Rat, LD_{50}, dermal	> 3170 mg/kg bw
Rat, LC_{50}, inhalation	> 3.6 mg/L of air (4 h, nose only, aerosol)
Rabbit, skin irritation	Not irritating (24 h)
Rabbit, eye irritation	Not irritating
Guinea-pig, skin sensitization (test method used)	Not sensitizing (Magnusson & Kligman)
Short-term studies of toxicity	
Target/critical effect	Decreased body-weight gain (rats and dogs), haematopoietic system (dogs)
Lowest relevant oral NOAEL	232 mg/kg bw per day (90-day study in rats)
	5.7 mg/kg bw per day (1-year study in dogs)
Lowest relevant dermal NOAEL	2000 mg/kg bw per day, highest dose tested (3-week study in rabbits)
Lowest relevant inhalation NOAEC	0.058 mg/L air (28-day study in rats)
Genotoxicity	
	Not genotoxic in vitro and in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Decreased body-weight gain (mice and rats)
Lowest relevant NOAEL	15 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Non-statistically significant increase in incidence of mammary gland tumours in female mice (higher than historical control range) and rats at 3000 ppm
Reproductive toxicity	
Reproduction target/critical effect	Reduction male fertility, decrease pup viability at birth and mean litter size at parentally toxic levels
Lowest relevant reproductive NOAEL	Parents: 51 mg/kg bw per day (rats)
	Reproductive and offspring toxicity: 51 mg/kg bw per day (rats)
Developmental target/critical effect	Embryotoxicity (rabbits) and fetotoxicity (rats) at maternally toxic doses
Lowest relevant developmental NOAEL	Maternal: 10 mg/kg bw per day (rabbits)

	Developmental: 30 mg/kg bw per day (rabbits)
Neurotoxicity/delayed neurotoxicity	
	No specific study; no findings in other studies
Other toxicological studies	
Toxicity of metabolites:	
Melamine	Oral LD_{50} in rat: 3161 mg/kg bw (males)
	Main toxic effects of dietary administration to rats and mice: calculi formation, inflammatory reactions and hyperplasia in the urinary bladder
	LOAEL calculus formation: about 150 mg/kg bw per day in rats (90 days)
	NOAEL hyperplasia: 150 mg/kg bw per day in rats (90 days)
	Induction of carcinomas of the urinary bladder in male rats at 225 mg/kg bw per day (2 years)
	Not carcinogenic in females rats or in mice of both sexes
	Not genotoxic in vitro and in vivo
	Non genotoxic mode of action
Medical data	
	No adverse effects on health in manufacturing personnel

Summary

	Value	Study	Safety factor
ADI	0–0.06 mg/kg bw	Dog, 1 year study of toxicity	100
ARfD	0.1 mg/kg bw	Rabbit, developmental toxicity, (maternal toxicity)	100

4.10 DIAZINON (022)

TOXICOLOGY

Diazinon is the ISO approved name for the contact organothiophosphate insecticide, *O,O*-diethyl *O*-2-isopropyl-6-methylpyrimidin-4-yl phosphorothioate (IUPAC). Diazoxon, the biologically active metabolite of diazinon, inhibits the activity of cholinesterase.

Diazinon has been reviewed by the JMPR on several occasions since the first evaluation in 1963. In 1966, an ADI of 0–0.002 mg/kg bw per day was established based on a NOEL of 0.02 mg/kg bw per day for inhibition of plasma cholinesterase activity in a 37–43-day study in humans. In 2001, the JMPR established an ARfD for diazinon. Although a new study of acute toxicity in humans was submitted, the ARfD of 0.03 mg/kg bw was based on a NOAEL of 2.5 mg/kg bw observed in a study of acute neurotoxicity in rats.

The present Meeting re-considered the ADI and ARfD for diazinon because the existing ADI was based on a study in men only, while a second study in male volunteers was not considered suitable as the basis for an ARfD in 2001. As inhibition of cholinesterase activity is the most sensitive toxicological end-point for diazinon, all previously considered studies that reported cholinesterase activity and five additional studies were reviewed by the present Meeting. The new data included the final report of the preliminary study of acute toxicity in humans that was considered by the JMPR in 2001, another repeat-dose study in humans, a short-term study of toxicity in rats and two published studies.

Unpublished studies in laboratory animals complied with good laboratory practice (GLP) and with the relevant OECD test guidelines. Studies in humans were conducted in accordance with principles such as those expressed in the Declaration of Helsinki[42] or equivalent statements prepared for use by national and/or multinational authorities.

Toxicological data

The oral LD_{50} for diazinon in rats ranged from 187 to 1160 mg/kg bw, while the dermal LD_{50} and inhalation LC_{50} were > 2150 mg/kg bw and > 2.3 mg/L, respectively.

Signs of acute toxicity after oral, dermal, or inhalational administration were those typically observed with most organophosphorus cholinesterase-inhibiting pesticides and included muscarinic effects (diarrhoea, salivation, pupil constriction), nicotinic effects (muscle fasciculations and fatigue) and central nervous system effects (ataxia, convulsions).

The most sensitive end-point observed in all species given single and repeated doses of diazinon was inhibition of cholinesterase activity. In studies designed to establish the time course of clinical signs and inhibition of cholinesterase activity in rats, there was an apparent sex difference in sensitivity to clinical signs, with females showing signs of poisoning at doses of 50 mg/kg bw or greater, while in males it was at doses of 250 mg/kg bw or greater. However, there was little difference in inhibition of cholinesterase activity between the sexes. The overall NOAEL in all studies of acute toxicity was 2.5 mg/kg bw on the basis of inhibition of cholinesterase activity in erythrocytes and in the brain at the next highest dose in both sexes.

In some repeat-dose dietary studies, female rats appeared to be more sensitive to inhibition of cholinesterase activity, while lacking clinical signs. This apparent sex difference in sensitivity for cholinesterase inhibition was confirmed in a 28-day dietary exposure study in rats in which cholinesterase activity was monitored in the blood and in regional areas of the brain. Significant dose-related reductions in erythrocyte and plasma cholinesterase activity were observed at 30 ppm (2.3 mg/kg bw per day) in both sexes, while significant dose-related inhibition of cholinesterase activity was observed in all tested regions of the brain (i.e. cerebellum, cerebral cortex, striatum, hippocampus and thoracic spinal cord) of females at 300 ppm (23 mg/kg bw per day), but only in the cerebellum of males. The greater incidence of treatment-related muscle fasciculations among females (14 out of 15) relative to males (3 out of 15) at the highest tested dose of 3000 ppm (210 mg/kg bw per day) is additional support for a sex difference in sensitivity.

In a 1-year study in dogs, clinical signs and reduced body-weight gain were observed in females at slightly lower doses, i.e. 150 ppm (5.9 mg/kg bw per day) in females and 300 ppm (10.9 mg/kg bw per day) in males.

The LOAEL for cholinesterase inhibition in erythrocytes in repeat-dose studies was 10 ppm (equivalent to 1 mg/kg bw per day) in a 92-day dietary study in rats. The highest NOAEL in the database was 5 ppm (equivalent to 0.5 mg/kg bw per day) in the 92-day study in rats.

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[42] Cristie B (2000) Doctors revise Declaration of Helsinki. *BMJ* 321:913.

In a study of acute toxicity in male volunteers given ascending doses of diazinon, cholinesterase activity was not inhibited in erythrocytes at 0.21 mg/kg bw, the second highest dose tested. The highest dose was ignored, as the group comprised a single volunteer. Repeat-dose studies in male volunteers given diazinon for 28–37 days showed that, while there was some inhibition of plasma cholinesterase activity at the highest tested dose of 0.03 mg/kg bw per day, no inhibition of erythrocyte cholinesterase activity was observed.

Toxicological evaluation

The Meeting identified inhibition of cholinesterase activity as the most sensitive end-point observed after single or repeated doses of diazinon in all species. The LOAEL for reduced cholinesterase activity in erythrocytes was 1 mg/kg bw per day and the NOAEL was 0.5 mg/kg bw per day. In considering the NOAEL and LOAEL identified in all repeat-dose studies, the Meeting concluded that all species appeared to be equally sensitive and the extent of cholinesterase inhibition was not dependent on duration of dosing, once steady state had been achieved within 4 weeks. After considering all previously evaluated data and the new studies, the Meeting established an ADI of 0–0.005 mg/kg bw based on the highest NOAEL of 0.5 mg/kg bw per day for inhibition of erythrocyte cholinesterase activity in a 92-day repeat-dose study in rats, and with a safety factor of 100.

The Meeting reaffirmed the ARfD of 0.03 mg/kg bw that was established by the 2001 JMPR. This ARfD was based on the NOAEL of 2.5 mg/kg bw identified in studies of acute toxicity and neurotoxicity in rats, and a safety factor of 100. This ARfD was supported by the NOAEL of 0.21 mg/kg bw identified in the study in humans given a single dose of diazinon, and a safety factor of 10.

An addendum to the toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Acute neurotoxicity[b]	Behavioural changes and cholinesterase inhibition in erythrocytes	2.5 mg/kg bw	150 mg/kg bw
	Time course of cholinesterase inhibition after a single dose[b]	Cholinesterase inhibition in erythrocytes and brain	2.5 mg/kg bw	25 mg/kg bw
Human	Acute toxicity[c]	No inhibition of cholinesterase activity	0.21 mg/kg bw	—
Rat	3-month studies of toxicity[a]	Cholinesterase inhibition in erythrocytes and brain	5 ppm, equal to 0.4 mg/kg bw per day	250 ppm, equal to 19 mg/kg bw per day
		Cholinesterase inhibition in erythrocytes[c]	5 ppm, equivalent to 0.5 mg/kg bw per day	10 ppm, equivalent to 1 mg/kg bw per day
	98–99 week study of toxicity[a]	Cholinesterase inhibition in erythrocytes and brain	1.5 ppm, equal to 0.07 mg/kg bw per day	125 ppm, equal to 6 mg/kg bw per day
Dog	1-year study of	Cholinesterase	0.5 ppm, equal to	150 ppm, equal to 4.5

	toxicity[a]	inhibition in erythrocytes and brain	0.02 mg/kg bw per day	mg/kg bw per day
Human	37 days	No inhibition of cholinesterase in erythrocytes	0.025[c]	—
	34 days		0.03[c]	
	28 days		0.03[c]	

[a] Dietary administration

[b] Gavage administration

[c] Highest tested dose

Estimate of acceptable daily intake for humans

0–0.005 mg/kg bw

Estimate of acute reference dose

0.03 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

RESIDUE AND ANALYTICAL ASPECTS

Diazinon has been evaluated by the JMPR several times and a number of maximum residue levels were estimated. The residue was defined as diazinon for regulatory and dietary intake assessment purposes. The present Meeting established an ADI of 0-0.005 mg/kg bw but the ARfD of 0.03 mg/kg bw remained unchanged.

Results of supervised trials, carried out on cranberry according the US registered uses, were submitted for evaluation.

Results of supervised residue trials

During the 1988 and 1989 growing seasons ten trials were conducted on cranberries in three regions of USA. Samples were collected at 7 day PHI following the total seasonal application rates of 6.72–13.45 (GAP or 1.3 × GAP), and 20.17 (double rate) kg ai/ha.

Samples were stored frozen from harvest to analysis for a maximum of 11 months. Storage stability data submitted to the 1993 JMPR indicated that diazinon and CGA-14128 (4-hydroxy-2-isopropyl-6-methylpyrimidine) residues were stable in/on frozen raw agricultural commodities (< -10^{o} C) for up to 26 months. Diazoxon was not stable (< 3 months).

The harvested cranberry samples were analyzed by a method with an LOQ of 0.01 mg/kg for each residue component measured. The concurrent recoveries of diazoxon, diazinon and CGA-14128 from cranberries fortified at 0.016-0.40 mg/kg ranged between 70-100% (82 ± 11, n = 7), 75-112% (94 ± 14, n = 8), and 106-125% (114 ± 8, n = 7), respectively.

The average residues (mg/kg) from treatments carried out according to 1.5 times the individual treatment rate and at 1.3 times the total seasonal application rates specified in GAP were in rank order: < 0.01, 0.01, 0.04, 0.05, 0.07, 0.08 and 0.13mg/kg

The Meeting estimated a maximum residue level of 0.2 mg/kg, HR of 0.13 mg/kg and STMR of 0.05 mg/kg, respectively.

DIETARY RISK ASSESSMENT

Long-term intake

As the ADI of the compound was revised, the long-term intake was recalculated using the current Codex MRLs or the estimated STMR values. The summary of calculations are included in Annex 3 of the report. The intake of diazinon residues calculated based on the 13 regional diets ranged from 7 to 50% of the maximum ADI (0.005 mg/kg bw).

The Meeting concluded that the long-term intake of residues from the use of diazinon on the commodities considered by the CCPR or JMPR is unlikely to present a public health concern.

Short-term intake

Since the ARfD was not changed the IESTI was only calculated for cranberries:

The GEMS/Food regional diet specifies the large portion sizes of cranberry of 3.53 g/kg bw for adults and 6.78 g/kg bw for children (both are from the USA).

The IESTIs of diazinon calculated on the basis of the large portion size and the estimated HR of 0.13 mg/kg are 1.53% and 2.9% of the ARfD for adults and children, respectively.

The Meeting concluded that the short-term intake of residues resulting from the use of diazinon on cranberry that have been considered by the JMPR is unlikely to present a public health concern.

4.11 DIMETHOATE (027)

RESIDUE AND ANALYTICAL ASPECTS

Dimethoate was evaluated by the JMPR on several occasions between 1965 and 1994 and under the CCPR Periodic Review Programme in 1998. The compound was re-evaluated in 2003 for residues and toxicology. The 2003 Meeting recommended a number of MRLs and established an acute reference dose (ARfD) of 0.02 mg/kg bw.

The 38th session of the CCPR in 2006 decided to advance the MRL of dimethoate in barley of 2 mg/kg to step 8, which was adopted by the 29th session CAC as a Codex standard. Apart from that, the Committee was informed that new residue information for barley would be submitted to the JMPR.

Results of supervised residue trials

Barley

Field trials conducted in northern Europe and involving one foliar application of dimethoate were made available to the Meeting.

GAP in Finland on cereals is for one application per season with a maximum rate of 0.32 kg ai/ha to be applied from leaf development to the end of tillering, before stem elongation. In seven trials on barley from northern Europe (two from the UK, two from France, two from Denmark and one from Germany) matching Finnish GAP residue levels of dimethoate were < 0.001 mg/kg in six trials and 0.002 mg/kg in one trial in grains. The omethoate residues in grains were < 0.001 (7) mg/kg.

The Meeting agreed that the MRL for barley recommended at the 1998 Meeting and advanced to step 8 by the 2006 CCPR was sufficient to accommodate the new residue data and the Finnish GAP, and that no further evaluation was required.

Barley straw and fodder, dry

Residues in barley straw and fodder, dry were evaluated by JMPR 1998. An MRL was not recommended but STMRs were estimated for dimethoate and omethoate separately. New field trials conducted in northern Europe and involving one foliar application of dimethoate were made available to the present Meeting.

GAP in Finland on cereals is for one application per season with a maximum rate of 0.32 kg ai/ha to be applied from leaf development to the end of tillering, before stem elongation. In 7 trials on barley from northern Europe (two from the UK, two from France, two from Denmark and one from Germany) matching Finish GAP, residue levels found were < 0.01 (6) and 0.02 mg/kg for dimethoate and < 0.01 (7) mg/kg for omethoate in straw.

The Meeting agreed that the STMRs of 0.495 mg/kg for dimethoate and 0.03 mg/kg for omethoate estimated by the 1998 JMPR for barley straw were sufficient to accommodate the new residue data and the Finnish GAP, and that no further evaluation was required.Further work

The Meeting noticed that the estimation of STMRs and HRs was not correct for some of the commodities calculated by the 2003 JMPR. The Meeting agreed to do a corrigendum based on the supervised residue trials data submitted to the 2003 JMPR. This should include consideration of new information on GAP and residue data.

4.12 DISULFOTON (074)

RESIDUE AND ANALYTICAL ASPECTS

Disulfoton, an insecticide acaricide, was evaluated for residues within the periodic review programme by the 1991 JMPR. Additional residue information was evaluated by the JMPR in 1994 and 1998. An ADI of 0.0003 mg/kg bw and an acute RfD of 0.003 mg/kg bw were established in 1991 and in 1996, respectively. Estimations of the short-term intake (IESTI) in 2002 by WHO (CCPR 34, CX/PR 02/03) resulted in lESTIs exceeding the acute reference dose (ARfD) of 0.003 mg/kg bw for broccoli, cabbage, cauliflower, lettuce, potato, Japanese radish and rice. In the interim Codex MRLs for potato, Japanese radish and rice were withdrawn.

At the 36th Session of CCPR, the Committee noted that the acute intake concerns had not been resolved even with the use of a probabilistic method (ALINORM 04/27/24, para 106). The Committee returned the MRLs of broccoli; cabbages, head; cauliflower; lettuce head and leaf to Step 6 awaiting refinements in the acute dietary intake probabilistic methodology (ALINORM 04/27/24, para 107).

At the 37th Session of CCPR the Committee decided to return all the MRLs currently at step 7 to step 6. Since this was the third time that the proposed MRLs were returned to Step 6 for intake concerns, the Committee also decided to request the JMPR to review alternate GAPs that may result in lower MRL recommendations (ALINORM 05/28/24, para 105).

The manufacturer submitted GAP information from Canada, Mexico, Japan and the USA on broccoli, cabbage, cauliflower, and lettuce.

Residue and GAP information were also submitted by Japan on Azuki bean, burdoc, cabbage, Chinese cabbage, cucumber, egg plant, common bean (pod), mitsuba, onion, Satsuma mandarin, pineapple, potato, Japanese radish, Chinese onion (rakkyo), soybean, Welsh onion, sugar cane, sweet pepper, tomato, upland wasabi and water melon.

Results of supervised residue trials on crops

Data from supervised trials which have not previously been evaluated on Azuki bean, burdock, cabbage, Chinese cabbage, cucumber, egg plant, common bean (pod), mitsuba, onion, Satuma mandarin, pineapple, potato, Japanese radish, Chinese onion, soybean, Welsh onion, sugar cane, sweet pepper, tomato, wasabi and water melon were provided by the Japanese government.

Trials from Japan were available only in summary form and could not be evaluated.

Data on broccoli, cabbage, cauliflower and lettuce which were reviewed in the 1991, 1994 and 1998 monographs were interpreted in the light of current GAP. The Meeting noted that current GAP was the same as that recorded in 1998.

Broccoli

In USA, disulfoton may be used on broccoli in the field as a soil injection or side dressing at 1.1 kg ai/ha with a PHI of 14 days.

In Canada, disulfoton may be used on broccoli in the field as a soil-application band or side dressing at 1.1 kg ai/ha with a PHI of 42 days.

In Mexico, disulfoton may be used on broccoli in the field as a soil-application band at 1 kg ai/ha after transplanting small plants.

In six US field trials where disulfoton was used as a soil spray (pre-plant) at 1.1 kg ai/ha and a side-dressing at 1.7–2.0 kg ai/ha, with PHIs of 14–29 days, residues in rank order were < 0.02, < 0.02, 0.03, 0.05, 0.09 and 0.11 mg/kg. The Meeting noted that the field trial application rates considerably exceeded the GAP rates, so the trial data could not be used.

The Meeting noted that a highest residue of 0.11 mg/kg for broccoli would be associated with IESTI values of 60% and 120% of the current ARfD (0.003 mg/kg).

None of the residue data relating to available alternative GAP suggests a lower maximum residue level to replace the current proposal of 0.1 mg/kg disulfoton on broccoli.

Cabbage

In USA, disulfoton may be used on cabbage in the field as a soil injection or side dressing at 2.2 kg ai/ha with a PHI of 42 days. In six US field trials where disulfoton was used as a soil spray (pre-plant) at 1.1 kg ai/ha and a side-dressing at 1.7 kg ai/ha, with PHIs of 41–42 days, residues in rank order were 0.02, 0.03, 0.06, 0.08, 0.17 and 0.17 mg/kg.

Six trials were insufficient for estimation of an HR. The Meeting noted that a highest residue of 0.17 mg/kg for head cabbage would be associated with IESTI values of 110% and 260% of the current ARfD (0.003 mg/kg).

In Canada, disulfoton may be used on cabbage in the field as a soil-application band or side dressing at 1.1 kg ai/ha with a PHI of 42 days. In one US field trial where disulfoton was used twice as a band at 1.1 kg ai/ha and a PHI of 42 days, the residue was < 0.02 mg/kg. In two US field trials where disulfoton was used as a soil spray (pre-plant) at 1.1 kg ai/ha and a side-dressing at 1.3–1.5 kg ai/ha, with PHIs of 39 and 42 days, residues were < 0.02 and < 0.02 mg/kg.

Three trials were insufficient for estimation of an HR.

In Japan, disulfoton may be used on cabbage in the field by soil incorporation in the row or in the planting furrow at 1.5–3 kg ai/ha. In four Japanese field trials where disulfoton was used twice at 2 or 4 kg ai/ha and with PHIs of 57–69 days, the residues in rank order were 0.063, 0.072, 0.073 and 0.096 mg/kg.

Four trials were insufficient for estimation of an HR.

In Mexico, disulfoton may be used on cabbage in the field as a soil-application band at 1 kg ai/ha after transplanting small plants. No residue data were available at this GAP.

None of the residue data relating to available alternative GAP suggests a lower maximum residue level to replace the current proposal of 0.2 mg/kg disulfoton on head cabbage.

Cauliflower

In Canada, disulfoton may be used twice on cauliflower in the field as a soil injection or side dressing at 1.1 kg ai/ha with a PHI of 30 days.

In four US field trials on cabbage where disulfoton was used three times as a side-dressing at 1.1 kg ai/ha, with PHIs of 28-40 days, residues in rank order were < 0.01, 0.01, 0.04 and 0.31 mg/kg.

In three US field trials on cabbage where disulfoton was used as a soil spray (pre-plant) at 1.1 kg ai/ha and with 2 side-dressings at 1.0 or 1.7 kg ai/ha, with PHIs of 28–30 days, residues in rank order were < 0.01, < 0.01, and 0.05 mg/kg. Residues in rank order for the seven trials were: < 0.01, < 0.01, < 0.01, 0.01, 0.04, 0.05 and 0.31 mg/kg.

The 1991 JMPR assumed that the value of 0.31 mg/kg 40 days after the last application was an outlier (JMPR Residue Evaluations, 1991, page 325). On re-examination of the study report (Di-Syston - Magnitude of residue on cauliflower, Report M 91154, 1987), the Meeting noted that there was no documented reason for classifying the residue value of 0.31 mg/kg as invalid. The Meeting therefore included the value in the evaluation.

From this use, the Meeting estimated an HR of 0.31 mg/kg for disulfoton on cauliflower. The Meeting noted that an HR of 0.31 mg/kg for cauliflower would be associated with IESTI values of 150% and 380% of the current ARfD (0.003 mg/kg).

In Mexico, disulfoton may be used on cauliflower in the field as a soil-application band at 1 kg ai/ha after transplanting small plants. No residue data were available at this GAP.

In USA, disulfoton may be used on cauliflower in the field as a soil injection or side dressing at 1.1 kg ai/ha with a PHI of 40 days.

In four US field trials where disulfoton was used three times as a side-dressing at 1.1 kg ai/ha, with PHIs of 38–43 days, residues in rank order were < 0.01, 0.01, 0.04 and 0.31 mg/kg. In four US field trials where disulfoton was used as a soil spray (pre-plant) at 1.1 kg ai/ha and two side-dressings at 1.0 or 1.7 kg ai/ha, with PHIs of 38 and 40 days, residues in rank order were < 0.01, < 0.01, < 0.01 and 0.01 mg/kg. Residues in rank order for the eight trials were: < 0.01, < 0.01, < 0.01, < 0.01, 0.01, 0.01, 0.04 and 0.31 mg/kg.

None of the residue data relating to available alternative GAP suggests a lower maximum residue level to replace the current proposal of 0.05 mg/kg disulfoton on cauliflower. On the contrary, the inclusion of 0.31 mg/kg as a valid residue for disulfoton use on cauliflower suggests that the recommended maximum residue level on cauliflower should be adjusted to a higher level.

From this use, the Meeting estimated HR and STMR values of 0.31 and 0.01 mg/kg respectively for disulfoton on cauliflower.

The Meeting estimated a maximum residue level of 0.5 mg/kg for disulfoton on cauliflower to replace the current recommendation of 0.05 mg/kg.

Lettuce

In Canada, disulfoton may be used on lettuce as a band application at seeding at 1.1–2.2 kg ai/ha. In three US leaf lettuce trials where disulfoton was used at 2.2–2.9 kg ai/ha and the lettuce were harvested 50–59 days later, disulfoton residues were < 0.03, 0.10 and 0.56 mg/kg.

Three trials were insufficient for estimation of an HR.

In USA, disulfoton may be used on lettuce in the field as a soil injection or side dressing at 2.2 kg ai/ha with a PHI of 60 days. The US and Canadian GAPs were accepted as essentially equivalent.

In Mexico, disulfoton may be used on lettuce as a band or furrow application at seeding at 1 kg ai/ha. In eight US lettuce trials where disulfoton was used at 1.1–1.2 kg ai/ha and the lettuce were harvested 60–116 days later, disulfoton residues were < 0.03, < 0.05, < 0.05, < 0.05, 0.22, 0.58, 0.64 and 1.1 mg/kg.

From this use, the Meeting estimated an HR of 1.1 mg/kg for disulfoton on lettuce. The Meeting noted that an HR of 1.1 mg/kg for lettuce would be associated with IESTI values of 180% and 280% of the current ARfD (0.003 mg/kg).

None of the residue data relating to available alternative GAP suggests a lower maximum residue level to replace the current proposal of 1 mg/kg disulfoton on head and leaf lettuce.

DIETARY RISK ASSESSMENT

Long-term intake

The estimates of long-term intake for disulfoton (ADI 0-0.0003 mg/kg bw) in 2002 for the five regional diets were 10–120% of the ADI[43]. The STMR of 0.01 mg/kg for cauliflower is unchanged, as a result the estimates of long-term intake are unchanged.

Short-term intake

The International Estimated Short-Term Intakes (IESTI) was calculated for cauliflowers. An ARfD of 0.003 mg/kg bw has been established by the JMPR. The IESTI represented 180% and 280% of the ARfD for the general population and children respectively. The information provided to the JMPR precludes an estimate that the dietary intakes calculated for cauliflowers would be below the acute reference dose.

[43] WHO. 2002. Dietary exposure in relation to MRL setting. Codex Committee on Pesticide Residues. CCPR, 34th Session. Document CX/PR 02/03.

4.13 ENDOSULFAN (032)

RESIDUE AND ANALYTICAL ASPECTS

Endosulfan was listed in the periodic re-evaluation programme at the 36th Session of the CCPR for periodic review by the 2006 JMPR. The toxicology of endosulfan was reviewed within the periodic review by the 1998 JMPR.

The Meeting received extensive information on the metabolism and environmental fate, methods of analysis, stability of residues in storage, registered use patterns, residue supervised trials data, farm animal feeding studies and the fate of residues during processing.

Animal metabolism

The Meeting received animal metabolism studies with endosulfan in rats, dairy cows, lactating sheep and laying hens.

Initial metabolism of endosulfan in rats involves either sulfoxidation to endosulfan sulfate, a fat-soluble metabolite, followed by desulfation to the diol, or direct hydrolysis to the diol followed by oxidation to the ether, the hydroxy ether, the dihydroxy ether, and to the main metabolite in urine and faeces, the lactone. A number of unidentified polar metabolites are probably the conjugates of known metabolites. The majority of an oral dose was excreted in the faeces (70–90%) and urine (9–20%) as polar metabolites. Highest radioactivity concentrations were observed in liver and kidney followed by fat. Repeated administration of radiolabeled endosulfan or a 2 year feeding study in rats did not show a bioaccumulation of residues in fatty tissues.

Dairy cows were dosed with [^{14}C]-endosulfan at a dose rate equivalent to 22 ppm in the diet for five consecutive days, equivalent to 0.64 mg/kg bw per day. Radioactivity was detected in all edible tissues and milk at between 0.05 and 3.57 mg/kg parent equivalent. The parent compound alpha and beta isomers were detected in tissues from 2 to 15%. The major metabolite identified in all tissues, including fat and milk, was endosulfan sulfate (12–89%) with endosulfan lactone being found in kidney and liver tissue, indicating that the endosulfan is readily cleaved following dosing to a dairy cow. Metabolites other than endosulfan sulfate reported in liver and kidney tissue were produced as a result of enzymatic and acid hydrolysis of polar material that predominated in these two tissues.

Following a single dose of [^{14}C]-endosulfan (methylene labelling) to two lactating East Friesian sheep at a dose rate equivalent to 0.3 ppm in the diet, approximately 90% of the administered ^{14}C-material was excreted in the urine and faeces. Endosulfan diol and endosulfan hydroxyether, but not parent, were found in urine while endosulfan was the major component of the residue in faeces. 1–2% of the radioactivity was found in milk collected 0–17 days after administration. The main metabolite was endosulfan sulfate with the highest concentration of 0.15 mg/kg (0–24 hours after dosing) and was clearly concentrated in cream. At sacrifice, 40 days after dosing, the radioactivity level was less than 0.02 mg eq/kg in most of the organs and tissues, with exemption of liver having a peak level of 0.03 mg eq/kg.

Laying hens were dosed with [^{14}C]-endosulfan at a dose rate equivalent to 10 ppm in the diet for 12 consecutive days; the radioactivity was detected in all edible tissues at a level ranging between 0.013 and 0.974 mg/kg parent equivalent. The major metabolite identified in all tissues (excluding egg white) was endosulfan sulfate (36–65%), with a small percentage of unchanged α- and β-endosulfan also seen, plus the products of hydrolysis and oxidation namely endosulfan diol and endosulfan lactone.

In summary, the primary residues found in animal tissues were the parent, endosulfan, both alpha and beta isomers, and to a larger extent, endosulfan sulfate. The metabolism studies are

consistent with the view that the parent is converted to the sulfate *in situ* and the sulfate is more likely to be measured in tissues than the parent compound. While liver appears to be the target organ for metabolism of endosulfan, the above residue components are clearly present in significant amounts in fat. The high presence of these metabolites in fat is consistent with endosulfan being a fat-soluble pesticide. However, endosulfan and endosulfan sulfate do not bioaccumulate in organisms due to the extensive metabolism with enzymatic hydrolysis of endosulfan and endosulfan sulfate forming more polar metabolites.

Plant metabolism

The meeting received plant metabolism studies with endosulfan on tomato, cucumber, apple, sugar beet and soybean.

Young tomato plants were treated three times with ^{14}C-labelIed endosulfan at intervals of 7 days, each time at an application rate of 635 g ai/ha. 90% of the total radioactive residues were extracted from tomato fruit with acetone/water and shown to consist of the parent isomers, α- and β-endosulfan and the metabolite endosulfan sulfate. In leaves, trace amounts of free and considerable amounts of conjugated endosulfan diol were also observed.

A young apple tree was treated with ^{14}C-labelled formulated endosulfan at a rate which corresponded to 1.5 kg ai/ha. 90% of the total radioactive residues could be extracted from apples with acetone/water. These residues consisted almost exclusively of the parent isomers α- and β-endosulfan and to a very low extent the metabolite endosulfan sulfate. In leaves, endosulfan sulfate occurred as a major metabolite accounting for approximately 50% of the total radioactive residues. Only traces of endosulfan diol could be detected. The portion of non-extractable residues increased up to approximately 10% at day 21 after treatment.

Cucumber plants were treated three times with ^{14}C -labelled endosulfan at intervals of 7 days, each time at a nominal application rate of 530 g ai/ha. The total radioactive residues in the leaves decreased from 185 mg/kg to 52 mg/kg parent equivalent 0 to 14 days after the last treatment. The corresponding levels in the fruit decreased only from 0.23 to 0.18 mg/kg eq. After 14 days and the third treatment with endosulfan, the major components α- and β-endosulfan and endosulfan sulfate contributed approximately 50% of the total radioactive residues. Several smaller components did not exceed 0.05 mg/kg eq each.

Sugar beet plants were treated twice at 630 g ai/ha each and harvested 21 days later. In roots, 93.4% of TRR were extractable leaving 6.6% of TRR non-extractable. The organo-soluble radioactivity in roots consisted mainly of endosulfan sulfate (59.6% of TRR) followed by α- and β-endosulfan. In sugar beet leaves, more than 93% of TRR were extractable. In total, 51.9% of the TRR were identified in the leaves. A further 32.7% of the TRR was characterized as polar radioactivity. α--endosulfan, β-endosulfan and endosulfan sulfate were the major residue components in all plant parts.

Soybean plants were treated twice at 530 g ai/ha each. Applications were made at forage stage 61 days before harvest and hay stage 38 days before harvest. In forage just after the first treatment 98.5% of TRR were extractable with 75.4% on the plant surface. In hay 87% of the TRR were extractable and in beans at harvest 94.5%. In beans and hay the major metabolite was endosulfan sulfate with respectively 78.4 and 51.2% of the TRR. β-endosulfan and α-endosulfan were detected at 5 and 1.5% of the TRR for these two parts of the plant, respectively.

The metabolism of endosulfan in plants was characterized by decreasing levels of α-endosulfan and increasing levels of β-endosulfan and the subsequent formation of endosulfan sulfate which is the major metabolite.

Environmental fate in soil

The aerobic degradation of endosulfan in soil starts with the modification of the 7-membered dioxathiepin ring. Oxidation results in the formation of the main metabolite endosulfan sulfate. The microbially induced hydrolysis of endosulfan and of endosulfan sulfate leads to ring opening of the 7-membered ring and formation of endosulfan diol. The endosulfan diol is then condensed to endosulfan ether (minor pathway) or oxidized to endosulfan hydroxy carboxylic acid and its condensation product endosulfan lactone. The chlorinated bicyclic carbon skeleton was shown to be completely degraded by considerable formation of labelled carbon dioxide in the soil metabolism study with ring labelled endosulfan sulfate.

The half lives in the laboratory were in the range of 12–39 days for α-endosulfan, 58–264 days for β-endosulfan and about 150 days for endosulfan sulfate. It should be noted here that the former laboratory degradation studies lack in the microbial activity due to the small soil samples employed and the long incubation period without re-fertilisation of the soil microbes. Therefore, degradation studies in the field are a more realistic approach. In the field, the degradation half life is shortened to 7–21 days under Southern European summer conditions. However at colder fall and winter temperatures, the half life increased to 75–93 days. It appears that the alpha isomer degrades faster (with a half life of 6–11 days) than the beta isomer (with a half life of 19–36 days) in the field.

The main soil metabolite endosulfan sulfate is more persistent than isomers of the parent, and degrades in the field with a half life of approximately 75–161 days depending on the study conditions. Other metabolites only appear at a low level in soil and are deemed not to be relevant.

A multi-year study showed only a slight increase in soil residue levels, from the first year, to form a relatively constant plateau level in subsequent years, even in Northern Europe with cold to moderate temperatures. There does not, therefore, appear to be significant long-term accumulation of endosulfan and its sulfate in soil. Furthermore, the plateau level decreased following termination of the application.

In a rotational crop study endosulfan residues taken up by root and leafy vegetable crops, sown immediately after soil treatment at a 6× exaggerated application rate, were generally lower than the corresponding residues in soil. The highest residues were 0.2 mg/kg in the leaf and 0.3 mg/kg in the tuber of carrots, being the critical crop at the application rate of 6.6 kg ai/ha. It should be noted that there were some varying residue levels reported applying to non-mature plants at the earlier samplings. Therefore, a significant reduction in the absolute residue level in rotational crops may be expected under normal circumstances, such as; when a 1× rate is used, when there is interception of the spray by the plants reducing the proportion reaching the (non-target) soil, and when partial degradation of the pesticide in soil could occur during the interval between application of endosulfan and planting of the rotational crop.

The Meeting concluded that the presence of endosulfan residues in succeeding crops from foliar application is unlikely to be significant.

Methods of residue analysis

Methods of analysis of residues of endosulfan in plants and animal products used GC/ECD.

The methods for plant material have been validated on a wide range of crops and processed products. The principle of most methods involves a solvent extraction step followed by different matrix dependant clean up steps such as GPC, Florisil or silica gel column chromatography. The final determination is carried out by GC mostly with ECD. For enforcement purposes of plant material the method derived from the Dutch multi-residue method MRM-1 is suitable. The limit of quantification (LOQ) is typically about 0.02 mg/kg for α-endosulfan, β-endosulfan and endosulfan sulfate.

For the analysis of animal matrices, after extraction with an appropriate solvent and partition in acetonitrile, α-endosulfan, β-endosulfan and endosulfan sulfate were determined after purification

by GC/ECD. The LOQ is typically about 0.025 mg/kg for α-endosulfan, β-endosulfan and endosulfan sulfate.

Stability of residues in stored analytical samples

The storage stability of endosulfan and its important metabolites was tested in plant materials and animal tissues and products. The results of all the studies indicate that the compounds are stable in frozen storage in the tested plant commodities for 18 to 24 months and in animal commodities for at least one year.

Definition of the residue

Based on the results of various plant and animal metabolism studies, endosulfan (α- and β- isomer) and its main metabolite endosulfan sulfate are the relevant residue components.

Results from metabolism studies on the distribution ratio of residues between muscle and fat show that the residues are fat soluble which is confirmed by the log P_{OW} of 4.6-4.7 for α-endosulfan and 4.3-4.8 for β-endosulfan and 3.8 for endosulfan sulfate. Endosulfan residues are considered as fat soluble.

The Meeting concluded that the residue definition for enforcement and dietary intake purposes in plant and animal commodities is the sum of α- and β- isomer and its main metabolite endosulfan sulfate.

Results of supervised residue trials

Citrus fruits

Endosulfan is registered for foliar application to citrus fruits in Angola, Australia, Central America, Chile, Morocco, Mozambique, Saudi Arabia and South Africa. The GAP in Australia for citrus fruits is 10.5 g ai/hL with a PHI of 3 days. Endosulfan residues from supervised trials conducted in Australia according to the GAP were: 0.03, 0.16 and 0.19 mg/kg for lemons; 0.07 and 0.11 mg/kg for mandarins; and 0.05 and 0.08 mg/kg for oranges.

The Meeting considered seven supervised trials insufficient to estimate a maximum residue level for citrus fruit and withdraw the previous recommendation for oranges, sweet, sour (0.5 mg/kg).

Pome fruits

Endosulfan is registered in apples in Australia, Canada, Central America, Chile, China, Japan, Namibia, Saudi Arabia, South Africa, the USA and Zimbabwe. Results of supervised trials in Australia were reported, but those trials were not conducted according to the GAP of Australia (66.5 g ai/hL and a PHI of 28 days).

Endosulfan residues from five trials in the USA according to the US GAP (3.36 kg ai/ha/year, three applications at 66.5 g ai/hL with a PHI 21 days) were 0.16, 0.27, 0.36, 0.54 and 0.77 mg/kg.

Endosulfan residue from one trial in South Africa following GAP (1.18 kg ai /ha and a PHI of 14 days) were 0.60 mg/kg. The Meeting considered that the residues were from the same population and thus could be combined. Endosulfan residues in trials that matched GAP in ranked order were: 0.16, 0.27, 0.36, 0.54, 0.60 and 0.77 mg/kg.

Endosulfan is registered in pear in Australia, Canada, Central America, Chile, Cyprus, Greece, Japan, South Africa and the USA. Results of four supervised trials in Australia were reported, but those trials were not conducted according to the GAP (66.5 g ai/hL and a PHI of 28 days).

The Meeting considered there were insufficient trials to recommend a maximum residue level for pome fruits. The previous recommendation of 1 mg/kg for pome fruit was withdrawn.

Cherries

Supervised trials on sweet and sour cherries were performed in the USA according to GAP (3.36 kg ai/ha/year, 2 × 260 g ai/hL with a PHI of 21 days; 350 EC formulation).

Endosulfan residues obtained in sour cherry trials were as follows:

EC formulation (airblast spray): 0.12, 0.29, 0.34, 0.37, 0.53, 0.54, 0.63 (2), 0.85, 1.1 mg/kg

WP formulation (airblast spray): < 0.05 (7), 0.06 (2), 0.09 mg/kg.

Endosulfan residues obtained in sweet cherry trials were as follows:

EC formulation (airblast spray): 0.14, 0.41, 0.44, 0.52, 0.57, 0.92, 1.4 mg/kg

EC formulation (mist blower): 0.1, 0.14, 0.16 mg/kg

WP formulation (airblast spray): < 0.05, 0.06, 0.08, 0.1, 0.14, 0.20, 0.34 mg/kg and

WP formulation (mist blower): 0.31, 0.72, 0.78 mg/kg.

The residues obtained using WP and EC formulations from airblast and mist blower sprayers do not represent the same population. As a result only residues obtained from the application of the EC formulation with an airblast sprayer were considered. The results for the trials on sour and sweet cherries were combined, resulting in endosulfan residues in ranked order were: 0.12, 0.14, 0.29, 0.34, 0.37, 0.41, 0.44, 0.52, 0.53, 0.54, 0.57, 0.63 (2), 0.85, 0.92, 1.1, and 1.4 mg/kg.

The Meeting recommended a maximum residue level for cherries of 2 mg/kg to replace the previous recommendation of 1 mg/kg, an HR value of 1.4 mg/kg and an STMR value of 0.53 mg/kg.

Apricot, nectarine and peach

The Meeting received results of supervised trials on apricot, nectarine and peach conducted in Australia, but there is no GAP for these commodities. For peach, supervised trials were also reported from Europe (no GAP available) and the USA. The US trials were not conducted according to the GAP (3.36 kg ai /ha/year, 2 × 340 g ai/hL with a PHI of 21 or 2 × 66.5 g ai/hL and a PHI of 30 days).

The Meeting considered there were insufficient trials to recommend a maximum residue level for apricot, nectarine, or peach. The previous recommendation for peach of 1 mg/kg was withdrawn.

Plums (including prunes)

Neither residue data nor information on GAP for the use of endosulfan in plums was submitted.

The Meeting recommended withdrawal of the previous recommendation of 1 mg/kg for plums (including prunes).

Grapes

Endosulfan is registered for use on grapes in Canada, Central America, Chile, Croatia, Japan, Namibia, South Africa, Turkey and the USA.

Endosulfan residues from one trial in the USA conducted according to the GAP (3.36 kg ai/ha/year, 3 × 70 g ai/hL and a PHI of 7 days) was 0.75 mg/kg.

The Meeting considered one supervised residue trial insufficient to estimate a maximum residue level for grapes. The previous recommendation for grapes of 1 mg/kg was recommended for withdrawal.

Pineapple

The Meeting received results of supervised trials conducted on pineapple in the USA. As these trials were not conducted according to the US GAP (2.5 kg ai/ha, 3.36 kg ai/ha/year, with a PHI of 7 days), the Meeting could not consider them for the estimation of a maximum residue limit for pineapple.

The Meeting recommended withdrawal of the previous recommendation of 2 mg/kg (Po).

Other tropical fruits (avocado, custard apple, litchi, mango, papaya, persimmon)

The Meeting received results of supervised trials conducted in Australia on avocado, custard apple, litchi, mango, pawpaw (papaya) and persimmon.

In Australia, the GAP specifies an application rate of 70 g ai/hL for avocado, custard apple, mango and persimmon and an application rate of 52.5 g ai/hL for litchi and papaya. The PHI is 7 days, except for avocado (14 days).

Endosulfan residues obtained from the trials in Australia according to the corresponding GAPs were 0.01 and 0.11 mg/kg for avocado; 0.1 and 0.35 mg/kg for custard apple; 1.0 and 1.3 mg/kg for litchi; 0.17 and 0.20 mg/kg for mango; 0.1 and 0.18 mg/kg for papaya; and 0.55 and 0.89 mg/kg for persimmons.

The Meeting decided to combine endosulfan residues for avocado, custard apple, mango and papaya for mutual support, the residues in ranked order were: 0.01, 0.1 (2), 0.11, 0.17, 0.18, 0.20 and 0.35 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg, an HR value of 0.35 mg/kg and an STMR value of 0.14 mg/kg for avocado, custard apple, mango and papaya.

The Meeting decided to combine endosulfan residues for litchi and persimmon for mutual support, with the residues being, in ranked order, 0.55, 0.89, 1.0, and 1.3 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg, an HR value of 1.3 mg/kg and an STMR value of 0.95 mg/kg for litchi and persimmon.

Onion, bulb

Neither residue data nor information on GAP on the use of endosulfan in onions was submitted.

The Meeting recommended withdrawal of the previous recommendation of 0.2 mg/kg for onion, bulb.

Cabbages, head

Endosulfan is registered for foliar application on cabbage in Australia, Canada, Central America, Chile, Japan, New Zealand, Turkey and the USA.

Endosulfan residues in head cabbages from two trials in the USA according to that countries GAP (1.27 kg ai /ha with a PHI of 7 days) were 0.05 and 0.24 mg/kg, and from two trials in Australia according to its GAP (0.735 kg ai /ha with a PHI of 7 days) 0.026 and 0.1 mg/kg. The Meeting considered four supervised trials insufficient to estimate a maximum residue level for cabbage.

The Meeting recommended withdrawal of the previous recommendations of 1 mg/kg for head cabbage and of 2 mg/kg for Savoy cabbage.

Brussels sprouts

Endosulfan is registered for foliar application to Brussels sprouts in Canada, Central America, Namibia, South Africa and the USA.

Two trials from the USA were done according to the Canadian GAP (0.7 kg ai /ha with a PHI of 7 days), resulting in endosulfan residues of 0.68 and 0.94 mg/kg.

The Meeting considered two supervised trials insufficient to recommend a maximum residue level for Brussels sprouts.

Broccoli

Endosulfan is registered for foliar application to broccoli in Australia, Canada, Central America and in the USA.

Endosulfan residues from 17 trials from the USA, according to the GAP (1.27 kg ai /ha with a PHI of 7 days) were 0.22, 0.26, 0.28, 0.36, 0.37, 0.56, 0.57, 0.74, 0.79, 0.88, 0.97, 1.07, 1.31, 1.32, 1.86, 2.04, and 2.40 mg/kg.

Endosulfan residues from three trials in Australia, conforming to that countries GAP (0.735 kg ai /ha with a PHI of 7 days) were 0.17, 0.29 and 0.60 mg/kg.

The Meeting considered the trials to all be from similar populations and decided to combine the data for the purpose of maximum residue level recommendation. Endosulfan residues in ranked order were (n = 20): 0.17, 0.22, 0.26, 0.28, 0.29, 0.36, 0.37, 0.56, 0.57, 0.60, 0.74, 0.79, 0.88, 0.97, 1.07, 1.31, 1.32, 1.86, 2.04, and 2.4 mg/kg.

The Meeting estimated a maximum residue level for broccoli of 3 mg/kg to replace the previous recommendation of 0.5 mg/kg, an HR value of 2.4 mg/kg and an STMR value of 0.67 mg/kg.

Cauliflower

Endosulfan is registered for foliar application to cauliflower in Australia, Canada, Central America, Japan, New Zealand and the USA.

Endosulfan residues in cauliflower from two US trials conforming to the Canadian GAP (0.875 kg ai/ha with a PHI of 7 days) were < 0.05 and 0.1 mg/kg. Residues from one Australian trial at GAP (0.735 kg ai/ha with a PHI of 7 days) was 0.09 mg/kg. The Meeting considered three supervised trials insufficient to recommend a maximum residue level for cauliflower.

The Meeting recommended withdrawal of the previous recommendations of 0.5 mg/kg for cauliflower.

Cucumber

The Meeting received results of supervised trials on cucumbers conducted in Europe, Australia and the USA. No GAP was available for cucumber in Europe. The GAP in Australia specifies an application concentration of 70 g ai/hL and a PHI of 3 days. The GAP in the USA specifies an application rate of 1.27 kg ai/ha (3.36 kg ai/ha/year) and a PHI of 2 days.

Endosulfan residues from 20 trials in the USA at the GAP, in ranked order, were 0.18, 0.19, 0.22, 0.23, 0.24, 0.28, 0.30 (2), 0.31 (2), 0.32 (3), 0.36 (2), 0.40, 0.42, 0.53, 0.58 and 0.64 mg/kg. Endosulfan residues from two trials on cucumbers in Australia at the GAP were 0.09 and 0.11 mg/kg. The combined residues in cucumber were 0.09, 0.11, 0.18, 0.19, 0.22, 0.23, 0.24, 0.28, 0.30 (2), 0.31 (2), 0.32 (3), 0.36 (2), 0.40, 0.42, 0.53, 0.58 and 0.64 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg to replace the previous recommendation of 0.5 mg/kg, an STMR value of 0.31 mg/kg and an HR value of 0.64 mg/kg.

Melons, except watermelon

The Meeting received results of supervised trials on melons conducted in Europe, Australia and the USA. No GAP was available for melons in Europe. The GAP in Australia specifies an application concentration of 70 g ai/hL and a PHI of 3 days. The GAP in the USA specifies an application rate of 1.27 kg ai/ha (3.36 kg ai/ha/year) and a PHI of 2 days.

Endosulfan residues from 12 trials in the USA at the GAP were 0.05, 0.22, 0.24, 0.30 (2), 0.34, 0.35, 0.40, 0.41, 0.45, 0.49 and 0.60 mg/kg in the whole fruit. Endosulfan residues from two trials on melons in Australia at the GAP were 0.55 and 1.2 mg/kg in the whole fruit. The combined residue data, in rank order, were: 0.05, 0.22, 0.24, 0.30 (2), 0.34, 0.35, 0.40, 0.41, 0.45, 0.49, 0.55, 0.60 and 1.2 mg/kg in the whole fruit.

No pulp samples were analyzed in the US and Australian trials. The Meeting decided to use results for pulp and whole fruit reported for trials in Southern Europe, obtaining pulp to whole fruit ratios of < 0.1, < 0.13, 0.17, < 0.25 (2), < 0.29, < 0.50, <1.0 (2) with a median of < 0.25.

Based on the whole fruit data, the Meeting estimated a maximum residue level of 2 mg/kg to replace the previous recommendation of 0.5 mg/kg. Based on the melon pulp vs. whole fruit residue ratio, the Meeting estimated an STMR value of 0.09 mg/kg and an HR value of 0.3 mg/kg for melon pulp.

Squash, summer

The Meeting received results of supervised trials on summer squash conducted in Spain and the USA and on zucchini in Australia.

Endosulfan residues from 12 trials in the USA at the GAP, in ranked order, were < 0.05, 0.05, 0.07, 0.08, 0.09, 0.13, 0.14, 0.15, 0.16 (2), 0.17 and 0.23 mg/kg. For zucchini, residues from four Australian trials, at the GAP, were 0.05, 0.06, and 0.09 (2) mg/kg. The combined summer squash and zucchini residues were < 0.05, 0.05, 0.05, 0.06, 0.07, 0.08, 0.09 (3), 0.13, 0.14, 0.15, 0.16 (2), 0.17 and 0.23 mg/kg.

The Meeting estimated a maximum residue level for summer squash of 0.5 mg/kg which confirms the previous recommendation, an STMR of 0.09 mg/kg and an HR of 0.23 mg/kg.

Pepper

Endosulfan is registered for use as a foliar spray on peppers in Australia, Canada, Cyprus, Greece, and the USA. The Meeting received results of supervised trials on peppers conducted in the USA, Australia and Spain. No GAP was available from Spain and the GAP from Greece did not specify a PHI.

Endosulfan residues in two trials from the USA according to Canadian GAP (1.125 kg ai/ha with a PHI of 2 days) were 0.05 and 0.22 mg/kg. Endosulfan residues in two Australian trials at the GAP (66.5 g ai/hL with a PHI of 3 days) were 0.36 and 0.40 mg/kg.

The Meeting considered four trials insufficient to recommend a maximum residue limit for peppers.

Tomato

Endosulfan is registered for use as a foliar spray on tomatoes in Angola, Australia, Canada, Central America, Chile, Cyprus, Ecuador, Greece, Japan, Morocco, Mozambique, Namibia, New Zealand, South Africa, Spain, the USA, Venezuela and Zimbabwe. The Meeting received results of supervised trials on tomatoes conducted in the USA, Australia, Germany, Greece, Italy, Portugal and Spain.

In the USA, endosulfan is registered for the use on tomatoes at 1.27 kg ai/ha (3.36 kg ai/ha/year) with a PHI of 2 days. In field trials in the USA that matched the GAP, the endosulfan residues were 0.03, 0.04, < 0.05, < 0.05, 0.07, 0.1, 0.16, 0.21, 0.22, 0.24, 0.25, 0.25, 0.25, 0.27, 0.27, 0.27, 0.27, 0.28, 0.29, 0.33, 0.33, 0.34, 0.35, 0.38, 0.42, 0.45, 0.45, 0.47, 0.66, 0.73, 0.83 and 0.85 mg/kg (n = 32).

In Australia, endosulfan residues from field trials after application of 0.15 – 0.17 kg ai/hL and a PHI of 3 days were < 0.005, 0.06, 0.07 and 0.09 mg/kg but did not match the GAP (66.5 g ai/hL).

Endosulfan residues conducted outdoor in Southern Europe according to the GAP of Spain (0.53 kg ai/ha and a PHI of 3 days) were: 0.03, 0.03, 0.04, 0.05, 0.07, 0.07, 0.1, 0.11, 0.13, 0.13, 0.13, 0.15, 0.15, 0.19, 0.19, 0.19, 0.21, 0.22, 0.24, 0.28, 0.43 and 0.79 mg/kg (n = 22).

Endosulfan residues conducted indoor in Southern Europe according to the GAP of Spain were: 0.05, 0.07, 0.09, 0.1, 0.11, 0.12, 0.16, 0.17, 0.19, 0.20, 0.21, 0.21, 0.21, 0.23, 0.24, 0.27, 0.28, 0.29, 0.32, 0.35, 0.37, 0.41, 0.60, 0.65 and 0.72 mg/kg (n = 25).

The Meeting agreed to combine the results of the trials in the USA and Southern Europe, resulting in endosulfan residues of (in ranked order):

0.03(3), 0.04, 0.04, < 0.05, < 0.05, 0.05, 0.05, 0.07 (4), 0.09, 0.1(3), 0.11, 0.11, 0.12, 0.13(3), 0.15, 0.15, 0.16, 0.16, 0.17, 0.19(4), 0.20, 0.21(5), 0.22, 0.22, 0.23, 0.24(3), 0.25(3), 0.27(4), 0.28(3), 0.29, 0.29, 0.32, 0.33, 0.33, 0.34, 0.35, 0.35, 0.37, 0.38, 0.41, 0.42, 0.43, 0.45, 0.45, 0.47, 0.60, 0.65, 0.66, 0.72, 0.73, 0.79, 0.83 and 0.85 mg/kg (n = 79).

The Meeting estimated a maximum residue level for tomatoes of 1 mg/kg to replace the previous recommendation of 0.5 mg/kg, an HR value of 0.85 mg/kg and an STMR value of 0.22 mg/kg.

Eggplant

The Meeting received results of supervised trials on eggplant from Australia. Four trials were conducted according to the GAP of Australia (0.735 kg ai/ha with a PHI of 7 days), resulting in endosulfan residues of < 0.005, < 0.005, 0.006 and 0.06 mg/kg.

The Meeting estimated a maximum residue level for eggplant of 0.1 mg/kg, an HR value of 0.06 mg/kg and an STMR value of 0.006 mg/kg.

Sweet corn

The Meeting received results of supervised trials on sweet corn from Australia. As no GAP was available for Australia, the Meeting was not able to recommend a maximum residue limit for sweet corn.

Lettuce and kale

Endosulfan is registered for use on lettuce and kale from the USA. No residue data for lettuce and kale were submitted.

The Meeting recommended withdrawal of the previous recommendations of 1 mg/kg for kale, lettuce, head and lettuce, leaf.

Spinach

Endosulfan is registered for use on spinach in the USA. No residue data for spinach were submitted.

The Meeting recommended withdrawal of the previous recommendations of 2 mg/kg for spinach.

Beans

Endosulfan is registered for use as a foliar spray on beans in Angola, Canada, Central America, Chile, Japan, Peru, Myanmar, Namibia, South Africa, the USA and Zimbabwe. The Meeting received results of supervised trials on beans from Germany, Australia and the USA.

Only one trial in the USA conformed to the US GAP (3.36 kg ai/ha/year with a PHI of 3 days). In this trial the total endosulfan residue was 0.64 mg/kg.

The Meeting considered four supervised trials insufficient to estimate a maximum residue level for beans. The previous recommendations for broad bean (green pods and immature seeds) and common bean (pods and/or immature seeds) of 0.5 mg/kg were withdrawn.

Peas

The Meeting received results of supervised trials on peas from Australia. No GAP was available for Australia, therefore the Meeting was not able to recommend a maximum residue limit for peas.

The Meeting recommended withdrawal of the previous recommendation for garden pea (young pods) of 0.5 mg/kg.

Soybean (dry)

Endosulfan is registered for use on soybean in Australia, Brazil, Central America, Chile, Iran and Zimbabwe.

The Meeting received results of supervised trials on soybeans from Australia and Brazil. The trials in Australia were not conducted according to the GAP of Australia (350 g ai/ha with a PHI of 1 day).

Eighteen trials conducted in Brazil conformed to the Brazilian GAP (0.525 kg ai/ha and a PHI of 30 days). Endosulfan residues obtained in these trials were < 0.02, 0.05, 0.08, 0.09, 0.1 (2), 0.15, 0.20 (3), 0.25, 0.30 (2), 0.31, 0.40, 0.42, 0.45 and 0.60 mg/kg.

The Meeting estimated a maximum residue level for soybeans of 1 mg/kg which confirms the previous recommendation, and an STMR value of 0.2 mg/kg.

Carrot and beetroot

The Meeting received results of supervised trials on carrot and beetroot from Australia. The GAP of Australia for carrot and beetroot specifies a maximum application rate of 0.735 kg ai/ha and a PHI of 14 days.

For carrot, four trials were conducted according to the GAP, with endosulfan residues being < 0.005, 0.04, 0.1 and 0.13 mg/kg. Only one trial on beetroot conformed to the GAP, resulting in 0.25 mg/kg of endosulfan.

The Meeting considered five supervised trials insufficient to estimate a maximum residue level for carrot and beetroot. The Meeting recommended withdrawal of the previous recommendation for carrot of 0.2 mg/kg.

Potato and sweet potato

Endosulfan is registered for use as a foliar spray on sweet potatoes in Australia, Japan and the USA and on potatoes in Australia, Canada, Central America, Chile, Iran, Japan, New Zealand, Peru, Turkey, the USA and Zimbabwe.

The Meeting received results of supervised trials on potatoes in Australia, Europe (no GAP), and the USA. Three trials in Australia were conducted according to the GAP of Australia (0.735 kg ai

/ha with a PHI of 14 days), resulting in endosulfan residues of < 0.005, 0.005 and 0.007 mg/kg. In a single trial reported in the USA, endosulfan residues < 0.05 mg/kg occurred at the rate of 5.56 kg ai/ha with 3 applications and a PHI of 1 day (US GAP: 3.36 kg ai/ha/year and a PHI of 1 day). Endosulfan residues in all trials on potatoes were below the LOQ of 0.05 mg/kg (even for two Australian trials conducted at a double application rate as compared to the GAP in Australia).

The Meeting received results of supervised trials on sweet potato in Australia and the USA. One trial in Australia was at the GAP (0.735 kg ai/ha with a PHI of 14 days) and the endosulfan residue was < 0.005 mg/kg. Sixteen trials in the USA were conducted according to the US GAP (3.36 kg ai/ha/year with a PHI of 1 day), resulting in endosulfan residues < 0.05 mg/kg.

The Meeting decided to use the results of supervised trials on sweet potato to support the recommendation for potato. The Meeting estimated a maximum residue level for potato and sweet potato of 0.05* mg/kg, an HR value of 0.05 and an STMR value of 0.05 mg/kg. The Meeting decided to withdraw the previous recommendations for potato and sweet potato of 0.2 mg/kg.

Sugar beet

Endosulfan is registered for foliar application to sugar beet in Canada, Chile and Japan. The Meeting received results of supervised trials on sugar beet in Italy. No GAP was available for Europe; therefore the Meeting was not able to recommend a maximum residue limit for sugar beet.

The Meeting recommended withdrawal of the previous recommendation of 0.1 mg/kg for sugar beet.

Celery

Endosulfan is registered for foliar application to celery in Canada, Central America, Australia and in the USA. The Meeting received results of supervised trials on celery from Australia and the USA.

Two trials in Australia were conducted according to Australian GAP (66.5 g ai/hL with a PHI of 7 days). Endosulfan residues were 0.29 and 1.1 mg/kg.

Twelve trials in the USA were conducted according to the GAP of the USA (1.12 kg ai/ha/year with a PHI of 4 days). Endosulfan residues were 1.0, 1.4, 1.8, 2.5, 2.6 (2), 2.9, 3.1 (2), 3.8, 4.1 and 5.0 mg/kg.

The Meeting considered the trials to all be from similar populations and decided to combine the residue data obtained from the US and Australian trials. Endosulfan residues in ranked order were: 0.29, 1.0, 1.1, 1.4, 1.8, 2.5, 2.6 (2), 2.9, 3.1 (2), 3.8, 4.1 and 5.0 mg/kg.

The Meeting estimated a maximum residue level for celery of 7 mg/kg to replace the previous recommendation of 2 mg/kg, an HR value of 5.0 mg/kg and an STMR value of 2.6 mg/kg.

Rhubarb

The Meeting received results of supervised trials on rhubarb in Australia. Endosulfan is not registered for use as a foliar spray on rhubarb in Australia and therefore the Meeting was not able to recommend a maximum residue limit for rhubarb.

Hazelnuts and macadamia nuts

Endosulfan is registered for foliar spraying on hazelnuts in Poland, Spain and Turkey and on macadamia nuts in Australia.

For hazelnuts, the Meeting received results of supervised trials from Italy. Two of the trials were performed according to the GAP of Spain (105 g ai/hL with a PHI of 30 days). Endosulfan residues were < 0.02 mg/kg.

For macadamia nuts, results of four supervised trials from Australia were reported. Three of the trials were conducted according to the GAP of Australia (70 g ai/hL with a PHI of 2 days) and one trial at 50% above the GAP. Endosulfan residues were < 0.005 mg/kg in all four trials.

The Meeting decided to use the results for hazelnuts and macadamia nuts for mutual support and estimated a maximum residue level for hazelnuts and macadamia nuts of 0.02(*) mg/kg, an HR of 0 mg/kg and a STMR of 0 mg/kg .

Cotton seed

Endosulfan is registered for use on cotton in Angola, Australia, Benin, Brazil, Burkina, Central America, China, Cyprus, Ecuador, Ethiopia, Greece, India, Iran, Ivory Coast, Madagascar, Mali, Morocco, Mozambique, Myanmar, Namibia, Pakistan, Peru, South Africa, Spain, Sudan, Thailand, Togo, Turkey, the USA, Venezuela and Zimbabwe. The Meeting received results of supervised trials on cotton conducted from Australia, Greece and Spain.

One trial in Australia, conducted according to Australian GAP (0.735 kg ai/ha with a PHI of 56 days), had a residue < 0.02 mg/kg.

Seven trials in Southern Europe with a CS formulation were according to the GAP of Southern Europe (0.84 kg ai/ha with a PHI of 21 days), resulting in endosulfan residues of < 0.02 (5) and 0.24 mg/kg. Three trials with an EC formulation in Southern Europe according the same GAP resulted in endosulfan residues of < 0.02 (3) and 0.06 mg/kg.

The Meeting considered the trials to all be from similar populations and decided to combine the residue data obtained from Australia and Southern Europe. Combined endosulfan residues, in ranked order, were: < 0.02 (9), 0.06 and 0.24 mg/kg.

The Meeting estimated a maximum residue level for cotton seed of 0.3 mg/kg to replace the previous recommendation of 1 mg/kg, and a STMR of 0.02 mg/kg.

Rape seed

Endosulfan is registered for use on oil seed in Australia. No residue data for rape seed were submitted.

The Meeting recommended withdrawal of the previous recommendation of 0.5 mg/kg for rape seed.

Sunflower seed

Endosulfan is registered for use on oil seed in Australia. No residue data for sunflower seed were submitted.

The Meeting recommended withdrawal of the previous recommendation of 1 mg/kg for sunflower seed.

Maize

Endosulfan is registered for use on cereals in Australia. No residue data for maize were submitted.

The Meeting recommended withdrawal of the previous recommendation of 0.1 mg/kg for maize.

Rice

Neither residue data nor information on GAP of the use of endosulfan in rice were submitted.

The Meeting recommended withdrawal of the previous recommendation of 0.1 mg/kg for rice.

Wheat

Endosulfan is registered for use on cereals (barley, oats, rye, wheat) in Australia and the USA. No residue data for cereals were submitted.

The Meeting recommended withdrawal of the previous recommendation of 0.2 mg/kg for wheat.

Cocoa beans

Endosulfan is registered for use on cocoa in Brazil, Cameroon, Ivory Coast, Malaysia and Nigeria. The Meeting received results of supervised trials on cocoa from Brazil, Ghana and the Ivory Coast.

The trials in Brazil were conducted at application rates below the rate specified in the Brazilian GAP (87.5 g ai/hL with a PHI of 30 days).

Eight trials from Ghana and one trial from the Ivory Coast were conducted according to the GAP of Cameroon (0.26 kg ai/ha, with a PHI of 28 day), resulting in endosulfan residues in beans of < 0.01 (9) mg/kg.

Nine trials from the Ivory Coast conformed to the GAP of the Ivory Coast (0.250 g ai/ha, with the PHI not specified). The highest residues from these trials were selected for consideration: < 0.01 (5), 0.01, 0.03 (2), 0.06, and 0.08 mg/kg.

Endosulfan residues obtained in the trials from Ghana and the Ivory Coast in ranked order were: < 0.01 (14), 0.01, 0.03 (2), 0.06 and 0.08 mg/kg.

The Meeting estimated a maximum residue level for cocoa beans of 0.2 mg/kg to replace the previous recommendation of 0.1 mg/kg, and an STMR value of 0.01 mg/kg.

Coffee beans

Endosulfan is registered for use on coffee in Brazil, Cameroon, Central America, Cuba, Ecuador, Namibia, Peru, South Africa, Sudan, Thailand and Zimbabwe.

Three trials from Colombia, two trials from Mexico, two trials from Guatemala and three trials from Brazil were conducted according to the GAP of Cuba (0.613 kg ai/ha with a PHI of 30 days). Endosulfan residues in ranked order were: < 0.01 (3), 0.01, 0.02 (2), 0.03, 0.06, 0.08 and 0.09 mg/kg.

The Meeting estimated a maximum residue level for coffee beans of 0.2 mg/kg to replace the previous recommendation of 0.1 mg/kg, and a STMR of 0.02 mg/kg.

Tea

Endosulfan is registered for use on tea in China, Japan and Malaysia. The Meeting received results of supervised trials from India, which could not be matched against provided GAPs from China, Japan or Malaysia. The Meeting was not able to recommend a maximum residue limit for tea.

The Meeting recommended withdrawal of the previous recommendation of 30 mg/kg for tea, green and black.

Fate of residues during processing

The hydrolysis of ^{14}C-endosulfan under conditions representing food processing operations was investigated. Following pasteurisation, baking, boiling and sterilisation simulation, α-endosulfan, β-endosulfan and the hydrolysis product endosulfan-diol were the main components found.

The effect of processing on the level of residues of endosulfan has been studied in oranges, apples, peaches, grapes, pineapples, tomatoes, potatoes, soybeans, coffee beans, cacao beans and tea.

The processing factors (PF) shown below were calculated from the total residues for the commodities for which MRLs, STMRs and HRs were estimated. The mean PF was calculated from three values, otherwise the median PF was calculated.

RAC	Processed product	No.	PF	Mean/median PF
Tomatoes	juice	10	< 0.1, < 0.12, < 0.16, < 0.16, < 0.17, < 0.20, < 0.20, 0.20, 0.27, 0.49	< 0.185
	paste	5	0.16, 0.33, 0.59, 1.0, 1.62, 1.63	0.59
	puree	5	< 0.1, 0.33, 0.51, 0.64, 0.66	0.51
	fruit, peeled and canned	4	0.075, 0.1, < 0.20, < 0.20	0.15
	fruit, unpeeled and canned	6	0.33, 0.44, 0.50, 0.50, 1.0,1.1	0.50
Soybeans	crude oil	3	1.17, 4.1, 4.33	3.2
Coffee beans	ground roast coffee	1	< 0.063	< 0.063
	instant coffee	1	< 0.063	< 0.063

Tomatoes were processed into juice, paste, puree, peeled canned fruit and unpeeled canned fruit with processing factors of < 0.185, 0.59, 0.51, 0.15 and 0.50, respectively. Based on the STMR value of 0.22 mg/kg for tomato, the STMR-Ps were 0.04 mg/kg, 0.13 mg/kg, 0.11 mg/kg, 0.03 mg/kg, 0.11 mg/kg, for residues in tomato juice, paste, puree, peeled canned fruit and unpeeled canned fruit, respectively.

Soya beans were processed into crude oil with a processing factor of 3.2. Based on the STMR value of 0.2 mg/kg for soya beans, the STMR-P was 0.64 mg/kg for soybean crude oil.

The Meeting recommended a maximum residue limit of 2 mg/kg for soybean crude oil, based on the highest residue of 0.6 mg/kg for soya beans and the processing factor of 3.2.

Coffee beans were processed into roasted coffee and instant coffee with a processing factor of < 0.063 for both. Based on the STMR value of 0.02 mg/kg for coffee beans, the STMR-Ps were 0.0013 mg/kg for roasted coffee and instant coffee.

For cotton seed, no processing studies were submitted. The previous recommendation of 0.5 mg/kg for cotton seed oil, crude, was recommended for withdrawal.

Farm animal dietary burden

The Meeting estimated the dietary burden of endosulfan residues in livestock (farm animals) on the basis of the livestock diets listed in Appendix IX of the *FAO Manual* (FAO 2002).

The maximum dietary burden calculations include the highest residues (HR) and STMR-P values which are used for the estimation of maximum residue levels in animal commodities such as milk, eggs, meat and offal. The STMR dietary burden calculations for livestock allow an estimate of the median residues in milk, eggs, meat and offal that can be used in the chronic dietary assessments and in this case STMR and STMR-P values for feeds are used.

The percentage dry matter (DM) is taken as 100% where highest residues and STMR values are expressed on a dry weight basis.

Calculation of the dietary burden for maximum residue estimation

Commodity	Group	Residue (mg/kg)	% DM	highest residue or STMR	*Diet content (%)*			Residue (mg/kg)		Contribution
					Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Cotton seed	SO	0.24	88	HR	*10*	*25*	*NU*	0.027	0.068	NU
Soya bean	VD	0.6	89	HR	*15*	*15*	*20*	**0.1**	**0.1**	**0.135**
Potato	VR	0.05	20	HR	*75*	*40*	*NU*	**0.19**	**0.1**	**NU**
Total					***100***	***80***	***20***	**0.32**	**0.27**	**0.13**

The calculated highest dietary burdens for beef cattle, dairy cattle and poultry are 0.32, 0.27 and 0.13 ppm, respectively.

Calculation of the dietary burden for STMR estimation

Commodity	Group	Residue (mg/kg)	% DM	highest residue or STMR	*Diet content (%)*			Residue (mg/kg)		Contribution
					Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Cotton seed	SO	0.02	88	STMR	*10*	*25*	*NU*	0.002	0.006	NU
Soya bean	VD	0.2	89	STMR	*15*	*15*	*20*	**0.034**	**0.034**	**0.045**
Potato	VR	0.05	20	STMR	*75*	*40*	*NU*	**0.188**	**0.1**	**NU**
Total					***100***	***80***	***20***	**0.22**	**0.14**	**0.04**

The STMR dietary burdens for beef cattle, dairy cattle and poultry are 0.22, 0.14 and 0.04 ppm, respectively.

Animal commodity maximum residue levels

The livestock dietary burdens used for the estimation of the maximum residue levels for animal commodities are 0.32 ppm for beef cattle, 0.27 ppm for dairy cattle and 0.13 ppm for poultry. The livestock dietary burdens used for the STMR estimation for dietary risk assessment are 0.22 ppm for beef cattle, 0.14 ppm for dairy cattle and 0.04 ppm for poultry.

For poultry, the maximum dietary burden is estimated as 0.13 ppm. As a poultry feeding study was not provided, the poultry metabolism study is used to estimate maximum residue levels for eggs and poultry tissues. In the poultry metabolism study, hens were orally dosed for 12 days at levels of ^{14}C endosulfan ranging 10 to 12 ppm. Scaling the TRR in eggs and poultry tissues for a maximum dietary burden of 0.13 ppm, residues in eggs, poultry muscle/fat and liver are 0.011 mg/kg, 0.013 mg/kg and 0.006 mg/kg respectively. The validated method of analysis for poultry tissues and eggs was conducted at concentrations of 0.025 mg/kg for each component of the residue definition, and as residues in poultry tissues and eggs are expected to be less than the validated LOQ of all of the components of the residue definition, the Meeting recommended maximum residue levels of 0.03* mg/kg for eggs, poultry meat and poultry edible offal. The STMR and HR values for eggs, poultry meat and poultry edible offal were 0.025 mg/kg.

For cattle, the maximum dietary burden for beef cattle and dairy cows is 0.32 and 0.27 ppm, respectively. The dietary burden for beef cattle will determine the estimates for meat, fat and edible offal while the dietary burden for dairy cows will determine the estimate for milk.

The maximum dietary burden of 0.32 ppm is below the lowest dose level in the cattle feeding study of 4 ppm. The target tissue for endosulfan residues in animal tissues is fat. The variation in residues in fat with dose level is significant and it is noted that at the 4 ppm dose level residues in

composite fat were 1.2, 1.4 and 1.7 mg/kg. Using the highest residue of 1.7 mg/kg and scaling to 0.32 ppm, leads to an estimated residue of 0.14 mg/kg in fat. The Meeting noted that as the samples in the feeding study were composited fats and not from individual fat depots and as residues in meat producing animals are likely to be higher than milk producing animals, the Meeting recommended a maximum residue level of 0.2 mg/kg in meat on a fat basis. The previous recommendation of 0.1 mg/kg (fat) for meat (from mammals other than marine mammals) was withdrawn.

Similarly, scaling for residues in liver and kidney against the highest residues in the dose group leads to estimates of 0.078 mg/kg for liver and 0.006 mg/kg in kidney. On the basis of the estimates, the Meeting recommended maximum residue levels of 0.1 mg/kg for liver and 0.03* mg/kg for kidney.

For milk, residues in whole milk following dosing at 4 ppm ranged from 0.05 mg/kg to 0.08 mg/kg. Scaling for a dietary burden of 0.27 ppm, leads to an estimate of 0.005 mg/kg endosulfan in whole milk. Endosulfan is defined as fat-soluble, and residues in cream following dosing at 12 ppm ranged 0.81–1.42 mg/kg. Based on a dietary burden of 0.27 ppm for a dairy animal, residues in cream result in an estimate of 0.032 mg/kg. The Meeting recommended maximum residue levels of 0.1 mg/kg for milk fat and of 0.01 mg/kg for whole milk. The previous recommendation of 0.004 mg/kg F was withdrawn.

For dietary risk assessment, the STMR values are 0.09 mg/kg for meat/fat, 0.0039 mg/kg for muscle, 0.003 mg/kg for milk, 0.034 mg/kg for cream or milk fat, 0.054 mg/kg for liver and 0.004 mg/kg for kidney. The estimated HR values were 0.14 mg/kg for meat/fat, 0.0056 mg/kg for muscle, 0.078 mg/kg for liver and 0.006 for kidney.

Definition of the residue (for compliance with the MRL and for estimation of the dietary intake): Sum of α-endosulfan, β-endosulfan and endosulfan sulfate. This definition applies to plant and animal commodities.

The residue is fat soluble.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of endosulfan 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 International Estimated Daily Intakes (IEDI) of endosulfan, based on estimated STMRs were 3–20% of the maximum ADI (0.006 mg/kg bw). 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.

Short-term intake

The International Estimated Short Term Intake (IESTI) of endosulfan calculated for the commodities for which residue levels were estimated. The results are shown in Annex 4.

The IESTI of endosulfan calculated on the basis of the recommendations made by the JMPR represented for children 0–390% and for the general population 0–210% of the ARfD (0.02 mg/kg bw). The IESTI for broccoli for children was 390% and for the general population 210% of the ARfD, for celery 270% for children and 120% for the general population, 120% for cherries for children, and 110% for tomato for children.

The Meeting concluded that the short-term intake of residues of endosulfan resulting from the uses that have been considered by the JMPR, except the uses on broccoli, celery, cherries and tomatoes, is unlikely to present a public health concern.

The Meeting noted that no residue data relating to an alternative GAP were submitted. The information provided to the JMPR precludes an estimate that the dietary intake would be below the ARfD for consumption of broccoli, celery, cherries and tomatoes by children and broccoli and celery for the general population.

The meeting noted that the ARfD of endosulfan was established in 1998. Since then improvements in the toxicological assessment have been made, including the introduction of compound specific assessment factors. Consequently, it is recommended that the ARfD of endosulfan be reassessed at a future meeting for possible refinements.

4.14 FENAMIPHOS (085)

RESIDUE AND ANALYTICAL ASPECTS

Fenamiphos is a systemic organophosphorus nematicide which is registered for use in more than sixty countries. It was reviewed by the JMPR on several occasions including the periodic review of toxicological data in 1997 and residue data in 1999. The current ADI is set at 0–0.0008 mg/kg bw and the ARfD at 0.003 mg/kg bw. The residue definition was "sum of fenamiphos and its sulfoxide and sulfone, expressed as fenamiphos."

Due to acute intake concerns, the MRL for peppers, tomato and watermelon were returned to Step 6 at the 34th, 35th, 36th, 37th and 38th Sessions of the Codex Committee on Pesticide Residues. The 37th Session of the CCPR in 2005 requested JMPR to review GAPs that might result in lower MRL recommendations and added fenamiphos in the Priority List. The 38th CCPR in 2006 reiterated the request to JMPR to consider alternative GAPs to determine whether lower MRLs for these commodities could be recommended.

The current Meeting received GAP information and new residue trial data on these commodities. In addition, it received new trial data on melons and egg plant. Although there was no acute intake concern associated with the MRL for melon, the data on melons were reviewed because the existing Codex MRL for watermelon was based melons trial data. The data on egg plant was not reviewed as this was outside the purview of the current Meeting.

Results of supervised residue trials

The Meeting received results of new trials on melons, watermelon, sweet peppers and tomato conducted in 1998–1999. Information from trials on these crops submitted to the 1999 JMPR was also used in the current evaluation. A number of trials with a CS formulation were reported by the 1999 JMPR but not used for estimating maximum residue levels because the GAP had been pending. As the GAP has since been approved, these trials were also included for consideration.

Labels from Australia, Greece, Italy, Portugal and Spain were made available to the Meeting.

The existing Codex MRL for watermelon, as recommended by the 1999 JMPR, was based on residues in melons from the supervised trials in accordance with GAP. Consequently, the Meeting again reviewed the results of supervised trials on melons although no short-term intake concern had previously been identified for melons.

Melons

The Meeting received the results of six new melon trials conducted in France, Italy and Spain using a CS formulation applied in a glasshouse. Nine indoor trials in Italy with a CS formulation; two field trials from Australia and two field trials from Brazil with an EC formulation; and four field trials from Guatemala, one field trial from Italy and four trials from Mexico with GR formulations were reviewed by the 1999 JMPR.

The relevant current GAP information is as follows:

Crop	Country	Form.	Application					Notes
			Timing	Method	Rate, kg ai/ha	No	PHI, days	
Melons/ watermelon	Italy	240CS	From transplanting to about 10 d later	In irrigation water	10	1	60	
Melons/ watermelon	Spain	240CS	Before start of flowering	Soil treatment	4.8-9.6	2	60	a
Cucurbits	Australia	400EC	Pre-planting or pre-transplanting	Soil treatment	9.6	1	-	
Melons	Brazil	400EC	At sowing	In irrigation water	4	1	-	
Melons	Guatemala	10GR		Spreading/incorp.	2.5-5.0	1	60	
		10GR		Spreading	5	1	60	
		15GR		Spreading/incorp.	2.6-5.1	1	60	
Melons	Italy	5GR		Soil incorporation	9.6-12	1	60	

a. First application, just before transplanting or sowing or immediately afterwards; and second application, during the rooting period before the start of flowering.

Six new indoor trials with a CS formulation were conducted in 1998 and 1999 and evaluated against the GAP of the countries where the trials were conducted. In the case of one French trial, Italian GAP was used. Five trials were in accordance with the maximum GAP and residues in fruit in rank order were: < 0.02 (3) and 0.04 (2) mg/kg.

Nine indoor trials were conducted with a CS formulation in Italy in 1996 and 1997. Although no information was available on the timing of application, the application rate, number of application and PHI were in accordance with the GAP of Italy. Residues in fruit at or around the PHI of 60 days were: < 0.02 mg/kg (7), 0.02 and 0.03 mg/kg.

The residues reported in pulp of samples taken 60 days after application were all below the LOQ of 0.02 mg/kg. However, pulp was not analyzed in the two trials that showed the residue level of 0.04 mg/kg in whole fruit taken 60 days after application. Regardless of compliance with GAP, where whole fruit analysis resulted in a residue concentration range of 0.03–0.05 mg/kg, residue levels in pulp were < 0.02– 0.03 mg/kg.

GAP in Argentina for a CS formulation allows one application at a rate of 3.2–4.0 kg ai/ha, with a PHI of 90 days but no trials matched this use pattern.

Two field trials from Australia with an EC formulation were conducted within GAP and residues in fruit were < 0.01 mg/kg (2). One field trial from Brazil with an EC formulation was conducted in accordance with Brazilian GAP and residues in fruit were < 0.02 mg/kg. Even with double rate, residues were still below the LOQ. No data were available for residues in pulp but they were expected to be around the same level as or lower than those in whole fruit.

There is no reported GAP for an EC formulation that would lead to lower residues.

Among trials using GR formulations were, one field trial from Guatemala, conducted in accordance with the current GAP of Guatemala, and four Mexican trials also within the GAP of Guatemala. Residues in fruit were: < 0.01 (4) and < 0.05 mg/kg. Residues in pulp were reported for the Mexican trials and were below the LOQ of 0.01 mg/kg.

Using the GAP of Costa Rica for the GR formulation (0.2–2.5 kg ai/ha, one application, with a 60 day PHI) would exclude trial results from Guatemala.

Watermelon

The Meeting also received the results of four new trials conducted on watermelon in Italy and Spain using a CS formulation in a greenhouse. The 1999 JMPR reviewed two field trials conducted in Italy with a GR formulation.

Among four new trials, two trials were in accordance with GAP and residues were: < 0.02 and 0.02 mg/kg.

In two Italian trials with the GR formulation, samples were not taken and analyzed 60 days after the application and therefore not used for estimating an HR.

The data were insufficient for estimating an HR for watermelon.

As the GAP for melons and watermelon is identical in many countries including Australia, Italy and Spain, the Meeting agreed to use data on melons for short-term intake estimation for watermelon as in the 1999 JMPR. As residue concentrations in pulp are not available for all trials following respective GAP, and the residue concentrations in whole fruit and pulp do not differ significantly due to the systemic nature of fenamiphos, the Meeting decided to use the residue concentrations in whole fruit to estimate an HR.

Since the residues arising from the use of these three formulations did not differ significantly, the Meeting concluded that it was not appropriate to disregard the results of trials with certain formulation(s) when estimating an HR. Based on the combined residues (< 0.01 (6), < 0.02 (11), 0.02, 0.03, 0.04 (2) and < 0.05 mg/kg), the Meeting estimated an HR of 0.04 mg/kg and noted that this HR would result in IESTI for general population being 120% and that for children being 310% of the ARfD (0.003 mg/kg bw).

The Meeting concluded that none of the residue data relating to available GAP suggests a lower maximum residue level than the current proposal.

However, as the residues in two new trials were 0.04 mg/kg, the Meeting decided to recommend a new maximum residue level of 0.05 mg/kg for fenamiphos in watermelon to replace the current proposal of 0.05* mg/kg. The Meeting estimated an STMR of 0.02 mg/kg and an HR of 0.04 mg/kg.

The Meeting noted that these recommendations are also valid for melons, except watermelon.

Peppers

The Meeting received the results of 10 new trials conducted from France, Greece, Italy, Portugal and Spain using a CS formulation in glasshouse. Four indoor trials in Italy, one indoor trial in Portugal and three indoor trials in Spain with a CS formulation; two field and two indoor trials in Spain with an EC formulation; and three field trials from Italy and one indoor and two field trials from Spain with a GR formulation were reviewed by the 1999 JMPR.

The relevant current GAP information is as follows:

Crop	Country	Form.	Application	Notes

			Timing	Method	Rate, kg ai/ha	No	PHI, days	
Peppers, Sweet	Italy	240CS	From transplanting to about 10 d later	In irrigation water	10	1	60	
Peppers, Sweet	Spain	10GR	Pre-planting or pre-sowing	Spreading/incorp.	5-10	1	60	
		400EC		Spraying	4.8-10	2	60	a
		240CS	Before start of flowering	Soil treatment	4.8-9.6	2	60	b

a. Up to two applications per season can be given, by dividing the dose in half if the duration of the crop makes it possible to observe the safety period. The first application should be before sowing or transplanting or immediately afterwards and the second during the rooting period of the crop before the start of flowering.

b. First application, just before transplanting or sowing or immediately afterwards; and second application, during the rooting period before the start of flowering.

Ten new trials were evaluated against the GAP of Italy/Spain. Four trials were conducted in compliance with GAP and residues found were: < 0.02 (3) and 0.02 mg/kg. In two other trials in Italy and two trials from Greece, although application took place after the specified timing residues were below the LOQ of 0.02 mg/kg.

Although no information was available on the timing of application, the application rate, number of applications and PHI of trials conducted with the CS formulation in 1996 and 1997 were in accordance with GAP in Italy. Residues at or around the PHI of 60 days were: < 0.02 (4), 0.02, 0.07, 0.08 and 0.11 mg/kg.

GAP in Argentina for a CS formulation allows one application at the rate of 3.2–4.0 kg ai/ha, with a PHI of 90 days but no trials matched this condition.

Three trials from Spain with an EC formulation were conducted in accordance with Spanish GAP and residues found were: 0.06, 0.08 and 0.26 mg/kg.

There is no reported GAP for the EC formulation that would lead to lower residues.

Three trials in Spain with GR formulation were conducted in accordance with GAP in Spain and residues were: < 0.05, 0.06 and 0.35 mg/kg.

The GAP in some countries allowed lower application rates for GR formulations (single application up to 1.2 kg ai/ha), however, no trials matched such GAP.

Since the residues arising from the use of these three formulations were not significantly different the Meeting concluded that it is not appropriate to disregard results from trials with certain formulation(s) when estimating HR. Based on combined residues (< 0.02 (7), 0.02 (2), < 0.05, 0.06 (2), 0.07, 0.08 (2), 0.11, 0.26 and 0.35 mg/kg) the Meeting estimated an HR of 0.35 mg/kg, the same value as that estimated by the 1999 JMPR. The IESTI for the general population is 100% and that for children is 110% of the ARfD.

The Meeting concluded that none of the residue data relating to available GAP suggests a lower maximum residue level to replace the current proposal of 0.5 mg/kg for fenamiphos in peppers.

Tomato

The Meeting received the results of seven new trials conducted in France, Greece, Italy, Portugal and Spain using a CS formulation in glasshouses. The 1999 JMPR reviewed four trials from Italy, two trials from Portugal and two trials from Spain with CS a formulation in greenhouse; five field trials from Australia, four field trials from South Africa and two field and two indoor trials from Spain with an EC formulation; one field trial from Australia, four field trials from Brazil, two field trials from

South Africa and two field trials from Spain with GR formulations; one field trial from South Africa with both GR and EC formulations; and one field trial from South Africa with an EW formulation.

The current relevant country GAPs are shown below.

Crop	Country	Form.	Application					Notes
			Timing	Method	Rate, kg ai/ha	No	PHI, days	
Tomato	Australia	400EC	Pre-planting or pre-transplanting	Spraying	9.6	1	-	
		10GR	Within 7 d of planting	Sprinkling	11	1	-	
		5GR	Within 7 d of planting	Sprinkling over soil	13	1	-	Not Tasmania
Tomato	Brazil	10GR	At planting	Incorporation	3-4	1	90	
Tomato	Italy	240CS	From transplanting to about 10 d later	In irrigation water	10	1	60	
Tomato	S. Africa	240CS 400EC 10GR	Pre-planting	Spraying Spraying/incorp. Spreading/incorp.	9.8	1 1 1	- - -	
Tomato	Spain	10GR	Pre-planting or pre-sowing	Spreading/incorp.	5-10	1	60	
		400EC		Spraying	4.8-10	2	60	a
		240CS	Before start of flowering	Soil treatment	4.8-9.6	2	60	b

a. Up to two applications per season can be given, by dividing the dose in half if the duration of the crop makes it possible to observe the safety period. The first application should be before sowing or transplanting or immediately afterwards and the second during the rooting period of the crop before the start of flowering.

b. First application, just before transplanting or sowing or immediately afterwards; and second application, during the rooting period before the start of flowering.

Seven new trials were evaluated against GAP in Italy/Spain. One trial was conducted in compliance with GAP and residues were < 0.02 mg/kg. In four other trials from Italy, where application took place later than the specified timing, residues of samples taken 60 days after application were below the LOQ of 0.02 mg/kg.

Although no information was available on the timing of application, application rate, number of applications and PHI, trials with a CS formulation conducted in 1996 and 1997 were in accordance with Italian GAP. Residues at or around the PHI of 60 days were: < 0.02 (5), 0.02, 0.09 and 0.14 mg/kg.

The GAP in Argentina for a CS formulation allows one application at a rate of 3.2–4.0 kg ai/ha, with a PHI of 90 days, however no trials matched this use pattern.

Four trials from Australia, with an EC formulation, were in compliance with Australian GAP and residues found were < 0.05 (3) and 0.15 mg/kg. In four trials from Spain matching Spanish GAP, residues found were < 0.02 (2), 0.13 and 0.27 mg/kg. As no field data was provided fro the trials from South Africa, data from those trials were not used in this evaluation.

The GAP in some countries for the EC formulation allow lower application rates, i.e., single applications at 2.8–3.4 or 3.2–4.0 kg ai/ha. However, no submitted trials matched such a GAP.

One trial from Australia, with a GR formulation, was in compliance with Australian GAP, had residues found of < 0.05 mg/kg. One trial from Brazil, in compliance with Brazilian GAP, had residues found of < 0.1 mg/kg. As no field data was provided for the trials from South Africa, data from those trials were not used in this evaluation.

Two trials from Spain were conducted in accordance with Spanish GAP with residue found of < 0.02 (2) mg/kg.

There is no reported GAP for GR formulations that would lead to lower residues.

Since the residues arising from the use of these three formulations were not significantly different, the Meeting concluded that it was not appropriate to disregard the results of trials with certain formulation(s) when estimating HR. Based on combined residues (< 0.02 (10), 0.02, < 0.05 (4), 0.09, < 0.1, 0.13, 0.14, 0.15 and 0.27 mg/kg), the Meeting estimated an HR of 0.27 mg/kg, similar to that estimated by the 1999 JMPR (0.30 mg/kg). The IESTI for general population is 100% and that for children is 280% of the ARfD.

The Meeting concluded that none of the residue data relating to available GAPs suggests a lower maximum residue level to replace the current proposal of 0.5 mg/kg for fenamiphos on tomato.

Definition of the residue: Sum of fenamiphos and its sulfoxide and sulfone, expressed as fenamiphos.

DIETARY RISK ASSESSMENT

Long-term intake

As the ADI had not been modified since the International Estimated Dietary Intakes of fenamiphos were calculated last time in 1999 (3–14% of the maximum ADI of 0.0008 kg/kg for five regional diets); and the STMRs estimated by the current Meeting for melons, except watermelon and watermelon were identical to those estimated in 1999, IEDI calculation was not conducted by the current Meeting.

Short-term intake

The International Estimated Short-Term Intakes (IESTIs) of fenamiphos by general population and by children were calculated for melons, except watermelon; and watermelon for which HRs were estimated. The ARfD is 0.003 mg/kg and the calculated IESTIs for children up to 6 years of age range from 90 to 310% and those for general population from 40 to 120% of the ARfD. The information provided to the JMPR precludes an estimate that the short-term dietary intake would be below the ARfD for consumption of watermelon by children and by the general population.

4.15 FENPROPATHRIN (185)

RESIDUE AND ANALYTICAL ASPECTS

Fenpropathrin, an insecticide/acaricide, was first evaluated by the JMPR in 1993 as a new compound. The JMPR allocated an ADI of 0-0.03 mg/kg and recommended 14 MRLs, later adopted by the Codex Alimentarius Commission as Codex MRLs. The residue definition is fenpropathrin (the residue is fat soluble).

At the 38th Session of the CCPR in 2006, the Delegation of India requested the elaboration of an MRL for tea. Fenpropathrin was added to the agenda of the current Meeting for evaluation pending availability of trial data on tea. The Meeting received the current label from India, results of supervised trials, a processing and plant metabolism study and methods of analysis.

Metabolism

Plant metabolism

The Meeting received studies conducted to determine metabolism of fenpropathrin in leaves.

The metabolism of radio-labelled fenpropathrin was investigated in cabbages grown and treated in a greenhouse. After foliar application of ^{14}C -fenpropathrin to cabbages the radioactive carbon on the surface of treated leaves decreased as ^{14}C in the leaves increased. Most of the recovered radiocarbon was in the treated leaves and less than 1.2% of the applied radioactive carbon was found in the untreated shoots. This indicates that fenpropathrin and its metabolites only slightly translocate from the site of application to other parts of the plant. The predominant radioactive component in the surface washes was the parent compound, fenpropathrin. The major radioactive components in leaves were fenpropathrin and the conjugates of metabolites with a –CH2OH group.

The fate of HCN and 2,2,3,3-tetramethylcyclopropanecarboxylic acid (TMPA) in abscised leaves of apple, cabbage, kidney bean, mandarin orange, tomato and vine was investigated. TMPA was readily converted in plants to more polar products. In orange, cabbages and bean plants, the malonyl glucoside was mainly formed. In tomato, the gentiobioside was predominant. Further work was carried out using $K^{14}CN$. There was a gradual increase in the amount of volatile ^{14}C trapped in NaOH solution, most of the radioactive carbon was considered to be $^{14}CO_2$. The study demonstrates that $H^{14}CN$ liberated on ester hydrolysis of fenpropathrin and its derivatives would be rapidly incorporated into β-cyanoalanine, asparagine, aspartic acid and γ-glutamyl-β-cyanoalanine, with ultimate formation of $^{14}CO_2$ and unextractable ^{14}C residues.

The Meeting confirmed that the residue definition of fenpropathrin is appropriate for leafy vegetables as well as for tea.

Methods of residue analysis

The Meeting received descriptions and validation data for methods of analysis used in the supervised trials on tea conducted in India.

Both methods use the same principle as that of the methods developed by the manufacturer and reviewed by the 1999 JMPR and involve extraction of fenpropathrin, partitioning, clean-up and analysis using GC-ECD. For one method, recovery test were conducted at a range of 0.05–2 mg/kg and procedural recoveries in this range were 88–96%. The limit of quantification was 0.05 mg/kg. For the second method, a recovery test was conducted at 0.283 mg/kg resulting in procedural recovery around 90%. No details for the procedural recovery tests were reported for either method.

Results of supervised trials on crops

The Meeting received information and results from a total of 12 supervised trials conducted in India on tea. The current product label from India was provided. No information was available for procedural recoveries in the analysis of samples from supervised trials.

Tea

Fenpropathrin (300 g ai/kg EC) is registered in India for use on tea at 0.05–0.06 kg ai/ha with a PHI of 7 days.

In ten trials, collected tea leaves were processed into black tea. In six trials this was achieved through withering, crush/tear/curl process, oxidation and drying while in another two trials by machine drying. In trials with conditions matching the registered use, residues of fenpropathrin were in rank order: < 0.05, 0.14, 0.14, 0.17 and 0.18 mg/kg. In one trial conducted with double rates, the residues in the black tea from the sample taken 7 days after treatment were < 0.05 mg/kg. In another trial conducted with half rates, the residues in black tea from the sample taken 7 days after treatment were 1.38 mg/kg. No information on the possible cause of the high residue concentration was available. Although the used rate was half of the Indian GAP rate, the Meeting decided to include this value for estimating the maximum residue level.

In two additional trials, collected tea leaves were air-dried to prepare green tea. In trials where conditions matching the registered use pattern, residues of fenpropathrin were 0.13 mg/kg.

Since growing conditions and application rate/method for black tea and green tea are equivalent with the only difference being in processing methods, the Meeting estimated a maximum residue level for tea, green, black on the basis of combined residue results: < 0.05 (2), 0.13, 0.14, 0.14, 0.17, 0.18 and 1.38 mg/kg.

The Meeting estimated a maximum residue level, STMR and HR at 2 mg/kg, 0.14 mg/kg and 1.38 mg/kg respectively.

Fate of residues during processing

The Meeting received information on the fate of fenpropathrin during the brewing of tea.

Black tea (50 g) from field trials at the maximum rate or green tea (50 g) from trials at the maximum rate or double rates was brewed by boiling in 100 mL of water in a flask. Tea samples and concentrated decoctions were analyzed. However, no information was available on procedural recoveries for the analysis of samples.

A transfer factor was used to indicate the amount of fenpropathrin transferred from tea leaves to water (decoction) during brewing. The transfer factor was tentatively calculated by dividing the total residue (mg) in the decoction (concentrated to 10 mL) by the total residue (mg) in tea leaves (50 g) assuming that the specific gravity of the decoction is the same as that of water. No estimation of the processing factor was possible as the residue levels in the decoction before concentration were too low to quantify. The results indicate that only a small amount of fenpropathrin was transferred into the decoction as predicted from the highly fat-soluble nature of the compound. Table 3 shows the calculated transfer factor.

Table 3. Transfer factor from tea to decoction.

Process	Transfer factor	Best estimate
Black tea - decoction	0.03, < 0.02, < 0.06 0.02, < 0.01, < 0.03	0.03
Green tea - decoction	0.01, < 0.008, < 0.01, < 0.02, < 0.08 0.01, < 0.004, < 0.006, < 0.01, < 0.03	0.01

Where the residues in black or green tea were below the LOQ, the transfer factor was not calculated.

Definition of the residue: fenpropathrin

The residue is fat soluble.

DIETARY RISK ASSESSMENT

Long-term intake

The long-term dietary intakes were estimated for the 13 cluster diets using maximum residue levels for fenpropathrin recommended by the 1999 Meeting and an STMR for tea estimated by the current. The maximum ADI is 0.03 mg/kg and the calculated intakes were 3–80% of the maximum ADI. The Meeting concluded that the long-term intake of residues of fenpropathrin resulting from the uses considered by the Meeting was unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intakes (IESTIs) of fenpropathrin by general population and by children were calculated for tea, green, black, for which an HR was estimated by the current Meeting. As it is not known if it is necessary to establish an ARfD, no the short-term intake assessment could be determined.

4.16 FLUDIOXONIL (211)

RESIDUE AND ANALYTICAL ASPECTS

Fludioxonil was first evaluated by the 2004 JMPR Meeting. The 2004 Meeting estimated an MRL of 0.7 mg/kg for foliar uses on pears, but did not recommend an MRL for pome fruit based on post-harvest use due to an insufficient number of trials performed at the maximum GAP. The present Meeting received information on the post-harvest use pattern, residue analysis, and post-harvest trials on apples and pears. Results of an apple processing study were also reported.

Methods of residue analysis

The Meeting concluded that adequate multi- and single-residue methods exist for both gathering data in supervised trials and processing studies and for the monitoring and enforcement of fludioxonil MRLs in commodities of plant origin.

Two single-residue methods (AG-597 and REM 133.04) were used for the analysis of fludioxonil in treated apples and pears and in samples resulting from an apple processing study. The LOQ of both methods was 0.02 mg/kg. In the case of method AG-597B, the overall average recovery was 97% with an average relative standard deviation of 9.8%. The analytical method REM 133.04 gave an overall average recovery of 81% with an average relative standard deviation of 14%.

Multiresidue methods, such as the previously reported method DFG S19 or recently developed QuEChERS method, are more suitable for routine monitoring of residues than the two single-residue methods AG-597B and REM 133.04.

Stability of pesticide residues in stored analytical samples

The JMPR 2004 Meeting concluded that fludioxonil residues are stable in apples and many other commodities for at least 24 months under deep freeze conditions (<-18°C). In the supervised trial and processing studies reported to the present Meeting, apple and pear samples were stored frozen for a maximum of 177 days (5.8 months).

Results of supervised trials on crops

The Meeting received supervised trial data for post-harvest treatments of pome fruit (apples and pears) conducted in the USA. Apples and pears were treated by post-harvest dip, drench, or spray using a 50% wettable powder formulation of fludioxonil. GAP for pome fruit specifies a maximum of two treatments, one on entering storage and a second on exit from storage for market distribution, at a single application rate of 0.5 kg ai/200,000 kg fruit (2.5 mg ai/kg fruit) for spray treatment (0.86 kg ai/hL for droplet-type applications using a low-volume concentrate; 0.24 kg ai/hL for high-volume jet-type sprays) and 0.06 kg ai/hL for dip/drench treatments.

Seventeen trials (seven on apples and ten on pears) were conducted as a single application at approximately the GAP rate. Eight trials (four on apples and four on pears) were conducted at the GAP rate with two sequential applications, involving 0.06 kg ai/hL dip/drench treatment followed by packing-line spray at 2.5 mg ai/kg fruit (2.85 mg ai/kg fruit, *i.e.* 114% GAP, was used in one trial on pears).

As GAP specifies two treatments, the Meeting regarded the eight trials with two sequential applications as an approximation of the maximum GAP. The residue levels on apples, in ranked order were: 2.0, 2.2, 2.4, and 2.5 mg/kg. The residue levels on pears, in ranked order were: 1.1, 1.2, 1.6, and 2.8 mg/kg (note: 1.6 mg/kg resulted from a dip treatment at 100% GAP followed by the spray treatment at 114% GAP). The Meeting decided to combine the data, thus the residue levels on pome fruit, in ranked order, were: 1.1, 1.2, 1.6, 2.0, 2.2, 2.4, 2.5, and 2.8 mg/kg. The Meeting estimated a maximum residue level for pome fruit of 5 mg/kg and an STMR of 2.1 mg/kg, and withdrew its previous recommendation for a maximum residue level of 0.7 mg/kg for pears

Fate of residues during processing

The Meeting received information on the fate of incurred residues of fludioxonil during commercial-type processing of apples into juice and purée. The processing factors and STMR-P values, based on an STMR of 2.1 mg/kg for pome fruits, are summarized in the table below.

Raw agricultural commodity	Processed commodity		
	Commodity	Processing factor	STMR-P (mg/kg)
Apple	Washed fruit	0.84	
	Juice, pasteurized	0.08	0.17
	Pomace, wet	1.4	2.9
	Pomace, dry	5.3	11
	Purée	0.12	0.25

The Meeting estimated a maximum residue level of 20 mg/kg for apple pomace, dry, based on the highest residue of 2.8 mg/kg in the pome fruit post harvest trials and the processing factor of 5.3.

Farm animal dietary burden

The Meeting estimated the maximum dietary burden of fludioxonil residues for farm animals (beef cattle, dairy cows, and poultry) using previously recommended MRLs and STMR-Ps for possible feed commodities and STMR-P for wet apple pomace estimated by the present Meeting. The table below shows the basis for the dietary intake calculation.

Commodity	Group	Maximum or highest residue level (mg/kg)	STMR or STMR-P	Dry matter (%)	Residue on dry wt (mg/kg)	*Dietary content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry

Apple pomace (wet)	AB		2.9	40	7.3	*40*	*20*		2.9	1.5	
Wheat forage	AF	0.05		25	0.20	*25*	*60*		0.05	0.12	
Rape forage	AM	0.05		30	0.17	*30*	*20*		0.05	0.03	
Maize grain	GC	0.05		88	0.06			*80*			0.05
Pea seed	VD	0.07		90	0.08	*5*		*20*	0.004		0.02
Total						***100***	***100***	***100***	**3.0**	**1.7**	**0.07**

The maximum dietary burdens of fludioxonil in beef cattle, dairy cows, and poultry (on the basis of diets listed in Appendix IX of the *FAO Manual*) are 3.0, 1.7, and 0.07 mg/kg, respectively. For comparison, the previously calculated dietary burdens were 0.07, 0.06, and 0.07 mg/kg, respectively (JMPR Report 2004).

Farm animal feeding studies

The 2004 Meeting received information on a ruminant feeding study, the results of which are summarized in the tables below. No study was available on poultry feeding.

Residues of fludioxonil and its metabolites (converted via oxidation to 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid), found in milk were:

Animal number	Dose level in diet	Residues (mg/kg) at dosing (day)						
		0 (pre-dosing)	1	3	7	14	21	26
2A	1x	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
2B	0.55 mg/kg	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
2C		< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
3A	3x	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
3B	1.6 mg/kg	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
3C		< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
4A	10x	< 0.01	< 0.01	< 0.01	< 0.01	**0.019**	**0.012**	< 0.01
4B	5.5 mg/kg	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
4C		< 0.01	< 0.01	**0.016**	**0.011**	**0.010**	**0.014**	< 0.01

Residues of fludioxonil and its metabolites (converted via oxidation to 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid) found in ruminant tissues were:

Animal number	Dose level in diet	Residues (mg/kg) at dosing (day)					
		Round muscle	Tenderloin muscle	Liver	Kidney	Perirenal fat	Omental fat
2A	1x	na	na	na	na	na	na
2B	0.55 mg/kg	na	na	na	na	na	na
2C		na	na	na	na	na	na
3A	3x	na	na	na	na	na	na
3B	1.6 mg/kg	na	na	na	na	na	na
3C		na	na	na	na	na	na
4A	10x	< 0.01	< 0.01	< 0.05	< 0.05	< 0.05	< 0.05
4B	5.5 mg/kg	< 0.01	< 0.01	< 0.05	< 0.05	< 0.05	< 0.05
4C		< 0.01	< 0.01	< 0.05	< 0.05	< 0.05	< 0.05

Animal commodity maximum residue levels

The addition of wet apple pomace to the list of possible feed items resulted in the estimated maximum dietary burden of 3.0, 1.7, and 0.07 mg/kg for beef cattle, dairy cows, and poultry, respectively.

Based on the information in Appendix IX of the *FAO Manual*, apple pomace is not a significant part of a poultry diet, thus the addition of this feed item did not change the previous estimation of maximum dietary burden and MRLs. The 2004 Meeting recommended MRLs of 0.01 (*) mg/kg for poultry meat and 0.05 (*) mg/kg for eggs and poultry offal. STMR values of 0 mg/kg were estimated for eggs, poultry meat, and poultry offal.

In the feeding study reported to the 2004 Meeting, no quantifiable residue of fludioxonil was found in the tissues of ruminants at the 5.5 mg/kg feeding level, which corresponds to 3.2-fold and 1.7-fold higher levels than the estimated maximum dietary burdens for dairy cows and beef cattle, respectively. Thus, the addition of wet apple pomace to the list of possible feed items did not change the recommendation of the 2004 Meeting.

The present Meeting confirmed the previous recommendations for a maximum residue level of 0.05* for edible offal and 0.01 (*) mg/kg for muscle and the STMR values of 0 mg/kg for both edible offal and muscle.

In milk, the highest residue level found was 0.019 mg/kg at the 5.5 mg/kg feeding level. Using this information and extrapolating to a 1.7 mg/kg feeding level (corresponding to the maximum dietary burden for dairy cows), the highest residues expected in milk would be below the reported LOQ of 0.01 mg/kg. This estimation is also supported by the results of the 1.6 mg/kg feeding study (a close approximation of the maximum dietary burden for dairy cows), which led to no quantifiable fludioxonil residues (< 0.01 mg/kg) in milk. This reaffirms the 2004 JMPR recommendation of the MRL of fludioxonil residue at the LOQ, 0.01 (*) mg/kg, and the STMR value for milk of 0 mg/kg.

Definition of the residue for compliance with MRLs and estimation of dietary intake in plant commodities: fludioxonil.

Definition of the residue for compliance with MRLs and estimation of dietary intake in livestock commodities: fludioxonil and metabolites determined as 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid and calculated as fludioxonil. Fludioxonil is fat-soluble.

DIETARY RISK ASSESSMENT

Long-term intake

The IEDIs of fludioxonil based on STMR and STMR-P values estimated for 47 commodities for the thirteen GEMS/Food regional diets were 0–2% of the ADI (Annex 3 of the Report). A similar result was obtained in 2004, when the Meeting concluded that the long-term dietary intake of fludioxonil residues is unlikely to present a public health concern.

Short-term intake

The 2004 Meeting decided that an ARfD for fludioxonil is unnecessary and concluded that the short-term dietary intake of fludioxonil residues is unlikely to present a public health concern.

4.17 HALOXYFOP (INCLUDING HALOXYFOP-R AND HALOXYFOP-R METHYL ESTER) (194)

TOXICOLOGY

Haloxyfop is the ISO approved name for (*R*/*S*)-2-[4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionic acid. It is a substituted phenoxypropionic acid derivative that has been developed as a selective herbicide for control of grass weeds in broadleaf crops. In the first formulations produced, the active substance was either racemic haloxyfop ethoxy ethyl ester or the racemic methyl ester. As it has been demonstrated that haloxyfop-R is the herbicidally active isomer, and essentially no activity is associated with the *S* isomer, a resolved methyl ester has been developed which is approximately 98% *R* isomer. When applied to plants, the esters are rapidly hydrolysed to the acid.

Haloxyfop (racemic), its sodium salt and its esters (racemic haloxyfop ethoxy ethyl ester and racemic haloxyfop methyl ester) were first evaluated by the JMPR in 1995, when the Meeting established an ADI of 0–0.0003 mg/kg bw based on a NOAEL of 0.03 mg/kg bw per day for liver tumours in a 2-year study in mice. New toxicological data had been made available since this date. Haloxyfop was re-evaluated at the request of the CCPR. New data on pharmacokinetics, dermal toxicity, genotoxicity and special studies of hepatocellular peroxisome proliferation had become available since the last evaluation.

All studies with haloxyfop-R methyl ester and pivotal studies with haloxyfop were certified as being compliant with GLP. Other studies were carried out before the OECD guidelines on GLP were promulgated. The quality of these studies was considered to be acceptable.

Numerous studies of the pharmacology and toxicology of various chemical forms of haloxyfop were available. Investigations with haloxyfop-R and its methyl ester were limited to studies of absorption, distribution, metabolism and excretion, acute toxicity, short-term studies of toxicity, and genotoxicity.

Biochemical aspects

Studies of pharmacokinetics and metabolism were conducted with racemic haloxyfop and haloxyfop-R methyl ester. Oral doses of haloxyfop-R methyl ester or haloxyfop were rapidly and extensively absorbed in all laboratory species tested (mice, rats, dogs and cynomolgus monkeys) and in humans (absorption half-life in men, 0.9 h). Irrespective of whether haloxyfop or haloxyfop-R methyl ester

was administered, haloxyfop was the only substance detected in the plasma. *S*-isomeric forms of haloxyfop underwent rapid and almost complete inversion to R-forms in rats, and it was assumed that this also occurred in other species. The highest concentrations of residue were in the liver and kidneys. Biphasic elimination was seen in dogs and cynomolgus monkeys, with a rapid initial phase (half-lives, 1–2 hours in dogs and 2.5 hours in monkeys) followed by a slow second phase (half-lives, 34 hours in dogs and 3 days in monkeys). There was little primary metabolism of haloxyfop in any species tested, but there was some conjugation. Glucuronidation occurred in mice and rats. The major route of elimination was the faeces in mice (recovered radiolabel: males, 79%; and females, 71%), male rats (55–77%) and male dogs (88%), but the urine was the major route of excretion in female rats (68–81%) and cynomolgus monkeys (99%). Men excreted 65–100% of a single oral dose in the urine.

The pharmacokinetics and metabolic data on haloxyfop-R methyl ester and haloxyfop suggest that the results of studies of oral toxicity with racemic haloxyfop methyl ester, haloxyfop or haloxyfop sodium salt should be relevant to the investigation of the toxicity of haloxyfop–R methyl ester and haloxyfop-R, as all stereoisomeric forms and esterified forms end up as the de-esterified R enantiomer.

Toxicological data

Haloxyfop administered orally was of moderate acute toxicity in mice, rats and cynomolgus monkeys, with apparently higher toxicity in male rats than in female rats (LD_{50} for haloxyfop-R methyl ester: males, 337 mg/kg bw; females, 545 mg/kg bw). Signs of gastric irritation were seen at high oral doses (1000 mg/kg bw) in one study in rats and signs of hepatotoxicity were seen in another study of acute toxicity in rats. Haloxyfop-R methyl ester was not irritant to the skin or eyes of rabbits and was not a skin sensitizer in guinea-pigs (Magnusson & Kligman and Buehler tests).

The toxicity of haloxyfop has been investigated in short-term studies in mice, rats, dogs and monkeys. In all these species haloxyfop caused hepatocellular hypertrophy, which was often associated with increased eosinophilia of the cytoplasm and a more homogeneous appearance to the cytoplasm than in controls. The lowest NOEL for this effect was 0.02 mg/kg bw per day in short-term studies of toxicity in mice and rats. A modest but consistent increase in serum alkaline phosphatase activity was seen in mice and rats at 2 mg/kg bw per day, with a NOAEL of 0.2 mg/kg bw per day. Hepatocellular hypertrophy was seen at 5 mg/kg bw per day or greater in a study in dogs, and at 10 mg/kg bw per day or greater in a study in monkeys. In addition to these effects on the liver, thyroid changes were seen and a NOAEL of 0.2 mg/kg bw per day was identified in the studies in dogs and monkeys. Small decreases in serum cholesterol concentrations and small increases in haematological parameters were measured in dogs receiving haloxyfop at doses below that producing hepatocellular hypertrophy, but were not regarded as toxicologically significant.

Repeated dermal doses of 40 mg/kg bw per day or more of haloxyfop-R methyl ester caused similar effects on the livers of male rats to those seen after repeated oral doses of rats with haloxyfop. A NOAEL was not identified.

Combined long-term studies of toxicity and carcinogenicity were conducted with haloxyfop in mice and rats. In mice, hepatocellular hypertrophy and liver tumours were seen. A dose-related positive trend in the number of animals having one or more liver masses, and statistically significant increases in the incidences of liver tumours (adenoma, and adenoma plus carcinoma in males; carcinoma in females) occurred. Only the increased incidence of liver carcinomas was greater than the historical control range. The LOAEL for production of liver tumours in mice was 0.6 mg/kg bw per day and the NOAEL was 0.065 mg/kg bw per day. Hepatocellular hypertrophy was seen in rats in the absence of an increase in tumour incidence, and the NOAEL was therefore identified as the highest dose tested (0.1 mg/kg bw per day in males, and 1 mg/kg bw per day in females). Haloxyfop was not carcinogenic in rats.

Haloxyfop and haloxyfop-R methyl ester gave negative results in a comprehensive range of studies of genotoxicity in vitro and in vivo. The Meeting concluded that haloxyfop, haloxyfop-R and haloxyfop-R methyl ester are unlikely to be genotoxic.

In order to confirm the hypothesis that the mouse liver tumours observed at 0.6 mg/kg bw per day were the result of a mode of action involving peroxisome proliferation, a series of special studies were performed, including studies in vitro and in vivo in mice, rats, guinea-pigs, dogs and cynomolgus monkeys treated orally. It was shown by electron microscopy that exposure to haloxyfop caused proliferation of hepatocellular peroxisomes in mice and rats at 10 mg/kg bw per day, but not in dogs and cynomolgus monkeys at up to 20 mg/kg bw per day. In mice, hepatic carnitine acyl transferase (CAT) was induced at 0.5 mg/kg bw per day or more, and other enzymes were induced at higher doses: catalase, glycerophosphate dehydrogenase (GPD), and fatty acid beta-oxidation (FAOX). Furthermore, several genes (ACO, CYP4A10 and CTE-I) that are associated with peroxisome proliferation were upregulated at 0.6 mg/kg bw per day. In rats, CAT, catalase, GPD and FAOX were induced. In guinea-pigs, acyl CoA oxidase (ACO) activity was increased modestly at 30 mg/kg bw per day. In dogs, electron microscopy showed no peroxisome proliferation at doses of up to 20 mg/kg bw per day, but there was increased hepatic activity of hepatic FAOX at doses of 5 mg/kg bw per day or more. Doses of up to 30 mg/kg bw per day did not cause hepatocellular peroxisome proliferation in cynomolgus monkeys and hepatic peroxisome FAOX activity was unaffected. Studies in vitro showed that peroxisome proliferation did not occur in human hepatocytes exposed to haloxyfop acid or to a positive control peroxisome proliferator (WY14,643) at doses that caused peroxisome proliferation in hepatocytes from mice.

The negative results of tests for mutagenicity indicate that the tumours in mice were not caused by a genotoxic mechanism. The Meeting used the IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans[44] in considering whether the mode of action by which the liver tumours were produced in mice was relevant to humans. It was concluded that the production of liver tumours in mice was by a mode of action that involved hepatocellular peroxisome proliferation and it was noted that this effect was not seen in dogs, cynomolgus monkeys or in cultured human hepatocytes. Hepatocellular peroxisome proliferation has been shown elsewhere to be associated with hepatocellular hyperplasia and liver tumours in rodents but not in non-rodent species. It has been well established[45] that chemicals that induce mouse liver tumours via peroxisome proliferator-induced receptor alpha (PPARα) agonism do not pose a risk of hepatocarcinogenesis in humans, because of quantitative dynamic differences in PPARα activation.

The Meeting concluded that haloxyfop is unlikely to pose a carcinogenic risk to humans based on the absence of genotoxicity and the recognition of a mode of action for production of the liver tumours in mice that is not relevant to humans.

Multigeneration studies with haloxyfop in rats showed no effects on reproduction at doses that were not maternally toxic. Low pup body weights (F_{1a}, F_{1b} and F_{2a} pup body weights, 5–10% lower than controls) and low litter weights (6–7% lower in litters of F_{1b} pups on postnatal days 14–21) were reported at 1 mg/kg bw per day in Sprague-Dawley rats in the two-generation study. The NOAEL was 0.065 mg/kg bw per day. In the three-generation study in Fischer 344 rats, the NOAEL was 0.05 mg/kg bw per day on the basis of low pup body weights seen at a dose of 1 mg/kg bw per day in the F_{1b} and F_{2a} pups during weaning and up to termination of the study at age 28 days. The overall NOAEL for the effects on pup body weight was 0.065 mg/kg bw per day.

In a study of developmental toxicity, the fetuses of rats given haloxyfop at a dose of 7.5 mg/kg bw per day showed delayed ossification of thoracic vertebrae. The NOAEL was 1 mg/kg bw

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[44] Boobis A, Cohen SM, Dellarco V et al. (2006) IPCS Framework For Analysing the Relevance of a Cancer Mode of Action for Humans. *Critical Reviews in Toxicology*, 36:781-792.

[45] Klaunig JE et al. (2003) PPARα agonist-induced rodent tumours: modes of action and human relevance. *Critical Reviews in Toxicology*, 3:655–780.

per day. Two studies of developmental toxicity were performed in rabbits. In the first, the NOAEL was 7.5 mg/kg bw per day on the basis of an increased incidence of a minor skeletal variation at 20 mg/kg bw per day. Increased maternal mortality, increased number of resorbed implantations and increased number of litters with resorptions were also seen at this dose. In the second study, there was no adverse effect on development, but there was increased maternal mortality at 15 mg/kg bw per day. The NOAEL was 7.5 mg/kg bw per day. The Meeting concluded that haloxyfop is not teratogenic.

No cases of adverse effects were reported in France between 1995 and 2002 among personnel involved in the production and formulation of haloxyfop-based products. A medical review of the health of 50 workers at the plant showed no adverse health findings that could be attributed to exposure to haloxyfop. In China, between January 1999 and January 2002, there were 82 reported incidents of alleged human health effects associated with a herbicidal product that contained haloxyfop-R methyl ester. The majority of the reported incidents concerned small accidental exposures involving minor symptoms. Intentional oral exposures to the commercial preparation were associated with drowsiness, lethargy, seizures, coma and death. These non-specific signs can be attributed either to the petroleum distillate solvent used as co-formulant or to haloxyfop, or both, since they are both contained at high levels (about 20% and 10%, respectively) in the commercial preparation.

The Meeting noted that there were no qualitative or quantitative differences in the toxicological properties of haloxyfop-R methyl ester and haloxyfop. None of the studies revealed any unexpected effects of haloxyfop-R methyl ester, and the quantitative dose–effect relationships of racemate and R enantiomer were very similar. The data on haloxyfop could therefore be used for the toxicological evaluation of haloxyfop-R methyl ester and haloxyfop-R.

The Meeting concluded that the existing database was adequate to characterize the potential hazard of haloxyfop, haloxyfop-R and their methyl esters to fetuses, infants and children.

Toxicological evaluation

The Meeting concluded that there were sufficient data to bridge the toxicology studies between haloxyfop and haloxyfop-R methyl ester. As the relative molecular mass of haloxyfop methyl ester is very close to that of haloxyfop, there is no need to compensate for differences in relative molecular mass when considering doses.

The Meeting established a group ADI of 0–0.0007 mg/kg bw for racemic haloxyfop, haloxyfop-R and their methyl esters based on a NOAEL of 0.065 mg/kg bw per day for low pup body weight in multigeneration studies in rats, and applying a safety factor of 100.

The Meeting established a group ARfD of 0.08 mg/kg bw for racemic haloxyfop, haloxyfop-R and their methyl esters on the basis of a NOAEL of 7.5 mg/kg bw per day for maternal mortality and increased number of resorptions at higher doses in a study of developmental toxicity in rabbits, and applying a safety factor of 100.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	36-week study of toxicity[a, e]	Toxicity	0.2 mg/kg bw per day	2 mg/kg bw per day
	2-year study of carcinogenicity[a,fe]	Toxicity	0.6 mg/kg bw per day[d]	—
		Carcinogenicity	0.065 mg/kg bw per	0.6 mg/kg bw per

			day[d]	day
Rat	16-week study of toxicity[a, b]	Toxicity	0.2 mg/kg bw per day	2 mg/kg bw per day
	2-year study of toxicity and carcinogenicity[a, e]	Toxicity	0.1 mg/kg bw per day	—
		Carcinogenicity	0.1 mg/kg bw per day	—
	Two-generation study of reproductive toxicity[a,e]	Maternal toxicity	1 mg/kg bw per day	—
		Offspring toxicity	0.065 mg/kg bw per day	1 mg/kg bw per day
	Developmental toxicity[b, e]	Maternal toxicity	7.5 mg/kg bw per day	—
		Fetotoxicity	1 mg/kg bw per day	7.5 mg/kg bw per day
Rabbit	Developmental toxicity[b, e]	Maternal toxicity	7.5 mg/kg bw per day	15 mg/kg bw per day
		Embryo- and fetotoxicity	7.5 mg/kg bw per day	15 mg/kg bw per day
Dog	1-year study of toxicity[a, e]	Toxicity	0.5 mg/kg bw per day	5 mg/kg bw per day
Monkey	13-week study of toxicity[c]	Toxicity	2 mg/kg bw per day	10 mg/kg bw per day

[a.] Dietary administration dietary concentrations adjusted weekly to maintain the intended dosages

[b.] Gavage administration

[c.] Nasogastric administration

[d.] Highest dose tested

[e] Study performed with haloxyfop

Estimate of acceptable daily intake for humans

0–0.0007 mg/kg bw

Estimate of acute reference dose

0.08 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 exposures

Critical end-points for setting guidance values for exposure to haloxyfop (including haloxyfop-R and haloxyfop-R methyl ester)

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and extensive
Distribution	Widely distributed with highest levels in liver and kidneys.
Potential for accumulation	None
Rate and extent of excretion	$t_{½}$ = 6.3 days for clearance from plasma to urine (human). Mostly excreted in urine.
	Main route of excretion is faeces in mice, male rats and dogs but urine in female rats, cynomolgus monkeys and men.
Metabolism in mammals	Oral haloxyfop methyl ester rapidly transformed to haloxyfop acid on absorption. Little primary metabolism, but some conjugation.
Toxicologically significant compounds in animals, plants and the environment	Haloxyfop
Acute toxicity	
Rat, LD_{50}, oral	300–337 mg/kg bw in males,
	545–623 mg/kg bw in females
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rabbit, dermal irritancy	Not irritating
Rabbit, eye irritancy	Not irritating
Guinea-pig, skin sensitization	Not sensitizing (Buehler, and Magnusson & Kligman)
Short-term studies of toxicity	
Target/critical effect	Liver
Lowest relevant oral NOAEL	0.2 mg/kg bw per day (serum alkaline phosphatase activity in mouse)
Lowest relevant dermal NOAEL	< 40 mg/kg bw per day (erythrocytes)
Genotoxicity	
	Not genotoxic in vitro or in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	None
Lowest relevant NOAEL	0.1 mg/kg bw per day (highest dose tested in male rats)
Carcinogenicity	No carcinogenic potential in the rat. Hepatocellular carcinoma in female mice associated with peroxisome proliferation (mode of action not relevant to humans)
Reproductive toxicity	
Reproductive target/critical effects	No reproductive effects
	Low pup weight
Lowest relevant reproductive NOAEL	Parental: 1 mg/kg bw per day (highest dose tested)
	Offspring: 0.065 mg/kg bw per day (pup weight)
Developmental target critical effect	Delayed ossification, resorptions

Lowest relevant developmental NOAEL	Maternal: 7.5 mg/kg bw per day (mortality)
	Developmental: 1 mg/kg bw per day (delayed ossification)
Neurotoxicity/delayed neurotoxicity	
	No specific study; no findings in other studies
Other toxicological studies	
Mechanism studies	Increased hepatocellular peroxisome proliferation in mice, rats and hepatocytes from guinea-pigs
	No effect on peroxisome proliferation in dogs, monkeys or hepatocytes from humans
Medical data	
	No adverse effects on health of manufacturing workers

Summary for racemic haloxyfop, haloxyfop-R and their methyl esters

	Value	Study	Safety factor
Group ADI	0–0.0007 mg/kg bw	Rat, two-generation study of reproductive toxicity	100
Group ARfD	0.08 mg/kg bw	Rabbit, studies of developmental toxicity	100

DIETARY RISK ASSESSMENT

Haloxyfop was evaluated for residues in 1995, 1996 and 2001 when the Meeting estimated a number of maximum residue levels for plant and animal commodities. As the trial data were primarily from the 1980's and GAP is likely to have drifted or changed significantly since then, the Meeting concluded that available residue data were not appropriate for estimating long-term or short-term intakes; and therefore no intake assessment was conducted by the current Meeting.

4.18 IMIDACLOPRID (206)

RESIDUE AND ANALYTICAL ASPECTS

Imidacloprid was evaluated by the JMPR in 2001 and 2002 when an ADI of 0-0.06 mg/kg bw per day and an ARfD of 0.4 mg/kg bw per day were established, and a number of maximum residue levels were estimated. The residues were defined as the sum of imidacloprid and its metabolites containing the 6-chloropyridinyl moiety for both regulatory and dietary intake assessment purposes.

Results of supervised trials carried out on cranberry according the US registered uses, were submitted for evaluation.

Results of supervised trials on crops

Five field trials were conducted with foliar applications at the maximum recommended rate (0.56 kg ai/ha). Mature cranberries were harvested at the recommended PHI (30 days) and 45 days post treatment.

The individual residue components were found to be stable under deep freeze conditions (< -20°C) for 655-656 days. The longest storage period of samples corresponded with the test period and confirmed the validity of residue data obtained.

Samples were analyzed for combined residues of imidacloprid and metabolites M09 (WAK 4140), M06 (WAK 3745), M01 (WAK 4103), and 6-CNA with a total residue method with average concurrent recovery of 102% obtained during the analysis of samples. The limit of quantification (LOQ) was 0.05 mg/kg. No quantifiable residues were observed in the samples (< 0.05 mg/kg).

Based on the results of these trials < 0.05 (5) mg/kg the Meeting estimated a maximum residue level of 0.05* mg/kg and values for STMR and HR of 0.05 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The GEMS/Food regional diets specify the following long-term cranberry consumption (g/day per person) for various cluster diets: A (0.1); D (0.3); F (0.6); M (2.5). The cranberry consumption in the other regions is nil.

The highest IEDI in the 13 GEMS/Food regional diets, based on estimated STMR was < 0.01% of the maximum ADI (0.06 mg/kg bw).

The Meeting concluded that the long-term dietary intake of imidacloprid residues from use on cranberry will add only marginally to the intake of residues from other uses considered by an earlier JMPR.

Short-term intake

The GEMS/Food regional diet specifies large portion sizes of cranberry as 3.53 g/kg bw for adults and 6.78 g/kg bw for children (both are from the USA).

The IESTIs of imidacloprid calculated on the basis of the large portion size and the estimated HR of 0.05 mg/kg are 0.04% and 0.1% of the ARfD for adults and children, respectively.

The Meeting concluded that the short-term intake of residues of imidacloprid resulting, from the use on cranberry that have been considered by the JMPR, is unlikely to present a public health concern.

4.19 METHOXYFENOZIDE (209)

RESIDUE AND ANALYTICAL ASPECTS

Methoxyfenozide was evaluated by the JMPR in 2003 and an ADI of 0-0.1 mg/kg bw per day and an ARfD of 0.9 mg/kg bw per day were established, and a number of maximum residue levels were estimated. The JMPR defined the residues as parent compound for compliance with MRLs and for dietary intake estimations.

Results of supervised trials carried out on cranberry according the US registered uses were submitted for evaluation.

Results of supervised residue trials on crops

Six trials were conducted on cranberries in four geographical regions of the USA and British Columbia, Canada. Each treated plot received four foliar broadcast applications of the test substance approximately according to GAP. Two replicate samples of mature or nearly mature cranberry fruit were collected around the registered PHI.

The harvested fruit samples were analyzed by a method determining the parent compound alone. The method was validated at 0.01 mg/kg level. The average recovery of 87% was obtained in the residue range of 0.01 and 1 mg/kg. Stability of residues (< -15^{o}C) was tested in three samples indicating that the residues were stable during the storage period.

The residues of parent methoxyfenozide found in fruit treated according to GAP in rank order were: 0.03, 0.03, 0.07, 0.10, 0.15 and 0.39 mg/kg.

The Meeting estimated a maximum residue level of 0.7 mg/kg, HR of 0.39 mg/kg and STMR of 0.085 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The GEMS/Food Consumption Cluster Diets specifies the following long-term cranberry consumption (g/day per person) for various cluster diets: A (0.1); D (0.3); F (0.6); M (2.5). The cranberry consumption in the other regions is nil.

The highest IEDI in the 13 GEMS/Food regional diets based on estimated STMR was < 0.01% of the maximum ADI (0.1 mg/kg bw).

The Meeting concluded that the long-term intake of residues of methoxyfenozide use on cranberry will not practically increase the intake of residues from other uses considered earlier by the JMPR.

Short-term intake

The GEMS/Food regional diet specifies the large portion size for cranberry of 3.53 g/kg bw for adults and 6.78 g/kg bw for children (both are from the USA).

The IESTIs of methoxyfenozide calculated on the basis of the large portion size and the estimated HR of 0.39 mg/kg are 0.15% and 0.3% of the ARfD for adults and children, respectively.

The Meeting concluded that the short-term intake of residues of methoxyfenozide resulting from the use on cranberry that has been considered by the JMPR is unlikely to present a public health concern.

4.20 PIRIMICARB (101)

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of pirimicarb were evaluated by the JMPR in 1976, 1978, 1979, 1981 and 1985. The compound was listed in the Periodic Re-Evaluation Programe at the 37th Session of the CCPR for periodic review by the 2006 JMPR. The toxicological review was conducted in 2004, when an ADI of 0-0.02 mg/kg bw and an ARfD of 0.1 mg/kg bw were established.

The Meeting received a full data package including animal and plant metabolism studies (goats, hens, apple trees, lettuce, potatoes and wheat), crop rotational studies, hydrolysis and photolysis studies in water, information on analytical methods, supervised residue trial data from use as a foliar spray on a range of fruit, vegetable, cereal and oil seed crops, processing studies and livestock feeding studies. GAP information was also submitted by the Netherlands.

Animal metabolism

The Meeting received information on the fate of orally dosed pirimicarb in the lactating goat and in laying hens. Experiments were carried out with pirimicarb ^{14}C labelled at the pyrimidinyl-2 position. Metabolism in laboratory animals (rats) was summarized and evaluated by the WHO panel of the JMPR in 2004.

Kinetic studies in rats have demonstrated that pirimicarb administered orally to male and female rats is rapidly and extensively absorbed (> 70% of the administered dose) and widely distributed. Radioactivity from [^{14}C]pyrimidinyl-labelled pirimicarb was excreted predominantly in the urine, while radioactivity from [^{14}C]carbamoyl-labelled pirimicarb was excreted predominantly in expired air. Tissue retention of radioactivity was low. Pirimicarb was extensively metabolized, giving rise to 24 metabolites, 17 of which were identified. The main metabolic pathway involves the loss of the carbamate moiety to produce a range of substituted hydroxypyrimidines, some of which are glucuronide conjugates.

One lactating Alpine goat orally treated twice daily for five consecutive days with ^{14}C-labelled pirimicarb at a calculated dose rate of 17 ppm feed, was sacrificed approximately 21 hours after the last dose. The largest amount of radioactivity was found in the urine and faeces, which contained around 63% and 11% of the total dose, respectively. The edible tissues (liver, kidney, muscle and fat) contained 1.3%, while milk contained 0.29%. The goat was monitored for expired ^{14}C-volatiles, but none were found. The overall recovery of the radioactivity was 77.3%.

After 5 days of treatment, the highest concentration of radioactive residues was found in the liver (0.46 mg/kg eq). Kidney, muscle and fat contained 0.34, 0.07, and 0.02 mg/kg eq, respectively. The total residue in the pm milk was higher than the residue in the am milk, indicating that a plateau was reached within 24 hours after dosing. Residue levels in milk during the dosing period were on average 0.054 mg/kg eq in the pm milk, while residue levels in the am milk were on average 0.03 mg/kg eq.

Neither pirimicarb nor any carbamate containing metabolites were detected in goat tissues or milk. The metabolites identified in liver, kidney and muscle were the hydroxypyrimidines R31805, R34865 and R31680. Individually these metabolites did not exceed 0.03 mg/kg eq in any tissue. The same three hydroxypyrimidine metabolites, plus a fourth closely related compound of the same structural type, were identified at very low levels (up to 0.01 mg/kg) in milk. The major part of the radioactivity remained unidentified: 65% in liver, 75% in kidney, 68% in muscle and 34% in milk. Each individual compound was < 10% of the total recovered radioactivity, and it is very unlikely that they comprised significant levels of any carbamate containing metabolite.

Ten white leghorn laying hens were orally dosed once daily for ten consecutive days with ^{14}C-labelled pirimicarb at a calculated dose rate of 7.7 ppm feed. The hens were sacrificed approximately 21–24 hours after the final dose. The largest amount of radioactivity was found in the excreta, which contained around 88% of the total dose. The edible tissues (liver, kidney, muscle and fat) contained around 0.6%, while eggs contained around 0.3%. The hens were monitored for expired ^{14}C-volatiles, but none were found. The overall recovery of the radioactivity was around 89%.

After 10 days of treatment, the highest concentration of radioactive residues was found in the liver (0.3 mg/kg eq). Kidney, breast muscle and fat contained 0.11, 0.14, and 0.02 mg/kg eq, respectively. The residue levels in egg yolk and white reached a plateau at day 6 and day 3, respectively. The residue levels at the plateau level were on average 0.13 mg/kg eq (range 0.11–0.15 mg/kg eq) in egg yolks and on average 0.08 mg/kg eq (range 0.065–0.088 mg/kg eq) in egg whites.

Neither pirimicarb nor any carbamate containing metabolites were found in hen tissues or eggs. The metabolites identified were the hydroxypyrimidines R31805, R34865 and R31680. In tissues, only compound R31680 exceeded 0.01 mg/kg eq, whilst in eggs only compound R34865 exceeded 0.01 mg/kg eq. A substantial part of the radioactivity remained unidentified: 64% in liver, 24% in kidney, 24% in breast muscle, 34% in thigh muscle, 17% in fat, 27% in egg white and 49% in egg yolk. It is however very unlikely that these unidentified fractions contain significant levels of any carbamate.

In conclusion, the metabolism of pirimicarb in farm animals was similar to that in laboratory animals. Goats and laying hens dosed with pirimicarb quickly detoxify the compound. Neither parent nor any carbamate containing metabolites were found in edible tissues, milk and eggs.

Plant metabolism

The Meeting received new information on the fate of pirimicarb after foliar treatment of apple trees, lettuce, potatoes and wheat which superseded the old metabolism studies carried out during the 1970s and early 1980s. Experiments were carried out with pirimicarb ^{14}C labelled at the pyrimidinyl-2 position. In all experiments an extensive set of carbamates, hydroxypyrimidines and guanidines was used as reference compounds.

Two apple trees, grown in pots in a caged area open to normal weather conditions in the UK, were sprayed with a WG formulation containing ^{14}C-labelled pirimicarb. The first tree was treated three times with 1.2 kg ai/ha and the second tree three times with 1.1 kg ai/ha. The first interval was 70 days, the second 46 days. Apples were harvested at 21 days after treatment (DAT). The total radioactive residues in the apples were 2.4 mg/kg eq and 1.7 mg/kg eq for the first and second tree, respectively. The major residue found in apples was parent pirimicarb (30% TRR). Other carbamates, hydroxypyrimidines, N,N-dimethylguanidine and urea were found at low levels (< 2% TRR). The polar residue (total 51% TRR) did not contain any significant levels of carbamates and comprised many different components including compounds with basic, strongly basic and neutral or acidic properties.

Lettuce plants were glasshouse grown in pots of sandy loam soil in the UK. Lettuce foliage was sprayed with a WG formulation containing ^{14}C- labelled pirimicarb. The first pot was treated three times with 0.255 kg ai/ha and the second pot three times with 0.265 kg ai/h at intervals of 7 days starting with 8 week old plants. The heads of mature lettuce plants were collected at 3 DAT (first pot) and 7 DAT (second pot). Total radioactive residues in lettuce leaves were 14 and 12 mg/kg eq at 3 and 7 days post-treatment, respectively. In the samples, 91% and 88% TRR could be extracted with MeOH, respectively. Pirimicarb and the carbamate metabolite demethyl pirimicarb together accounted for the majority of the radioactivity (68.7% and 59.3%). Three other carbamates and two hydroxypyrimidines were identified at much lower levels (≤ 2%).

Potato plants were grown in pots in sandy loam soil in a caged area open to normal weather conditions in the UK. Potato foliage was sprayed with a WG formulation containing ^{14}C- labelled pirimicarb. Two separate experiments were conducted: a low dose where 0.78 kg ai/ha was applied

twice at an interval of 13 days, and a high dose where four applications were made at 2.8 kg ai/ha with an interval of 7, 6 and 8 days. The first spray application was 108 days after planting. Potato tubers were harvested at 17 and 18 days post-treatment from the low and high dose trials, respectively. The total radioactive residues found in tubers were 0.04 and 0.23 mg/kg eq for the low and high dose experiment, respectively. In the low dose experiment, 95.1% of the total recovered radioactivity could be extracted. Neither parent nor any metabolites containing the carbamate moiety were found. The majority of the residue (90.2%) was comprised of highly polar water-soluble components, e.g., 1,1-dimethylguanidine, methylguanidine, of which no single metabolite exceeded 0.01 mg/kg eq. In the high dose experiment, 95.0% of the total recovered radioactivity could be extracted. Trace amounts of parent (1.7%), carbamates demethyl pirimicarb (1.0%) and demethyl formamido pirimicarb (0.7%) and a hydroxypyrimidine R31805 (1.1%) were identified. The principal metabolites, identified in the polar water-soluble fractions (81.6%), were N,N-dimethylguanidine (15.8%) and N-methylguanidine (3.5%).

In the UK field grown wheat was transplanted into a circular tub placed in a caged area open to normal weather conditions. Transplanting was carried out 55 days prior to the first treatment. Wheat foliage was sprayed with a WG formulation containing ^{14}C- labelled pirimicarb. The crop was sprayed twice at rates of 0.28 and 0.29 kg ai/ha, respectively. The first treatment was at growth stage BBCH 70 - 80 (just after completion of the flowering stage) and the second treatment was 35 days later. Wheat was collected at 14 days post-treatment, with grain heads separated from the straw. Total radioactive residues found in wheat straw and grain were 16 mg/kg eq and 0.72 mg/kg eq, respectively. The metabolism of pirimicarb in straw and grain is very similar. For grain and straw 86.6% and 80.1% of the total recovered radioactivity was extracted, respectively. Pirimicarb itself was the major residue (25.2% in grain, 13.4% in straw). Other identified compounds were demethyl pirimicarb (2.8% in grain, 4.4% in straw) and demethyl formamido pirimicarb (1.3% in grain, 1.7% in straw) and hydroxypyrimidine R31805 (1.6% in grain, 1.2% in straw). The remaining radioactivity comprised highly polar, water soluble constituents, including guanidines.

In conclusion, studies on the nature of residues in primary crops have demonstrated that pirimicarb undergoes very extensive metabolism resulting in a diverse range of metabolites. The early stages of metabolism, as demonstrated by the lettuce study, but also exhibited in other crops studies, involve modification of the dimethylamino moiety on position 2 of the pyrimidine ring and loss of the carbamate moiety. Loss of the carbamate moiety produces hydroxypyrimidine metabolites. The main metabolic route involves degradation of pirimicarb to demethyl pirimicarb and further degradation of both these compounds to the corresponding hydroxypyrimidines R31805 and R34865.

Further degradation of the hydroxypyrimidines takes place, resulting in ring opening of the pyrimidine and further degradation to form low molecular weight polar molecules such as the guanidines.

Although the metabolism of pirimicarb is qualitatively comparable to that in animals, the turnover in plants is much lower and substantial amounts of parent and carbamate-containing metabolites can still be present at harvest.

Environmental fate in soil

The Meeting received confined and field rotational crop studies.

A confined rotational crop study was undertaken to determine the accumulation and metabolic fate of ^{14}C-labelled pirimicarb under field conditions. The crops used were lettuce, radish and millet. A single application of pirimicarb at a rate of 1.48 kg ai/ha was made to bare soil (sandy loam) in Visalia, California, USA. Crops were planted into the soil 29, 61, 119 days after treatment and were harvested at maturity. Millet was also harvested at the forage and hay stages. The total radioactive residues in the crops declined significantly as the plantback or rotation interval increased. Millet straw had the highest residues at all rotations (5 mg/kg eq at a plantback of 29 DAT), while the lowest residue was found in the radish root (0.029 mg/kg eq at a plantback of 119 DAT). Leafy, root

and small grain crops all show comparable metabolic profiles. Low levels of pirimicarb (< 0.001–11.5% of the total recovered radioactivity) and carbamate metabolites (demethyl pirimicarb 0.213–14.5%, demethyl formamido pirimicarb < 0.001–4.14% and R35140 < 0.001–5.88%) were found in some samples and levels of carbamates decreased as the rotation interval increased. Other identified compounds were hydroxypyrimidines (R31805, R34865 and R31680) and guanidine (R12378).

Two supervised field trials were carried out in the USA (Whitakers, North Carolina (NC) and Visalia, California (CA)) to determine the magnitude of residues of pirimicarb in rotational crops (millet, mustard and turnip). At each site two plots were used with a primary crop of lettuce. Pirimicarb as a WG formulation was applied on the first plot four times at 0.56 kg ai/ha with 5 day intervals. On the second plot a combination of a single application at 0.37 kg ai/ha + two applications at 0.56 kg ai/ha with a 5 and 10 day interval were made. In NC the last application was at the vegetative growth stage, in CA at the full grown vegetative growth stage. The formulation was applied as a broadcast treatment using a tractor mounted sprayer. The soil type was USDA sandy loam. The lettuce was removed and separate plots of millet, mustard and turnip were planted back at 30, 60 and 120 days after the last application. The rotated crops were sampled at normal harvest for the rotational crop.

No residues of pirimicarb or its metabolites demethyl pirimicarb, demethyl formamido pirimicarb and R238177 were measured in any of the samples from North Carolina from any of the plant back intervals (< 0.01 mg/kg, each analyte). Low pirimicarb and demethyl pirimicarb residues were measured in some of samples from the Californian trials. The highest total pirimicarb residues were found in millet forage (0.05–0.07 mg/kg eq) and mustard leaves (0.03–0.04 mg/kg eq) from the 30 day planting interval. No residues of R238177 were measured in any of the samples (< 0.01 mg/kg).

Environmental fate in water-sediment systems

The Meeting received information on the hydrolysis and photolysis of pirimicarb in water. Pirimicarb was shown to be hydrolytically stable under acidic, neutral and alkaline conditions. However, pirimicarb was rapidly degraded by photolysis in aqueous solution with DT_{50} values of 3.2 hours and 2.28 hours at pH 5 and 7, respectively. After a period equivalent to 31 hours summer sunlight, only 1.2% and 1.4% of the total applied radioactive parent remained at pH 5 and 7. The major degradation products formed are demethyl formamido pirimicarb, hydroxypyrimidine R31805 and N,N-dimethylguanidine(sulfate), which accounted for up to 17.9%, 27.8% and 14.1% of the radioactivity applied, respectively at pH 5 and 16.4%, 25.5% and 26.9% at pH 7.

Methods of analysis

The Meeting received data on analytical methods for enforcement and monitoring of pirimicarb and its carbamate metabolites (demethyl pirimicarb, demethyl formamido pirimicarb, and R238177) in plant commodities and pirimicarb and demethyl pirimicarb in animal commodities. The Meeting also received information on analytical methods used in the study reports.

Analytical methods for enforcement and monitoring

Method RAM 265 is intended for use as an enforcement-monitoring method for the determination of pirimicarb and its carbamate metabolites (demethyl pirimicarb, demethyl formamido pirimicarb, and R238177) in plant commodities. The method is also used in study reports (see below). In general, LOQs of 0.01 mg/kg can be reached. The Meeting noted that method RAM 265 is considered a special method and cannot be included in a multi-residue method because of the acid treatment required for the conversion of demethyl formamido pirimicarb into demethyl pirimicarb.

Method DFG S19 is intended for use as an enforcement-monitoring method for the determination of pirimicarb and its carbamate metabolite (demethyl pirimicarb) in animal commodities. Method DFG S19 is a published German multi-residue method and results show that pirimicarb and its metabolite can be incorporated into this existing method. The published method consists of GC technology. Newer studies use HPLC-MS/MS with the S19 method. LOQs of 0.01 mg/kg were reported for milk, muscle, kidney, liver, fat and eggs.

Analytical methods used in study reports

In the course of time, numerous analytical methods to determine pirimicarb and its metabolites have been described. They include methods PPRAM 15 (1972-1997, several versions), PPRAM 38 (1978), RAM 265 (1995-2004, several versions), RAM 277 (2000-2004), RAM 319 (2000-2002) and RAM 360 (2001). Most methods were developed for the determination of pirimicarb and its carbamate metabolites demethyl pirimicarb and demethyl formamido pirimicarb, while some versions of method RAM 265 and methods RAM 319 and RAM 360 also measure the metabolite R238177.

In general, extracts were left to stand overnight or incubated for 1 hour at 50 °C to ensure the conversion of any demethyl formamido pirimicarb into demethyl pirimicarb. After an optional clean-up step (depending on commodity) pirimicarb and demethyl pirimicarb were analysed by GC-NPD, HPLC-MS/MS (APCI, positive ion mode or with fluorescence detection). Modifications of the methods mainly concerned the clean-up and changed GC or HPLC conditions. The reported LOQ for each analyte was usually 0.01 mg/kg. In some cases the LOQ had to be raised to 0.05 mg/kg because of matrix interferences, e.g., in cabbage, fodder and straw.

Stability of residues in stored analytical samples

The Meeting received data on the stability of residues in various crops and milk.

Storage stability studies on apple, cauliflower, cabbage, cucumber, tomato, Iceberg lettuce, snap beans, potato, artichoke, asparagus, wheat grain and straw and seeds from oilseed rape fortified with a mixture of pirimicarb, demethyl pirimicarb and R238177 show that residues are stable for up to 12 months when stored at -18 °C.

The storage stability of pirimicarb residues in stonefruit, berries and other small fruits, bulb vegetables, Brussels sprouts, courgettes and melons, peppers and sweet corn, kale, turnip tops, mustard leaves, beans without pods and peas with or without pods, carrots and turnip roots, pulses (dry peas, dry broad beans) and sunflower seeds, barley (straw and grains), maize (grain, forage, fodder), and millet (grain, forage, hay, straw) was not specifically investigated but the storage stability in these commodities can be extrapolated from other crops with high water content, e.g., apples and tomatoes, and other dry crops with starch and proteins, e.g., wheat grain and seeds from oilseed rape.

Residues of pirimicarb, demethyl pirimicarb and demethyl formamido pirimicarb are stable in milk for up to 24 months when stored at -14 °C. No storage stability data are available on meat, edible offal and fat; however metabolism studies show that it is unlikely that any carbamate containing residue will occur in animal tissues.

Definition of the residue

In animals, pirimicarb is quickly detoxified and neither parent nor any other carbamate containing metabolites were found in edible tissues, milk and eggs.

Because of the lack of a better indicator molecule the Meeting agreed that parent pirimicarb should be the compound of interest in animal commodities, both for enforcement and for dietary risk assessment.

It was concluded from the low magnitude of residues in animal fat and the log P_{ow} of 1.7 of the parent that the residue is not fat-soluble.

In plants, the major residue is the parent pirimicarb. Metabolites include carbamates, hydroxypirimidines and guanidines. The only metabolites of significance were demethyl pirimicarb and demethyl formamido pirimicarb. Hydroxypyrimidines and guanidines are not of toxicological concern. The 2004 JMPR concluded that demethyl pirimicarb and demethyl formamido pirimicarb have toxicological profiles similar to that of pirimicarb itself. Metabolite (2-dimethylamino-6-hydroxymethyl-5-methylpyrimidin-4-yl dimethylcarbamate) (R238177) is the 6-hydroxymethyl metabolite of pirimicarb. The current JMPR decided that in the absence of specific data, the toxicological properties of pirimicarb itself can be assumed for this 6-hydroxymethyl metabolite.

The Meeting noted that in the residue trials, this metabolite was virtually always below the LOQ except in some trials on currants and peppers, where measurable residues were found, in one instance up to 0.08 mg/kg. The Meeting decided that the 6-hydroxymethyl metabolite does not have to be included in the residue definition for dietary risk assessment.

Definition of the residue in plant commodities for compliance with MRLs: pirimicarb.

Definition of the residue in plant commodities for estimation of dietary intake: sum of pirimicarb, demethyl pirimicarb and demethyl formamido pirimicarb, expressed as pirimicarb.

Definition of the residue in animal commodities for compliance with MRLs and estimation of dietary intake: pirimicarb.

Results of supervised trials on crops

Supervised trials were available for the use of pirimicarb as a foliar spray on the following crops: citrus (mandarins, oranges), apples, stone fruit (cherries, peaches, nectarines and plums), berry fruit (currants, gooseberries, raspberries, blackberries and strawberries), onions, brassica vegetables (cabbage, cauliflower, broccoli, Brussels sprouts and kale), cucumber, summer squash, melons, tomatoes, peppers, sweetcorn, lettuce, legumes and pulses, carrots, sugar beet, potato, globe artichoke, asparagus, cereals (barley, wheat and maize), oil seed rape and sunflower.

Trial data or relevant GAP was not submitted for alfalfa (fodder); alfalfa forage (green); celery; cotton seed; endive; leek; parsley; pecan; spinach; sweet corn (corn-on-the-cob) and watercress, for which current recommendations for maximum residue levels exist.

The Meeting agreed to withdraw its previous maximum residue level recommendations for these commodities.

Analytical methods used in the trials measured residues of pirimicarb and also the combined residues of demethyl pirimicarb (R34836) and demethylformamido pirimicarb (R34885), the latter being converted to and measured as R34836. In most trials the methods were also able to measure 2-dimethylamino-6-hydroxymethyl-5-methylpyrimidin-4-yl dimethylcarbamate), the 6-hydroxymethyl metabolite of pirimicarb (R238177).

The Meeting agreed to use residue results for pirimicarb for the estimation of maximum residue limits and to combine the results for pirimicarb and for demethyl pirimicarb plus demethylformamido pirimicarb, expressed as pirimicarb (adjustment factor of 1.06) for the estimation of STMRs and HRs. In this appraisal, the term ‘total pirimicarb residues’ refers to these combined residues of pirimicarb and the listed de-methyl metabolites, expressed as pirimicarb.

The ratio of the de-methyl metabolites and parent compound varied in different crops and in some cases this may lead to STMR and/or HR values (based on the total pirimicarb residues) being established at levels higher than the estimated maximum residue level, as this is based on the parent compound only. In addition, the Meeting agreed that because residues of the demethyl metabolites did not generally contribute significantly to the total residue, they would only be included in the total where they were reported at levels above the LOQ. This approach is shown in the following example:

Pirimicarb (mg/kg)	Demethyl pirimicarb plus demethylformamido pirimicarb (mg/kg)	Total pirimicarb residues, expressed as pirimicarb (mg/kg)
< 0.01	< 0.01	< 0.01
0.1	< 0.01	0.1
0.2	0.1 [× 1.06]	0.31

Oranges, sweet, sour

The results of residue trials in Italy and Spain on oranges were made available to the Meeting.

GAP for citrus in Spain is for foliar spray applications of 0.05 kg ai/hL (PHI of 7 days). In trials from Italy and Spain, matching this GAP, pirimicarb residues in whole fruit were: 0.11, 0.11, 0.25, 0.27, 0.37 and 0.40 mg/kg (n = 6). Total pirimicarb residues in orange pulp in these trials were: < 0.01 (5) and 0.01 mg/kg.

Mandarin

The results of residue trials in Italy and Spain on mandarins were made available to the Meeting.

GAP for citrus in Spain is for foliar spray applications of 0.05 kg ai/hL (PHI of 7 days). In trials from Italy and Spain, matching Spanish GAP, pirimicarb residues in whole fruit were: 0.35, 0.68, 0.77, 0.87, 1.2, 1.2, 1.8 and 2.2 mg/kg (n = 8). Total pirimicarb residues in mandarin pulp in these trials were: < 0.01, 0.01, 0.01, 0.01, 0.02, 0.03, 0.04 and 0.08 mg/kg (n = 8).

The Meeting agreed that the data for oranges and mandarins were sufficient to support a citrus fruit commodity group maximum residue level and estimated a maximum residue level of 3 mg/kg for pirimicarb on citrus fruit and based on the mandarin data, estimated an STMR of 0.015 mg/kg and HR of 0.08 mg/kg for total pirimicarb residues in the edible portion of citrus fruit.

The Meeting also agreed to withdraw its previous recommendations of 0.5 mg/kg for oranges (Sweet and Sour) and 0.05 (*) mg/kg for citrus fruit (except oranges, Sweet, Sour) as these were being replaced by the recommendation for citrus fruit.

Apples

The results of residue trials in France, Germany, Italy, Spain and UK on apples were made available to the Meeting.

GAP for deciduous fruit crops in Spain is for foliar spray applications of 0.05 kg ai/hL (PHI of 7 days) and in trials from France, Italy and Spain matching this GAP, pirimicarb residues in whole fruit were: 0.03, 0.05, 0.12, 0.13, 0.15, 0.15 and 0.25 mg/kg (n = 7). Total pirimicarb residues in apples these trials were: 0.03, 0.07, 0.15, 0.18, 0.19, 0.21 and 0.30 mg/kg (n = 7).

In Netherlands, GAP for apples and pears is for up to two applications of 0.025 kg ai/hL (PHI 7 days) and in trials from France and UK matching this GAP, residues of pirimicarb were: 0.05, 0.14, 0.15, 0.16, 0.18, 0.28, 0.3 and 0.88 mg/kg (n = 8). Total pirimicarb residues in apples these trials were: 0.05, 0.16, 0.17, 0.17, 0.2, 0.3, 0.33 and 0.91 mg/kg (n = 8).

The Meeting noted that the two residue populations were similar and agreed to use a combined data set of: 0.03, 0.05, 0.05, 0.12, 0.13, 0.14, 0.15, 0.15, 0.15, 0.16, 0.18, 0.25, 0.28, 0.3 and 0.88 mg/kg (n = 15) for pirimicarb residues in apples and 0.03, 0.05, 0.07, 0.15, 0.16, 0.17, 0.17, 0.18, 0.19, 0.2, 0.21, 0.3, 0.3, 0.33 and 0.91 mg/kg for total pirimicarb residues.

The Meeting agreed that the data on apples could be used to support a pome fruit commodity group maximum residue level and estimated a maximum residue level of 1 mg/kg for pirimicarb on pome fruit (confirming the existing recommendation) and estimated an STMR of 0.18 mg/kg and HR of 0.91 mg/kg for total pirimicarb residues in pome fruit.

Cherries

The Meeting received results of residue trials in France, Germany, Italy, Spain and UK on cherries.

GAP for deciduous fruit crops in Spain is for foliar spray applications of 0.05 kg ai/hL (PHI of 7 days) and in trials from France, Italy and Spain matching this GAP, pirimicarb residues in whole fruit were: 0.28, 1.1, 1.2, 1.4 and 1.9 mg/kg (n = 5). Total pirimicarb residues in flesh of cherries in these trials were: 0.36, 1.3, 1.3, 1.8 and 2.1 mg/kg (n = 5).

GAP for stone fruits in the Czech Republic is for foliar spray applications of up to 0.038 kg ai/hL (PHI 7 days) and in trials from Germany, France and UK matching this GAP, pirimicarb residues in whole fruit were: 0.43, 0.69, 0.71 and 0.89 mg/kg (n = 4). Total pirimicarb residues in flesh of cherries in these trials were: 0.49, 0.78, 0.82, and 0.99 mg/kg (n = 4).

The Meeting noted that the two residue populations appeared to from similar populations and agreed to use a combined data set of: 0.28, 0.43, 0.69, 0.71, 0.89, 1.1, 1.2, 1.4 and 1.9 mg/kg (n = 9) for pirimicarb residues in cherries and 0.36, 0.49, 0.78, 0.82, 0.99, 1.3, 1.3, 1.8 and 2.1 mg/kg (n = 9) for total pirimicarb residues.

Peaches (and nectarines)

The Meeting received results of residue trials in France, Italy and Spain on peaches and nectarines.

GAP for deciduous fruit crops in Spain is for foliar spray applications of 0.05 kg ai/hL (PHI 7 days) and eight trials on peaches and four trials on nectarines from France, Italy and Spain matched this GAP.

Pirimicarb residues in nectarines were 0.09, 0.17, 0.22 and 0.36 mg/kg and total pirimicarb residues in two of these trials were 0.27 and 0.41 mg/kg in nectarine flesh. In peaches, pirimicarb residues were 0.09, 0.15, 0.22, 0.25, 0.32, 0.34 0.39 and 1.2 mg/kg and in six of these trials, total pirimicarb residues in peach flesh were 0.13, 0.29, 0.37, 0.39, 0.46 and 1.4 mg/kg.

The Meeting noted that the residues from the nectarine and peach trials were from similar populations and agreed to combine the results. Pirimicarb residues in whole fruit were: 0.09, 0.09, 0.15, 0.17, 0.22, 0.22, 0.25, 0.32, 0.34, 0.36, 0.39 and 1.2 mg/kg (n = 12). Total pirimicarb residues in flesh of peaches and nectarines in eight of these trials were: 0.13, 0.27, 0.29, 0.37, 0.39, 0.41, 0.46 and 1.4 mg/kg (n = 8).

Plums

The Meeting received results of residue trials in France, Germany, Italy, Spain and UK on plums.

GAP for deciduous fruit crops in Spain is for foliar spray applications of 0.05 kg ai/hL (PHI 7 days) and in trials from France, Italy and Spain matching this GAP, pirimicarb residues in whole fruit were: 0.1, 0.15, 0.17, 0.29 and 0.3 mg/kg (n = 5). Total pirimicarb residues in flesh of plums in four of these trials were: 0.11, 0.19, 0.22 and 0.36 mg/kg (n = 4).

In Netherlands, GAP for plums is for up to two applications of 0.038 kg ai/hL (PHI 7 days) and in trials from Germany and UK matching this GAP, residues of pirimicarb were: 0.08, 0.1, 0.15 and 0.27 mg/kg (n = 4). Total pirimicarb residues in flesh of plums in these trials were: 0.09, 0.11, 0.17 and 0.30 mg/kg (n = 4).

In the Czech Republic, GAP for plums is for up to two applications of 0.038 kg ai/hL (PHI 14 days) and in trials from Germany and UK matching this GAP, residues of pirimicarb were: 0.12, 0.20, 0.21, 0.21, 0.24, 0.28, 0.32 and 0.34 mg/kg (n = 8). Total pirimicarb residues in flesh of plums in these trials were: 0.13, 0.21, 0.24, 0.28, 0.28, 0.31, 0.37 and 0.43 mg/kg (n = 8).

The Meeting noted that the three sets of residue results were from similar populations and agreed that they could be combined. Pirimicarb residues in whole fruit were: 0.08, 0.1, 0.1, 0.12, 0.15,

0.15, 0.17, 0.20, 0.21, 0.21, 0.24, 0.27, 0.28, 0.29, 0.3, 0.32 and 0.34 mg/kg (n = 17). Total pirimicarb residues in the flesh were: 0.09, 0.11, 0.11, 0.13, 0.17, 0.19, 0.21, 0.22, 0.24, 0.28, 0.28, 0.30, 0.31, 0.36, 0.37 and 0.43 mg/kg (n = 16).

The Meeting agreed that the data on peaches, nectarines, cherries and plums could be used to support a 'stone fruit' commodity group maximum residue level and estimated a maximum residue level of 3 mg/kg for pirimicarb on stone fruit and based on the cherry data, estimated an STMR of 0.99 mg/kg and HR of 2.1 mg/kg for total pirimicarb residues in the flesh of stone fruit.

The Meeting also agreed to withdraw its previous maximum residue level recommendations of 0.5 mg/kg for peaches and for plums (including prunes) because they were being replaced by the maximum residue level for stone fruit.

Currants (and gooseberries)

The Meeting received results of residue trials in Germany on currants and gooseberries.

In Netherlands, GAP for currants and gooseberries is for up to two applications of 0.025 kg ai/hL (PHI 7 days) and seven currant trials and one gooseberry trial from Germany matched this GAP.

Pirimicarb residues in currants were 0.07, 0.08, 0.09, 0.14, 0.18, 0.23 and 0.28 mg/kg (n = 7) and in gooseberries, the pirimicarb residue was 0.13 mg/kg. The Meeting agreed to combine the currant and gooseberry results as mutually supporting data. The combined data set for currants and gooseberries were: 0.07, 0.08, 0.09, 0.13, 0.14, 0.18, 0.23 and 0.28 mg/kg (n = 8). Total pirimicarb residues were: 0.08, 0.08, 0.11, 0.14, 0.16, 0.18, 0.25 and 0.3 mg/kg (n = 8).

Raspberries

The Meeting received results of residue trials in Germany on raspberries and blackberries.

In Netherlands, GAP for raspberries and blackberries is for up to 2 applications of 0.025 kg ai/hL (PHI 7 days) and three raspberry trials from Germany matched this GAP.

Pirimicarb residues in raspberries were 0.23, 0.34, and 0.76 mg/kg (n = 3). Total pirimicarb residues were: 0.24, 0.36 and 0.82 mg/kg (n = 3).

Strawberries

The Meeting received results of residue trials in Italy and Spain on outdoor strawberries and in France, Italy, Spain and UK on protected strawberries.

GAP in the Czech Republic for berry fruit is for up to 0.25 kg ai/ha, PHI 7 days and in Belgium, GAP is for up to 0.2 kg ai/ha (PHI 7 days), no residue trials matched these GAPs. In two outdoor trials in Italy matching the GAP in France (up to 0.375 kg ai/ha (PHI 15 days), residues of pirimicarb were 0.08 and 0.12 mg/kg and total pirimicarb residues were: 0.09 and 0.14 mg/kg.

The Meeting agreed the data were not sufficient to estimate a maximum residue limit for strawberries and agreed to withdraw the previous recommendation of 0.5 mg/kg.

The Meeting agreed that the data on currants, gooseberries and raspberries could be used to support a 'berry fruit (except grapes and strawberries)' commodity group maximum residue level and estimated a maximum residue level of 1 mg/kg for pirimicarb on berries and other small fruits (except grapes and strawberries) and based on the raspberry data, estimated an STMR of 0.36 mg/kg and HR of 0.82 mg/kg for total pirimicarb residues in berries and other small fruits (except grapes and strawberries).

The Meeting also agreed to withdraw its previous maximum residue level recommendation of 0.5 mg/kg for blackberries; currant, Black and raspberries, Red, Black, because they were being replaced by maximum residue level for berries and other small fruits (except grapes and strawberries).

Onions, bulb

The Meeting received results of residue trials on bulb onions from France, Germany, Italy, Spain and UK.

GAP for vegetables in Spain is for foliar spray applications of 0.05 kg ai/hL (PHI 3 days for vegetables except cucurbits) and in trials from Italy and Spain matching this GAP, pirimicarb residues in onion bulbs were: < 0.01 (4), 0.01, 0.02, 0.05 and 0.06 mg/kg (n = 8). Total pirimicarb residues in these trials were: < 0.01, < 0.01, < 0.01, ≤ 0.01, 0.01, 0.02, 0.07 and 0.09 mg/kg (n = 8)

In the Czech Republic, GAP for onions and garlic is for up to two applications of 0.025 kg ai/ha (maximum) with a PHI of 14 days. In six trials from Germany, France and UK matching this GAP, residues of pirimicarb were all < 0.01 (n = 6) and total pirimicarb residues were also < 0.01 (6).

The Meeting agreed to use the trials matching the GAP from Spain and estimated a maximum residue level of 0.1 mg/kg for pirimicarb in onion, bulb (to replace the existing recommendation of 0.5 mg/kg) and estimated an STMR of 0.01 mg/kg and an HR of 0.09 mg/kg for total pirimicarb residues.

Garlic

The Meeting also agreed to extrapolate the results for onion, bulb to garlic and estimated a maximum residue level of 0.1 mg/kg for pirimicarb in garlic (to replace the existing recommendation of 0.5 mg/kg) and estimated an STMR of 0.01 mg/kg and an HR of 0.09 mg/kg for total pirimicarb residues in garlic.

Cauliflower

The Meeting received results of residue trials in France and UK on cauliflowers.

In the Czech Republic, GAP for brassica vegetables is for up to two applications of 0.25 kg ai/ha (PHI 3 days). Trials from UK matched this GAP except for the higher number of applications. The Meeting noted that the residue half-life for pirimicarb in cauliflowers was less than 7 days, and that the residue contribution from treatments applied more than 14 days before harvest would not be significant.

The Meeting agreed to use the results of the UK trials matching the GAP of the Czech Republic but with 2–5 applications (at 7–14 day intervals). Pirimicarb residues in these trials were: 0.01, 0.01, 0.01, 0.02, 0.02, 0.03, 0.04, 0.04, < 0.05, < 0.05, < 0.05, < 0.05, 0.05 and 0.05 mg/kg (n = 14). Total pirimicarb residues were: 0.01, 0.01, 0.01, 0.02, 0.02, 0.04, 0.04, < 0.05, < 0.05, < 0.05, < 0.05, 0.05, 0.05 and 0.06 mg/kg (n = 14).

Broccoli

The Meeting received results of residue trials in UK on broccoli.

In the Czech Republic, GAP for brassica vegetables is for up to 2 applications of 0.25 kg ai/ha (PHI 3 days). Trials from UK matched this GAP except for the higher number of applications. The Meeting noted that the residue half-life for pirimicarb in broccoli was less than 7 days, and that the residue contribution from treatments applied more than 14 days before harvest would not be significant.

The Meeting agreed to use the results of the UK trials matching the GAP of the Czech Republic but with 2-5 applications (at 14 day intervals). Pirimicarb residues in these trials were: < 0.01, < 0.01, < 0.01, < 0.01, 0.01, 0.39 and 0.41 mg/kg (n = 7). The total pirimicarb residues were: < 0.01, < 0.01, < 0.01, < 0.01, 0.01, 0.48 and 0.5 mg/kg (n = 7).

Brussels sprouts

The Meeting received results of residue trials in Germany and UK on Brussels sprouts.

In the Czech Republic, GAP for brassica vegetables is for up to two applications of 0.25 kg ai/ha (PHI 3 days). Trials from UK and Germany matched this GAP except for the higher number of applications. The Meeting noted that the residue half-life for pirimicarb in Brussels sprouts was less than 7 days, and that the residue contribution from treatments applied more than 14 days before harvest would not be significant.

The Meeting agreed to use the results of the trials from Germany and UK matching the GAP of the Czech Republic but with 2-5 applications (at 10-35 day intervals). Pirimicarb residues in these trials were: 0.04, 0.04 and 0.05 mg/kg (n = 3). The total pirimicarb residues were: 0.05, 0.05 and 0.06 mg/kg (n = 3).

In Germany, the GAP for brassica vegetables is for up to 3 applications of 0.125 kg ai/ha (PHI 7 days) and in two broccoli trials from Germany matching this GAP, pirimicarb residues for both were 0.02 mg/kg and the total pirimicarb residues were also 0.02 mg/kg.

The combined results from the trials matching the GAPs of the Czech Republic and Germany were: 0.02, 0.02, 0.04, 0.04 and 0.05 mg/kg (n = 5) for pirimicarb and the total pirimicarb residues were: 0.02, 0.02, 0.05, 0.05 and 0.06 mg/kg (n = 5).

Cabbage, head

The Meeting received results of residue trials in Germany and UK on cabbage.

In France, GAP for cabbage is 0.375 kg ai/ha (PHI 7 days) and in trials from France, Germany and UK, matching the GAP of France, pirimicarb residues were: 0.01, 0.03, < 0.05, < 0.05, < 0.05, < 0.05, < 0.05 and 0.06 mg/kg (n = 8). Total pirimicarb residues were: 0.02, < 0.05, < 0.05, < 0.05, < 0.05, < 0.05, < 0.05, 0.06 and 0.12 mg/kg (n = 8).

The Meeting agreed that the data on broccoli, Brussels sprouts, cauliflower and cabbage (head) could be used to support a 'brassica vegetables' commodity group maximum residue level and estimated a maximum residue level of 0.5 mg/kg for pirimicarb on brassica (cole or cabbage) vegetables and estimated an STMR of 0.05 mg/kg (based on the cabbage data) and HR of 0.5 mg/kg (based on the broccoli data) for total pirimicarb residues in brassica (cole or cabbage) vegetables.

The Meeting also agreed to withdraw its previous maximum residue levels of 1 mg/kg for broccoli; Brussels sprouts; cabbages, head and cauliflower, and of 0.5 mg/kg for kohlrabi as they would be replaced by the maximum residue level for brassica (cole or cabbage) vegetables.

Cucumbers and squash, summer

The Meeting received results of residue trials in Italy and Spain on outdoor cucumbers and in France, Italy, Spain and UK on protected cucumbers. Results from trials on protected courgettes in France and outdoor courgettes in Italy were also provided to the Meeting.

Cucumbers: GAP for cucumbers in Netherlands is for foliar spray applications of 0.025 kg ai/hL, up to 0.37 kg ai/ha (PHI 1 day). While matching residue trials data for outdoor cucumbers were not available, pirimicarb residues on protected cucumbers from trials in France, Italy, Spain and UK, matching the GAP of Netherlands were: 0.09, 0.1, 0.13, 0.14, 0.15, 0.17, 0.24, 0.29 and 0.41 mg/kg. Total pirimicarb residues in these trials were: 0.12, 0.14, 0.16, 0.18, 0.18, 0.21, 0.27, 0.33 and 0.44 mg/kg.

In France, GAP for cucumbers is for up to two applications of 0.375 kg ai/ha (PHI 3 days) and two outdoor cucumber trials in Italy matched this GAP. Pirimicarb residues in these trials were < 0.01 and 0.22 mg/kg. Total pirimicarb residues were < 0.01 and 0.24 mg/kg.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 7 days) and two outdoor cucumber trials in Spain matched this GAP. Pirimicarb residues in these trials were 0.02 and 0.02 mg/kg. Total pirimicarb residues were 0.02 and 0.04 mg/kg.

Squash, summer: GAP for summer squash in Netherlands is for foliar spray applications of 0.025 kg ai/hL, up to 0.37 kg ai/ha (PHI 1 day). While matching residue trials data for outdoor summer squash were not available, pirimicarb residues on protected summer squash (courgettes) from trials in France, matching the GAP of Netherlands were 0.11 and 0.14 mg/kg, with total pirimicarb residues in these trials being 0.11 and 0.15 mg/kg.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 7 days) and outdoor summer squash trials in France and Italy matched this GAP. Pirimicarb residues in these trials were < 0.01, < 0.01, 0.01 and 0.02 mg/kg. Total pirimicarb residues in these trials were < 0.01, < 0.01, 0.01 and 0.03 mg/kg.

The Meeting noted that the residues in the protected cucumber and protected summer squash trials matching the Netherlands GAP were from similar populations and agreed to combine them as mutually supporting data for cucumbers and squash, summer. Pirimicarb residues in the combined data set were: 0.09, 0.1, 0.11, 0.13, 0.14, 0.14, 0.15, 0.17, 0.24, 0.29 and 0.41 mg/kg (n = 11). Total pirimicarb residues in these combined trials were: 0.11, 0.12, 0.14, 0.15, 0.16, 0.18, 0.18, 0.21, 0.27, 0.33 and 0.44 mg/kg (n = 11).

The Meeting agreed that the data on cucumbers and summer squash could be used to support a 'fruiting vegetables, cucurbits (except melons and watermelons)' commodity group maximum residue level and estimated a maximum residue level of 1 mg/kg for pirimicarb on fruiting vegetables, cucurbits (except melons and water melons) and estimated an STMR of 0.18 mg/kg and HR of 0.44 mg/kg.

The Meeting also agreed to withdraw its previous maximum residue levels of 1 mg/kg for cucumber and gherkin because they were being replaced by the recommendation for maximum residue levels for fruiting vegetables, cucurbits (except melons and water melons).

Melons, except watermelons

The Meeting received results of residue trials in Italy and Spain on outdoor and protected melons.

GAP for melons in France is for foliar spray applications of up to 0.375 kg ai/ha (PHI 3 days). Residue trials from Italy and France, for both outdoor melons (4) and protected melons (4) matched this GAP.

Pirimicarb residues in outdoor melons were 0.03, 0.06, 0.06 and 0.11 mg/kg (n = 4). Total pirimicarb residues in melon flesh were 0.02, 0.03, 0.05 and 0.09 mg/kg.

In protected melons, pirimicarb residues were: 0.02, 0.04, 0.04 and 0.13 mg/kg (n = 4), and total pirimicarb residues in melon flesh were: 0.01, 0.02, 0.02 and 0.04 mg/kg (n = 4).

The Meeting noted that the two data sets were from similar populations and agreed to use the results of the outdoor and protected melon trials to give a combined data set of: 0.02, 0.03, 0.04, 0.04, 0.06, 0.06, 0.11 and 0.13 mg/kg (n = 8) for pirimicarb in whole melons. Total pirimicarb residues in the flesh were: 0.01, 0.02, 0.02, 0.02, 0.03, 0.04, 0.05 and 0.09 mg/kg (n = 8).

The Meeting estimated a maximum residue level of 0.2 mg/kg for pirimicarb in melons, except watermelon and estimated an STMR of 0.025 mg/kg and an HR of 0.09 mg/kg for total pirimicarb residues in the pulp.

Tomatoes

The Meeting received results of residue trials in France, Italy and Spain on outdoor tomatoes and in France, Italy, Spain and UK on protected tomatoes.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits) and in outdoor tomato trials from France, Italy and Spain, matching this GAP, pirimicarb residues were: 0.02, 0.03, 0.07, 0.08, 0.09, 0.1, 0.1 and 0.16 mg/kg. Total pirimicarb residues in these trials were: 0.03, 0.03, 0.1, 0.1, 0.11, 0.12, 0.14 and 0.18 mg/kg.

In trials on protected tomatoes in France and UK matching the GAP of Netherlands (up to 0.37 kg ai/hL with a 1 day PHI), pirimicarb residues were: 0.07, 0.08, 0.1, 0.1, 0.1, 0.17, 0.2 and 0.2 mg/kg and total pirimicarb residues were 0.07, 0.08, 0.1, 0.1, 0.1, 0.17, 0.2 and 0.2 mg/kg.

In trials on protected tomatoes in Spain and Italy matching the GAP of Spain, pirimicarb residues were: 0.05, 0.11, 0.21 and 0.22 mg/kg and total pirimicarb residues were 0.07, 0.13, 0.23 and 0.25 mg/kg.

The Meeting noted that the results of the outdoor tomato trials, the protected tomato trials matching the GAP of Spain and the protected tomato trials matching the GAP of Netherlands appeared to be from similar populations and the Meeting agreed to combine all the tomato residue results. The combined residues of pirimicarb were: 0.02, 0.03, 0.05, 0.07, 0.07, 0.08, 0.08, 0.09, 0.1, 0.1, 0.1, 0.1, 0.1, 0.11, 0.16, 0.17, 0.2, 0.2, 0.21 and 0.22 mg/kg (n = 20). Total pirimicarb residues in these trials were: 0.03, 0.03, 0.07, 0.07, 0.08, 0.1, 0.1, 0.1, 0.1, 0.1, 0.11, 0.12, 0.13, 0.14, 0.17, 0.18, 0.2, 0.2, 0.23 and 0.25 mg/kg (n = 20).

Peppers, sweet

The Meeting received results of residue trials in Italy and Spain on outdoor peppers and in France, Italy, Spain and UK on protected peppers.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits) and in outdoor pepper trials from Italy and Spain, matching this GAP, pirimicarb residues were: 0.01, 0.02, 0.03, 0.03, 0.04, 0.05, 0.07 and 0.07 mg/kg. Total pirimicarb residues in these trials were: 0.01, 0.03, 0.03, 0.04, 0.06, 0.07, 0.08 and 0.09 mg/kg.

In trials on protected peppers in France, Italy, Spain and UK matching the GAP of Spain, pirimicarb residues were: < 0.01, 0.01, 0.04, 0.05, 0.05, 0.08, 0.08, 0.14, 0.15 and 0.18 mg/kg. Total pirimicarb residues in these trials were: < 0.01, 0.01, 0.04, 0.05, 0.06, 0.08, 0.08, 0.17, 0.19 and 0.22 mg/kg.

The Meeting noted that the combined results of the outdoor and protected pepper trials appeared to be from the same population and the Meeting agreed to combine all the pepper residue results. The combined residues of pirimicarb were: < 0.01, 0.01, 0.01, 0.02, 0.03, 0.03, 0.04, 0.04, 0.05, 0.05, 0.05, 0.07, 0.07, 0.08, 0.08, 0.14, 0.15 and 0.18 mg/kg (n = 18). Total pirimicarb residues in these trials were: < 0.01, 0.01, 0.01, 0.03, 0.03, 0.04, 0.04, 0.05, 0.06, 0.06, 0.07, 0.08, 0.08, 0.08, 0.09, 0.17, 0.19 and 0.22 mg/kg (n = 18).

The Meeting agreed that the data on tomatoes and peppers could be used to support a 'fruiting vegetables, other than cucurbits, mushrooms, edible fungi and sweet corn (kernels and corn-on-the-cob)' commodity group maximum residue level and estimated a maximum residue level of 0.5 mg/kg for pirimicarb on fruiting vegetables, other than cucurbits (except mushrooms, fungi, edible (not including mushrooms), sweet corn (kernels) and sweet corn (corn-on-the-cob)) and estimated an STMR of 0.105 mg/kg and HR of 0.25 mg/kg, based on the tomato data.

The Meeting also agreed to withdraw its previous maximum residue levels for eggplant (1 mg/kg); peppers, chili (2 mg/kg); peppers, Sweet (1 mg/kg) and tomatoes because they were being replaced by the maximum residue level for fruiting vegetables, other than cucurbits (except mushrooms, fungi, edible (not including mushrooms), sweet corn (kernels) and sweet corn (corn-on-the-cob)).

Dried chilli peppers

The Meeting agreed to apply a default dehydration factor of 10 (in the absence of specific processing information) to the above estimated maximum residue level, STMR and HR and estimated a maximum residue level of 5 mg/kg for pirimicarb in dried chilli peppers and an STMR of 1.05 mg/kg and HR of 2.5 mg/kg for total pirimicarb residues.

Sweetcorn

The Meeting received results of residue trials in France on sweetcorn.

In France, GAP is 0.2 kg ai/ha (PHI 7 days) and in trials from France matching this GAP, pirimicarb residues in sweetcorn kernels were: < 0.01, < 0.01, < 0.01 and 0.02 mg/kg (n = 4). Total pirimicarb residues in these trials were: < 0.01, < 0.01, < 0.01 and 0.02 mg/kg (n = 4).

The Meeting estimated a maximum residue level of 0.05 mg/kg for pirimicarb in sweet corn (kernels) and estimated an STMR of 0.01 mg/kg and an HR of 0.02 mg/kg for total pirimicarb residues in sweet corn kernels. The Meeting agreed to withdraw the previous recommendation for sweetcorn (corn on the cob) of 0.05* mg/kg.

Lettuce

The Meeting received results of residue trials on outdoor lettuce from France and UK and on protected lettuce from France, Italy, Spain and UK. These trials were conducted using a range of different lettuce types, most of which (where identified) were the 'Iceberg' type head lettuce or the more loosely packed 'Butterhead' type of leafy lettuce.

In outdoor lettuce trials from France and UK matching the Netherlands GAP of 0.25 kg ai/ha (PHI 7 days), pirimicarb residues were: < 0.01, < 0.01, 0.01 and 0.02 mg/kg and total pirimicarb residues were < 0.01, 0.07, 0.11 and 0.33 mg/kg.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits) and while no outdoor lettuce trials matching this GAP were available, in protected lettuce trials in France, Spain and UK matching the GAP of Spain , pirimicarb residues were: 0.6, 0.84, 0.86, 1.2, 1.4, 1.5, 1.7 and 2.3 mg/kg (n = 8). Total pirimicarb residues in these trials were: 1.3, 2.0, 2.1, 2.3, 2.3, 2.4, 2.8 and 3.0 mg/kg (n-8).

Five trials on protected lettuce in France matched the German GAP of 0.125 kg ai/ha (PHI 7 days) but with two applications at 7-12 day intervals rather than the GAP maximum of 3 applications at least 10 days apart. The Meeting noted that the residue contribution from treatments made more than 21 days before harvest would be insignificant, and agreed the use these trials. Pirimicarb residues were: 0.1, 0.1, 0.23, 0.25 and 0.28 mg/kg. Total pirimicarb residues were 0.38, 0.53, 0.65, 0.76 and 0.92 mg/kg.

The Meeting noted that the residues in the protected lettuce trials were higher than in the outdoor crops and agreed to use the results of the protected lettuce trials. The combined residues of pirimicarb were: 0.1, 0.1, 0.23, 0.25, 0.28, 0.6, 0.84, 0.86, 1.2, 1.4, 1.5, 1.7 and 2.3 mg/kg (n = 13). Total pirimicarb residues in these trials were: 0.38, 0.53, 0.65, 0.76, 0.92, 1.3, 2.0, 2.1, 2.3, 2.3, 2.4, 2.8 and 3.0 mg/kg (n = 13).

The Meeting estimated a maximum residue level of 5 mg/kg for pirimicarb in lettuce, head (replacing the existing recommendation of 1 mg/kg) and estimated an STMR of 2 mg/kg and an HR of 3 mg/kg for total pirimicarb residues.

The Meeting also noted that in the nine protected lettuce trials where the lettuce type could be classified as either head lettuce (7 trials) or leaf lettuce (2 trials), the results appeared to be from similar populations, and agreed to use the results to estimate a maximum residue level of 5 mg/kg for

pirimicarb in lettuce, leaf and estimated an STMR of 2 mg/kg and an HR of 3 mg/kg for total pirimicarb residues.

Kale

The Meeting received results of residue trials in UK on kale.

In the Czech Republic, GAP for brassica vegetables is for up to 2 applications of 0.25 kg ai/ha (PHI 3 days). Six trials on kale from UK matched this GAP but in three trials an additional application was made 16-17 days before sampling. The Meeting noted that the residue half-life for pirimicarb in kale was less than 3 days and that the residue contribution from treatments applied more than 14 days before harvest would not be significant.

The Meeting agreed to use the results of these trials from UK matching the GAP of the Czech Republic but with 2 or 3 applications. Pirimicarb residues in kale leaves and petioles from these trials were: < 0.05, 0.05, 0.07, 0.08, 0.09 and 0.15 mg/kg (n = 6). Total pirimicarb residues were: 0.20, 0.26, 0.27, 0.34, 0.35 and 0.60 mg/kg (n = 6).

The Meeting estimated a maximum residue level of 0.3 mg/kg for pirimicarb in kale and estimated an STMR of 0.31 mg/kg and an HR of 0.6 mg/kg for total pirimicarb residues.

Beans (except broad bean and soya bean)

The Meeting received results of residue trials in France, Germany, Greece, the Netherlands and Spain on fresh beans.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits) and in trials from Greece and Spain, matching this GAP, pirimicarb residues were: 0.09, 0.22, 0.36, 0.39 and 0.4 mg/kg. Total pirimicarb residues in these trials were: 0.15, 0.27, 0.49, 0.55 and 0.59 mg/kg.

GAP for legume vegetables in Germany is for up to 3 applications of 0.25 kg ai/ha, at least 10 days apart (PHI 3 days). The Meeting agreed to use matching residue trials data with 2 applications (7-12 days apart) from France and Germany as the final applications contributed the majority of the residues. In these trials, pirimicarb residues were: 0.04, 0.23, 0.25 and 0.26 mg/kg and total pirimicarb residues were 0.1, 0.26, 0.31 and 0.38 mg/kg.

In France, GAP for green beans is 0.375 kg ai/ha (PHI 7 days) and in trials from France, Germany and Netherlands, matching this GAP, pirimicarb residues were: 0.03, 0.07, 0.1, 0.13, 0.16, 0.21, 0.21, 0.22, 0.28 and 0.31 mg/kg. Total pirimicarb residues in these trials were: 0.09, 0.19, 0.22, 0.23, 0.24, 0.25, 0.27, 0.38, 0.42 and 0.44 mg/kg.

The Meeting noted that the results of these trials appeared to be from the same population and agreed to combine all of the bean (with pods) residue results. The combined residues of pirimicarb were: 0.03, 0.04, 0.07, 0.09, 0.1, 0.13, 0.16, 0.21, 0.21, 0.22, 0.22, 0.23, 0.25, 0.26, 0.28, 0.31, 0.36, 0.39 and 0.4 mg/kg (n = 19). Total pirimicarb residues in these trials were: 0.09, 0.1, 0.15, 0.19, 0.22, 0.23, 0.24, 0.25, 0.26, 0.27, 0.27, 0.31, 0.38, 0.38, 0.42, 0.44, 0.49, 0.55 and 0.59 mg/kg (n = 19).

Broad bean, shelled (succulent)

The Meeting received results of residue trials in UK on broad beans.

In Germany, GAP is for up to 3 applications of 0.25 kg ai/ha, at least 10 days apart (PHI 3 days). The Meeting considered that the residue contribution from applications made more than 20 days before harvest would be negligible and agreed to use matching residue trials data with 2 applications (7-12 days apart) from UK. In these trials, pirimicarb residues were: 0.01, 0.02, 0.03 and 0.04 mg/kg and total pirimicarb residues were 0.01, 0.03, 0.05 and 0.06 mg/kg.

Peas, shelled

The Meeting received results of residue trials in France, Italy and UK on fresh peas (without pods).

In France, GAP for peas is 0.375 kg ai/ha (PHI 7 days) and in ten trials from France, Italy and UK, matching this GAP, pirimicarb residues in peas (without pods) were all < 0.01 (n = 10).

Peas

The Meeting received results of residue trials in Germany and Netherlands on peas (with pods).

In two trials in Germany and Netherlands, matching the GAP in France (0.375 kg ai/ha, PHI 7 days), pirimicarb residues were < 0.01 and < 0.01 mg/kg and total pirimicarb residues were also < 0.01 and < 0.01 mg/kg.

The Meeting agreed that the data on peas and beans (with and without pods) could be used to support a 'legume vegetables (except soya beans)' commodity group maximum residue level and using the results for beans (with pods), estimated a maximum residue level of 0.7 mg/kg for pirimicarb on legume vegetables (except soya beans) and estimated an STMR of 0.27 mg/kg and HR of 0.59 mg/kg.

The Meeting also agreed to withdraw its previous maximum residue levels of 0.1 mg/kg for beans, shelled; 1 mg/kg for common bean (pods and/or immature seeds) and 0.2 mg/kg for peas (pods and succulent=immature seeds) because they were being replaced by the maximum residue level for legume vegetables (except soya beans).

Beans and peas (dry)

Residue results on beans (dry) and peas (dry) were made available to the Meeting from trials in France and Spain.

Beans (dry): In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits). In three trials on beans grown in France for dry bean production, matching the GAP of Spain, pirimicarb residues in beans (dry) were: 0.03, 0.04 and 0.09 mg/kg and total pirimicarb residues were 0.06, 0.08 and 0.14 mg/kg.

Peas (dry): In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits). In five trials on peas grown in France and Spain for dry pea production, matching the GAP of Spain, pirimicarb residues in peas (dry) were: < 0.01, < 0.01, 0.05, 0.08 and 0.12 mg/kg and total pirimicarb residues were < 0.01, < 0.01, 0.07, 0.1 and 0.15 mg/kg.

The Meeting noted that the results on dry peas and beans were mutually supportive as they appeared to be from similar populations. The combined results for pirimicarb were: < 0.01, < 0.01, 0.03, 0.04, 0.05, 0.08, 0.09 and 0.12 mg/kg (n = 8) and total pirimicarb residues were < 0.01, < 0.01, 0.06, 0.07, 0.08, 0.1, 0.14 and 0.15 mg/kg (n = 8).

The Meeting agreed that the data on peas, dry and beans, dry could be used to support a 'pulse (except soya beans)' commodity group maximum residue level and estimated a maximum residue level of 0.2 mg/kg for pirimicarb on pulses (except soya beans) and estimated an STMR of 0.075 mg/kg and HR of 0.15 mg/kg .

Carrots

The Meeting received results of residue trials in France, Italy and Spain on carrots.

In France, GAP for carrots is 0.375 kg ai/ha (PHI 7 days). In eight trials from France, Spain and Italy, matching the GAP of Spain, pirimicarb residues were all < 0.01 (8) and total pirimicarb residues were also all < 0.01 (8) mg/kg (n = 8).

Sugar beet

The Meeting received results of residue trials in France, Italy, Spain and UK on sugar beet.

In Spain, GAP for sugar beet is 0.05 kg ai/hL (PHI 3 days). In two trials from Italy matching this GAP, pirimicarb residues were: < 0.01 and < 0.01 mg/kg and total pirimicarb residues were also < 0.01 and < 0.01 mg/kg.

In the Czech Republic, GAP for sugar beet is 0.25 kg ai/ha (PHI 7 days). In trials from UK matching the GAP in the Czech Republic, pirimicarb residues were: < 0.01 (17), 0.01, 0.01 and 0.02 mg/kg (n = 20) and the total pirimicarb residues were also < 0.01 (17), 0.01, 0.01 and 0.02 mg/kg (n = 20).

The Meeting noted that these two data sets appeared to be from the similar populations, and agreed to combine them. The residues of pirimicarb were: < 0.01 (19), 0.01, 0.01 and 0.02 mg/kg (n = 22) and the total pirimicarb residues were < 0.01 (19), 0.01, 0.01 and 0.02 mg/kg (n = 22).

Potatoes

The Meeting received results of residue trials in France, Germany, Spain and UK on potatoes.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits). In two potato trials from Spain matching this GAP, pirimicarb residues were: < 0.01 and < 0.01 mg/kg and total pirimicarb residues were also < 0.01 and < 0.01 mg/kg.

In the Czech Republic and in Netherlands, GAP for potatoes is for up to two applications of 0.25 kg ai/ha (PHI 7 days). In trials from Germany and UK matching these GAPs, pirimicarb residues were all < 0.01 mg/kg (n = 5) and total pirimicarb residues were also < 0.01 mg/kg (n = 5).

The Meeting noted that these two data sets appeared to be from the same population, and agreed that they could be combined. Residues of pirimicarb were: < 0.01 (7) mg/kg and the total pirimicarb residues were also < 0.01 (7) mg/kg.

The Meeting agreed that the data on carrots, sugar beet and potatoes could be used to support a 'root and tuber vegetables' commodity group maximum residue level and estimated a maximum residue level of 0.05 mg/kg for pirimicarb on root and tuber vegetables and estimated an STMR of 0.01 mg/kg and HR of 0.02 mg/kg based on the sugar beet data.

The Meeting also agreed to withdraw its previous maximum residue levels of 0.05 (*) mg/kg for beetroot; parsnip; potato; radish; sugar beet and 'turnip (garden) because they were being replaced by the maximum residue level for root and tuber vegetables

Artichokes, globe

The Meeting received results of residue trials in France, Italy and Spain on globe artichokes.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits). In six trials from Spain and Italy, matching the GAP of Spain, pirimicarb residues were: 0.33, 0.42, 0.44, 0.73, 1.9 and 2.6 mg/kg and total pirimicarb residues were: 0.44, 0.51, 0.53, 0.85, 2.1 and 2.8 mg/kg.

In six trials from France, matching the French GAP (0.375 kg ai/ha, PHI 7 days), pirimicarb residues were: 0.07, 0.16, 0.18, 0.23, 0.3 and 0.46 mg/kg and total pirimicarb residues were: 0.09, 0.19, 0.22, 0.27, 0.41 and 0.56 mg/kg.

The Meeting noted that the results of the trials matching the GAPs in Spain and in France appeared to be from different populations and agreed to use the results from the trials matching the GAP in Spain.

The Meeting estimated a maximum residue level of 5 mg/kg for pirimicarb in artichoke, globe and estimated an STMR of 0.69 mg/kg and an HR of 2.8 mg/kg for total pirimicarb residues.

Asparagus

The Meeting received results of residue trials in Germany on asparagus.

In France, GAP for asparagus is 0.375 kg ai/ha, applied to the ferns (once harvesting is completed for the season) with a PHI of 200 days (before the new spears are harvested the next season).

In four trials from Germany and Greece, involving application rates higher than in the French GAP, but with similar PHIs, pirimicarb residues were all < 0.01 mg/kg (n = 4) and total pirimicarb residues were also all < 0.01 mg/kg (n = 4).

The Meeting agreed that because residues were all < 0.01 mg/kg in newly emerged spears from treated plants, the results of these trials could be used and the Meeting estimated a maximum residue level of 0.01 (*) mg/kg for pirimicarb in asparagus and estimated an STMR of 0 mg/kg and an HR of 0 mg/kg for total pirimicarb residues.

Barley

The Meeting received results of residue trials in France and UK on winter barley.

In the Czech Republic, GAP for cereals is for up to two applications (0.15 kg ai/ha), up to the 'soft dough' growth stage (BBCH 85). While the label also states a PHI of 14 days, the Meeting agreed to use trials that matched the crop growth stage instruction as being a better indication of GAP.

In trials from France and UK, matching the Czech Republic GAP (with PHIs ranging from 20 to 29 days), pirimicarb residues were: < 0.01 (6), 0.01 and 0.03 mg/kg and total pirimicarb residues were: < 0.01 (6), 0.01 and 0.05 mg/kg.

Wheat

The Meeting received results of residue trials in France and UK on winter wheat.

In the Czech Republic, GAP for cereals is for up to two applications (0.15 kg ai/ha), up to the 'soft dough' growth stage (BBCH 85). While the label also states a PHI of 14 days, the Meeting agreed to use trials that matched the crop growth stage instruction as being a better indication of GAP.

In trials from France and UK, matching the Czech Republic GAP (with PHIs ranging from 21 to 46 days), pirimicarb residues were all < 0.01 mg/kg (n = 8) and total pirimicarb residues were also all < 0.01 mg/kg (n = 8).

Maize

The Meeting received results of residue trials in France on maize.

In France, GAP for maize is 0.2 kg ai/ha, up to the end of flowering, with a PHI of 80 days for grain and 60 days for animal forage. In trials from France, Germany and Italy, matching the GAP in France, pirimicarb residues were: < 0.01 (12) and 0.02 mg/kg (n = 13) and total pirimicarb residues were: < 0.01 (12) and 0.04 mg/kg (n = 13).

The Meeting agreed that the data on wheat, barley and maize could be used to support a 'cereal grains (except rice)' commodity group maximum residue level and estimated a maximum residue level of 0.05 mg/kg for pirimicarb on cereal grains (except rice) and estimated an STMR of 0.01 mg/kg (based on the maize data) and HR of 0.05 mg/kg (based on the barley data) for total pirimicarb residues.

The Meeting also agreed to withdraw its previous maximum residue levels of 0.05 mg/kg (*) for barley, oats and wheat because they were being replaced by a maximum residue level for cereal grains (except rice).

Rape seed

The Meeting received results of residue trials in France, Spain and UK on oil seed rape.

In Spain, GAP is 0.25 kg ai/ha (PHI 21 days) and in two trials from Spain, matching this GAP, pirimicarb residues were < 0.01 and < 0.01 mg/kg total pirimicarb residues were also < 0.01 and < 0.01 mg/kg.

GAP for oil seed rape in the Czech Republic is 0.21 kg ai/ha, with no PHI specified, and in six trials from UK and France, matching this GAP, with PHIs of 14–17 days, pirimicarb residues were: < 0.01 (5) and 0.02 mg/kg and total pirimicarb residues were also ≤ 0.01 (5) and 0.02 mg/kg.

The Meeting agreed to use the results from the trials matching the Czech Republic GAP to estimate a maximum residue level of 0.05 mg/kg for pirimicarb in rape seed (to replace the existing recommendation of 0.2 mg/kg) and estimated an STMR of 0.01 mg/kg and an HR of 0.02 mg/kg for total pirimicarb residues.

Sunflower seed

The Meeting received results of residue trials in France, Italy and Spain on sunflower.

In France, GAP is 0.25 kg ai/ha (PHI 21 days) and in twelve trials from Italy and Spain, matching this GAP, pirimicarb residues were < 0.01, < 0.01, < 0.01, 0.01, 0.01, 0.01, 0.01, 0.03, 0.03, 0.03, 0.03 and 0.05 mg/kg and total pirimicarb residues were: < 0.01, < 0.01, < 0.01, 0.01, 0.01, 0.01, 0.02, 0.03, 0.03, 0.04, 0.04 and 0.07 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg for pirimicarb in sunflower seed and estimated an STMR of 0.015 mg/kg and an HR of 0.07 mg/kg for total pirimicarb residues.

Residues in animal commodities

Animal feed commodities

The Meeting noted that the two demethyl pirimicarb metabolites can occur in animal feeds at levels averaging about 50% of the total pirimicarb residues, and these metabolites can therefore be a significant component of diet.

Because animal transfer studies have only been conducted with the parent compound, the Meeting considered there was insufficient information to determine the behaviour of the dimethyl carbamate metabolites in animals, and agreed to use the total pirimicarb residue values instead of just parent pirimicarb residue values to estimate STMRs and highest residues for animal feeds in order to avoid under-estimating the potential for residues of pirimicarb metabolites to transfer into animal commodities.

Bean forage (green)

The Meeting received information on residues in bean forage from trials on fresh beans from Spain, on broad beans from UK and beans (dry) from France.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI of 3 days, except for cucurbits) and in two common bean trials from Spain, matching this GAP, total pirimicarb residues in vines (without pods) were: 3.5 and 7.0 mg/kg.

GAP for legume vegetables in Germany is for up to 3 applications of 0.25 kg ai/ha, at least 10 days apart (PHI 3 days). The Meeting considered that the final applications contributed the majority of the residues and agreed to use data from residue trials with 2 applications (7–12 days apart) from the UK. In these trials, total pirimicarb residues in broad bean forage (without pods) were: 0.21, 0.42, 0.51 and 0.73 mg/kg.

In three trials on beans from France, grown for dry bean production, matching the GAP of Spain, total pirimicarb residues in bean forage (including empty pods) were: 0.34, 0.44 and 0.64 mg/kg.

The total pirimicarb residue results in forage (with or without empty pods) from common beans, broad beans and beans grown for dry bean production were: 0.21, 0.34, 0.42, 0.44, 0.51, 0.64, 0.73, 3.5 and 7 mg/kg.

The Meeting noted that the residues in the common bean forage (3.5 and 7.0 mg/kg) were significantly higher than in the vines (with or without empty pods) from the other bean varieties, and agreed to use these results to estimate STMRs and highest residues for bean forage.

The Meeting estimated an STMR of 5.25 mg/kg and a highest residue of 7 mg/kg for total pirimicarb residues (fresh weight) in bean forage (green) for the purposes of calculating animal dietary burden.

Pea hay or pea fodder (dry)

The Meeting received information on residues in pea foliage from trials on fresh peas in France and on peas grown for dry pea production in France and Spain.

In France, GAP for peas is 0.375 kg ai/ha (PHI 7 days) and in two trials from France, matching this GAP, pirimicarb residues were 0.02 and 0.44 mg/kg and total pirimicarb residues in vines and empty pods were: 0.09 and 0.62 mg/kg.

In Spain, GAP for vegetables is 0.05 kg ai/hL (PHI 3 days except cucurbits). In five trials on peas in France and Spain, matching Spanish GAP, pirimicarb residues in vines and empty pods were 0.34, 0.89, 2.7, 2.9 and 14 mg/kg and total pirimicarb residues were: 0.72, 1.6, 4.1, 4.6 and 18 mg/kg.

The Meeting noted that the residues in the pea forage from the trials matching the GAP of Spain were significantly higher than those matching the GAP in France, and agreed to use the higher results to estimate STMRs and highest residues for pea forage.

Allowing for the standard 25% dry matter for pea vines (*FAO Manual* p 148*)*, the Meeting estimated a maximum residue level of 60 mg/kg (dry weight) for pea hay or pea fodder, dry and estimated an STMR of 16.4 mg/kg and a highest residue of 72 mg/kg (dry weight) for total pirimicarb residues for the purposes of calculating animal dietary burden.

Maize forage

The Meeting received results of residues in maize forage from trials conducted in France, Germany and Italy.

In France, GAP for maize is 0.2 kg ai/ha, up to the end of flowering, with a PHI of 60 days for animal forage. In six trials from France and Italy, matching the GAP in France, pirimicarb residues were all < 0.01 mg/kg (n = 6) and total pirimicarb residues were also all < 0.01 mg/kg (n = 6).

The Meeting estimated an STMR of 0 mg/kg in maize forage and a highest residue of 0 mg/kg for total pirimicarb residues (fresh weight) for the purposes of calculating animal dietary burden.

Barley straw and fodder, dry

The Meeting received results of residues in barley straw from trials on winter barley in France and UK.

In the Czech Republic, GAP for cereals is for a maximum of two applications, up to the ‘soft dough’ growth stage (BBCH 85).

In trials from France and UK, matching the GAP of the Czech Republic (with PHIs ranging from 20 to 29 days), pirimicarb residues in barley straw were: < 0.01, < 0.01, 0.02, 0.02, 0.02, 0.03, 0.08 and 0.13 mg/kg and total pirimicarb residues were: < 0.01, < 0.01, 0.04, 0.04, 0.04, 0.07, 0.11 and 0.22 mg/kg (n = 8).

Wheat straw and fodder, dry

The Meeting received results of residues in wheat straw from trials on winter wheat in France and UK.

In the Czech Republic, GAP for cereals is for a maximum of two applications, up to the 'soft dough' growth stage (BBCH 85).

In trials from France and UK, matching the Czech Republic GAP (with PHIs ranging from 21 to 46 days), pirimicarb residues were: < 0.01, < 0.01, 0.02, 0.02, < 0.05, 0.07 and 0.16 mg/kg (n = 7) and total pirimicarb residues were: < 0.01, < 0.01, 0.05, 0.08, < 0.09, 0.23 and 0.33 mg/kg (n = 7).

Maize fodder

The Meeting received results of residues in maize fodder from trials conducted in France, Germany and Italy.

In France, GAP for maize is 0.2 kg ai/ha, up to the end of flowering, with a PHI of 80 days for grain. In trials from France, Germany and Italy, matching the GAP in France, pirimicarb residues in maize fodder were: < 0.01 (10) and 0.02 (3) mg/kg (n = 13) for pirimicarb and total pirimicarb residues were: < 0.01 (9), < 0.01, 0.02 (3) mg/kg (n = 13).

The Meeting noted that the results from the wheat straw, barley straw and maize fodder trials appeared to be from the similar populations and agreed to combine the residues to estimate a commodity group maximum residue level, STMR and highest residue. Pirimicarb residues were: < 0.01 (14), 0.02 (8), 0.03, < 0.05, 0.07, 0.08, 0.13 and 0.16 mg/kg (n = 28) and total pirimicarb residues were: < 0.01 (13), < 0.01, 0.02 (3) 0.04, 0.04, 0.04, 0.05, 0.07, 0.08, < 0.09, 0.11, 0.22, 0.23 and 0.33 mg/kg (n = 28).

The Meeting estimated a maximum residue level of 0.3 mg/kg for pirimicarb in straw and fodder (dry) of cereal grains except rice and for the purposes of calculating animal dietary burden, estimated an STMR of 0.015 mg/kg and a highest residue of 0.33 mg/kg for total pirimicarb residues.

Sugar beet leaves or tops

The Meeting received information on residues in sugar beet leaves from trials on sugar beet in France, Italy, Spain and UK.

In Spain, GAP for sugar beet is 0.05 kg ai/hL (PHI 3 days). In two trials from Italy matching this GAP, total pirimicarb residues in sugar beet leaves were: 2.1 and 4.3 mg/kg.

In the Czech Republic, GAP for sugar beet is 0.25 kg ai/ha (PHI 7 days). In trials from UK matching the GAP in the Czech Republic, the total pirimicarb residues in sugar beet leaves were: 0.14, 0.45, 0.50, 0.53, 0.59, 0.66, 0.86, 1.2, 1.3 and 3.4 mg/kg (n = 10).

The Meeting noted that these two data sets appeared to be from the same population, and agreed to combine them. The total pirimicarb residues in sugar beet leaves were: 0.14, 0.45, 0.48, 0.53, 0.59, 0.66, 0.86, 1.2, 1.3, 2.1, 3.4 and 4.3 mg/kg (n = 12).

The Meeting estimated an STMR of 0.76 mg/kg (fresh weight) and a highest residue of 4.3 mg/kg (fresh weight) for the total pirimicarb residues in sugar beet leaves or tops for the purposes of calculating animal dietary burden.

Fate of residues during processing

Pirimicarb is stable under the standard hydrolysis conditions used to mimic food processing. The only carbamate degradate to be observed was demethyl pirimicarb at < 0.8% of the total radioactivity and this metabolite was also found in plant metabolism studies.

The Meeting received information on the fate of incurred residues of pirimicarb during the processing of apples, plums, tomatoes, Brussels sprouts, head cabbage, kale, potatoes and barley. The processing factors (PF) shown below were calculated from the total residues for the commodities for which MRLs, STMRs and HRs were estimated.

RAC	Processed product	No.	PF	Median PF
Apples	juice	4	0.50, 0.74, 0.75, 1.00	0.745
	sauce	4	0.20, 0.50, 0.50, 1.00	0.5
	wet pomace	1	1.66	1.66
Plums	prunes	4	1.69, 1.92, 2.07, 2.82	2.0
Tomatoes	juice	5	0.50, 0.62, 0.70, 0.86, 1.54	0.70
	puree	5	0.62, 0.64, 1.49, 2.19, 2.33	1.49

Apples were processed into juice, sauce and wet pomace with processing factors of 0.745, 0.5 and 1.66, respectively. Based on the STMR value of 0.18 mg/kg for pome fruit, the STMR-Ps were 0.13 mg/kg, 0.09 mg/kg and 0.3 mg/kg for total pirimicarb residues in apple juice, sauce and wet pomace, respectively.

Plums were processed into dried prunes with a median processing factor of 2. Based on the STMR of 0.23 mg/kg and the HR of 0.43 mg/kg for plums, the STMR-P was 0.46 mg/kg and the HR-P was 0.86 mg/kg for total pirimicarb residues in prunes.

Tomatoes were processed into juice and puree with processing factors of 0.7 and 1.49. Based on the STMR value of 0.105 mg/kg for tomato, the STMR-Ps were 0.07 mg/kg and 0.16 mg/kg for total pirimicarb residues in tomato juice and puree.

Farm animal dietary burden

The Meeting estimated the dietary burden of pirimicarb residues in farm animals from the diets listed in Appendix IX of the FAO Manual (FAO, 2002). One feed commodity only from each Codex Commodity Group is used. Calculation from the highest residue values provides the concentrations in feed suitable for estimating MRLs for animal commodities, while calculation from the STMR values for feed is suitable for estimating STMR values for animal commodities. In the case of processed commodities, the STMR-P value is used for both intake calculations.

Estimated maximum dietary burden of farm animals

Commodity	CC	Residue (mg/kg)	Basis	DM %	Residue ÷ DM	*Diet content (%)*			Residue contribution, mg/kg		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Apple wet pomace	AB	0.3	STMR-P	40	0.75	***40***	***20***		0.3	0.15	
Pea, field hay	AL	72	Highest residue	100	72.00	***25***	***50***		18	36	
Bean forage (Note)	AL	7	Highest residue	35	20.00	*30*	*30*				
Barley straw	AS	0.33	Highest	89	0.37	*10*	***20***			0.074	

Commodity	CC	Residue (mg/kg)	Basis	DM %	Residue ÷ DM	*Diet content (%)*			Residue contribution, mg/kg		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
			residue								
Millet straw	AS	0.33	Highest residue	90	0.37	*10*	*10*				
Oats straw	AS	0.33	Highest residue	90	0.37	*10*	*10*				
Rye straw	AS	0.33	Highest residue	90	0.37	*10*	*10*				
Sorghum stover	AS	0.33	Highest residue	88	0.38	*25*	*15*				
Wheat straw	AS	0.33	Highest residue	88	0.38	***10***	*10*		0.038		
Sugar beet tops	AV	4.3	Highest residue	23	18.7	***20***	***10***		3.74	1.87	
Barley grain	GC	0.05	Highest residue	88	0.06	*50*	*40*	*75*			
Corn grain	GC	0.05	Highest residue	88	0.06	***5***	*40*	***80***	0.003		0.045
Corn, pop grain	GC	0.05	Highest residue	88	0.06	*80*	*40*	*80*			
Millet grain	GC	0.05	Highest residue	88	0.06	*50*	*40*	*70*			
Oats grain	GC	0.05	Highest residue	89	0.06	*50*	*40*	*80*			
Rye grain	GC	0.05	Highest residue	88	0.06	*40*	*40*	*50*			
Sorghum grain	GC	0.05	Highest residue	86	0.06	*40*	*40*	*80*			
Wheat grain	GC	0.05	Highest residue	89	0.06	*50*	*40*	*80*			
Pulse seed (Note)	VD	0.15	Highest residue	90	0.17	*20*	*20*	*20*			
Carrot culls	VR	0.02	STMR-P	12	0.17	*25*	*25*				
Potato culls	VR	0.02	STMR-P	20	0.10	*75*	*40*				
TOTAL		.				*100*	*100*	*100*	**22**	**38.1**	**0.08**

Consumption value from soya bean forage
Consumption value from pea seed

Estimated mean dietary burden of farm animals

Commodity	CC	Residue (mg/kg)	Basis	DM %	Residue ÷ DM	*Diet content (%)*			Residue contribution, mg/kg		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Apple wet pomace	AB	0.3	STMR-P	40	0.75	***40***	***20***		0.3	0.15	
Pea, field hay	AL	16.4	STMR	100	16.40	*25*	***50***			8.2	
Bean forage (Note)	AL	5.25	STMR	35	15.00	***30***	*30*		4.5		
Barley straw	AS	0.015	STMR	89	0.02	*10*	*60*				
Millet straw	AS	0.015	STMR	90	0.02	*10*	*10*				
Oats straw	AS	0.015	STMR	90	0.02	*10*	*10*				
Rye straw	AS	0.015	STMR	88	0.02	*10*	*10*				
Sorghum stover	AS	0.015	STMR	88	0.02	*25*	*15*				
Wheat straw	AS	0.015	STMR	88	0.02	*10*	*10*				
Sugar beet tops	AV	0.76	STMR	23	3.30	***20***	***10***		0.66	0.33	
Barley grain	GC	0.01	STMR	88	0.01	*50*	*40*	*75*			
Corn grain	GC	0.01	STMR	88	0.01	*80*	*40*	*80*			

Commodity	CC	Residue (mg/kg)	Basis	DM %	Residue ÷ DM	*Diet content (%)*			Residue contribution, mg/kg		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Corn, pop grain	GC	0.01	STMR	88	0.01	*80*	*40*	*80*			
Millet grain	GC	0.01	STMR	88	0.01	*50*	*40*	*70*			
Oats grain	GC	0.01	STMR	89	0.01	*50*	*40*	*80*			
Rye grain	GC	0.01	STMR	88	0.01	*40*	*40*	*50*			
Sorghum grain	GC	0.01	STMR	86	0.01	*40*	*40*	*80*			
Wheat grain	GC	0.01	STMR	89	0.01	*50*	*40*	***80***			0.009
Pulse seeds (Note)	VD	0.075	STMR	90	0.08	***10***	***20***	***20***	0.008	0.017	0.017
Carrot culls	VR	0.01	STMR-P	12	0.08	*25*	*25*				
Potato culls	VR	0.01	STMR-P	20	0.05	*75*	*40*				
TOTAL		.				*100*	*100*	*100*	**5.47**	**8.7**	**0.026**

Consumption value from soya bean forage
Consumption value from pea seed

Farm animal feeding studies

The Meeting received information on feeding studies with lactating cows and laying hens.

A residue transfer study in livestock was conducted with four groups of three Friesian cows that were fed for 28 to 29 days with diets containing pirimicarb. Pirimicarb was applied as a spray to grass 'nuts' tumbling in a drum of a cement mixer. The treated grass nuts were mixed with untreated grass nuts and hay to obtain an actual total feed intake of 18 kg/cow per day. Actual pirimicarb levels in the treated nuts were 423 ppm corresponding to actual feeding levels of 0, 24, 71 and 235 ppm. One cow from each group was slaughtered on day 28 and one cow on day 29, each within 24 hours of the final dose. The remaining cow from each group was maintained on a control diet for a further 7 days before slaughter. Milk was collected at morning and afternoon milking at 2–3 day intervals throughout the study. Liver, kidney muscle, and fat (subcutaneous, peritoneal) were taken for analysis.

No parent was found at any of the feeding levels (< 0.04 mg/kg). R34386 (including R34855) was only found at the highest feeding level (235 ppm) in the range < 0.02–0.088 mg/kg. Residues did not accumulate and declined rapidly when pirimicarb feeding ceased. No parent and no R34836 (including R34855) were found at any of the feeding levels in kidney and liver (< 0.01 mg/kg). Parent and metabolite R34386 (including R34855) were only occasionally found in muscle or fat at levels up to 0.02 mg/kg. Milk samples from control animals were < 0.005 mg/kg for each analyte, except for the day 3 milk sample, where a value of 0.01 mg/kg was found for parent and day 17 and day 26 milk samples, where a value of 0.005 mg/kg was found for R34836.

A residue transfer study in laying hens was conducted with four groups of 40 laying hens + four cockerels. The hens were fed for up to 28 days with basal layers' diet containing pirimicarb at actual feeding levels of 0.083, 1.5, 4.6 and 14.3 ppm parent eq, followed by a recovery period of 14 days on untreated feed. Eggs (10 per treatment group) were collected on days 1, 3, 7, 11, 15, 21, 25 and 27 (treatment period) and days 31, 35, 39 and 42 (post-treatment period). Eggs were separated into whites and yolks. On each day, the white and yolk samples from each group were pooled. Five hens from each group were sacrificed on days 21, 28, 35 and 42 of the trial. No residues were found in pooled egg yolk and pooled egg white samples (< LOQ for each analyte) at any feeding level. No residues were found in pooled composite tissue samples (muscle, skin with fat) at any feeding level (< LOQ for each analyte). Residues in liver were at or below the LOQ: < 0.01 to 0.01 mg/kg for parent and < 0.04 to 0.04 mg/kg for R34836 (including R34855).

Residues in animal commodities

In the feeding study where lactating cows were dosed at 24 and 71 ppm, no pirimicarb residues were detected in tissues and milk. Therefore no residues are to be expected at the maximum calculated dietary burden of 22 mg/kg feed for beef cattle and 38 mg/kg for dairy cattle.

In the feeding study where laying hens were dosed at 1.5, 4.6 and 14.3 ppm, no pirimicarb residues were detected in tissues and eggs. No residues are to be expected at the maximum calculated dietary burden of 0.08 mg/kg feed for poultry.

The Meeting estimated a maximum residue level of 0.01* mg/kg in meat (from mammals except marine mammals), to replace the existing recommendation of 0.05 (*) mg/kg, and estimated HRs and STMRs of 0 mg/kg.

The Meeting also estimated a maximum residue level of 0.01* mg/kg in edible offal (mammalian) and estimated HRs and STMRs of 0 mg/kg.

For milks, the Meeting estimated a maximum residue level of 0.01* mg/kg to replace the existing recommendation of 0.05 (*) mg/kg, and estimated an STMR of 0 mg/kg.

The Meeting estimated a maximum residue level of 0.01* mg/kg in poultry meat, poultry offal and eggs and estimated HRs and STMRs of 0 mg/kg.

DIETARY RISK ASSESSMENT

Long term intake

The evaluation of pirimicarb has resulted in recommendations for MRLs and STMRs for raw and processed commodities. Consumption data were available for 53 food commodities and were used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 1–10% of the maximum ADI of 0.02 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of pirimicarb ((including the demethyl carbamate metabolites) 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 pirimicarb was calculated for the food commodities (and their processing fractions) for which maximum residue levels and HRs were estimated and for which consumption data were available. The results are shown in Annex 4.

The IESTI varied from 0–40% of the ARfD (0.1 mg/kg bw) for the general population. The IESTI varied from 0–70% of the ARfD for children 6 years and below. The Meeting concluded that the short-term intake of residues of pirimicarb (including the demethyl carbamate metabolites) from used considered by the Meeting was unlikely to present a public health concern.

4.21 PIRIMIPHOS-METHYL (086)

TOXICOLOGY

Evaluation for an acute reference dose

Pirimiphos-methyl is an organophosphorus insecticide and acaricide. Toxicological monographs for pirimiphos-methyl were prepared by the Joint Meeting in 1974, 1976 and 1992. In 1992, an ADI of 0–0.03 mg/kg bw was established based on a NOAEL of 0.25 mg/kg bw per day in a 28-day and a 58-day study in human volunteers, and a safety factor of 10.

At the request of the CCPR, the requirement for an ARfD was considered on the basis of data from previous evaluations as well as new studies. A number of studies previously evaluated by the JMPR were considered to be possibly relevant for establishing an ARfD and were re-evaluated.

Pirimiphos-methyl was being considered by WHO as a larvicide treatment for drinking-water. For that reason, the WHO programme on Guidelines for drinking-water quality had recommended that pirimiphos-methyl be evaluated toxicologically by JMPR.

For pirimiphos-methyl, the specifications were established by JMPS and published as *WHO specifications and evaluations for public health pesticides*: *pirimiphos-methyl* (2006).[46]

The pivotal studies with pirimiphos-methyl were certified as being compliant with GLP. Other available studies were carried out before the OECD guidelines on GLP were implemented. However, the quality of these studies was considered to be acceptable.

Biochemical aspects

No new toxicokinetic studies were available for the present evaluation. The evaluation made by the 1992 JMPR indicated that peak plasma concentrations of radioactivity (after administration of [C^{14}]pirimiphos-methyl) are reached 0.5 hours after an oral dose. Pirimiphos-methyl is rapidly excreted. After oral administration of pirimiphos-methyl to male rats, 80.7% and 7.3% of the administered dose was excreted via the urine and faeces, respectively, within 24 hours. In dogs, 48 hours after dosing at either 18.4 or 16.7 mg/kg bw, urinary excretion was 64.4% or 82.5% and faecal excretion 17.3% or 13.3%, respectively.

As a thiophosphate, pirimiphos-methyl requires metabolic activation (from P=S to P=O) to inhibit acetylcholinesterase activity. No data were available on the interindividual variability of P=S oxidation. Pirimiphos-methyl is highly lipophilic (log K_{ow} = 4.2).

Toxicological data

The acute oral toxicity of pirimiphos-methyl is low. In the rat, acute oral LD_{50} values range from 1667 to 2050 mg/kg bw. The clinical signs observed in the LD_{50} experiments are typical of those resulting from inhibition of acetylcholinesterase activity, i.e. incontinence, salivation, chromolacrimation, tremors, fibrillations, fasciculations and prostration.

A number of 28-day and 90-day studies with pirimiphos-methyl were performed in rats and dogs. In all these studies, inhibition of cholinesterase activity was the critical end-point. The overall NOAEL from the studies in rats was 8 ppm, equivalent to 0.4 mg/kg bw per day. The NOAEL in a 90-day study in dogs was 2 mg/kg bw per day. There were no indications that dogs are more sensitive

[46] Available from http://www.who.int/whopes/quality/en/Pirimiphos_methyl_eval_may_06.pdf.

than rats to the effects of pirimiphos-methyl. In these short-term studies it appeared that inhibition of erythrocyte acetylcholinesterase activity reached maximum levels only after 2 weeks of treatment.

In a study of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 12 mg/kg bw per day on the basis of a reduction in erythrocyte acetylcholinesterase activity at day 19 at 24 mg/kg bw per day. No toxicologically relevant effects in fetuses were observed. The NOAEL for embryo-fetotoxicity was 48 mg/kg bw per day. In dams treated at 48 mg/kg bw per day, brain cholinesterase activity was still significantly inhibited at day 29, i.e. 11 days after the last dose.

Two single-dose studies of neurotoxicity in rats were available. In the first, after administration of a high dose (1000 mg/kg bw) of pirimiphos-methyl, maximum inhibition (61%) of brain acetylcholinesterase activity was found after 24 hours. Partial recovery was apparent at 48–72 hours. In the second single-dose study of neurotoxicity, rats treated with pirimiphos-methyl at 150 or 1500 mg/kg bw showed dose-dependent reductions in erythrocyte and brain acetylcholinesterase activity 24 hours after administration. In the animals at the highest dose, brain acetylcholinesterase activity had only partially recovered by day 15 after treatment. On the basis of the inhibition in brain cholinesterase activity at 24 h, the NOAEL was 15 mg/kg bw.

In one 28-day and one 56-day study in humans, pirimiphos-methyl was administered orally at a dose of 0.25 mg/kg bw per day. In neither study was inhibition of erythrocyte acetylcholinesterase activity nor any other toxicologically relevant effect observed.

Toxicological evaluation

The critical effect caused by pirimiphos-methyl is inhibition of acetylcholinesterase activity in the nervous system. Pirimiphos-methyl is not embryo-fetotoxic.

In establishing an ARfD, the Meeting concluded that it is appropriate to use data on inhibition of acetylcholinesterase activity in rats from a single-dose study of neurotoxicity in which a NOAEL of 15 mg/kg bw was identified. Based on this NOAEL, the Meeting established an ARfD of 0.2 mg/kg bw, using a safety factor of 100.

The Meeting considered that it was not appropriate to use a chemical specific adjustment factor, although the occurrence and severity of the adverse effects of acetylcholinesterase inhibitors (directly related to the level of inhibition of cholinesterase activity in the nervous system) are considered to depend on C_{max} rather than AUC. In fact, the Meeting observed that:

- Peak plasma concentrations of radioactivity (after administration of [C^{14}]pirimiphos-methyl) are reached 0.5 hours after an oral dose, while maximal inhibition of brain acetylcholinesterase activity appears to occur after about 24 hours.
- Pirimiphos-methyl is highly lipophilic (log K_{ow} = 4.2). As a thiophosphate, it requires metabolic activation (from P=S to P=O) to inhibit acetylcholinesterase activity. No data are available on the interindividual variability of P=S oxidation.
- The recovery of brain cholinesterase activity is slow.

A toxicological monograph was prepared.

Levels relevant for risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Acute neurotoxicity [a]	Neurotoxicity	15 mg/kg bw	150 mg/kg bw
Human	28-day, 56-day toxicity	(Neuro-)toxicity	0.25 mg/kg bw	—[b]

[a] Gavage administration

[b] Highest dose tested

Estimate of acute reference dose

0.2 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 exposures

DIETARY RISK ASSESSMENT

Short-term intake

The International Estimated Short-Term Intakes (IESTIs) of pirimiphos-methyl, from its uses as a larvicide, for the general population and for children for commodities which STMRs or HRs were estimated by the Meeting in 2003 and 2004 where information on consumption was available (Annex 4). The ARfD is 0.2 mg/kg bw and the calculated IESTIs for children up to 6 years of age ranged from 0 to 30% and those for the general population from 0 to 10% of the ARfD. The Meeting concluded that the short-term intake of residues of pirimiphos-methyl from uses considered by the 2003 and 2004 Meeting were unlikely to present a public health concern.

In addition to its agricultural use, pirimiphos-methyl is being considered by WHO as a larvicide treatment for drinking-water. The manufacturer recommends direct addition of pirimiphos-methyl at 1 mg/L to water. Assuming that an adult weighing 60 kg would consume 2 l of drinking-water containing pirimiphos-methyl at a concentration of 1 mg/L, this would be equal to an oral exposure of 0.033 mg/kg bw. This is similar to the ADI of 0–0.03 mg/kg bw, established by JMPR 1992, and less than the established ARfD of 0.2 mg/kg bw.

In addition to this safety assessment, the WHO programmes concerned would consider efficacy of the treatment and additional relevant exposure scenarios before recommending such a treatment and deriving drinking-water guideline values.

4.22 PROPAMOCARB (148)

RESIDUE AND ANALYTICAL ASPECTS

Propamocarb, a carbamate fungicide, was evaluated by JMPR three times in the 1980´s and the last time in 2005, when an ADI of 0–0.4 mg/kg bw and an ARfD of 2 mg/kg bw were established. The residue evaluation of the compound was completed by the current Meeting within the periodic review program.

Data submitted by the manufacturers and evaluated at this Meeting include metabolism in animal and plant, degradation in soil, residues in succeeding crops, analytical methods, residue trials and processing studies. The Government of Japan submitted GAP information and summary tables of residue trials.

Animal metabolism

A study was conducted with a lactating cow orally dosed twice daily for seven consecutive days at 11.5 mg/kg [^{14}C]-propamocarb HCl equivalents in the diet (2.0 mg/kg bw/day). Over 70% of the administered dose was excreted in the urine and total radioactive residues (TRR) in tissues and bile accounted for 0.7% of the administered dose. Cumulative radioactivity recovered in the milk (0.599 mg/kg) accounted for 0.46% of the administered dose. The residues in the milk were always higher in the afternoon, with a mean of 0.054 ± 0.008 mg/kg propamocarb HCl eq (n = 7), and a maximum of 0.057 mg/kg on day 6 than in the morning (mean: 0.035 ± 0.003 mg/kg propamocarb HCl eq. (n = 7) and the maximum of 0.037 mg/kg on day 5). No residues (< 0.01 mg/kg) were found in milk fat. TRR was higher in liver (0.415 mg/kg) and muscle contained < 0.02 mg/kg.

Propamocarb represented 24.6% TRR in muscle (0.005 mg/kg), 23.5% in kidney (0.025 mg/kg), 6.2% TRR in liver (0.026 mg/kg) and 6.0% TRR in milk (0.003 mg/kg). The compound was either oxidized to form propyl propamocarb N-oxide (Met IV), dimethylated at the di-methyl amine group or hydroxylated at the propyl side chain following cyclisation to form propamocarb oxazolidin-2-one (Met VI). Met IV was the main metabolite found in kidney, liver and muscle (40–49% TRR or 0.008 to 0.203 mg/kg), Met VI was mainly found in urine (59% TRR). 2-hydroxy propamocarb was the main metabolite in milk, with 37.5% TRR (0.022 mg/kg). N-desmethyl propamocarb metabolite was found in milk, muscle and faeces (< 10% TRR), but not in kidney and liver.

Rat metabolism studies provided to the Meeting and extensively reviewed by the 2005 JMPR has shown a pathway and metabolism profile similar to that found in cow.

Metabolism in plants

In one study conducted in the USA in 1996 on spinach, ^{14}C -propamocarb was applied twice as a foliar spray at 2.53 kg ai/ha. Samples were harvested immediately following the first application (day 0), just prior to the second application (day 20) and three days after the second application (day 23). Samples were extracted with acidic methanol and extracted filter cake re-extracted with acidic methanol in a Soxhlet system. On average, TRR ranged from 203 to 236 mg/kg propamocarb HCl equivalents, with over 97% TRR being extracted. Propamocarb was the main residue found in the sample extracts, with over 75% TRR. Metabolites IV, VI, 2-hydroxyl and N-desmethyl propamocarb corresponded to < 7.5% TRR

In one study conducted in UK in 2002 in lettuce, ^{14}C -propamocarb was applied three times to soil at 72.2 kg ai/ha followed by three foliar applications in a greenhouse at 1.08 kg ai/ha. Plants were harvested 38 days after final soil treatment and 21 days after final foliar treatment. Samples were extracted sequentially with methanol and water and the remained plant residues re-extracted by refluxing with 2M HCl and 2M NaOH. TRR in the samples harvested after soil applications was 8.2 mg/kg propamocarb HCl eq., of which only 2.8% TRR (0.23 mg/kg) was the parent compound. Most of the residues (54.4% TRR) was found in an unidentified polar region. Samples harvested 21 days after the foliar treatments had a TRR of 10.7 mg/kg, of which 91% was extracted with methanol and 0.2% remained unextracted. About 90% of the radioactivity found in the methanol and water extracts was identified as propamocarb and three unknown regions accounted each for < 4% TRR. The presence of radioactive residues in the control samples (0.35 mg/kg) suggests the incorporation of volatile radioactive products, probably $^{14}CO_2$, into the structure of the plant.

Three metabolism studies conducted with potato were submitted to the Meeting. In two greenhouse studies conducted in Germany in 1989/1994, plants were treated three times by foliar application, at 2.45 kg ai/ha and potato tubers harvested approximately 6 weeks after the final treatment. In the first study, TRR present in the samples corresponded, on average, to 0.82 mg/kg propamocarb HCl equivalents, of which 45.5% was extracted with acidic methanol. The ^{14}C residue present was equally distributed between peel and flesh. Propamocarb represented 49.6% TRR, partitioning mainly in the methanol fraction. One metabolite, representing 8.6% TRR or 0.07 mg/kg, had the same chromatographic behaviour as propyl-propamocarb-N-oxide (Met IV). In the second

study, 90% of the radiolabelled material was recovered after acidic methanol or acetonitrile extraction followed by alkaline and acid hydrolysis of the remaining material. About 32% TRR was present in the organic extract and 6.6% was unextracted. HPLC analysis using normal and reverse phase showed about 7% TRR of the sample being identified as propamocarb and approximately 50% TRR as d-glucose.

In a field study conducted with potato in UK in 2001, ^{14}C -Propamocarb was applied six times as a foliar spray at 2.2 kg ai/ha and at 10.8 kg ai/ha. Samples were harvested approximately 7 days after the last treatment and extracted with methanol, water and refluxed in HCl and NaOH base. At the lower spray rate, TRR corresponded to 0.112 mg/kg propamocarb HCl eq. in tuber, 0.05 mg/kg in peel, 0.02 mg/kg in flesh and 85.9 mg/kg in foliage. Values for samples from the higher rate ranged from 0.05 to 476 mg/kg. Unextracted residues ranged from 4.8 to 12.2% TRR. Chromatographic and MS analysis of extracts from the lower rate treatment showed < 2% TRR as propamocarb in tuber and 28.6% TRR in foliage. Residues were mainly found in an unidentified chromatographic region (77.4 and 30% TRR in tuber and foliage). Three metabolites were tentatively identified in both samples: hydroxypropyl propamocarb (0.5% TRR in the tuber), N-desmethyl propamocarb (only detected in foliage at 5.7% TRR) and propyl propamocarb N-oxide (Met IV), present at 3.2% TRR in the tuber (0.004 mg/kg). No unchanged propamocarb was released from the foliage water extract from the higher rate treatment after acid, base and enzyme treatment

In a greenhouse study conducted in Germany in 1998, cucumbers were grown in soil treated once with ^{14}C propamocarb HCl applied at 2.9 kg ai/ha (11.8 mg ai/plant) and harvested at 30 days post treatment. Hydroculture-grown cucumbers were treated once at a rate of 53.4 mg ai/plant and sampled with a PHI of 21 days. Samples were extracted using maceration and soxhlet with acidic methanol. Propamocarb residues represented 19.3% TRR in cucumber extracts from the soil treatment and 58.4% TRR in hydroponic treatment. Unextracted residues represented, on average, 6.5% TRR. Polar metabolites represented 59.2 and 32.1% TRR, respectively and the remaining ^{14}C residues detected were incorporated into natural products.

In one greenhouse study conducted with tomato in UK in 2001, ^{14}C -Propamocarb was applied four times to soil at 0.007 (1×) or 0.036 kg ai/ha (5×) and as a single foliar treatment at 2.2 kg ai/ha. Samples were extracted by maceration with methanol and water, with further acid and basic extraction as necessary. Tomato samples from soil treatments harvested at 14 to 35 days PHI showed, on average, 64.3% TRR present in the methanol extract. From 46.5 to 85.7% TRR of the foliar treated samples harvested after 7 to 28 days were found in the methanol extracts. Propamocarb was not detected in the 14 days 1× soil treated sample, but was the major component of the 7 days foliar treated tomato sample (75.2% TRR; 0.065 mg/kg). The appearance of residues in the control plants, an unknown region observed also in chromatograms of treated plants, suggest the incorporation of volatile ^{14}C into plant natural products.

In summary, in spinach, lettuce and tomato treated with propamocarb as a foliar spray, the parent compound was the main residue (> 70% TRR). Lettuce, cucumber and tomato grown on treated soil showed < 20% TRR as propamocarb, but the majority of the radioactivity found was unidentified polar compounds. The parent propamocarb amounted to 1.9 to 49.6% TRR in potato plants sprayed with propamocarb. In all studies, there was evidence of volatile ^{14}C incorporation into plant material. Results from the spinach and potato studies showed that metabolites are formed by hydroxylation of the terminal propyl chain, N-demethylation and N-oxidation of the parent molecule. No metabolites were found in the samples in larger amounts than the 5% TRR.

Rotational Crops

In a confined rotational crop study, bare soil was treated at approximately 6 kg ai/ha, representing 1.2 times the annual maximum application rate for propamocarb. Leafy lettuce, radish and wheat were planted 30 days, 120 days and 365 days after treatment. In crops planted in the 30 day aged soil, total residues ranged from 0.36 (radish roots) to 2.33 mg/kg (wheat straw), and declined sharply in crops planted in soil aged 120 days and 365 days to a maximum of 0.09 mg/kg propamocarb HCl eq.

Propamocarb was found in all acidic methanol sample extracts from the 30 day aged soil and was the major component (15.4% TRR in wheat straw to 67.4% TRR in radish tops), except for wheat grain, where the oxazolidine metabolite (Met VI) represented 19.9% TRR. 2-hydroxy propamocarb, N-oxide (Met IV) and desmethyl propamocarb (wheat only) were not present in any sample at levels < 10% TRR. The remainder residue was a complex mixture of highly polar components. Residues released after acid and base hydrolysis (< 10% TRR) indicated a similar pattern of metabolites.

In rotational field studies conducted in 10 American states (11 trials) in 1997, four applications at 1.68 kg ai/ha of propamocarb were made to soil with a five day interval. Wheat, sugar beets, table beets, dry beans and soybeans were planted 30, 60 or 365 days after the final soil treatment. Samples of wheat grain, forage, hay and straw, soybean seed, forage and hay, beets root and tops, and dry bean were harvested at typical sampling times. Wheat was the only crop grown on 30 days aged soils which contained residues at or above LOQ. Therefore, only wheat samples were analysed from all crops grown on 60 days aged soil.

As samples from the 60 day aged soil were generally < LOQ (0.05 mg/kg), samples from the 365-day were not analysed. Residues were detected only in wheat hay and forage samples from the 30 day aged soil. Residues were in the range of 0.051 to 0.229 mg/kg or both hay and forage.

Environmental fate in soil

In five studies conducted from 1978 to 1986 with ^{14}C-propamocarb hydrochloride incubated under aerobic conditions at 15 or 25^{o}C in loamy sand soil containing 200 mg/kg labelled compound, propamocarb degraded very rapidly with a half life (DT_{50}) ranging from 10 to 28 days. In three studies conducted at 10 or 20^{o}C, clay loam, loamy silt, loamy sand and silty sand soils were incubated with propamocarb incorporated at the rates of 0.00361 or 3.61 kg ai/ha, for 120 days. Degradation of the parent compound was slower in a clay loam soil with a higher clay and organic carbon content, reaching 27.1% TRR at the end of the study at 20^{o}C. Half life determined in the soils ranged from 10.9 days in loamy sand to 29.7 days in silty sand soil. Lower incubation temperature decreased the degradation rate of propamocarb in loamy silt soil with half lives of 11.7 and 25.3 days at 20^{o}C and 10^{o}C, respectively. The study using Borstel soil at 10°C indicated that the rate of degradation slowed with depth, with DT_{50} values ranging from 73.7 days at 20 cm to 267 days at 90 cm, probably due to decreasing microbial activity and organic carbon content in deeper soil layers.

In a study conducted with 4 sandy loam soils and 2 clay loam soils incubated with 250mg/kg and 10 mg/kg ^{14}C-propamocarb HCl at 20 and 10 ^{o}C for 120 and 365 days, the majority of the radioactivity was assigned to propamocarb, decreasing to a maximum of 22.1% TRR in the soil with the lowest organic carbon and biomass content (sandy loam). This soil also had the highest half life among the soils (87.7 days) while for the others DT_{50} ranged from 14.1 to 42.2 days. Up to ten non-identified metabolites, none of them being present above 10% TRR, were found in the soil extracts from all the studies.

One study conducted in sterilized and non-sterilized German standard soil suggests that soil degradation of propamocarb is mediated by micro-organisms.

Degradation of ^{14}C-propamocarb hydrochloride under anaerobic conditions was much slower than in an aerobic environment, with a half life in loamy sand soil at 25^{o}C of 459 days. The half life of propamocarb in flooded sandy loam soil treated with 250 mg/kg or 10 mg/kg and kept under anaerobic conditions in the dark at 20^{o}C was 308.2 and 65.7 days respectively. Propamocarb was quickly removed from the water phase (DT_{50} of 14.7 days at 250mg/kg rate). The major degradation product, which was not identified, reached a maximum of 6.6% TRR in the system after 365 days. In one study to investigate the photolysis of propamocarb on soil surface, the estimated half life under irradiated conditions was 35.4 days.

One field dissipation study was conducted in the USA with sandy loam and loamy sandy soils, bare or covered with turf grass, treated four times at 9.35 kg ai/ha rate. DT_{50} in bare soils, thatch

and grass ranged from 13.2 to 23.7 days. No propamocarb residues (< 0.002 mg/kg) were detected during the four month period in bare soil layer deeper than 30 cm.

In summary, propamocarb is not expected to accumulate in soil. The compound degrades relatively fast to many unidentified products (each < 10% TRR) under aerobic conditions at 10–25°C, with half life ranging from 10 to 87.7 days, with the longer times occurring in soils with lower organic matter content, possibly due to lower microbial activity. Under anaerobic conditions, propamocarb degradation was very slow in bare or flooded soil (DT_{50} > 300 days). The compound is rapidly transferred from the water to the soil in a flooded system.

Analytical methods

The residue methods used to analyse propamocarb were validated using the free base or the hydrochloride. Plant materials can be extracted with 1% acetic acid and the compound quantified by HPLC/MS/MS (electrospray ionization) at m/z 102 and or 144. Avocado extracts requires a partition step with n-hexane to remove the fat before the chromatography. Some methods also include a C18 SPE clean up step of the acid extract before the final determination. These methods were validated in many laboratories, at levels from 0.01 mg/kg to 10 mg/kg, for lettuce, chicory witloof, peppers, potato, processed potato, spinach, leek, onion, cabbage, cauliflower, Brussels sprout, broccoli, cucumber, avocado, melon and wheat grain. In most cases mean recoveries were within the acceptable levels (70–120%) with a maximum CV of 20% (n = 2–9). LOQ was 0.01 mg/kg, as propamocarb (free base) or propamocarb HCl.

In some laboratories, plant materials were extracted with acidified methanol, the extract basified with NaOH solution and cleaned up with a series of extraction procedures with chloroform, acidic water and di-isopropyl ether. The free base formed was quantified by GC/N/FID or GC/MSD. This method was validated for many crops at levels from 0.05 to 10 mg/kg, with mean recovery and CV falling within the acceptable levels (n = 2–8). LOQ was either 0.05 or 0.1 mg/kg, as propamocarb HCl.

Propamocarb can be extracted from animal products with 1.0% HCl in methanol and residues analyzed by HPLC-MS/MS. Validation at fortification levels of 0.01 mg/kg (LOQ) and 0.10 mg/kg, as propamocarb (free base), for animal tissues, milk and eggs gave recoveries from 83 to 101% and CV < 20% (n = 5).

Residues of propamocarb hydrochloride can be extracted from soil using HCl or acidified methanol, followed by a sequence of clean-up steps of the extract (chloroform/1N HCl/di-isopropyl ether) and the free base determined by GC/N/FID or GC/MSD. The method was successfully validated from 0.026 to 50 mg/kg in four different studies. In another method, propamocarb was extracted with HCl, the extract was cleaned-up on a C18 column, the final extract was basified with ammonia solution and the free base was determined by LC-MS/MS. LOQ was 0.02 mg/kg, with a mean recovery of 89% and CV of 8% (n = 5).

Stability of pesticide residues in stored analytical samples

Propamocarb residues are stable under frozen conditions, up to 26 months of storage in tomato samples fortified at 0.5 mg/kg (> 75% remained). At 5 mg/kg level, the average residue was 67% after 14.5 months of storage. Lettuce samples fortified at 0.5 and 5.0 mg/kg and stored for 14 were stable under frozen conditions (over 85% of the residues remained).

Residue definition

Metabolism studies conducted in spinach, lettuce and tomato treated with propamocarb as a foliar spray have shown that the parent compound was the main residue (> 70% TRR). Lettuce, cucumber and tomato grown on treated soil and potato samples after foliar treatment showed < 50% TRR as

propamocarb. In these cases, the majority of the radioactivity (> 50% TRR) was present as unidentified polar metabolites, probably from ^{14}C incorporation into plant material, as d-glucose.

As propamocarb was the major compound present in treated plants, the Meeting agreed that the residue definition in plants for both enforcement and dietary intake purposes is propamocarb (free base).

Propamocarb represented a maximum of 24.6% TRR in cow tissues, while propyl propamocarb N-oxide (Met. IV) was the main compound detected in kidney, liver and muscle (40–49% TRR) and 2-hydroxy propamocarb was the main metabolite in milk (37.5% TRR). No metabolism study on poultry was provided.

Although propamocarb is not the main residue found in animal tissues and milk, no analytical method determining the metabolites is available that would be suitable for enforcement. No residues are expected in feed. The Meeting agreed that the residue definition for animal products for both enforcement and dietary intake purposes is propamocarb.

Propamocarb HCl has a log $P_{OW} < 0$ and animal metabolism studies have shown that it does not concentrate in fat. The Meeting concluded that propamocarb is not fat soluble.

Residues from supervised trials

Formulations containing propamocarb hydrochloride, alone or co-formulated with other active substances were used in the trials. When residues were reported in the studies as propamocarb hydrochloride, the values were multiplied by 0.84 and expressed as propamocarb.

Metabolism studies conducted in lettuce using soil treatment at a rate corresponding to 72.2 kg ai/ha have shown that < 3% TRR represented propamocarb residues in leaves after 38 days. The Meeting agreed that the seedbed drench application is not expected to contribute to final residues in crops treated with additional foliar sprays and or drip irrigation/soil drench. Consequently the trial, in which seedbed drench applications were made at higher or lower than GAP, was considered for MRL estimation.

No residue data was submitted for celery, beetroot, Brussels sprouts and strawberry. The Meeting agreed to withdraw the previous recommendations for these crops

Onion

In Europe, propamocarb is registered for use on onions in Poland (PHI of 7 days), Sweden (PHI of 30 days) and UK (PHI of 133 days). In seven trials conducted in France, Germany, the Netherlands, Spain and UK, propamocarb was applied four times at rates from 0.75–2.9 kg ai/ha and samples collected at 0 and/or 14 days. Residues, as propamocarb, ranged from < 0.008 to 0.29 mg/kg.

As no trials were conducted according to GAP, the Meeting did not recommend a maximum residue level for propamocarb in onions.

Cabbage

Propamocarb is registered to be used in Europe as a foliar application (Germany), as a seedbed or soil drench (Greece, Spain and UK) or both treatments (Italy and Netherlands). In Italy, GAP is 2 applications at 16 kg ai/ha seedbed drench applications and 3 × 1.1–2.2 kg ai/ha foliar treatment, with a PHI of 20 days.

Seventeen trials conducted in France, Germany, Italy and Spain in 2000/2001 using 72 and 36 kg ai/ha seedbed drench followed by two applications at 2.2–3.8 kg ai/ha foliar, head cabbage samples were collected from day 30 up to day 138. In one trial, samples harvested within 22 days PHI gave residues of 0.03 mg/kg.

As only one trial was conducted according to GAP, the Meeting could not recommend a maximum residue level for propamocarb in cabbage.

The Meeting also withdrew its previous recommendation for propamocarb in cabbage of 0.1 mg/kg.

Cauliflower

Propamocarb is registered to be used in Europe as a foliar application (e.g. Belgium and Germany), as a seedbed or soil drench (Greece) or both treatments (Italy, the Netherlands and UK). In Italy, GAP is 2 × 16 kg ai/ha seedbed drench up to 3 × 1.1–2.2 kg ai/ha foliar, with a PHI of 20 days. In the Netherlands, GAP is 2 × 3.61 kg ai/ha seedbed drench and 2 × 2.2–3.6 kg ai/ha foliar, with a PHI of 14 days.

Twenty three trials were conducted in France, Germany, Greece, Italy, Spain and UK from 2000 to 2002 using 72.2 and 36.1 kg ai/ha seedbed drench followed by 2 × 2.2–3.8 kg ai/ha foliar. In four trials, residues in cauliflower heads at 14 or 21 days PHI were 0.008, 0.02, 0.05 and 0.09 mg/kg. In the other trials samples harvested 30 to 138 days after the last application gave residues ranging from < 0.008 to 0.02 mg/kg.

The Meeting confirms the previous recommendation of a maximum residue level of 0.2 mg/kg for propamocarb in cauliflower and also recommends a STMR of 0.035 mg/kg and a HR of 0.09 mg/kg.

Fruiting vegetables, cucurbits

Cucumber

Thirty seven trials were conducted with propamocarb in cucumber in Europe and the USA from 1991 to 2004. In Europe, propamocarb is registered to be used as a seed treatment, soil treatment, within irrigation and/or foliar treatment.

In Spain, one label allows one seedbed drench treatment at 14.4–21.7 kg ai/ha, two soil drench treatments at 0.15 to 0.50 kg ai/hL, one treatment through dripper equipment at 1.4–2.1 kg ai/ha and two foliar treatments at rates of 0.144–0.22 kg ai/hL with a 3 day PHI (F/GH). Five trials were conducted in France, Greece, Italy and Spain using two seedbed drench applications at 72/36 kg ai/ha, followed by one drip irrigation treatment at 1.7–3 kg ai/ha, two spray applications at 1.7–3 kg ai/ha (0.36–0.6 kg ai/hL) and another drip irrigation treatment at the same previously applied rate. Nine trials were conducted in Germany and Spain using one seedbed drench (29 kg ai/ha), two soil drenches (1.7–2.9 kg ai/ha, up to 1.5 kg ai/hL), two spray applications (1.7–3.2 kg ai/ha, approximately 0.5 kg ai/hL) and two more soil drench application at the same rate as previously applied. Four trials used seedbed drench (16 kg ai/ha) and drip irrigation application (1.5–2.7 kg ai/ha). These 18 trials are within the Spanish GAP giving residues within 3 days PHI of 0.40, 0.54, 0.59, 0.60, 0.70, 0.80 (2), 0.83, 1.0 (4), 1.3, 1.4 (2), 1.7, 1.8 and 4.8 mg/kg.

In Germany, propamocarb can be used as a foliar application at 4 × 2.2 kg ai/ha. In eight trials conducted in the country in 1991/1992, within GAP, residues at 4 days PHI were 0.60, 0.68, 0.90 (3), 1.0 and 1.3 mg/kg.

Four trials using drench/drip irrigation treatment conducted in Germany, the Netherlands and Spain did not match any European GAP.

In the USA, propamocarb can be used as a foliar application at 5 × 1.0 kg ai/ha. In seven trials conducted in that country in 1997, according to GAP, residues at 2 days PHI were 0.26, 0.29, 0.32, 0.61, 0.62, 0.69 and 0.75 mg/kg.

In four trials conducted in Japan according to GAP, residues at 21 days were 0.34, 0.37, 0.39 and 0.42 mg/kg. These trials could not be considered by the Meeting as only a summary data was provided.

Residues from 33 trials conducted according to GAP in Europe and USA in cucumber gave residues within the same range and can be combined as 0.26, 0.29, 0.32, 0.40, 0.54 (2), 0.59, 0.60 (2), 0.61, 0.62, 0.68, 0.69, 0.70, 0.75, 0.80 (2), 0.83, 0.90 (3), 1.0 (5), 1.3 (2), 1.4 (2), 1.7, 1.8 and 4.8 mg/kg.

Melons

A total of 48 trials were conducted with propamocarb in melons in Europe, where the compound is registered in many countries. In Spain, the product can be applied up to four times as a seedbed drench at 15.9 kg ai/ha and as a drip irrigation treatment at 1.1–1.6 kg ai/ha with a PHI of 14 days. In nine trials conducted in Germany, Italy, Portugal and Spain from 2001–2004 conforming to Spanish GAP (two seedbed drench application), propamocarb residues in fruit were < 0.008 (3), 0.04, 0.12, 0.21, 0.45, 1.0 and 1.4 mg/kg. In four trials, melon pulp was also analysed, giving residues of 0.06, 0.08, 0.17 and 0.53 mg/kg.

In Italy, the product can be used as a seedbed incorporation after drilling (2 × 57.8–86.6 kg ai/ha) and as a foliar treatment (2 × 1.1–2.2 kg ai/ha) and a PHI of 20 days. In 13 trials conducted in France, Italy, Greece and Spain in 2000/2001 at 2 × 20–24 kg ai/ha (seedbed drench) followed by two foliar applications at 2–2.2 kg ai/ha, residues in fruit 20 days after treatment were 0.04, 0.07, 0.08 (2), 0.17 (3), 0.25, 0.3, 0.59, 0.67 (2) and 2.2 mg/kg. Residues in melon pulp were < 0.01, 0.01 (3), 0.02 (5), 0.03 (2), 0.08 and 0.17 mg/kg. As the seedbed drench application is unlikely to contribute significantly to the final residues after the foliar application, these trials can be considered to be within the Italian GAP. In nine other trials conducted at the same rate, samples harvested up to 14 days after the last application gave residues in the fruit ranging from 0.10 to 0.90 mg/kg.

In Germany, propamocarb can be used up to four times as a foliar application in the field at 2.2 kg ai/ha and a PHI of 4 days. In France, it can be applied up to six times at 1.1 kg ai/ha with a 3 day PHI. Seventeen trials conducted at 3 to 5 applications at 1.1 or 2.2 kg ai/ha can be considered as being within German or French GAP, giving residues in the fruit at a 3 day PHI of 0.10, 0.11, 0.12, 0.14, 0.23, 0.24, 0.28, 0.38 (2), 0.40, 0.44 (2), 0.57, 0.65, 0.92 and 1.1 mg/kg. Melon pulp was analyzed in 15 trials, giving residues of < 0.04 (5), 0.04, < 0.08 (6), 0.07, 0.13 and 0.21 mg/kg.

In seven trials conducted with propamocarb in cantaloupe in the USA in 1997 according to GAP (five foliar applications at 1 kg ai/ha), propamocarb residues at a two day PHI were 0.29 (2), 0.34, 0.44, 0.66, 0.77, and 1.4 mg/kg.

Residues in melon fruit from 39 trials conducted in Europe and in seven trials conducted on cantaloupe in the USA according to GAP can be combined as < 0.008 (3), 0.04 (2), 0.07, 0.08 (2), 0.10, 0.11, 0.12 (2), 0.14, 0.17 (3), 0.21, 0.23, 0.24, 0.25, 0.28, 0.29 (2), 0.34 (2), 0.38 (2), 0.40, 0.44 (3), 0.45, 0.49, 0.57, 0.59, 0.65, 0.66, 0.67 (2), 0.77, 0.92, 1.0, 1.1, 1.4, 1.42 and 2.2 mg/kg.

Residues in melon pulp from 32 trials were < 0.01, 0.01 (3), 0.02 (5), 0.03 (2), < 0.04 (5), 0.04, 0.06, 0.07, < 0.08 (6), 0.08 (2), 0.13, 0.17(2), 0.21 and 0.53 mg/kg.

Summer squash

In six trials conducted with propamocarb in summer squash in the USA in 1997 according to GAP (five foliar applications at 1 kg ai/ha), residues of propamocarb at a 2 day PHI were, 0.37, 0.43, 0.49, 0.64, 0.99 and 1.1 mg/kg.

In the USA and in some European countries, GAP for propamocarb is for the crop group cucurbits. The Meeting, therefore, agreed to combine the residue population of cucumber, melons and summer squash from 85 trials conducted in Europe and USA to make recommendations for the crop

group of fruiting vegetables, cucurbits. The residues were, in rank order: < 0.008 (3), 0.04 (2), 0.07, 0.08 (2), 0.1, 0.11, 0.12 (2), 0.14, 0.17 (3), 0.21, 0.23, 0.24, 0.25, 0.26, 0.28, 0.29 (3), 0.32, 0.34 (2), 0.37, 0.38 (2), 0.4 (2), 0.43, 0.44 (3), 0.45, 0.49 (2), 0.54 (2), 0.57, 0.59 (2), 0.60 (2), 0.61, 0.62, 0.64, 0.65, 0.66, 0.67 (2), 0.68, 0.69, 0.7, 0.75, 0.77, 0.8 (2), 0.83, 0.90 (3), 0.92, 0.99, 1.0 (6), 1.1 (2), 1.3 (2), 1.4 (3), 1.42, 1.7, 1.8, 2.2 and 4.8 mg/kg.

The Meeting recommends a maximum residue level of 5 mg/kg for propamocarb in fruiting vegetables, cucurbits.

The Meeting recommends a STMR of 0.59 mg/kg and a HR of 4.8 mg/kg for propamocarb in fruiting vegetables, cucurbits, except melons and watermelons.

Based on the residue data on melon pulp, the Meeting recommends a STMR of 0.04 mg/kg and a HR of 0.53 mg/kg for melons and watermelons.

The Meeting withdraws its previous recommendation for propamocarb in cucumber of 2 mg/kg.

Sweet pepper

Thirty five trials were conducted with propamocarb hydrochloride in sweet pepper in Europe and the USA from 1997 to 2004 using drench, drip irrigation or foliar treatment.

Propamocarb is registered in Europe and the USA for drench, drip and/or foliar treatment. In Spain, the product can be applied twice as a seedbed treatment after sowing (15.9 kg ai/ha) and up to four times as a drip irrigation treatment (1.1–1.6 kg ai/ha) with a 3 day PHI. In the Netherlands, up to three seedbed drench applications at 36.1 kg ai/ha and up to 5 drench/drip applications at 1.0/0.72 kg ai/ha are allowed, with a three day PHI.

In 18 trials conducted in greenhouses in Belgium, Italy, the Netherlands, Spain and Greece, using two seedbed applications followed by four soil drip or drench applications according to Spanish GAP, residues at three days PHI were < 0.008 (8), 0.008 (2), 0.02, 0.03, 0.06, 0.08, 0.10, 0.14, 0.15, 0.16 mg/kg as propamocarb. In three trials conducted at higher rates, residues at three days PHI ranged from < 0.008 to 0.05 mg/kg.

In the USA, propamocarb can be used in peppers as foliar application at 5 × 1.26 kg ai/ha with a 5 day PHI. In 10 trials conducted in that country according to GAP, residues were 0.07, 0.16, 0.20, 0.23, 0.26, 0.27, 0.32, 0.62, 0.98, 1.8 mg/kg. These trials gave residues at a higher range than trials conducted in Europe using drench/drip applications and the two residue population could not be combined.

The Meeting agreed to recommend a maximum residue level, based on USA trials, of 3 mg/kg, a STMR of 0.265 mg/kg and a HR of 1.8 mg/kg for propamocarb in sweet peppers.

The Meeting withdraws its previous recommendation for propamocarb in sweet peppers of 1 mg/kg.

Eggplant

Propamocarb is not registered for use in eggplant in the USA. In Europe, the compound has the same GAP as for sweet peppers. The Meeting agreed to use the residue trial data for sweet peppers in Europe to recommend a maximum residue level of 0.3 mg/kg, a STMR of 0.008 mg/kg and a HR of 0.16 mg/kg for propamocarb in eggplant.

Tomato

Forty five trials were conducted with propamocarb hydrochloride in tomato in Europe and the USA from 1997 to 2004.

Propamocarb is registered in Europe and USA for drench, drip and/or foliar treatment. In Spain, the product can be applied twice as a seedbed treatment after sowing (15.9 kg ai/ha) and up to four times as a drip irrigation treatment (1.1–1.6 kg ai/ha) with a 3 day PHI. In the Netherlands, up to three seedbed drench applications at 36.1 kg ai/ha and up to five drench/drip applications at 1.0/0.72 kg ai/ha are allowed, with a three day PHI.

In two trials conducted in greenhouses in Spain and Germany using seedbed drench followed by drench or dripping according to Spanish GAP, residues at three days PHI were < 0.008 and 0.08 mg/kg. In 16 trials conducted at higher GAP rates or number of application gave residues from < 0.008 to 0.05 mg/kg three days after the last application. In 9 trials conducted using drench treatment (1 to 2 × 15.9–72.2 kg ai/ha) followed by drench/dripping irrigation (2 to 4 treatments at 0.6–4.3 kg ai/ha), residues after three days ranged from < 0.008 to 0.07 mg/kg.

In the USA, propamocarb can be used in tomato as foliar application at 5 × 1.3 kg ai/ha and 5 days PHI. In 18 trials conducted in the country according to GAP, residues were 0.14, 0.16, 0.23, 0.25, 0.34, 0.37, 0.38, 0.40, 0.51, 0.52 0.60, 0.61 (2), 0.65, 0.68, 0.86, 0.94 and 1.4 mg/kg. Clearly, these trials gave residues at a higher range than the two trials conducted in Europe using drench/drip application and the two residue populations cannot be combined.

The Meeting agreed to recommend maximum residue level based on USA trials of 2 mg/kg, a STMR of 0.515 mg/kg and a HR of 1.4 mg/kg for propamocarb in tomato.

The Meeting withdrew its previous recommendation for propamocarb in tomato of 1 mg/kg.

Lettuce

Propamocarb is registered in lettuce in Europe and the USA. Sixty eight trials were conducted in leaf and head lettuce as a drench and/or foliar spray in France (21), Germany (18), Greece (3), Italy (3), the Netherlands (2), Spain (7) and USA (14) between 1993 and 2002.

GAP in some countries in Europe include two seedbed drench (SD) and two foliar (F) treatments, the rates being 1.6 g ai/m^2 (16 kg ai/ha) (SD) /1.1–1.6 kg ai/ha (Field, F, and Greenhouse, GH) in Italy, with 14 days PHI. In 12 trials (F or GH) conducted in Germany, Greece, Italy, the Netherlands and Spain at Italian GAP, residues at 14 days PHI were 0.92, 1.8, 3.9, 4.0, 4.5, 7.1, 8.1, 9.4, 9.8, 10, 11 and 13 mg/kg. Thirty two field trials were conducted in France, Germany, Greece, Italy and Spain using 2 seedbed drench applications at 72.2 and 36.1 kg ai/ha and 2 foliar applications at 1.66 kg/kg ai/ha. Residues at 14 days PHI determined in 28 trials were 0.7, 1.0 (2), 1.9, 2.0, 2.8, 3.2, 3.3, 4.2, 4.4, 4.7, 6.0, 6.5, 7.4, 7.9, 8.1, 9.2, 13 (2), 14, 15, 16 (2), 17, 21, 29, 31 and 40, mg/kg. In other four trials samples were harvested only after 21 days.

In Belgium, Germany and UK (F/GH), only foliar treatment is recommended, with three applications at 1.1 to 1.4 kg ai/ha and 21 days PHI. In 10 greenhouse trials conducted in France within UK GAP residues at 21 days PHI were 1.2, 1.7, 4.9, 6.5, 14, 15, 20, 24, 39 and 40 mg/kg; In other six trials with four applications, residues ranged from 14 to 40 mg/kg.

The 50 residue trials conducted with propamocarb in Europe can be combined as 0.7, 0.92, 1.0 (2), 1.2, 1.7, 1.8, 1.9, 2.0, 2.8, 3.2, 3.3, 3.9, 4.0, 4.2, 4.4, 4.5, 4.7, 4.9, 6.0, 6.5 (2), 7.1, 7.4, 7.9, 8.1 (2), 9.2, 9.4, 9.8, 10, 11, 13 (3), 14 (2), 15 (2), 16 (2), 17, 20, 21, 24, 29, 31, 39 and 40 (2) mg/kg.

GAP in the USA is four foliar applications at 1.68 kg ai/ha, two days PHI. In 14 trials conducted in the USA in leafy and head lettuce according to GAP, residues were 8.2, 9.7, 10, 11 (2), 17, 19, 31, 41 (2), 48, 51, 60 and 86 mg/kg. Residues in the head without the wrapper leaves of head lettuce ranged from 0.21 to 8.0 mg/kg.

In four trials conducted in Japan at GAP (3 × 1.28 kg ai/ha), residues at 14 days PHI were 0.28, 0.60, 1.6 and 1.8 mg/kg. These trials could not be considered by the Meeting as only summary data was provided.

The 64 European and USA trials can be combined to give one residue population as 0.7, 0.92, 1.0 (2), 1.2, 1.7, 1.8, 1.9, 2.0, 2.8, 3.2, 3.3, 3.9, 4.0, 4.2, 4.4, 4.5, 4.7, 4.9, 6.0, 6.5 (2), 7.1, 7.4, 7.9, 8.1 (2), 8.2, 9.2, 9.4, 9.7, 9.8, 10 (2), 11 (3), 13 (3), 14 (2), 15 (2), 16 (2), 17 (2), 19, 20, 21, 24, 29, 31 (2), 39, 40 (2), 41 (2), 48, 51, 60 and 86 mg/kg.

The Meeting recommended a maximum residue level of 100 mg /kg, a STMR of 9.9 mg/kg and a HR of 86 mg/kg for propamocarb in lettuce, head and leaf.

The Meeting withdrew its previous recommendation for propamocarb in lettuce, head of 10 mg/kg.

Spinach

Propamocarb is registered in Italy as seed, soil and foliar treatments. As a foliar treatment, the label recommends up to three applications at 1.1–2.2 kg ai/ha with a 20 day PHI. Seven trials were conducted in Belgium, Germany, Italy and Spain three applications at 1.3–1.6 kg ai/ha. In four trials, samples were analysed at a 21 day PHI, giving residues of propamocarb of 0.41, 8.4, 14 and 29 mg/kg.

The Meeting recommended a maximum residue level of 40 mg /kg, a STMR of 11.2 mg/kg and a HR of 29 mg/kg for propamocarb in spinach.

Potato

Thirty two trials were conducted with propamocarb HCl between 1990 and 2003 using foliar application in Europe and the USA. In one trial conducted in France and in 11 trials conducted in Germany according to German or UK GAP (6 × 0.94–0.99 kg ai/ha) at a 7 day PHI the residues, as propamocarb, were < 0.01 (2), < 0.08 (8) and 0.17 (2) mg/kg. In two German trials, residues measured in peeled tuber gave residues of < 0.08 (2) mg/kg. Nineteen trials were conducted in the USA, 18 of those at GAP (5 applications at 1.0 kg ai/ha), giving residues at 14 days PHI of < 0.05 (16) and 0.05 (2) mg/kg, measured as propamocarb. One trial conducted at higher rate gave residues of < 0.05 mg/kg.

In summary, residues according to GAP, were < 0.01 (2), ≤ 0.05 (16), 0.05 (2), < 0.08 (8) and 0.17 (2) mg/kg, as propamocarb. The Meeting recommended a maximum residue level of 0.3 mg/kg, a STMR of 0.05 mg/kg and a HR of 0.17 mg/kg for propamocarb in potato.

Radish

In Europe, propamocarb is registered in radish in Germany and the Netherlands with a 14 day PHI. In six trials conducted in Germany using one seed treatment and one foliar treatment at GAP rate (7.22 g/kg seed/0.722 kg ai/ha), root samples were collected from day 21 to 48 days after the last application, giving residues up to 11 mg/kg as propamocarb. In one trial, samples were collected 14 days after the last application, giving residues of 0.33 mg/kg. In four trials conducted in the Netherlands using two foliar applications within the GAP rate (1.08 kg ai/ha) residues at 14 days were 0.27, 0.30, 0.36, 0.42 mg/kg as propamocarb. Two trials conducted at higher or lower rates gave residues within the same range. Residues from five trials conducted according to GAP were 0.27, 0.30, 0.33, 0.36, 0.42 mg/kg

The Meeting recommended a maximum residue level of 1 mg/kg, a STMR of 0.33 mg/kg and a HR of 0.42 mg/kg for propamocarb in radish.

The Meeting withdrew its previous recommendation for propamocarb in radish of 5 mg/kg.

Chicory

In France, propamocarb is approved for application to chicory by spraying onto roots at the start of forcing at 72.2 kg ai/ha with a PHI of 21 days. In five trials conducted according to GAP in France in 1998, residues in the leaves were 0.46, 0.50, 0.60, 0.70 and 0.90 mg/kg as propamocarb. In five trials conducted in France, Germany and Netherlands at 106 kg ai/ha, residues in leaves at 21 days ranged from 0.41 to 3.6 mg/kg.

Propamocarb is also registered in France and Luxembourg to be used via a nutrient solution at 9 g/hL and 21 days PHI. In 10 trials conducted in France, Germany and Netherlands propamocarb was applied using a nutrient solution or irrigation system at 12.2 to 47.1 g/hL rate. Residues in leaves within 21 days PHI ranged from 0.03 to 0.35 mg/kg.

The Meeting recommended a maximum residue level of 2 mg /kg, a STMR of 0.60 mg/kg and a HR of 0.90 mg/kg for propamocarb in chicory.

Ginger

Results from four trials conducted at two sites in Japan with propamocarb HCl in ginger in 1986 were submitted to the Meeting as a summary table. GAP in Japan is up to five drench applications at 0.11–0.16 kg ai/hL with a 30 day PHI. The trials conducted at 3 × 0.213 kg ai/hL gave residues in the tubers at 30 days ranging from 0.64 to 4.5 mg/kg, as propamocarb.

As no trials were conducted according to GAP, the Meeting could not recommend a maximum residue level for propamocarb in ginger.

Fate of residues in processing

Four field trials were conducted in Germany with cabbage in 2001 with propamocarb hydrochloride applied twice as a drench treatment with a further two foliar applications at approximately double the maximum label rate. Samples of whole head cabbage were taken 27–31 days after the last application and processed to sauerkraut and cooked cabbage according to industrial processing procedures. Residues in cabbage head ranged from 0.05 to 0.84 mg/kg propamocarb hydrochloride. Residues decreased in sauerkraut and sauerkraut juice with mean/median processing factors (PF) of 0.33/0.15 and 0.49/0.33. PFs for the pasteurized products were 0.36/0.18 and 0.41/0.32, respectively. Residues also decreased in cooked cabbage, with a mean/median PF of 0.34/0.17.

In one study conducted with potatoes in the USA propamocarb hydrochloride was applied as a foliar spray at an exaggerated rate (2.5 × GAP). Potatoes were processed into potato flakes, potato chips, wet peel, and dry peel. Details of the processing procedures were not given. No residues were found in any raw potato or processed product (< 0.05 mg/kg).

In one study conducted in tomato in the USA in 1996, propamocarb was applied five times as a foliar spray at an exaggerated rate (5 × GAP rate). Tomatoes were harvested at normal maturity three days after the last application and three sub-samples were taken to be processed individually into tomato purée and tomato paste using a procedure that simulates typical commercial practices. Residues in RAC ranged from 10.3 to 11 mg/kg, as propamocarb. Residues concentrated in purée and paste, with a mean/median PF of 1.3/1.4 and 3.1/3, respectively.

Based on the STMR of 0.515 mg/kg for propamocarb in tomato and the median PF, the Meeting recommends a STMR of 0.721 for propamocarb in tomato purée and a STMR of 1.54 for propamocarb in tomato paste.

Residues in animal commodities

Feeding studies

No animal feeding studies were provided to this Meeting. Data from one metabolism study conducted with a lactating cow dosed with propamocarb at 2 mg/kg bw per day for seven days have shown that propyl propamocarb N-oxide (Met. IV) was the main compound detected in kidney, liver and muscle (40–49% TRR, up to 0.203 mg/kg propamocarb eq. in liver) and 2-hydroxy propamocarb was the main residue in milk (37.5% TRR or 0.022 mg/kg eq.). Propamocarb represented a maximum of 24.6% TRR, present at levels < 0.03 mg/kg.

Dietary burden of farm animals

From all the commodities for which propamocarb uses were considered by the JMPR, potato processed products are the only ones included in the animal diets according to the *FAO Manua*l (FAO 2002). In two trials conducted with potato according to GAP, residues in washed peel, were < 0.08 mg/kg. As wet peel represents 75% and 40% of beef cattle and dairy cattle diets respectively, no animal dietary burden is expected from the uses of propamocarb considered by the JMPR.

Residues in animal commodities

The Meeting recommended a maximum residue level of 0.01(*) mg/kg and a STMR of 0 mg/kg for propamocarb in eggs, milks, edible offal (mammalian), poultry edible offal, poultry meat and meat (from mammals other than marine mammals). The Meeting also recommends an HR of 0.01 mg/kg for eggs, edible offal (mammalian), poultry edible offal, poultry meat and meat (from mammals other than marine mammals).

DIETARY RISK ASSESSMENT

Long-term intake

The ADI for propamocarb is 0-0.4 mg/kg bw. The International Estimated Daily Intake (IEDI) for propamocarb was estimated for the 13 GEMS/Food cluster diets using the STMR or STMR-P values estimated by the current Meeting for 11 plant commodities. The results are shown in Annex 3. The IEDI ranged from 0 to 1% ADI. The Meeting concluded that the long-term intake of residues of propamocarb from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The ARfD for propamocarb is 2 mg/kg bw. The International Estimated Short Term Intake (IESTI) for propamocarb 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% ARfD for the general population and from 0 to 80% ARfD for children. In both populations, the highest intake came from the consumption of lettuce. The Meeting concluded that the short-term intake of residues of propamocarb from uses that have been considered by the JMPR is unlikely to present a public health concern.

4.23 PROPARGITE (113)

RESIDUE AND ANALYTICAL ASPECTS

Propargite [2-(4-*tert*-butylphenoxy)cyclohexyl prop-2-ynyl sulfite] was first evaluated by the JMPR for residues in 1977 and toxicology in 1978, with subsequent evaluations in 1978, 1979, 1980 and 1982. A periodic review (toxicology) was conducted by JMPR in 1999 when an ADI of 0-0.01 mg/kg bw was estimated and it was concluded that an acute reference dose was not necessary. A periodic review of residues was conducted in 2002 and MRLs were recommended for many crops and animal commodities. MRLs for beans (dry), pears, potato, pears, strawberry and walnuts were among those not proposed because of insufficient data or GAP information.

The CCPR (36th Session, 2004, paragraph 141, ALINORM 04/27/24) retained the existing Codex MRLs for beans (dry), pear, potato, strawberry and walnuts for 4 years under the periodic review procedure so that additional data could be provided to support these MRLs.

Information on registered uses and data from supervised residue trials in USA on beans (dry), potato and walnuts, together with additional information on methods of analysis and residue stability in stored analytical samples, were provided to the Meeting by the USA manufacturer and additional information on GAP and summaries of residue trials in Japan on citrus, apples, peaches, cherries, grapes and tea were provided by the Japanese manufacturer. No information was provided for pears or strawberries.

Analytical methods

The meeting received analytical method descriptions and validation data for propargite in beans (dry), walnuts and potato. These methods involved minor variations on a method ME-208, capable of determining both propargite and the metabolite t-butyl phenoxy cyclohexanol (TBPC). These methods were previously evaluated by JMPR in 2002.

The reported methods involved the acetonitrile extraction of residues in homogenized plant matrices, with the filtered extract being washed with hexane before being mixed with 10% NaCl and partitioned into either petroleum ether or hexane. After concentration and clean-up using a Florisil® column, the extracts were evaporated to dryness or near dryness. In some studies (potato and dry beans), the primary metabolite (TBPC) was then derivatised by incubation with triethylamine and heptafluorobutyric anhydride. Extracts were then resuspended in either hexane or toluene and analyzed for propargite using a gas chromatograph equipped with a mass selective detector (GC-MSD) in the selected ion monitoring mode. Residues of the TBPC metabolite were not reported as this is not included in the residue definition for either compliance with MRLs or for dietary intake estimation. Limits of quantification (LOQs) for these methods were 0.02 mg/kg for beans (dry) and walnuts (nutmeat) and 0.01 mg/kg for potato.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of propargite in various commodities under freezer storage (-16 to -20 °C). These studies were among those previously assessed by JMPR in 2002, where it was noted that with the exception of forage and fodder crops, more than 70% of propargite residues remained in frozen samples stored for about one year.

The Meeting agreed with the previous JMPR conclusion that propargite residues were stable in most frozen plant commodities for about one year, and could be applied to beans (dry), walnuts and potato, based on studies provided for alfalfa (seed, foliage and alfalfa hay), barley grain, almond kernels and on the potato study previously evaluated by the 2002 JMPR.

Results of supervised trials on crops

The Meeting received reports of supervised trials conducted in USA, where propargite was applied to a range of bean varieties grown for dry bean production, chick-peas, potato and walnuts and also received summaries of residue trials in Japan on citrus, apples, peaches, cherries, grapes and tea.

The Meeting agreed that the MRLs recommended at the 2002 Meeting for these latter commodities (citrus, apples, peaches, cherries, grapes and tea) were sufficient to accommodate residues arising from the Japanese GAPs, and that no further evaluation was required.

Beans (dry), chick-peas (dry)

Field trials conducted in USA on a range of bean varieties grown for dry bean production, and on chick-peas, involving two foliar applications of propargite were made available to the Meeting. Information on one additional trial on red kidney beans was provided to the JMPR 2002.

GAP in USA for *Lupinus, Phaseolis and Vicia spp* grown for dry bean production and for chick-peas, i.e., crops within the USA 'beans (dry)' group, is for up to two applications per season, with a maximum rate of 2.8 kg ai/ha, a 21 day interval between treatments with a PHI of 14 days. In six of the bean trials from USA matching the USA GAP, residues in beans (dry) were: 0.02, 0.07, 0.08, 0.1, 0.11 and 0.16 mg/kg and in one chick-pea trial, residues were 0.21 mg/kg.

The Meeting agreed that the results of the above trials could be combined and used to mutually support recommendations for beans (dry) and chick-peas, and could be extrapolated to similar commodities for which GAP existed in USA. The combined results were: 0.02, 0.07, 0.08, <u>0.1</u>, 0.11, 0.16 and 0.21 mg/kg.

The Meeting estimated maximum residue levels of 0.3 mg/kg and STMRs of 0.1 mg/kg for beans (dry), lupin (dry), broad bean (dry) and chick-pea (dry).

Potato

Field trials conducted in USA involving two foliar applications of propargite on potatoes, were made available to the Meeting.

GAP in USA for potatoes is for up to two applications per season, with a maximum rate of 2.5 kg ai/ha, a 21 day interval between treatments and a PHI of 14 days. In eight USA trials matching USA GAP, reported residue levels in potato tubers were: < 0.01 (6), 0.01 and 0.02 mg/kg. In a further four trials with a shorter treatment interval of 14 days, but otherwise matching the USA GAP, residue levels were all < 0.01 mg/kg. The Meeting agreed to combine the data from these two sets of trials, as the different spray intervals were not expected to influence the residue levels present in the tubers. The residue levels in the combined set of 12 trials were: < 0.01 (10), 0.01 and 0.02 mg/kg.

The Meeting estimated a maximum residue level of 0.03 mg/kg for potato and estimated an STMR of 0.01 mg/kg.

Walnuts

Field trials conducted in USA on walnuts, involving two foliar (air blast) applications of propargite were made available to the Meeting.

GAP in the USA for walnuts allows up to two applications per season, with a maximum rate of 2.5 kg ai/ha, a 21 day interval between treatments and a PHI of 21 days. In six USA trials matching USA GAP, reported residue levels in walnut kernels (nutmeat) were: < 0.02(2), 0.02, 0.08, 0.13 and 0.14 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg for walnuts and estimated an STMR of 0.05 mg/kg.

Animal commodity maximum residue levels

The Meeting noted that the GAP for dry bean varieties in USA included a condition that treated vines or trash should not be used for animal forage or fodder, and that the potential contribution to the farm animal dietary burden from residues in potato culls would be insignificant (when compared to the contribution from other fruit and vegetable by-products such as citrus pulp).

The Meeting therefore concluded that the farm animal dietary burden estimated by the JMPR in 2002 was still valid and confirmed the existing maximum residue limits and STMRs estimated for propargite in animal commodities.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of propargite has resulted in recommendations for new maximum residue limits and STMR values for several new commodities. Data on consumption were available for 32 commodities from this and previous evaluations, and this data was used to calculate dietary intake. The results are shown in Annex 3.

The IEDIs in the 13 GEMS/Food cluster diets, based on the estimated STMRs were 3–30% of the maximum ADI (0.01 mg/kg bw). The Meeting concluded that the long-term dietary intake of residues of propargite from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The 2002 JMPR concluded that it was unnecessary to establish an ARfD for propargite. The Meeting therefore concluded that the short-term dietary intake of residues of propargite from uses that have been considered by the JMPR is unlikely to present a risk to consumers.

4.24 PROPICONAZOLE (160)

RESIDUE AND ANALYTICAL ASPECTS

Propiconazole was last evaluated by the JMPR in 1987 1991,1994 and 2004 when an ADI of 0-0.07 mg/kg bw and ARfD of 0.3 mg/kg bw were established, and a number of maximum residue levels were estimated. The residue was defined as propiconazole for regulatory and dietary intake assessment purposes.

Results of supervised trials, carried out on cranberry according the US registered uses, were submitted for evaluation.

Results of supervised trials on crops

During the 1995 and 1999 growing seasons three field trials were conducted with maximum dosage on cranberries in two geographical regions of the USA.

For each trial, four broadcast foliar applications of propiconazole were made with single application rates of 0.42 kg ai/ha. The samples were collected at 43 and 44 days (US GAP: max application rate is 0.42 kg ai/ha with a PHI of 45 days)

The cranberry samples were analysed with a total residue method determining propiconazole and its metabolite as 2,4 dichlorobenzoic acid by capillary gas chromatography. The concurrent recoveries ranged from 71 to 120% with an average of 93% and standard deviation of 14.6%.

Concurrent storage stability tests indicated that the residues in samples spiked at 1.0 mg/kg level and stored at < -20^{o}C for 92 days did not degrade.

The residues measured in samples at harvest and expressed as propiconazole equivalent were: 0.2, 0.23 and 0.53 mg/kg.

The 1994 JMPR reported that over 30 days after the last application the proportion of the parent compound in the total residue was 8–11%, 21% and 18–23% in peanut, grapes and grape leaves, respectively (Evaluation 1994, part 1, vol 2. p1048). The residue composition obtained in various kinds of plant matrices indicate that the parent compound would not amount to more than 25% of the total residue in plant commodities including cranberry 45 days after last application.

Taking into account the proportion of parent compound in propiconazole residues in plant commodities, and the minimum data requirement (3 trials) specified for commodities which are insignificant in trade and do not raise any intake concern (2004 JMPR Report, pp. 30-31), the Meeting estimated a maximum residue level of 0.3 mg/kg an HR of 0.13 mg/kg and STMR of 0.058 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The GEMS Food specifies the following long-term cranberry consumption (g/day per person) for various cluster diets: A (0.1); D (0.3); F (0.6); M (2.5). The consumption of cranberry in the other regions is nil.

The highest IEDI in the 13 GEMS/Food regional diets, based on estimated STMR, was < 0.01% of the maximum ADI (0.07 mg/kg bw).

The Meeting concluded that the long-term intake of residues of propiconazole use on cranberry will not practically increase the intake of residues from other uses considered earlier by the JMPR.

Short-term intake

The GEMS/Food regional diet specifies the large portion sizes of cranberry of 3.53 g/kg bw for adults and 6.78 g/kg bw for children (both from the USA).

The IESTIs of propiconazole calculated on the basis of the large portion size and the estimated HR of 0.13 mg/kg are 0.15% and 0.3% of the ARfD for adults and children, respectively.

The Meeting concluded that the short-term intake of residues resulting from the use of propiconazole on cranberry that have been considered by the JMPR is unlikely to present a public health concern.

4.25 PYRACLOSTROBIN (210)

RESIDUE AND ANALYTICAL ASPECTS

Pyraclostrobin was evaluated by the JMPR in 2003 and an ADI of 0-0.03 mg/kg bw per day and an ARfD of 0.05 mg/kg bw per day were established. The 2004 JMPR defined the residues as parent compound for compliance with MRLs and for dietary intake calculations, and estimated a number of maximum residue levels in various commodities.

Additional information on registered uses and results of supervised trials were submitted for evaluation. The Meeting evaluated the new data together with those included in the 2004 evaluation for those commodities only for which recommendations were not made by the 2004 JMPR.

The samples were analysed with analytical methods based on LC/MS/MS detection providing an LOQ of 0.02 mg/kg for pyraclostrobin and its major metabolite 500M07 (BF500-3, methyl-N-[[[1-(4-chlorophenyl)-pyrazol-3-yl]oxy]-o-tolyl]carbamate). The methods are described in detail in the 2004 Evaluations. The applicability of the methods was confirmed with concurrent recovery tests in each study. The average recoveries were typically between 80 and 99% for pyraclostrobin and 500M07. No interference of plant matrices was observed in most of the studies.

The storage intervals of samples from sampling to analysis were within the period covered by the storage stability tests reported by the 2004 JMPR.

Results of supervised trials on crops

Apple

A total of 25 field trials were conducted in different representative apple growing areas in Belgium, Germany, France, Italy and the Netherlands according to corresponding GAP, i.e., 3–4 applications at 0.067–0.1 kg ai/ha with a PHI of 6–8 days.

The residues determined were: 0.03, 0.034, 0.041, 0.051, 0.057, 0.058, 0.064, 0.07, 0.07, 0.081, 0.095, 0.101, <u>0.104</u>, 0.118, 0.12, 0.131, 0.139, 0.142, 0.143, 0.163, 0.167, 0.184, 0.276, 0.289, 0.29 mg/kg.

The 2004 JMPR reported Brazilian trials conducted with 0.15 and 0.3 kg ai/ha which are 1.5× and 3× above the Brazilian GAP rate. The residues in apples ranged from < 0.02 to 0.38 mg/kg 14 days after the last of four treatments with 0.15 kg ai/ha.

Taking into account that early applications do not affect the residues and based on the residue data derived from trials performed in accordance with the European GAP, the Meeting estimated a maximum residue level of 0.5 mg/kg, HR of 0.29 mg/kg and STMR level of 0.104 mg/kg.

Raspberry

Nine trials were carried out in accordance with US GAP (four applications at 0.196 kg ai/ha with a 0 day PHI). The residues in mature fruit were: 0.5, 0.51, 0.63, 0.78, <u>0.78</u>, 0.89, 0.94, 1.03, 1.28 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg, HR of 1.28 mg/kg and STMR value of 0.78 mg/kg for raspberry.

Stone fruits

The 2004 JMPR evaluated numerous trials carried out in USA and estimated maximum residue levels for peaches (0.5 mg/kg), cherries (1 mg/kg) and plums (0.3 mg/kg). The pyraclostrobin residues from European trials performed according to Hungarian and Italian GAP were also reported. They ranged

between < 0.02–0.21 mg/kg for cherry (n = 16), < 0.02–0.1 mg/kg for plum (n = 13) and < 0.02–0.13 for peach (n = 14). These residues are covered by the maximum residue levels estimated by the JMPR based on US residue trial data.

No residue trials on apricot was reported but as apricot is now included on the label in Canada and USA (5 applications at 0.134 kg ai/ha, with 10 and 0 day PHI respectively) and Hungary (2–3 applications at 0.067 kg ai/ha, with a 7 day PHI), the Meeting concluded that maximum residue levels for stone fruit can be estimated taking into account the cherry residues reported by the 2004 JMPR. Pyraclostrobin residues in cherries from 12 US trials were 0.25 (2), 0.27, 0.34, 0.38, 0.42, 0.43, 0.48, 0.50 (2), 0.51, 0.63 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg, HR of 0.63 mg/kg and a STMR of 0.43 mg/kg for stone fruits, and withdraws its previous recommendations made for cherry, peach and plum (including prunes).

Leek

Eleven supervised field trials were performed on leeks according to GAP in Belgium and The Netherlands (maximum of 3 applications at 0.1 kg ai/ha with a PHI of 14 days). The corresponding residues were 0.05, 0.12, 0.15, 0.16, 0.19, 0.22(2), 0.24, 0.25, 0.29, 0.42 mg/kg.

The meeting estimated a maximum residue of 0.7 mg/kg, HR of 0.42 and an STMR of 0.22 mg/kg.

Brassica vegetables

Broccoli and cauliflower

Thirteen field trials were conducted in different representative cauliflower and broccoli growing areas in Europe consisting of three applications at a rate of 0.067 kg ai/ha of pyraclostrobin. The applications took place at about 28, 21 and 14 days prior to harvest.

The residues in cauliflower at about 14 days after the last application (corresponding to GAP in several EU countries) were: < 0.02 (6), 0.04 mg/kg.

The residues in broccoli at about 14 days after last application were: < 0.02 (5), 0.03 mg/kg.

The medians of residue populations in broccoli and cauliflower are not significantly different and the residue data can be combined.

The combined residues are: ≤ 0.02 (11), 0.03, 0.04 mg/kg.

Trials were also performed with 0.1 kg ai/ha (1.5× recommended rate) and resulted in somewhat higher residues: < 0.02 (8), 0.04, 0.04, and 0.18 mg/kg.

Based on the GAP of 0.067 kg ai/ha dose, the Meeting estimated a maximum residue level of 0.1 mg/kg, HR of 0.04 mg/kg and STMR of 0.02 mg/kg for flowerhead brassicas.

Brussels sprouts

Nine field trials were conducted in Brussels sprouts in the United Kingdom, The Netherlands, Denmark, Germany, Sweden and France. Three applications were made according to GAP at rates of 0.067 kg ai/ha for pyraclostrobin. The samples taken at around 14 days contained residues of: < 0.02 (3), 0.03 (2), 0.06, 0.08, 0.1, and 0.14 mg/kg.

Trials were also carried out at a rate of 0.1 kg/ha (1.5× GAP). Samples taken at around 14 days after last application contained residues of: 0.04, 0.06, 0.06, 0.07, 0.11, 0.12, 0.13, and 0.21 mg/kg.

The Meeting took into account the residues derived from applications performed according to GAP and estimated a maximum residue level of 0.3 mg/kg, HR of 0.14 mg/kg and an STMR of 0.03 mg/kg.

Cabbage

Fifteen field trials were conducted in different representative head cabbage growing areas in the EU. The cabbages were treated with pyraclostrobin in accordance with GAP, i.e., three applications at a rate of 0.067 kg ai/ha.

A further 12 field trials were conducted with about four applications at a rate of 0.1 kg ai/ha, 1.5× the GAP rate. The residues ranged between non-detected (LOQ = 0.02 mg/kg) and 0.08 mg/kg.

The samples taken at around the PHI of 14 days from fields treated according to GAP contained residues of: $\underline{< 0.02}$ (11), 0.04, 0.05, 0.09, and 0.09 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg, HR of 0.09 mg/kg and STMR of 0.02 mg/kg.

Fruiting vegetables

Cucumber

Supervised field trials were conducted at eight sites in the USA applying six sequential applications (7 ± 1 day apart) at a rate of 0.224 kg ai/ha and a total seasonal rate of 1.34 kg ai/ha. The US GAP allows four applications at a rate of 0.224 kg ai/ha.

The samples collected at 0 day PHI contained residues of: 0.03, 0.05, 0.06, $\underline{0.07}$, $\underline{0.09}$, 0.12, 0.14, and 0.41 mg/kg.

The Brazilian GAP specifies 4 sequential applications at rate of 0.1 kg ai/ha and a PHI of 7 days. Four trials carried out according to GAP resulted in residues below the LOQ (0.02 mg/kg) in all samples.

The medians of the two residue populations are different and were not combined.

The Meeting noted that cucumber is a rapidly growing crop and the early applications are made when the fruits are not present on the plants, therefore the residue pattern is not affected by the early treatments. Consequently, the Meeting considered that residue values derived from six sequential applications could be used, and estimated a maximum residue level of 0.5 mg/kg, HR of 0.41 mg/kg and an STMR of 0.08 mg/kg for cucumber.

Cantaloupe

In eight US trials pyraclostrobin was applied six times at a rate of 0.224 kg ai/ha, corresponding to US GAP. The residues in found directly after last application (day 0) were: 0.05, 0.08, 0.09, $\underline{0.1}$, $\underline{0.11}$, 0.12, 0.12, and 0.13 mg/kg.

The Meeting estimated for cantaloupe a maximum residue level of 0.2 mg/kg, HR of 0.13 mg/kg and STMR of 0.105 mg/kg.

Peppers

Seven field and six greenhouse trials were conducted on peppers with three applications at a rate of 0.1 kg ai/ha in Europe according to Italian GAP. The residues of pyraclostrobin in fruit samples collected 2−3 days after the final application ranged between < 0.02 and 0.25 mg/kg. There was no significant difference between the residue populations of field grown or greenhouse grown peppers.

The combined residues were: 0.03(4), 0.06, 0.07, 0.08, 0.09, 0.13(4) and 0.30 mg/kg.

The residues of pyraclostrobin from European trials were lower than the residues reported from trials conducted according to US GAP (six applications at 0.224 kg ai/ha with a 0 day PHI): 0.14, 0.22, 0.82 mg/kg. The two residue populations have different median values and cannot be combined.

The Meeting concluded that the residue data base reflecting the higher residue population derived from US GAP was not sufficient for estimating maximum residue level for bell peppers or chilli peppers, and used the results of trials performed according to maximum GAP in Europe. The Meeting estimated a maximum residue of 0.5 mg/kg, HR of 0.30 mg/kg and STMR of 0.08 mg/kg.

Eggplant

The 2004 JMPR estimated a maximum residue level for tomatoes of 0.3 mg/kg, an HR of 0.21 mg/kg and an STMR of 0.12 mg/kg for outdoor application based on the US GAP.

Twenty six field and greenhouse trials performed according to the GAP in Poland (three applications at a rate of 0.067–0.1 kg ai/ha with a PHI of 3 days) resulted in residues 2–3 days after the final application in the ranges of < 0.02 to 0.13 mg/kg. There was no significant difference between the residue populations of field and greenhouse tomatoes.

The residue levels estimated, based on the critical US GAP, covers the residues obtained in European trials.

Since the evaluation in 2004, US and Canadian labels authorising the use of the compound on eggplant became available (six applications at 0.224 kg ai/ha with a 0 day PHI) which is the same as that for tomato. Furthermore, the Meeting noted that there was no difference between residues derived from outdoor and protected growing conditions of tomato.

The Meeting concluded that the residue levels estimated for tomato can be applied for eggplant as well, and estimated a maximum residue level of 0.3 mg/kg, an HR of 0.21 mg/kg and a STMR of 0.12 mg/kg.

Kale

In the United Kingdom pyraclostrobin is registered for use as three applications at a rate of 0.067 kg ai/ha and a PHI of 14 days. Six field trials were conducted in curly kale in Denmark, the UK, the Netherlands and Sweden with four applications at 0.1 kg ai/ha. The applications were done about 5, 4, 3 and 2 weeks prior to commercial harvest. Samples were taken from 0 to 20–21 days after final application.

The residues in samples taken at 14 days were: 0.02, 0.06, 0.09, 0.26, 0.31, and 0.61 mg/kg.

The meeting considered that the early application does not affect the residues at harvest, and estimated a maximum residue level of 1 mg/kg, HR of 0.61 mg/kg and STMR of 0.175 mg/kg for kale.

Lettuce, head

In USA, pyraclostrobin has approval in lettuce for four applications at 0.117–0.23 kg ai/ha with a 0 day PHI. Supervised field trials performed on head lettuce with four applications at 0.224 kg ai/ha rate resulted in residues of: 1.95, 3.69, 4.96, 13.7, 14.9, and 19.7 mg/kg.

Seventeen field trials were carried out in typical growing regions of Europe according to GAP (two applications at 0.1 kg ai/ha and PHI of 14 days). Samples collected at around 14 days contained residues of: < 0.02 (6), 0.03, 0.04(4), 0.06, 0.08(3), 0.28, and 0.38 mg/kg.

Eight trials on lettuce were performed in greenhouse according to European GAP. The residues detected in lettuce head 14 days after the last application were: 0.03, 0.04, 0.13, 0.23, 0.29, 0.33, 0.75, and 0.81 mg/kg.

The US GAP would lead to an estimated maximum residue level of 40 mg/kg, an HR value of 19.7 mg/kg and a median residue of 9.33 mg/kg for lettuce head. This residue level would result in an estimated intake of 390% of the ARfD.

Consequently, in accordance with the principles of alternative GAP as described in Section 2.2, the Meeting considered the next lowest GAP and used the residues in greenhouse lettuce treated according to the European GAP for the estimation of maximum residue level of 2 mg/kg, HR of 0.81 mg/kg and an STMR of 0.26 mg/kg for lettuce head.

Snap beans

The 2004 JMPR was not able to recommend a maximum residue level for snap beans as there was no GAP at that time. The present meeting was provided with the US Label (GAP: two applications at 0.087–0.13 kg ai/ha dose with a 7 day PHI).

The nine field trials reported to the 2004 JMPR were performed with a rate of 0.224 kg ai/ha for individual treatments and total seasonal applied amount of 0.448 kg ai/ha.

The residues of pyraclostrobin in ranked order were: < 0.02, 0.04, 0.08, 0.1, 0.1, 0.11, 0.12, 0.13, 0.16 mg/kg.

As all trials were performed with a dosage corresponding to 1.7× maximum rate, the Meeting agreed that maximum residue level for snap beans could not be estimated.

Peas

A total of 21 field trials were conducted in vining peas in France, the United Kingdom, Germany, Denmark and Sweden applying pyraclostrobin twice with a target rate of 0.067 and 0.1 kg ai/ha. The samples were taken at earliest commercial harvest (corresponding to approximately 8–14 days after the last application). In all green pea samples the residues were below the LOQ of 0.02 mg/kg. As the PHI in France is 35 days, no residues can be expected in green peas.

The Meeting estimated for green peas a maximum residue level, HR and STMR values of 0.02* and 0.02, 0.02 mg/kg, respectively.

Soybean

The US GAP consists of two applications at a rate of 0.1–0.2 kg ai/ha with a PHI of 21 days and a seasonal maximum of 0.41 kg ai/ha. In 17 field trials the rate of pyraclostrobin applied was double that of the GAP with a total application rate of 0.448 kg ai/ha/season. The immature seeds were harvested at five days contained residues in the range of < 0.02 and 0.3 mg/kg.

The mature seeds collected from the 17 trials, sampled 28 days after the second application, were found to not contain any detectable residues (LOQ of 0.02 mg/kg).

In eight trials performed approximating Brazilian GAP (two applications at 0.075 kg ai/ha with a 14 day PHI) the residues were: < 0.02 (7) and 0.03 mg/kg.

As the majority of samples (84%) contained non-detectable residues at day 5 post application, and no residue was detectable in mature seeds, using this supportive information the Meeting concluded that the Brazilian data and GAP enable the estimation of maximum residue limits of 0.05 mg/kg, and STMR values 0.02 mg/kg for soybeans.

Spelt

No special residue trials were performed for spelt. However, as spelt is a registered crop in Belgium and Luxembourg with the same GAP as wheat, the Meeting concluded that the residue levels estimated by the 2004 JMPR for wheat grains are applicable to spelt as well.

Sunflower seed

The US GAP allows two applications with 0.1–0.2 kg ai/ha applied at 7–14 days intervals with a 21 day PHI. Field trials were performed by applying 0.224 kg ai/ha twice and collecting samples 21 days after the final application. The residues in ranked order were: < 0.02, 0.02, 0.04, 0.05, 0.06, 0.06, 0.1, and 0.22 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.055 mg/kg for sunflower seed.

Coffee

To complement the data submitted to the 2004 JMPR, additional field trials were carried out in Brazil with target rates of 0.1 kg ai/ha and 0.2 kg ai/ha (GAP is 0.2 kg ai/ha). The coffee bean samples, collected at full ripening stage (red coffee berry), were taken 45 days after the last application and contained residues of: < 0.02 (4), < 0.02, 0.03, 0.03, 0.11, 0.15, and 0.15 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg, and an STMR of 0.025 mg/kg for coffee beans.

Hops

A total of 12 field trials were conducted in the representative areas for hop cultivation in Germany with application rates of 0.21 to 0.30 kg ai/ha. Green hop cones were sampled immediately after the last application and at about 14, 21 and 28 days later.

During the last two samplings the collected green cones were divided into two parts. One part was deep-frozen and the other part was dried for 6 hours at 60°C and was then deep-frozen on the following day.

The residues in dried cones were: 1.1, 1.7, 2.1, 3.5, 4.5, 5.1, 7.2, and 7.4 mg/kg

The formulations and the spray volumes used did not have any observable effect on the magnitude of residues.

Six field trials were conducted in the US, where there is no GAP, with three applications at approximately 0.25 kg ai/ha applied in concentrate (low-volume) and dilute (high-volume) spray solutions. Hop cone samples were taken 0, 7 and 14 days after the last application. These were dried on the field prior to shipment for analysis. The residues in dried cones taken at day 14 were: 7.4, 7.6, 7.8, 9.3, 11 and 12 mg/kg.

The Meeting considered the residues determined in dried cones in German trials, and estimated a maximum residue of 15 mg/kg, and an STMR of 4.0 mg/kg for dried hop cone.

Animal feed commodities

Soybean forage

Seventeen field trials were performed in USA according to GAP. The label specifies a minimum of 14 day interval between last application and feeding forage to animals. The residues in soybean forage at

day 14 after the last application were: 0.75, 0.82, 0.90, 1.01, 1.10, 1.24, 1.30, 1.34, 1.60, 1.69, 1.75, 1.85, 2.37, 2.70, 2.74, 2.81, and 3.22 mg/kg.

The Meeting estimated highest residue of 3.22 mg/kg and an STMR of 1.6 mg/kg for soybean forage.

Fate of residue during processing

Hops

Hops were treated three times at a rate of 0.097–0.113 kg ai/ha in the Netherlands and Germany. Samples were taken 20–22 days after the final application (GAP 3 applications at 0.057–0.25 kg ai/ha with a PHI of 21 days). The green cone samples were dried and processed in a pilot plant in Germany.

The beer obtained from dried hops containing 1.57–4.75 mg/kg pyraclostrobin did not contain any detectable residues (< 0.04 mg/kg). The Meeting estimated an average processing factor of < 0.0156. Based on the STMR for hops (3.5 mg/kg), the estimated STMR-P for beer is 0.055 mg/kg.

Soybean seed

A single field trial was conducted applying pyraclostrobin at five times the maximum recommended rate (two applications of 1.12 kg ai/ha, 7 days apart) in order to obtain detectable residues in soybean seed. The harvested seeds underwent laboratory scale processing that simulated commercial practice. The average processing factors for hull was 1.46. The meal and refined oil did not contain any detectable residues. The calculated processing factor was 0.58 for both commodities. Based on the STMR for soybean (0.02 mg/kg), the estimated STMR-P for refined soybean oil is 0.012 mg/kg.

Sunflower seed

Sunflower seeds derived from crops treated twice with pyraclostrobin at five times the maximum recommended rate, were processed to meal and refined oil. The meal and refined oil did not contain any detectable residues resulting in a processing factor of < 0.014. Based on the STMR for sunflower (0.055 mg/kg), the estimated STMR-P for refined oil is 0.00077 mg/kg.

Farm animal dietary burden

The animal dietary burden estimated by the 2004 JMPR is based on peanut hay (7.28–14.4 mg/kg) and the cereal fodder (5.4–10.8 mg/kg) and is substantially larger than what would be expected from peanut forage (0.97 mg/kg) or feeding leafy vegetables. The farm animal dietary burden estimated by the 2004 JMPR is therefore not affected by the potential use of treated soybean, kale and other vegetables as animal feed.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes of pyraclostrobin, based on the STMRs estimated for 59 commodities included those which were evaluated by the 2004 JMPR for the 13 GEMS/Food regional diets were in the range of 0 to 7% of the maximum ADI (0.03 mg/kg bw per day). The Meeting concluded that the long-term intake of residues of pyraclostrobin resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term intake

The IESTI of pyraclostrobin calculated on the basis of the recommendations made by the JMPR represented 0–80% of the ARfD (0.05 mg/kg bw) for children and 0–30% for the general population.

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

4.26 QUINOXYFEN (222)

TOXICOLOGY

Quinoxyfen is the ISO approved name for 5,7-dichloro-4-(4-fluorophenoxy) quinoline, a halogenated quinoline fungicide acting against powdery mildew in cereal crops. The proposed fungicidal mechanism of action is disruption of signal transduction by targeting of G-proteins.

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

In dietary exposure studies with quinoxyfen, variable levels of incorporation were used to achieve an approximately constant level of exposure throughout the study. All the pivotal studies contained certificates of GLP compliance.

The 2005 CCPR selected quinoxyfen as the second compound for a FAO/WHO/OECD pilot project on work-sharing (see General Consideration 2.14). The text of the working paper was based extensively on existing documents prepared by regulatory authorities in Australia, the European Union and the United States of America (USA).

Biochemical aspects

Phenyl- and quinoline-ring ^{14}C-labelled material was used to investigate the absorption, distribution, metabolism and excretion of quinoxyfen in rats. Differences in findings for each type of radiolabel were due to extensive cleavage of the ether bond. Absorption was rapid, with peak plasma concentrations of radioactivity (2–3 µg equivalents/g) seen within 1 hours at a dose of 10 mg/kg bw. There were no data on tissue concentrations of radioactivity corresponding to the plasma C_{max}. Excretion of the quinoline radiolabel was relatively rapid (68–85% in 24 h) and predominantly in the faeces (approximately 70%) following absorption and subsequent secretion in the bile (approximately 50%). With the phenyl label, there was no marked difference between the proportion found in the urine or in the faeces. After most of the dose had been excreted (48 h), the highest concentrations of quinoline radiolabel were found in perirenal fat (0.12–0.35%/g), ovaries (0.07%/g), liver (0.03–0.05%/g), and kidneys (0.01–0.03%/g) with levels generally higher in females than in males. At 72 hours after administration, the longest duration investigated, 1–2% of the radioactivity remained in the carcass and tissues. Metabolism involved cleavage of the ether linkage to give 4-fluorophenol and 5,7-dichloro-4-hydroxy quinoline and conjugation (unidentified) of both fluorophenyl and quinoline moieties; there was also direct conjugation to the fluorophenyl ring of intact quinoxyfen. There were no significant differences either between the sexes or between single or repeated administration at 10 mg/kg bw. Saturation of absorption and metabolism was evident at 500 mg/kg bw.

Toxicological data

Quinoxyfen was of low acute toxicity when administered orally (LD_{50} > 5000 mg/kg bw in rats), dermally (LD_{50} > 2000 mg/kg bw in rabbits) or by inhalation (LC_{50} > 3.4 mg/L in rats). Quinoxyfen

was not irritating to skin, was slightly irritating to the eyes and was found to be a skin sensitizer using the maximization assay, but not when the Buehler method was used.

In short-term studies of toxicity with quinoxyfen, changes in liver weight and pathology and body-weight gain were the most consistently identified effects. In mice, increased liver weight, slight to moderate hepatocyte hypertrophy and very slight hepatocellular necrosis were present after 13 weeks of treatment at 500 mg/kg bw per day. The NOAEL for short-term toxicity in mice was 100 mg/kg bw per day. In rats, increased liver weight, and slight hepatocyte hypertrophy with increased basophilia were produced by doses of 100 mg/kg bw per day or above, with very slight hepatocellular necrosis being observed at 250 mg/kg bw per day. The hepatic effects seen in the rat after 13 weeks at 100 mg/kg bw per day were reversible within 4 weeks, but some effects persisted at 250 mg/kg bw per day. In dogs, slight vacuolation of hepatocytes—considered by the investigators to be suggestive of dilated endoplasmic reticulum rather than lipid accumulation—was observed after 4 weeks of treatment at 250, 500 and 1000 mg/kg bw per day, with hepatocellular necrosis in females at 500 and 1000 mg/kg bw per day. In the 13-week study in dogs, slight hepatocellular hypertrophy was seen in one male at 100 mg/kg bw per day, the highest dose used in the study. In the 1-year study in dogs, increased hepatocyte size and serum ALP activity (two- to threefold) was seen in both sexes at 200 mg/kg bw per day.

Other findings in rats included reductions in body-weight gain and food consumption of males and/or females after 4 or 13 weeks of treatment at doses of $\geq$ 100 mg/kg bw per day. Kidney weight was increased at 250 mg/kg bw per day after 13 weeks of treatment. The NOAEL was 10 mg/kg bw per day on the basis of reduced body-weight gain at 100 mg/kg bw per day; however, it was noted that the NOAEL in the 2-year study in rats was 20 mg/kg bw per day. In dogs, reduced body weight or body-weight gain and reduced food consumption were seen in males and/or females after treatment at doses of greater than 100 mg/kg bw per day; but not after 13 weeks of treatment at doses of up to and including 100 mg/kg bw per day. Effects consistent with haemolytic anaemia and compensatory response (haematopoiesis in the spleen and liver) were manifest at 200 mg/kg bw per day in the 1-year study in dogs, and the NOAEL was 20 mg/kg bw per day.

In a 28-day study of dermal exposure, rats were given quinoxyfen for 5 days per week at doses of up to 1000 mg/kg bw per day (equal to 714 mg/kg bw per day averaged over the study). There were no findings of systemic or local toxicity. The NOAEL was 714 mg/kg bw per day.

In an 80-week study, mice received diets containing quinoxyfen at variable concentrations to give mean intakes of 0, 20, 80 or 250 mg/kg bw per day. There were no treatment-related changes in survival, or incidences of tumours or non-neoplastic lesions. The only significant findings were at the highest dose: reductions in body-weight gain in both sexes and increased relative kidney and liver weights in females. There was no evidence for carcinogenicity with quinoxyfen in this study. The NOAEL was 80 mg/kg bw per day.

In a 104-week study, rats received diets containing quinoxyfen at variable concentrations to given mean intakes of 0, 5, 20 or 80 mg/kg bw per day. There were no treatment-related changes in survival or tumour incidences. The only significant findings were at the highest dose: an increase in liver weight at 20 mg/kg bw per day after 24 months was not considered to be adverse as there was no dose-related response and no associated histopathology findings. Clinical chemistry changes included increased concentration of blood urea nitrogen (BUN) in males and increased concentration of cholesterol in females. Relative liver and kidney weights were increased in both sexes at 24 months, although hepatocyte hypertrophy was increased in males at 12 months it was not seen after 24 months. The incidence of glomerulonephropathy was increased in males at 24 months. Quinoxyfen was not carcinogenic in this study. The NOAEL was 20 mg/kg bw per day, which was also the overall NOAEL in rats.

Quinoxyfen produced negative results in an adequate range of studies of genotoxicity in vitro and in vivo. The Meeting concluded that quinoxyfen was unlikely to be genotoxic.

On the basis of the absence of carcinogenicity in rodents and the absence of genotoxicity, the Meeting concluded that quinoxyfen is unlikely to pose a carcinogenic risk to humans

In a two-generation study of reproductive toxicity, there were no treatment-related differences in reproductive indices or in pup survival at doses of up to 110 mg/kg bw per day, the highest dose tested. The NOAEL for toxicity in parents and offspring was 20 mg/kg bw per day based on a slight but consistent reduction in body-weight gain in pups during lactation and hepatocyte hypertrophy in parental males, in the absence of clinical chemistry examinations of serum enzyme activities.

In studies of developmental toxicity in rats, the NOAEL for maternal toxicity, fetotoxicity and teratogenicity was 1000 mg/kg bw per day, the limit dose. In the study of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 80 mg/kg bw per day on the basis of a reduction in food consumption, reductions in maternal body-weight gain, poor condition and an increased incidence of abortions at 200 mg/kg bw per day. The abortions were noted to occur after 10 or more doses and in the presence of overt maternal toxicity, and were therefore not considered to be related to direct fetal toxicity. Quinoxyfen was not fetotoxic or teratogenic in rabbits under the conditions of this study.

Investigative studies were conducted on liver enzyme induction and hepatic effects in rats and mice treated with quinoxyfen for 2 weeks. In mice, significant increases in the activities of monoxygenase enzymes occurred at 1500, 6000 or 12000 ppm. Hepatocellular hypertrophy was reported at 6000 ppm (equivalent to 890 mg/kg bw per day) and above. The NOAEL for liver enzyme effects in mice was 400 ppm (equivalent to 55 mg/kg bw per day). In rats, only *p*-nitroanisole *O*-demethylase activity was investigated; this enzyme showed increased activity at doses of 2500 ppm or above for 2 weeks. The NOAEL was 500 ppm (equal to 45 mg/kg bw per day) for both sexes. There were no treatment-related histopathological changes in the liver of rats exposed for 2 weeks at doses of up to 12500 ppm (equal to approximately 1700 mg/kg bw per day), a dose producing significant mortality. The NOAELs for xenobiotic enzyme induction after 2 weeks exposure to quinoxyfen are above the NOAELs in the studies used to derive the ADI.

In a study of acute neurotoxicity in rats, quinoxyfen exhibited no systemic toxicity or evidence of neurotoxicity at 2000 mg/kg bw. In an investigation conducted as part of the long-term study of toxicity in rats, the administration of quinoxyfen over a period of 12 months did not produce any effect on motor activity or functional observations, nor on histopathology of the peripheral or central nervous system.

Workplace-monitoring data have confirmed three cases of skin sensitization associated with the handling of quinoxyfen in the initial phases of development and manufacture. No other adverse findings have been associated with the production, formulation or use of quinoxyfen.

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

Toxicological evaluation

The Meeting established an ADI for quinoxyfen of 0–0.2 mg/kg bw based on NOAELs of 20 mg/kg bw per day identified in three studies: the 24-month study in rats, on the basis of reduced body-weight gain, liver and kidney effects at 80 mg/kg bw per day; the 1-year study in dogs, on the basis of reduced food consumption and body-weight gain, haematological effects, and liver effects at 200 mg/kg bw per day; and the two-generation study of reproductive toxicity in rats, based on a reduction in body-weight gain in pups at 110 mg/kg bw per day during lactation; and with the application of a 100-fold safety factor**.**

The Meeting noted that quinoxyfen was not acutely toxic after short-term dosing, that there were no adverse findings in a study of acute neurotoxicity and that quinoxyfen did not exhibit specific developmental toxicity. The Meeting concluded that the establishment of an ARfD was unnecessary.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	18-month study[#]	Toxicity	80 mg/kg bw per day	250 mg/kg bw per day
		Carcinogenicity	250 mg/kg bw per day[a]	—
Rat	Study of acute neurotoxicity[b]	Toxicity	2000 mg/kg bw per day[a]	—
	Two-generation study of reproductive toxicity[c]	Reproduction	110 mg/kg bw per day[a]	—
		Offspring	20 mg/kg bw per day	110 mg/kg bw per day
		Parental	20 mg/kg bw per day	110 mg/kg bw per day
	Developmental toxicity[b]	Maternal	1000 mg/kg bw per day[a]	—
		Developmental	1000 mg/kg bw per day[a]	—
	2-year study[c]	Carcinogenicity	80 mg/kg bw per day[a]	—
		Toxicity	20 mg/kg bw per day	80 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal	80 mg/kg bw per day	200 mg/kg bw per day
		Developmental	80 mg/kg bw per day	200 mg/kg bw per day
Dog	1-year study[c]	Toxicity	20 mg/kg bw per day	200 mg/kg bw per day

[a] Highest dose tested

[b] Gavage administration

[c] Dietary study, variable concentrations used to give constant dose in mg/kg bw per day

Estimate of acceptable daily intake for humans

0–0.2 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 exposures

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

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption	Rapid and moderately extensive; about 70% of a dose of 10 mg/kg bw in rats, lower at higher doses.
Distribution	No data corresponding to C_{max}. Highest residual radioactivity in perirenal fat, skin, ovaries, liver, and kidneys
Potential for accumulation	Equivocal: 1–2% remaining at 72 h; log K_{ow} > 4
Rate and extent of excretion	Relatively rapid. For quinoline-ring label quinoxyfen in rats at 2 days: 13–20% in urine; 68–78% in faeces; for phenol label approximately 40% in urine and faeces
Metabolism in animals	Extensive hydrolytic cleavage to form 4-fluorophenol and 5,7-dichloro-4-hydroxyquinoline with subsequent conjugation. Some conjugation of uncleaved quinoxyfen.
Toxicologically significant compounds	Parent
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rabbit, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 3.4 mg/L of air (maximum achievable concentration)
Skin irritation	Not irritating
Eye irritation	Slight irritant
Guinea-pig, skin sensitization (test method used and result)	Positive in maximization test, negative in Buehler test
Short-term studies of toxicity	
Target/critical effect	Food consumption/body-weight gain; liver (rats, mice, dogs); haematological effects (dogs)
Lowest relevant oral NOAEL	20 mg/kg bw per day (1-year study in dogs)
Lowest relevant dermal NOAEL	714 mg/kg bw per day (28-day, 20-exposure, study in rats)
Genotoxicity	Negative in a battery of tests in vitro and in vivo. No genotoxic potential.
Long-term studies of toxicity and carcinogenicity	
Target/critical effect (rats)	Kidney & liver weight (both sexes) and glomerulonephrosis (males); body weight.
Lowest relevant NOAEL / NOEL	20 mg/kg bw per day (2-year study in rats)
Carcinogenicity	No evidence of treatment related tumorigenicity in rats or mice
Reproductive toxicity	
Reproduction target / critical effect	No effects on reproductive indices Reduction in body-weight gain in offspring during lactation

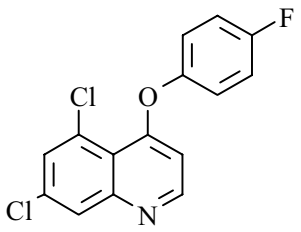
Lowest relevant reproductive NOAEL	20 mg/kg bw per day (parents and offspring) 110 mg/kg bw per day (reproduction)
Developmental target / critical effect	No specific fetal effects
Lowest relevant developmental NOAEL	80 mg/kg bw per day (maternal toxicity in rabbits). 80 mg/kg bw per day (fetal effects)
Neurotoxicity / delayed neurotoxicity	
Acute neurotoxicity	No adverse effects
12-month investigation of neurotoxicity within a long-term study in rats	No neurotoxic effects.
Other toxicological studies	
Induction of liver xenobiotic metabolizing enzymes (2-week dietary study):	NOAELs: 45 mg/kg bw per day (rats); 55 mg/kg bw per day (mice)
Medical data	
	Sensitization in production-plant personnel. No other adverse effects reported.

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.2 mg/kg bw	Rat, 2-year study; dog, 1-year study; rat, study of reproductive toxicity	100
ARfD	Unnecessary	—	—

RESIDUE AND ANALYTICAL ASPECTS

Chemical name: 5,7-dichloro-4-quinolyl 4 fluorophenyl ether



Animal metabolism

The Meeting received results of an animal metabolism study in lactating goats. Two goats were orally dosed with phenoxy ^{14}C-quinoxyfen (purity > 98%), twice daily for five consecutive days, at a rate of 10.7 mg quinoxyfen/kg feed. Similarly, two goats were treated with quinoline ^{14}C-quinoxyfen, twice daily for five consecutive days, at a rate of 11.7 mg quinoxyfen/kg feed.

Urine-faeces-cage wash accounted for 77–80% of the total administered dose. Milk contained 0.5–0.9%, liver 0.9–1.3%, and kidney 0.0–0.05%. The radioactive residue appeared to plateau in milk on day 4. Total radioactive residues (TRRs) in tissues and milk from use of the phenoxy labelled quinoxyfen were 0.34 mg/kg in kidney, 1.0 mg/kg in liver, 0.032 mg/kg in muscle, 0.20 mg/kg in omental fat, and 0.11 mg/kg in milk (16 hours after final dose); and from the use of the quinoline labelled quinoxyfen, 1.5 mg/kg in liver, 0.22 mg/kg in kidney, 0.032 mg/kg in muscle, 0.32 mg/kg in perirenal fat, and 0.064 mg/kg in milk.

Quinoxyfen was identified in milk (30–40% TRR), kidney (2–4% TRR), liver (10–20% TRR), and fat (50–97% TRR). DCHQ (5,7-dichloro-4-hydroxyquinoline) and/or 4-fluorophenol, resulting from cleavage of the ether linkage, was/were found in small amounts (< 5% TRR) in milk, kidney, and liver. Enzyme deconjugation of liver extracts indicated additional substantial quantities of these two compounds (13–20% TRR) present as conjugates. Less than 5% TRR was attributed to isomeric hydroxy quinoxyfens in liver, milk, and subcutaneous fat. 2-Oxo-quinoxyfen was found in milk at a maximum of 1.4% TRR.

The metabolism in goat and rat are qualitatively similar. Cleavage of the ether linkage to form 4-fluorophenol and DCHQ is seen in both animals. Isomers of fluorophenyl-ring hydroxylated quinoxyfen were found in the rat (bile and faeces), whereas isomers of quinoline-ring hydroxylated quinoxyfen (2-oxo) were found in the goat metabolism study. The latter were at very low levels (< 0.1% of the administered dose for the 2-oxo quinoxyfen) in the rat.

The Meeting concluded that the major metabolite in ruminant commodities from the oral administration of quinoxyfen is the parent quinoxyfen. Degradation from cleavage of the ether linkage generates free DCHQ and 4-fluorophenol. Another minor pathway involves formation of hydroxy derivatives.

Plant metabolism

The Meeting received plant metabolism studies for the foliar application of phenoxy- and quinoline-labelled [^{14}C] quinoxyfen, in separate experiments, to winter wheat, sugar beets, grapes, cucumber and tomato.

In each crop tested, parent quinoxyfen was found to be a significant to very major portion of the TRR: 8–27% TRR in wheat straw, 25% TRR in sugar beet root, 19–30% TRR in sugar beet tops, 93–98% TRR in grapes, 64–74% TRR in cucumber fruit, and 63–65% TRR in tomato fruit. DCHQ (7% TRR) and 4-fluorophenol (17% TRR) were found in sugar beet tops, indicative of ether bond cleavage. CFBPQ (2-chloro-10-fluoro(1)benzopyrano (2,3,4-de)quinoline), a product of photolysis, was also found in sugar beet tops (3–5% TRR) and possibly in wheat straw at 2% TRR. The 2-oxo quinoxyfen and p-hydroxyphenoxy quinoxyfen metabolites were tentatively identified at low concentrations (< 5% TRR) in several crops. Much of the unidentified extractable radioactivity in

wheat straw was found to be multicomponent and of an acidic anionic nature (about 20% TRR) not related to conjugates of quinoxyfen with natural products.

About ≥ 20% of the TRR in mature wheat straw was characterized as lignin, and 25% was associated with cellulose. About 13–53% TRR in wheat grain (100% TRR = 0.03 mg/kg) was associated with starch. About 10% TRR in tomato was associated with lignin, cellulose, and hemicellulose.

Quinoxyfen was shown to have no tendency to translocate in grape vines. Radiolabeled material applied only to some vine leaves did not move to the fruit or to untreated leaves.

The Meeting concluded that quinoxyfen is a major portion of the residue when applied in a foliar fashion to several crop types (grapes, cucumber and tomato). In wheat quinoxyfen was extensively metabolized with portions of the molecule becoming associated with natural plant constituents. Minor metabolic pathways were cleavage of the ether bond, photolysis, and hydroxylation of the quinoline or phenyl rings.

Environmental fate

The Meeting received information on the aqueous hydrolysis, aerobic soil metabolism, aqueous photolysis, and soil photolysis of quinoxyfen. Confined rotational crop studies with radiolabeled quinoxyfen were also provided.

Quinoxyfen is stable under aqueous hydrolysis at pH 7 and 9, but degrades slowly under acidic hydrolysis conditions. The half-life at pH 4 at 25^{o} C is about 75 days. The hydrolysis product was identified as DCHQ.

Quinoxyfen is relatively stable under conditions of dark aerobic soil metabolism. After 200 days, 53–81% of the quinoxyfen applied to various soil types remained. Some 0–27% had been converted to 2-oxo quinoxyfen, and 0–5% was present as DCHQ. About 15–25% of the original quinoxyfen had become bound to the soil. Less than 2% had been converted to carbon dioxide. Half lives of 90 to 500 days were calculated for the various soil types.

Quinoxyfen degraded in aqueous solution under artificial light (298 nm) to yield CFBPQ and DCHQ (minor). Half lives under typical use conditions were calculated to vary from 7 to 16 hours. Other work under natural sunlight conditions in water and water sediment systems showed the rapid loss of quinoxyfen, with no quinoxyfen remaining after 1 day. CFBPQ formed, but rapidly degraded

In contrast, quinoxyfen degraded slowly on the surface of sandy loam soil when exposed to simulated natural light. The half life was estimated to be equivalent to > 2 years in spring in England. DCHQ was identified in minor amounts, but the major metabolite remained unknown.

The uptake of radiolabeled quinoxyfen from soil into three succeeding crops (turnips, sunflower and cabbage) was reported. The quinoxyfen was applied at a rate equivalent to 400 g ai/ha, typical of the maximum seasonal use rate. Mature crop parts contained very low levels of radioactive residue, 0.4–3.5 µg/kg.

The Meeting concluded that quinoxyfen is relatively stable under aerobic conditions in soil and at neutral and alkaline pH in water, it undergoes rapid photolytic degradation in water systems, and that residues of quinoxyfen in rotational crops are unlikely.

Methods of Analysis

The Meeting received information for analytical methods for the quantitative determination of quinoxyfen in a variety of crops. The methods were used for data collection in the supervised field trials and livestock feeding studies, and several of the methods were validated by independent laboratories for use as enforcement methods. The methods were typically validated at 0.01 mg quinoxyfen/kg matrix for fruits, vegetables, and grains, with some exceptions (sugar beet tops, 0.2

mg/kg; barley and wheat straw and hops, 0.05 mg/kg). The methods were validated at 0.001 mg/kg for milk, and at 0.01 mg/kg for muscle, kidney, fat, and eggs. Bovine liver was problematic, and adequate recoveries were not achieved at levels of 0.01–1.0 mg/kg. Recovery in liver was 40% to 60%.

The various analytical methods for determination of residues of quinoxyfen in plant and animal matrices follow similar partitioning, clean-up and quantification procedures. Generally, quinoxyfen residues are extracted from plants and animal tissues samples with acidic acetonitrile. After addition of sodium bicarbonate solution to an aliquot of the extract, quinoxyfen is partitioned into hexane, which is then evaporated to dryness. The residue is reconstituted in hexane prior to an aminopropyl solid phase extraction using 1% acetone in hexane to elute quinoxyfen residues. The eluate is evaporated to dryness and reconstituted in 0.1% corn oil in tri-methyl pentane (TMP). Quinoxyfen is quantified either by gas chromatography with mass selective detection (GC-MSD) or by HPLC with UV absorbance. Specific methods differ in the clean-up steps, e.g., the use of gel permeation chromatography for livestock matrices.

The Meeting concluded that adequate analytical methods exist for the determination of quinoxyfen in crops and livestock commodities (except liver) both for data collection and MRL enforcement purposes.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of quinoxyfen in a variety of crop and livestock matrices. In all cases, quinoxyfen was shown to be stable in the macerated matrices under conditions of frozen storage for an interval at least as great as the storage interval of supervised field trial or livestock feeding samples.

Quinoxyfen was stable under conditions of frozen storage for at least 80 days in cherries, 365 days in grapes, 255 days in grape juice and raisins, 530 days in wheat grain and straw, 110 days in dried hops, 280 days in lettuce, 980 days in strawberry, 320 days in bell pepper, 250 days in melons, 240 days in milk, 190 days in kidney and muscle, and 220 days in fat. Quinoxyfen appeared to be unstable in liver, 60% remaining at 240 days, but the correction for the average concurrent recovery yields a percent remaining of 93%.

The Meeting concluded that quinoxyfen is stable in a variety of analytical crop, processed commodity, and livestock commodity samples under frozen storage conditions.

Residue definition

The plant and ruminant metabolism studies show that a major portion of the residue is parent quinoxyfen. There was no indication that substantial portions of quinoxyfen exist as conjugates in the metabolic mixtures. In plant studies, significant degradation with reincorporation of the radiolabel into natural products was indicated.

No metabolism study in poultry was provided. The poultry feeding study utilized radiolabeled quinoxyfen, but no attempts were made to identify the radiolabeled residues in eggs and tissues.

The available analytical methods determine only quinoxyfen.

The residue definition in Australia, the European Union, and the United States is quinoxyfen.

Ruminant feeding studies show that quinoxyfen preferentially accumulates in fat as opposed to muscle (10:1). Likewise the quinoxyfen ratio between cream and whole milk was about 8 to 1. The goat metabolism study indicated that the TRR in the various fats was about 10× those in muscle. Finally, the octanol/water partition coefficient for quinoxyfen is 4.7.

The Meeting concluded that the residue definition for both enforcement and dietary exposure considerations for plant commodities and for farm animal commodities is quinoxyfen. The Meeting also decided that quinoxyfen is fat-soluble.

Results of supervised trials on crops

The Meeting received supervised trials data for the foliar application of quinoxyfen as a suspension concentrate formulation (SC) to a variety of crops, including cherries, grapes, strawberries, currants, melons, peppers, lettuce, sugar beets, wheat, barley, and hops.

Cherries

Field trials are reported from the USA (GAP: 250 g/L SC, 0.12 kg ai/ha, five applications per season, 7 day PHI). The ranked order of residue values on cherries (pitted) for 13 trials conducted at maximum GAP is: 0.03, 0.05, 0.08 (2), 0.11 (2), 0.12, 0.13 (2), 0.14 (2), 0.15, and 0.27 mg/kg. The Meeting estimated an STMR of 0.12 mg/kg, HR of 0.27 mg/kg and a maximum residue level of 0.4 mg/kg.

Grapes

Field trials are reported from France (GAP: 250 g ai/L SC, 0.05 kg ai/ha, three applications per year at 7–10 day intervals, 21 day PHI), Germany (GAP: 250 g ai/L EC, 0.005 kg ai/hL, four applications maximum at 10–14 day intervals, 21 day PHI, the application volume depends on the growth stage), Italy (GAP: 250 g ai/L SC, 0.008 kg ai/hL, five applications maximum per year at 8–14 day intervals, 28 day PHI), Spain (GAP: 250 g ai/L SC, 0.075 kg ai/ha, 0.008 kg ai/hL, five applications maximum per year at 10–18 day intervals 30 day PHI for wine grapes, 21 day PHI for table grapes), US (GAP: 250 g ai/L SC, 0.12 kg ai/ha, five applications maximum per season or 0.60 kg ai/ha/year at 7–21 day interval, 14 day PHI), Canada (GAP: no label, use USA), and Australia (GAP: 250 g ai/L SC, 0.005 kg ai/hL, three applications maximum at 7–14 day intervals, 14 day PHI).

The trials in France and Germany consisted of 6, 7, or 10 repeat applications. Applications made more than 30 days before harvest will not contribute significantly to the final residue. With the 6–13 day retreatment intervals and a 21 day PHI, only the last three applications will contribute to the residue. The ranked order of residues from trials conducted at the maximum GAP with the additional repeat applications (n=9) in France and Germany is: 0.02, 0.04, 0.04, 0.05, 0.05, 0.06, 0.09, 0.13, and 0.36 mg/kg.

The ranked order of the residue values on grapes for eight trials conducted at the maximum GAP in Italy is: 0.04, 0.06, 0.07, 0.10, 0.17, 0.18, 0.30, 0.49 mg/kg. The ranked order of the residue values on grapes for trials conducted at the maximum GAP in Spain is: 0.02, 0.04, 0.08, 0.22 mg/kg.

The ranked order for 13 trials in the US conducted at the maximum GAP is: 0.06, 0.08 (2), 0.09, 0.13 (2), 0.15 (3), 0.18, 0.22, 0.24, 0.44 mg/kg. The ranked order for two trials in Canada conducted at the maximum GAP of the US is: 0.22, 0.29 mg/kg.

Fifteen trials conducted in Australia comply with the PHI of 14 days, 0.01, 0.05, 0.06, 0.09 (2), 0.15 (2), 0.17, 0.18, 0.23, 0.41, 0.45, 0.54, 0.82, 1.1 mg/kg

The trial residue values from France, Germany, Italy, Spain, Canada, US, and Australia appear to be from the same population and are combined (n = 51) in rank order: 0.01, 0.02 (2), 0.04 (4), 0.05 (3), 0.06 (4), 0.07, 0.08 (3), 0.09 (4), 0.10, 0.13 (3), 0.15 (5), 0.17 (2), 0.18 (3), 0.22 (3), 0.23, 0.24, 0.29, 0.30, 0.36, 0.41, 0.44, 0.45, 0.49, 0.54, 0.82, and 1.1 mg/kg. The Meeting estimated an STMR of 0.13 mg/kg, HR of 1.1 mg/kg and a maximum residue level of 2 mg/kg.

Strawberries

Field trials were reported to the Meeting from Germany (GAP: 250 g ai/L SC, 0.12 kg ai/ha, 0.006 kg ai/hl, two applications per season, 14 day PHI) and the USA (250 g ai/L SC, 0.11 kg ai/ha, four applications per season (0.44 kg ai/ha/season), 1 day PHI).

The residue values in ranked order from the eight trials in Germany at maximum GAP were: 0.01, 0.02, 0.04, 0.05, 0.07, 0.09, 0.12, and 0.16 mg/kg.

The residue values in ranked order from the six trials in the USA at maximum GAP are: 0.16, 0.18, 0.24, 0.41, 0.46, and 0.56 mg/kg. The values of Germany and the USA are not from the same population.

Using the residue values (n=6) from the USA, the Meeting estimated as STMR of 0.32 mg/kg, HR of 0.56 mg/kg and a maximum residue level of 1 mg/kg.

Currants

Supervised field trial studies for the foliar application of quinoxyfen to black currants in Germany were reported to the Meeting. The GAP is: 240 g ai/L, 0.075 kg ai/ha, 0.0075 kg ai/hL, three applications per year, 14 day PHI.

The residue values in ranked order (n=7) for trials conducted at maximum GAP were: 0.04, 0.05, 0.06, 0.20, 0.28, 0.30, and 0.40 mg/kg.

The Meeting estimated an STMR of 0.20 mg/kg, HR of 0.40 mg/kg and a maximum residue level of 1 mg/kg.

Melons

Field trials on melons were reported from Spain (GAP: 250 g ai/L SC, 0.0075 kg ai/hL, three applications per year, 7 day PHI), Italy (GAP: 250 g ai/L SC, 0.006 kg ai/hL, 7 day PHI), Greece (No label available, use GAP Italy), and the USA (GAP: 250 g ai/L SC, 0.11 kg ai/ha, four applications per year, 3 day PHI).

The residues in ranked order for whole melons from six trials at maximum GAP in Italy and two trials in Greece are: 0.01 (2), 0.02 (4), and 0.03 (2) mg/kg; and the residues in ranked order for the pulp only were: < 0.01 (6) and 0.02 (2) mg/kg.

The residues in ranked order for whole melons from eight trials at maximum GAP in Spain are: 0.01 (4) and 0.02 (4) mg/kg; and the residues in ranked order for the pulp only are: ND - < 0.01 (8) mg/kg.

The residues in ranked order for whole melons (cantaloupes) from six trials at maximum GAP in the USA (taking into account the permitted maximum total seasonal rate) are: < 0.01, 0.02, 0.03 (3), and 0.05 mg/kg. No data were provided on pulp.

The data from the various countries are from the same population and are combined (n=22) in ranked order, for whole melon: 0.01 (7), 0.02 (9), 0.03 (5), and 0.05 mg/kg; and for pulp (n=16), 0.01 (14) and 0.02 (2) mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg and HR of 0.02 mg/kg for quinoxyfen in melon pulp and a maximum residue level of 0.1 mg/kg for quinoxyfen in/on whole melon, except watermelon in both cases.

Peppers

A field trial residue study was reported from the USA (GAP: 250 g ai/L SC, 0.15 kg ai/ha, four applications per year, 0.60 kg ai/ha/year, 3 day PHI).

The residues (n=11) in ranked order for quinoxyfen residues on peppers from application at maximum GAP were: 0.01, 0.02, 0.09, 0.12, 0.15 (2), 0.16, 0.17, 0.23, 0.52, and 0.64 mg/kg.

The Meeting estimated an STMR of 0.15 mg/kg, HR of 0.64 mg/kg and a maximum residue level of 1 mg/kg for peppers (bell and non-bell).

Lettuce

A field study report was provided for the foliar application of quinoxyfen to lettuce (leaf and head) in the USA. The GAP in the USA is: 250 g ai/L SC, 0.11 kg ai/ha, four applications per season and 0.44 kg ai/ha/season, and a PHI of 1 day.

Seven trials on head lettuce were at maximum GAP, with residues in ranked order of: 0.91, 1.0, 1.2, 1.4, 2.1, 3.1, and 5.3 mg/kg. Six trials on leaf lettuce were at maximum GAP, with residues in ranked order of: 1.3, 2.9, 3.4, 4.3, 6.9, and 13 mg/kg.

The Meeting estimated an STMR of 1.4 mg/kg, HR of 5.3 mg/kg and a maximum residue level of 8 mg/kg for lettuce (head).

The Meeting estimated an STMR of 3.8 mg/kg, HR of 13 mg/kg and a maximum residue level of 20 mg/kg for lettuce (leaf).

Sugar beet roots

Field trial data were received from Germany (GAP: 500 g ai/LC SC, 0.12 kg ai/ha, two applications per season, 28 day PHI), UK (GAP: 500 g ai/L SC, 0.15 kg ai/ha, two applications, 28 day PHI), and France (GAP: 500 g ai/L SC, 0.15 kg ai/ha, one application, 28 day PHI).

The residue values for trials conducted in the three European countries at maximum GAP in ranked order are: < 0.01 (4), 0.01 (3), 0.02 mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg and a maximum residue level of 0.03 mg/kg for sugar beet roots.

Wheat grain

Wheat grain trials were reported from France, Germany, and the UK. The GAPs are: 500 g ai/L SC, 0.15 kg ai/ha, one application in France with a PHI of 56 days; 500 g ai/L SC, 0.25 kg ai/ha, one application in Germany at growth stages BBCH 25–32 (tillering), and in the UK 500 g ai/L SC, 0.15 kg ai/ha, two applications until growth stage BBCH 49 (about 60 days PHI).

Some trials in Greece were evaluated against the GAP of France. The trials in North France were evaluated against the GAP of Germany.

The trials in Greece were not within the maximum GAP of France. The trials were conducted at rates in excess of the maximum GAP, and they resulted in finite residue values (> LOQ). Some trials (n=21) in France, Germany, and the UK conducted at or in excess of the maximum GAP of the respective countries yielded residue values below the LOQ. The residue values in ranked order were: < 0.01 (21) mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg and a maximum residue level of 0.01 (*) mg/kg for wheat grain.

Barley grain

Barley grain trials were reported from France, Germany, and the UK. The GAPs are: 500 g ai/L SC, 0.15 kg ai/ha, one application in France with a PHI of 56 days; 500 g ai/L SC, 0.25 kg ai/ha, one application in Germany at growth stages BBCH 25–32 (tillering), and in the UK 500 g ai/L SC, 0.15 kg ai/ha, two applications until growth stage BBCH 49 (about 60 days PHI).

All trials in Europe were conducted above the maximum GAP. Eight trials provided residue values below the limit of quantitation. The ranked order of residues is < 0.01 (8) mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg and a maximum residue level of 0.01 (*) mg/kg for barley grain.

Wheat straw

Wheat trials were reported from France, Germany, and the UK. The GAPs are: 500 g ai/L SC, 0.15 kg ai/ha, two applications per season one application in France with a PHI of 56 days; 0.25 kg ai/ha, one application in Germany at growth stages BBCH 25–32 (tillering), and in the UK 500 g ai/L SC, 0.15 kg ai/ha, two applications until growth stage BBCH 49 (about 60 days PHI). Some trials in Greece were evaluated against the GAP of France (South). The trials in the UK and in North France were evaluated against the GAP of Germany.

The residues in rank order in wheat straw (n=16) were: < 0.05 (5), 0.07, 0.09, 0.11, 0.13 (2), 0.19 (2), 0.21, 0.23, 0.27, 0.36 mg/kg. On a dry weight basis (88% DM) the values are: < 0.06 (5), 0.08, 0.10, 0.12, 0.15 (2), 0.22 (2), 0.24, 0.26, 0.31, 0.41 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.14 mg/kg.

Barley straw

Barley trials were reported from France, Germany, and the UK. The GAPs are: 500 g ai/L SC, 0.15 kg ai/ha, two applications per season one application in France with a PHI of 56 days; 0.25 kg ai/ha, a application in Germany at growth stages BBCH 25–32 (tillering), and 500 g ai/L SC, 0.15 kg ai/ha, two applications until growth stage Zadoks 49 (about 60 days PHI) in the UK. The trials in the UK and in North France were evaluated against the GAP of Germany.

The residues in barley straw in rank order (n=6) are: 0.22 (2), 0.30, 0.58, 1.23, 2.94 mg/kg. On a dry weight basis (89% DM) the values are: 0.25 (2), 0.34, 0.65, 1.38, 3.30 mg/kg. The Meeting estimated a maximum residue level of 5 mg/kg and an STMR of 0.50 mg/kg. The highest residue is 3.3 mg/kg.

Hops (dry)

Hops trials were reported from Germany (GAP: 250 g/L SC, 0.011 kg ai/hl, four applications or 0.5 kg ai/ha/season, PHI 28 days) and from the USA (GAP: 250 g/L SC, 0.15 kg ai/ha, four applications or 0.6 kg ai/ha/season, PHI 21 days).

Six trials in Germany were conducted at the maximum seasonal GAP, but with three applications rather than four. The sum of the three applications was within 30% of the seasonal maximum GAP. The residue values in ranked order were: 0.03, 0.04, 0.07, 0.37, 0.41, and 0.55 mg/kg.

Four trials in the USA were conducted at the maximum season GAP, with three applications rather than four. The residue values in ranked order were: 0.39, 1.2, and 2.2 mg/kg.

The trials in the USA and in Germany are not from the same population. The three trials in the USA provide insufficient data for the estimation of an STMR and maximum residue level.

Using the six trials from Germany, the Meeting estimated and STMR of 0.22 mg/kg and a maximum residue level of 1 mg/kg for residues of quinoxyfen in hops (dry).

Spices

Using a default processing (dehydration) factor of 10, the Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 1.5 mg/kg for dried chili peppers based on the maximum residue level and STMR of pepper

Sugar beet tops

Field trial data were received from Germany (GAP: 500 g ai/LC SC, 0.12 kg ai/ha, two applications per season, 28 day PHI), UK (GAP: 500 g ai/L SC, 0.15 kg ai/ha, two applications, 28 day PHI), and France (GAP: 500 g ai/L SC, 0.15 kg ai/ha, one application, 28 day PHI).

Three trials from Germany and four trials from the UK were conducted at the maximum GAP. The residue values from Germany in ranked order were: 0.10 (2) and 0.27 mg/kg. The residue values from the UK in ranked order are: 0.13, 0.22, 0.36, and 0.37 mg/kg. The combined values (n=7) in ranked order were: 0.10 (2), 0.13, 0.22, 0.27, 0.36, and 0.37 mg/kg.

The Meeting estimated an STMR of 0.22 mg/kg and a highest residue level of 0.37 mg/kg.

Fate of residues in storage

The effect of storage upon the fate of quinoxyfen residues was not reported to the Meeting.

Fate of residues during processing

Information on the fate of quinoxyfen in the processing of wheat, barley, and grapes was reported to the Meeting. No information was supplied on the fate of radiolabeled quinoxyfen under general processing conditions.

Winter wheat which had received foliar treatment with quinoxyfen was processed into flour and bread in separate studies in France and the UK. The wheat grain contained no residues (< 0.01 mg/kg) and while there was no apparent concentration of residue in bran, flour, or bread, no processing factors could be calculated.

Barley in the UK was treated at an exaggerated rate with quinoxyfen, and the grain at normal harvest was processed into malt and beer by a simulated commercial process. The processing factor for malt was 0.5 and that for beer was < 0.1. Using the STMR for barley (0.01 mg/kg), the Meeting estimated an STMR-P of 0.001 mg/kg for beer.

Processing studies for the conversion of grapes to wine were reported from France, Germany, and Italy. In all cases, the grapes had quantifiable field incurred residues of quinoxyfen. Three trials were conducted for the preparation of white wine and two for the preparation of red wine. The processing factor varied from 0.004 to 0.03, with a median and average value of 0.01. Applying this processing factor to the STMR of grapes (0.15 mg/kg), the Meeting estimated an STMR-P of 0.015 mg/kg for wine (from grapes).

A processing study for the conversion of grapes to raisins and grape juice was reported from the USA. Grapes with a quantifiable field incurred residue of quinoxyfen were processed in separate commercial-type procedures into raisins and pasteurized grape juice. The processing factors for raisins and juice were 0.66 and 0.06, respectively. Using the STMR value for grapes (0.15 mg/kg), the Meeting estimated STMR-Ps of 0.099 mg/kg and 0.009 mg/kg for raisins and grape juice, respectively.

Farm animal dietary burden

The Meeting estimated the dietary burden of quinoxyfen residues in farm animals on the basis of the diets listed in Appendix IX of the *FAO Manual*. Calculation from MRLs, highest residues and STMR-P values provides the levels in feed suitable for estimating MRLs for animal commodities, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage of dry matter is taken as 100% when MRLs and STMR values are already expressed as dry weight.

Estimated maximum dietary burden of farm animals

Commodity	Group	Residue (mg/kg)	Basis of Residue	Dry matter (%)	Diets			Residue contribution (mg/kg)		
					Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Barley grain	GC	0.01	MRL	88	50	30	80	0.006	0.005	0.009
Sugar beet leaves (tops)	AV	0.37	HR	23	20	10	-	0.32	0.16	-
Barley Straw	AS	3.3	HR	89	10	60		0.33	1.98	
TOTAL					80	100	80	0.66	2.14	0.01

The calculated maximum dietary burdens for beef cattle, dairy cows and poultry are 0.66, 2.1, and 0.01 ppm, respectively.

Estimated STMR dietary burden of farm animals

Commodity	Group	Residue (mg/kg)	Basis of Residue	Dry matter (%)	Diets			Residue contribution (mg/kg)		
					Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Barley grain	GC	0.01	STMR	88	50	30	80	0.006	0.003	0.009
Sugar beet leaves (tops)	AV	0.22	STMR	23	20	10	-	0.19	0.10	-
Barley Straw	AS	0.50	STMR	89	10	60	-	0.05	0.30	
TOTAL					80	100	80	0.25	0.40	0.01

The calculated STMR dietary burdens for beef cattle, dairy cows and poultry are 0.25, 0.40, and 0.01 ppm, respectively.

Farm animal feeding studies

The Meeting received two feeding studies for dairy cattle and a radiolabeled quinoxyfen feeding study for poultry (chickens). Friesian cows were fed for 28 consecutive days with diets containing 0.2, 0.6, 2.0, or 20 ppm quinoxyfen. Residues in whole milk reached a plateau by day 7 of 0.001, 0.002, and 0.007 mg/kg for 0.2, 0.6, and 2.0 ppm dosing levels, respectively. At the 20 ppm dosing level, the quinoxyfen residue spiked to 0.37 mg/kg on day 7 and then declined to an apparent plateau of 0.16 ppm by the final day.

At the 0.2 ppm feeding level, the maximum and average (n=3 cows) residue in whole milk (day 27) was < 0.001 mg/kg. In cream, the maximum residue was 0.007 mg/kg and the average residue was 0.003 mg/kg. At the 0.6 ppm feeding level, the maximum and average (n=3 cows) in whole milk (day 27) was 0.002 mg/kg and 0.002 mg/kg, respectively. In cream, the maximum residue was 0.02 mg/kg, and the average residue was 0.015 mg/kg.

At the 0.2 ppm feeding level, the maximum and average residues in liver, kidney, muscle, and fat were ND and ND, < 0.01 and < 0.01 mg/kg, ND and ND, and 0.02 and 0.01 mg/kg, respectively.

At the 0.6 feeding level, the maximum and average residues in liver, kidney, muscle, and fat were < 0.01 and < 0.01 mg/kg, < 0.01 and < 0.01 mg/kg, ND and ND, and 0.02 and 0.012 mg/kg, respectively.

At the 0.6 ppm feeding level, the maximum and average residues in milk were 0.002 mg/kg each. The maximum and average values in cream were 0.022 mg/kg and 0.016 mg/kg, respectively. The maximum and average residue values in liver and kidney were < 0.01 mg/kg each. The maximum and average values in muscle were ND (< 0.002 mg/kg). The maximum and average values in fat were 0.02 and 0.12 mg/kg, respectively.

At the 2 ppm feeding level, the maximum and average residues in milk were 0.010 and 0.0088 mg/kg, respectively. The maximum and average residues in cream were 0.077 and 0.068 mg/kg, respectively. The maximum and average residues in liver, kidney, and muscle were < 0.01 mg/kg. The maximum residue in fat was 0.10 mg/kg, and the average was 0.09 mg/kg.

Quinoxyfen total residues, mg/kg

Dietary burden (ppm) Feeding level [ppm]		Cream	Milk	Muscle		Liver		Kidney		Fat	
		Mean	Mean	Highest	Mean	Highest	Mean	Highest	Mean	Highest	Mean
MRL, beef cattle	(0.66)			(< 0.01)		(< 0.01)		(< 0.01)		(0.02)	
	[0.6]			[< 0.002]		[< 0.01]		[< 0.01]		[0.02]	
MRL, dairy cattle	(2.1)	(0.068)	(0.0088)								
	[2]	[0.068]	[0.0088]								
STMR beet cattle	(0.25)				(0.002)		(0.002)		(< 0.01)		(0.01)
	[0.2]				[< 0.002]		[< 0.002]		[< 0.01]		[0.01]
STMR dairy cattle	(0.40)	(0.01)	(0.002)								
	[0.2/0.6]	[0.003/0.016]	[< 0.001/0.002]								

A *poultry feeding* study consisted of four groups of 10 Isa Brown laying hens fed at the following dose levels: 0.1, 0.3, and 1.0 ppm of diet/ day. The hens were fed gelatin capsules containing a *radiolabelled* (mixture of ^{14}C-quinoline label and ^{14}C-phenoxy label) ^{14}C-quinoxyfen. Each daily dose was administered in a single capsule at the same time each day for 28 days. Only TRR was determined in the eggs and tissues. These levels were very low at a 0.1 ppm diet with maximum values of 0.003 mg/kg in eggs, 0.009 mg/kg in liver, 0.004 mg/kg in kidney, 0.0 mg/kg in muscle, and 0.013 mg/kg in fat. At the 1.0 ppm feeding level, TRR values were 0.025 mg/kg in eggs, 0.097 mg/kg in liver, 0.049 mg/kg in kidney, 0.009 mg/kg in muscle, and 0.063 mg/kg in fat. However, the TRR was not characterized or identified.

Animal commodity maximum residue levels

The Meeting estimated the following maximum residue levels for mammalian commodities, based on the cow feeding studies and the calculated dietary intake (see above): muscle, 0.01 (*) mg/kg; fat, 0.02 mg/kg; edible offal, 0.01 (*) mg/kg; milk fat, 0.2 mg/kg; milk, 0.01 mg/kg. The Meeting likewise estimated the following STMR values: muscle, 0.002 mg/kg; fat, 0.01 mg/kg; edible offal 0.01 mg/kg; milk fat, 0.02 mg/kg; milk, 0.002 mg/kg. The milk fat estimations assume that cream is 50% fat. Although the metabolic profile in poultry was not determined, the feeding study with radiolababeled quinoxyfen demonstrated very low levels of total residue at a feeding level of 0.1 ppm, the estimated dietary burden of poultry. Therefore, the MRLs for poultry commodities are estimated at the LOQs of the analytical method, 0.01 (*) mg/kg for each of poultry egg and edible offal, and 0.02 mg/kg meat

(fat). The STMRs are based on the TRR values and are estimated to be: eggs, 0.003 mg/kg; offal, 0.009 mg/kg; muscle, 0 mg/kg; and fat 0.013 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDI) of quinoxyfen, based on the STMRs estimated for 15 commodities for the thirteen GEMS/Food cluster diets were in the range of 0% to 1% of the ADI (Annex 3). The Meeting concluded that the long-term intake of residues of quinoxyfen resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term intake

The 2005 JMPR decided that an acute RfD is unnecessary. The Meeting therefore concluded that the short-term intake of quinoxyfen residues is unlikely to present a public health concern.

4.27 TEMEPHOS (WATER)

TOXICOLOGY

Temephos (*O*,*O*,*O*'*O*'-tetramethyl *O*,*O*'-thiodi-*p*-phenylene bis(phosphorothioate)) is an organophosphate insecticide. Temephos is one of the compounds recommended by WHO for mosquito larvicide treatment in potable water. No ADI had been established previously. For that reason, the WHO Drinking-water Guidelines programme recommended that temephos be evaluated toxicologically by JMPR. Temephos has not been previously evaluated by the JMPR.

For temephos, the specifications were established by JMPS and published as *WHO specifications and evaluations for public health pesticides*: *temephos* (1999).[47]

Several studies with temephos, including studies of acute oral toxicity, dermal toxicity inhalation toxicity, irritancy, skin sensitization, genotoxicity and special studies of neurotoxicity in hens, were certified as being compliant with GLP. Other available studies were carried out before the OECD guidelines on GLP were promulgated. The Meeting noted that the reports of some of the critical studies were available only as brief published articles that lacked some of the details normally required for completing an adequate risk assessment.

Biochemical aspects

When given to rats as an oral dose, temephos was rapidly absorbed. At least 40% of the administered dose was absorbed into the blood plasma. Clearance was rapid (mostly within 48 h), with about 40% of an orally administered dose being excreted in the urine and about 60% recovered in the faeces. Very little of the orally administered dose remained in tissues, but most (about 3% of the administered material) was in adipose tissue.

Metabolism in rats is by *S*-oxidation to form the primary toxicant, temephos sulfoxide, and by carboxylesterase-mediated hydrolysis to form 4,4'-thiodiphenol. Temephos and these primary metabolites can undergo secondary metabolism by glucuronidation or sulfation to form conjugates.

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[47] Available from http://www.who.int/whopes/quality/en/temephos.pdf

Toxicological data

Temephos was of low acute oral toxicity in rats ($LD_{50,}$ 4000–13000 mg/kg bw) and the mouse (LD_{50}, 2062 mg/kg bw).

Temephos did not cause irritancy to rabbits' eyes or to the skin of rabbits or guinea-pigs. It was not a skin sensitizer when tested on guinea-pigs in the Buehler test.

In short-term studies with temephos administered in the diet or by gavage in rats (28–92 days), rabbits (30–35 days) and dogs (90–129 days), acetylcholinesterase activity in erythrocytes and, in some instances, in the brain was measured and animals were observed for clinical signs. The overall NOAEL for clinical signs was 10 mg/kg bw per day as derived from a study in rats treated by gavage for 28- and 44-days and from a study in rabbits treated by gavage for 35 days. This NOAEL is supported by the absence of clinical signs at 5.4 and 30 mg/kg bw per day, the highest doses tested, in the multigeneration study in rats and in a study of developmental toxicity in rabbits treated by gavage, respectively. Additional support is provided by the presence of mild signs in dogs given diets containing temephos at a concentration of 500 ppm for about 11 weeks, approximately equivalent to 25 mg/kg bw per day. The NOAEL for biologically significant (i.e. 20% greater than control values) inhibition of brain acetylcholinesterase activity was 54 ppm (2.3 mg/kg bw per day) in a 90-day dietary study in rats. In a 90-day dietary study in dogs, "marked" inhibition (no control values provided) in brain and > 95% inhibition of erythrocyte acetylcholinesterase activity were reported after treatment at 500 ppm (25 mg/kg bw per day), and there was no inhibition of erythrocyte acetylcholinesterase activity at 18 ppm (about 1 mg/kg bw per day). The overall NOAEL for biologically significant (i.e. 20% greater than control values) inhibition of erythrocyte acetylcholinesterase activity was 1.8 mg/kg bw per day in a 99-day dietary study in rats. Occasional and inconsistent reductions of erythrocyte acetylcholinesterase activity observed at lower doses in some studies in rats were not considered to be significant. The Meeting noted that between 80% and more than 90% inhibition of erythrocyte acetylcholinesterase activity was not associated with clinical signs of cholinergic toxicity in a 99-day dietary study in rats or in a limited 129-day dietary study in dogs, and this suggested that inhibition of erythrocyte acetylcholinesterase activity was not an appropriate indicator of inhibition of the activity of acetylcholinesterase in the peripheral nervous system. Consequently, the Meeting considered that the critical end-point for human risk assessment was inhibition of brain acetylcholinesterase activity and the NOAEL was 2.3 mg/kg bw per day.

In a study in human male volunteers who were prisoners, 10 men were given temephos at a dose of 1.1 mg/kg bw per day for 4 weeks and 9 men took temephos at a dose of 4.27 mg/kg bw per day for 5 days. There was no inhibition of cholinesterase activity in the plasma or in erythrocytes. This study in human volunteers who were prisoners was considered to be ethically acceptable according to the standards of the time it was performed (1967), although it would not be acceptable by current standards applied to new studies. The Meeting considered that the doses and the outcomes in this study in humans were not sufficiently well described for the results of this study to be used in isolation to set an ADI or an ARfD.

Hepatotoxicity was inconsistently seen in a series of briefly reported experiments in rabbits. However, there was no evidence of any hepatotoxicity at doses of up to 30 mg/kg bw per day in a well-conducted and well-reported study of developmental toxicity in rabbits.

In a long-term combined study of toxicity and oncogenicity in rats, no adverse effects on neoplastic or non-neoplastic pathology were found at any dietary dose tested, up to the highest dose of 15 mg/kg bw per day. Cholinesterase activities were not measured in this study.

Temephos gave uniformly negative results in an adequate range of tests for genotoxicity in vitro and in vivo. The Meeting concluded that temephos is unlikely to be genotoxic.

Studies of reproductive toxicity in rats showed that temephos did not adversely affect reproduction when given as oral doses of up to 125 ppm (5.4 mg/kg bw per day) for up to three generations. In a one-generation study, temephos at a dose of 500 ppm (22.5 mg/kg bw per day)

inhibited erythrocyte cholinesterase in mothers (90%) and in 21-day-old pups (30%), but other doses were not tested. There was no developmental toxicity or hepatotoxicity in rabbits given temephos at oral doses of up to 30 mg/kg bw per day.

Studies in hens showed that temephos did not have the potential to cause organophosphate-induced delayed neuropathy and did not cause demyelination of nerves.

Although, for the purposes of vector control, temephos is used at a concentration of up to 1 mg/L in drinking-water, only one report of an investigation of possible effects in exposed people was available. Approximately 2000 people were exposed to drinking-water containing temephos for 19 months without any adverse effects on plasma or erythrocyte cholinesterase activity. No illness attributable to the treatment was seen and all eight babies born during the study period were normal. The drinking-water was treated monthly with temephos. The intended concentration of 1 ppm was not achieved and only one sample contained temephos at a concentration of more than 0.5 ppm.

Toxicological evaluation

Temephos is recommended by WHO for addition to potable water as larvicide treatment at an application rate not exceeding 1 mg/L. Assuming that an adult weighing 60 kg would consume 2 l per day of drinking-water containing temephos at 1 mg/L, this would be equal to an oral exposure of 0.033 mg/kg bw. However, given the limited solubility of temephos in water, incomplete dissolution in drinking-water would be expected and this could result in actual exposures being appreciably less than this estimate. Consequently, 0.033 mg/kg bw per day was regarded as a worst-case upper limit of exposure.

Some of the studies that were critical to the assessment were of poor quality. The Meeting considered that the database was insufficiently robust to serve as the basis for establishing an ADI or an ARfD for temephos.

The Meeting concluded that the relevant NOAEL for human risk assessment is 2.3 mg/kg bw per day on the basis of inhibition of brain acetylcholinesterase activity in rats. This NOAEL provides a margin of exposure (MoE) from the estimated oral exposure derived from drinking-water treated with temephos of about 70. The MoE for clinical signs and the, possibly secondary, effects on development and reproduction are in the range of > 160 (highest dose tested in rat multigeneration study) to 900 (study of developmental toxicity in rabbits). In addition, reassurance is provided by the MoEs of 130 and 33 provided by the absence of clinical signs and erythrocyte cholinesterase inhibition in the poorly described study in volunteers treated for 5 or 14 days, respectively.

In addition to this safety assessment, the concerned WHO programmes will consider efficacy of the treatment and additional relevant exposure scenarios before further recommending such a treatment and deriving water-guideline values.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	28-day and 44-day study of toxicity[b]	Clinical signs	10 mg/kg bw per day	100 mg/kg bw per day
	90-day study in rats[a]	Inhibition of acetylcholinesterase in brain	2.3 mg/kg bw per day[d]	—
	2-year study of toxicity and carcinogenicity[a]	Carcinogenicity (cholinesterase activity not measured)	300 ppm (15 mg/kg bw per day)[d]	—

	Three-generation study of reproduction[a]	Maternal	125 ppm (5.4 mg/kg bw per day)[d]	—
		Offspring	125 ppm (5.4 mg/kg bw per day)[d]	
Rabbit	35-day study of toxicity[b]	Clinical signs	10 mg/kg bw per day[d]	—
	Study of developmental toxicity[b]	Maternal	30 mg/kg bw per day[d]	—
		Developmental	30 mg/kg bw per day[d]	—
Dog	90-day study of toxicity[a]	Inhibition of acetylcholinesterase in erythrocytes	18 ppm (0.9 mg/kg bw per day)	700/500 ppm (35/25 mg/kg bw per day)
		Inhibition of acetylcholinesterase in brain	—	700/500 ppm (35/25 mg/kg bw per day)[e]
	129-day study of toxicity[a]	Inhibition of acetylcholinesterase in erythrocytes	10 ppm (0.6–0.8 mg/kg bw per day)	50 ppm (3–4 mg/kg bw per day)
Chickens	Neurotoxicity[b]	No organophosphate-induced delayed neurotoxicity observed	1705 mg/kg bw[e]	—
Humans	Investigation of clinical signs and effects on cholinesterase activities in erthrocytes and plasma[c]	No adverse effects reported	1.1 mg/kg bw per day for 4 weeks or 4.27 mg/kg bw per day for 5 days[e]	—

[a] Dietary administration

[b] Oral gavage

[c] Administration in a drink

[d] Highest dose tested

[e] Only dose at which measurements of the critical end-point were made.

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	At least 40% of administered dose absorbed.
Distribution	Most of the retained residues were in the fat (about 0.5% of administered dose)
Potential for accumulation	Low
Rate and extent of excretion	Most of the administered oral dose recovered in the urine and faeces within 48 hours. About 40% in urine.

Metabolism in mammals	By hydrolysis and *S*-oxidation plus conjugation.
Toxicologically significant compounds	Temephos and temephos sulfoxide
Acute toxicity	
Rat, LD_{50}, oral	4000 to 13 000 mg/kg bw
Rat, LD_{50}, dermal	2000 to > 4000 mg/kg bw
Rat, LC_{50}, inhalation	> 4.79 mg/L
Rabbit, skin irritancy	Non-irritant
Rabbit, eye irritation	Non-irritant
Guinea-pig, skin sensitization (test method)	No skin sensitizing potential (modified Buehler test)
Short-term studies of toxicity	
Critical effects	Inhibition of brain acetylcholinesterase activity
Lowest relevant oral NOAEL	2.3 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	25 mg/kg bw per day (rabbit)
Genotoxicity	
	Not genotoxic (on the basis of tests in vitro)
Long-term studies of toxicity and carcinogenicity	
Critical effects	No adverse effects detected at any dose tested (cholinesterase activities not measured)
Lowest relevant oral NOAEL	15 mg/kg bw per day (rats, highest dose tested)
Carcinogenicity	Not carcinogenic in rats
Reproductive toxicity	
Reproductive target/critical effects	None
Lowest relevant reproductive NOAEL	5.4 mg/kg bw per day (rats, highest dose tested)
Developmental critical effect	None
Lowest relevant developmental NOAEL	10 mg/kg bw per day for maternal toxicity
	30 mg/kg bw per day (highest dose tested) for developmental effects
Neurotoxicity studies in hens	
Lowest relevant neurotoxicity NOAELs	1705 mg/kg bw (highest dose tested caused no neuropathy)
Observations in humans	
Volunteer studies	No effects on plasma or erythrocyte cholinesterase activity at 1.1 mg/kg bw per day for 4 weeks, or at 4.27 mg/kg bw per day for 5 days

4.28 THIABENDAZOLE (065)

TOXICOLOGY

Evaluation for an acute reference dose

Thiabendazole, the ISO approved name for 2-(4-thiazolyl)-1*H*-benzimidazole (CAS No. 148-79-8), is a benzimidazole compound used as a systemic fungicide in agriculture. Thiabendazole is also used as a broad-spectrum anthelmintic in various animal species, for control of parasitic infestations in humans, and in materials protection (as a preservative in adhesives, coatings, paper, textiles and paints).

The toxicology of thiabendazole was evaluated by the JMPR in 1970 and 1977. In 1977, the Meeting established an ADI of 0–0.3 mg/kg bw on the basis of the absence of effects at 3 mg/kg bw per day in a 6-month study in human volunteers, and a safety factor of 10.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) reviewed the toxicology of thiabendazole in 1992, 1997 and 2002. In 1997, the Committee established an ADI of 0–0.1 mg/kg bw. In 2002, the Committee established a conservative ARfD of 0.1 mg/kg bw based on NOAELs for haemolytic anaemia in repeat-dose studies of toxicity in rats and dogs, in view of the lack of more appropriate acute toxicity data.

Following the JECFA evaluation of thiabendazole in 2002, the sponsor conducted several studies of acute toxicity with thiabendazole administered by gavage or in the diet that were designed specifically to derive an ARfD and to determine the pharmacokinetic events that apply under these exposure scenarios. At the request of CCPR at its Thirty-eighth Session, thiabendazole was re-evaluated at the present Meeting in order to establish an ARfD. The Meeting also reviewed some relevant data from previous evaluations (studies of reproductive toxicity and developmental toxicity, as well as data from humans).

All new studies with thiabendazole were certified as complying with GLP.

Toxicological data

Previously evaluated studies

Studies to establish median lethal doses of thiabendazole given orally (LD_{50} values > 2000 mg/kg bw) did not provide any indication of acute effects.

In 2002, JECFA considered that emesis in dogs and effects on the kidney, haematopoietic system and development were relevant end-points for establishing an ARfD.

Clinical effects: In dogs, the NOAEL for emesis was 40 mg/kg bw per day. Common side-effects reported in humans receiving therapeutic doses (25 mg/kg bw or greater, twice per day for 1–10 days) included anorexia, nausea, vomiting and dizziness. In a study in volunteers, in which controls were given a placebo, a dose of 125 mg of thiabendazole given twice per day for 24 weeks (equivalent to 3.6 mg/kg bw per day for a 60 kg person) did not cause significant changes in subjective side-effects.

Kidney effects: In single-dose studies in mice, renal toxicity, mainly in the proximal tubules, was observed at doses of 250 mg/kg bw and higher, and consisted of histopathological changes including mitochondrial swelling and ultimately necrosis of epithelial cells. Effects were most severe 2–3 days after dosing; after that time, tissue repair processes began. Apart from tubular dilatation, all effects were either fully or partly reversed within 10 days of administration. The NOAEL was 125 mg/kg bw.

Haematological effects: Changes indicative of anaemia were occasionally seen early in 4- or 13-week studies in rats and 14- and 53-week studies in dogs. As histopathological changes indicative of anaemia occurred after one or several doses, they were considered by the 2002 JECFA to be relevant for assessing acute exposure. The NOAELs for these effects in rats and dogs were 9 and 10 mg/kg bw per day, respectively. However, in single-dose studies in rats treated by gavage assessed by the present Meeting (JMPR 2006), no treatment-related changes in haematology parameters were observed at up to 1000 mg/kg bw, the highest dose tested.

In a study in volunteers, 50 men received an oral dose of 125 mg of thiabendazole twice per day for 24 weeks (equivalent to 3.6 mg/kg bw per day for a 60 kg person), and 50 other men were given a placebo. Thiabendazole did not affect haematological parameters in blood after 4, 12 or 24 weeks of treatment. However, histopathological examinations, which in animals were more sensitive indicators of haematotoxicity, were obviously not performed.

Developmental effects: As teratogenic effects and early resorptions may be induced by a single dose within a certain sensitive period, these effects on the fetus are particularly relevant to setting an ARfD. Five studies were provided for assessment by the 2006 JMPR. In a published study in mice, teratogenic effects were observed after a single oral dose on day 9 of gestation. These effects consisted of deformed limbs at doses of 480 mg/kg bw and higher (NOAEL, 270 mg/kg bw) and fusion of vertebrae and ribs at 240 mg/kg bw and higher (NOAEL, 130 mg/kg bw). Excessive maternal mortality and lack of data on other maternotoxic effects compromised the interpretation of this study and the 2006 JMPR considered this study as supplementary information only. In another study in mice, no teratogenic effects were observed when thiabendazole was given at doses of up to 200 mg/kg bw per day on days 6–15 of gestation. Thiabendazole was not teratogenic in rats at doses of up to 80 mg/kg bw per day, the highest dose tested.

Increased rates of resorption were observed in mice and rabbits, but not in rats. In mice, the NOAEL for this effect was 700 mg/kg bw per day when the animals were treated by gavage on days 7–15 of gestation, and 1400 mg/kg bw after a single dose administered by gavage on day 9 of gestation. Rabbits exposed on days 6–18 of gestation showed increased rates of resorption (mainly early resorption) at oral doses of 120 mg/kg bw per day and higher, with a NOAEL of 24 mg/kg bw per day. In another study in rabbits, rates of resorption were increased at 600 mg/kg bw per day, with a NOAEL of 150 mg/kg bw per day.

In another study in mice treated by gavage on days 6–15 of gestation, decreases in the number of implantations and in the number of live fetuses were observed at doses of 100 mg/kg bw per day and higher. The NOAEL was 25 mg/kg bw per day. The effects on implantation were considered to result from a direct effect of the substance since they were seen within the first few days after treatment, before maternal toxicity (decrease in food consumption and body weight) was observed.

Studies evaluated for the first time at this meeting

Single-dose studies of toxicity: Three single-dose studies of toxicity in rats were provided for assessment by the 2006 JMPR. In the gavage studies, dose-related effects including reduced activity, tiptoe gait, landing foot splay and reduced motor activity were observed for up to 24 hours after 100 or 200 mg/kg bw and for up to 3 days after 1000 mg/kg bw. At this, the highest dose, there was also a transient reduction in body weight compared with controls. There were no treatment-related changes in haematology parameters. As the neuroactive effects observed at 100 mg/kg bw were marginal, the NOAEL was 100 mg/kg bw. In the dietary study, no treatment-related effects on clinical signs, FOB assessment, motor activity or body weight were observed at up to 600 ppm (equal to 46 mg/kg bw), the highest dose tested.

Toxicokinetic studies: Toxicokinetic studies that compared the gavage and dietary routes of administration showed that different kinetic profiles of thiabendazole were obtained, particularly with respect to C_{max}, which was shown to be much higher by the gavage route than by the dietary route. The administration of an aqueous slurry of diet as a model for residues of thiabendazole in food

commodities containing a high residue of thiabendazole demonstrated that by this more relevant route of exposure the kinetic behaviour of thiabendazole was closer to the situation seen in the dietary study. Therefore the results of the dietary study would be more appropriate for deriving the ARfD. However, the substance was not tested at doses high enough to produce any toxic effects.

Toxicological evaluation

After considering the data available to the present Meeting as well as the 2002 JECFA evaluation, the Meeting established an ARfD of 0.3 mg/kg bw for women of childbearing age on the basis of the NOAEL of 25mg/kg bw per day identified on the basis of reduction of implantations at doses of 100 mg/kg bw per day and higher in a study of developmental toxicity in mice, and a safety factor of 100. This value was supported by a NOAEL of 24 mg/kg bw per day identified on the basis of increases in resorptions at doses of 120 mg/kg bw per day and greater in a study of developmental toxicity in rabbits.

The Meeting established an ARfD of 1 mg/kg bw for the general population on the basis of a NOAEL of 100 mg/kg bw identified on the basis of some slight neuroactive effects at doses of 200 mg/kg bw and greater in a study of acute toxicity in rats treated by gavage, and a safety factor of 100.

An addendum to the toxicological monograph was prepared.

Levels relevant to acute dietary risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Developmental toxicity[b]	Maternal toxicity	25 mg/kg bw per day	100 mg/kg bw per day
		Developmental toxicity	25 mg/kg bw per day	100 mg/kg bw per day
Rat	Single-dose toxicity study	Toxicity	100 mg/kg bwb	200 mg/kg bw
			600 ppm, equal to 46 mg/kg bw[a,c]	—
Rabbit	Developmental toxicity[b]	Maternal toxicity	24 mg/kg bw per day	120 mg/kg bw per day
		Developmental toxicity	24 mg/kg bw per day	120 mg/kg bw per day

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

Estimate of acute reference dose

0.3 mg/kg bw for women of childbearing age

1 mg/kg bw for the general population

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

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

RESIDUE AND ANALYTICAL ASPECTS

Thiabendazole is authorized as a post-harvest fungicide on citrus in many countries. It was evaluated several times by JMPR in the period 1970-1981. The 1997 JMPR reviewed it under the CCPR Periodic Review Programme and proposed withdrawal of the existing CXL for citrus fruits of 10 mg/kg. The residue definition, agreed for compliance with MRLs and estimation of dietary intake for plant commodities, is thiabendazole; that for compliance with MRLs for animal commodities is the sum of thiabendazole and 5-hydroxythiabendazole. For estimation of dietary intake for animal commodities it is the sum of thiabendazole, 5-hydroxythiabendazole and its sulfate conjugate. The JMPR 2000 received new data from Spain on the basis of which an MRL of 3 mg/kg was proposed. At the CCPR meeting in 2003, the delegation from Morocco had commented that the proposed MRL for thiabendazole on citrus fruits of 3 mg/kg would need to be increased to support the country's use pattern. At that meeting the delegation of Morocco was invited to submit data to JMPR. During the CCPR meeting in April 2004 the MRL for citrus fruits was returned to Step 6 pending receival of the data.

The current Meeting received data from residue trials to support the uses of thiabendazole as a post-harvest treatment on citrus fruits in Morocco.

Methods of analysis

For the analysis of the samples from supervised trials conducted in Morocco two methods from the open literature were used. The first one is an old spectroscopic method with UV detection developed in France in 1974. Limited validation was carried out (on whole fruits at 0.1, 0.5 and 1 mg/kg fortification levels, one fortified sample at each fortification level). The recoveries yielded were 96–102%, with an LOQ of 0.1 mg/kg.

The second method was a reversed phase HPLC method (standard CEN method). The recoveries for thiabendazole were tested only for whole fruits at one fortification level (0.1 mg/kg, 3 replicate fortified samples) and were found to be in the range of 82–84%. The LOQ was estimated to be 0.01 mg/kg.

Results of supervised trials on crops

Citrus fruits

The Meeting received, for evaluation, post-harvest application data from trials conducted in Morocco during 2003 and 2004. Thiabendazole, formulated as 500 SC, was applied to oranges (15 trials) and clementine mandarins (8 trials) according to the nationally authorized use pattern (GAP). This consisted of a spray application, mixed with wax, at a rate of 0.375 kg ai/hL. Treated fruit samples were stored frozen at 4–6°C from harvest to analysis. Samples were taken for analysis < 2 days, 3, 4, 5, 11 or 15 days after application. Whole orange samples were analysed in 2003, while in 2004 peel and pulp were analysed separately.

The residue levels in whole oranges treated according the GAP, in ranked order, were: 1.6 (2), 1.8 (2), 2.1, 2.2, 2.5, 3.3 (2), 3.4 (2), 3.8, 4, 4.2 and 5.2 mg/kg.

Those in orange pulp were: < 0.1 and 0.84 mg/kg.

The residue levels in whole mandarins treated according to the GAP, in ranked order, were: 1.3, 2.4, 2.7 (3), 2.8, and 3.5 (2) mg/kg.

Those in mandarin pulp were: 0.03, 0.04, 0.09, < 0.1 (11), 0.12, and 0.37 mg/kg.

The Meeting agreed to combine the data for whole oranges and mandarins to give a data set for whole citrus fruits. The combined citrus fruits data (23 values), in rank order were: 1.3, 1.6 (2), 1.8 (2) 2.1, 2.2, 2.4, 2.5, 2.7 (3), 2.8, 2.9, 3.3 (2), 3.4, (2), 3.5, 3.8, 4, 4.2, and 5.2 mg/kg. Residue levels in citrus pulp, in rank order were: 0.03, 0.04, 0.09, < 0.1 (12), 0.12, 0.37 and 0.84 mg/kg.

On the basis of the trials carried out according to the Moroccan GAP the Meeting estimated a maximum residue level of 5 mg/kg for thiabendazole in citrus, replacing the previous recommendation of 3 mg/kg. The Meeting also estimated a median and a highest residue for whole fruits of 2.7 and 5.2 mg/kg respectively, for use in the calculation of the farm animal dietary burden. The Meeting recommended an STMR of 0.1 mg/kg and a HR of 0.84 mg/kg for citrus fruits.

Fate of residues in edible portion

The results from the 2004 trials provide information about distribution of residues between peel and pulp. These show that the majority of the residue remains on the peel. In only a few cases detectable residues of 0.03–0.84 mg/kg were found in the pulp. However, it should be noted that the sensitivity of the analytical method used on the majority of the samples was unsatisfactory (LOQ = 0.1 mg/kg). The distribution factors (DF) for residues into pulp ranged between 0.01 and 0.25, with a median DF of 0.1.

Farm animal dietary burden

The Meeting noted that the additional animal dietary burden from residues in citrus treated according to the Morocco GAP would be insignificant when compared to the contribution from wet potato peel calculated in 2000. This accounts for 2% of the total dietary burden for beef cattle and 4% for dairy cattle when using the highest residue, and 2% and 3% respectively, when using the median from whole fruits.

DIETARY RISK ASSESSMENT

Long-term intake

The IEDI of thiabendazole was estimated for the 13 cluster diets using the STMRs estimated by a previous JMPR for avocado, cattle kidney, cattle liver, cattle meat, cattle milk, mango, melon, papaya, pome fruit, potato and strawberry and the STMR for citrus fruits estimated by the current JMPR. The maximum ADI established in 1997 is 0.1 mg/kg bw and the calculated IEDIs were 2–20% of this ADI (Annex 3). The Meeting concluded that the intake of residues of thiabendazole resulting from the uses considered by a previous JMPR and by the current JMPR was unlikely to present a public health concern.

Short-term intake

The IESTIs of thiabendazole by general population and by children was calculated for commodities for which STMRs or HRs was estimated by the 2000 Meeting and the current Meeting (Annex 4). The current JMPR estimated two ARfDs for thiabendazole: one for general population; and the other for women of child-bearing age. The ARfD for general population is 1 mg/kg bw and the calculated IESTIs for children up to 6 years range from 0 to 60% and those for general population from 0 to 20% of this ARfD. The ARfD for women of child-bearing age is 0.3 mg/kg bw and the calculated IESTIs for women of child-bearing age range from 0 to 70% of this ARfD. The Meeting concluded that the short-term intake of residues of thiabendazole resulting from the use considered by the current JMPR is unlikely to present a public health concern.

4.29 THIACLOPRID (223)

TOXICOLOGY

Thiacloprid, (*Z*)-3-(6-chloro-3-pyridylmethyl)-1,3-thiazolidin-2-ylidenecyanamide (IUPAC), is an insecticide of the neonicotinoid class. It acts as an agonist of the nicotinic acetylcholine receptor in the central nervous system, thus disturbing synaptic signal transmission. Thiacloprid is an acute contact and stomach poison, with systemic properties. Thiacloprid was evaluated at the request of CCPR and had not been evaluated previously by JMPR.

All pivotal studies with thiacloprid were certified to be GLP compliant.

Biochemical aspects

After oral administration to rats, [^{14}C]methylene- or [^{14}C]thiazolidine-labelled thiacloprid was rapidly and almost completely absorbed after a single low dose (1 mg/kg bw) and about 10% less well absorbed after a single high dose (100 mg/kg bw), with maximum plasma concentrations of radioactivity occurring at 1–3 hours or 3–4 hours, respectively. Radioactivity was widely distributed throughout the body. Tissue residues at 48 hours after dosing accounted for less than 1% ([^{14}C]methylene label) or up to about 3% ([^{14}C]thiazolidine label) of the administered dose, with liver, kidneys, lung, adrenals and thyroid containing the highest residues. Excretion of radioactivity was rapid, primarily via urine (60–83%) and to a lesser extent via faeces (up to 34%) and exhaled air (<1%), with >90% of an administered low dose excreted within 48 hours. Intravenous administration (1mg/kg bw) revealed that the faecal radioactivity was largely due to biliary excretion. Thiacloprid was extensively metabolized and a total of 25 metabolites were identified. Metabolic transformations included *C*- and *N*-hydroxylation, *S*-oxidation and methylation, oxidative ring cleavage and methylene bridge cleavage, glucuronic acid, glycine and pentose sulfate conjugations.

Mechanistic studies showed that in males, plasma concentrations of thiacloprid had reached a peak on day 8 and decreased slightly from day 15 onwards, while in females, thiacloprid concentrations had reached a peak on day 8 and remained relatively constant for the duration of the study (28 days). Also in pregnant rats, concentrations of thiacloprid in plasma increased during pregnancy and reached a peak at the end of gestation.

Toxicological data

Thiacloprid was of moderate acute toxicity after oral (LD_{50}, 396–836 mg/kg bw) and inhalation (LC_{50}, 1.223 to > 2.535 mg/L) exposure in rats, with females being more sensitive than males. Thiacloprid was of low acute dermal toxicity (LD_{50} > 2000 mg/kg bw) in rats. Thiacloprid was not a skin irritant in rabbits, it was a slight eye irritant in rabbits, and it was not a skin sensitizer in guinea pigs.

In short-term studies of toxicity, the liver was the primary target organ of thiacloprid in rodents. In both rats and mice, a dose-dependent induction of liver enzymes occurred which was associated with increased liver weight, centrilobular hypertrophy and changes in the cytoplasm of the hepatocytes. In female mice, an increase in fatty vacuolization and hypertrophy of the adrenal X-zone was also seen. Changes in circulating hormone concentrations (e.g. T4, T3 and thyroid-stimulating hormone, TSH) and effects on the rat thyroid (e.g. increased weight, hypertrophy and increased mitotic rate of follicular cells) were observed as a consequence of the liver enzyme induction. Similar toxicological profiles were seen in rats after exposure via the dermal and inhalation routes. After oral and dermal administration to rats, the enzyme induction and increased liver weight were shown to be

reversible by the end of a 5-week or 2-week recovery period. The thyroid follicular cell hypertrophy was also shown to be at least partly reversible after dermal administration and a 2-week recovery period.

In a 14-week feeding study in mice, the NOAEL was 50 ppm (equal to 19.9 mg/kg bw) based on marked vacuolization in the adrenal X zone in females at 250 ppm and above. Effects at higher doses included liver changes (increased weight, hypertrophy of hepatocytes) in both sexes and increased adrenal weights in females at 1250 ppm and above.

In a 2-week study in rats treated by gavage, the NOAEL was 20 mg/kg bw per day on the basis of reduced body-weight gain and reduced feed intake at 60 mg/kg bw per day. In a 2-week feeding study in rats, the NOAEL was 100 ppm (equal to 9.8 mg/kg bw per day) on the basis of decreased body weights in females and thyroid effects (increased mitosis) in males at 500 ppm and above. In a 13-week feeding study with a 5-week recovery period in rats, the NOAEL was 400 ppm (equal to 28.6 mg/kg bw per day) on the basis of reduced body weight, clinical chemistry changes (increased cholesterol and protein concentration in plasma) and thyroid effects (increased weight) at 1600 ppm. The hypertrophy of hepatocytes in males at 1600 ppm was not completely reversible during the recovery period.

In a 5-day study in rats given thiacloprid by inhalation followed by a 2-week recovery period, the NOAEC was 0.019 mg/L (equal to 4.6 mg/kg bw per day) on the basis of clinical signs, reduced body weight and decreased thymus weights at 0.205 mg/L. All effects had resolved by the end of the recovery period. In a 4-week study in rats treated by inhalation, the NOAEC was 0.018 mg/L (equal to 4.4 mg/kg bw per day) on the basis of clinical signs, reduced body weights, liver toxicity in females (increased plasma levels of cholesterol, AP and bile acids) and thyroid effects in males (increased weight, hypertrophy of follicular epithelium) at 0.143 mg/L.

In a 4-week study in rats treated dermally, the NOAEL for systemic toxicity was 300 mg/kg bw per day on the basis of thyroid follicular cell hypertrophy at 1000 mg/kg bw per day. Hypertrophy of hepatocytes and thyroid follicular cells of males at 1000 mg/kg bw per day was partially reversible after a 2-week recovery period. The NOAEL for skin reactions was 1000 mg/kg bw per day, the highest dose tested.

In dogs, the liver was also the main target organ but enzyme induction and the subsequent changes in thyroid hormone levels were less pronounced than in rodents. In a 15-week feeding study in dogs, the NOAEL was 250 ppm (equal to 8.5 mg/kg bw per day) on the basis of reduced T4 levels, liver effects (increased weight, enzyme induction) and prostate effects (increased weight, hypertrophy of the glandular epithelium) at 1000 ppm and above. In a 52-week feeding study in dogs, the NOAEL was 250 ppm (equal to 8.3 mg/kg bw per day) on the basis of decreased T4 levels, liver effects (hepatocellular cytoplasmic changes) and prostate effects (increased weight and size) at 1000 ppm.

Thiacloprid gave negative results in an adequate battery of studies of genotoxicity in vitro and in vivo.

The Meeting concluded that thiacloprid was unlikely to be genotoxic.

Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. As in short-term studies, the liver was the primary target organ, with induction of liver enzymes being the most sensitive end-point in both rats and mice. Effects on other organs, such as thyroid, adrenals, ovaries and uterus were considered to be secondary to the increased liver enzyme activities and the subsequent hormonal imbalances. The increased incidences of lens fiber degeneration and retinal atrophy in female rats at the intermediate doses (50 and 500 ppm) were not considered to be treatment-related when compared with the data for historical controls, rather they were caused by the low survival rate of females in the control group. The increased incidences of degenerative changes in the nervous system and skeletal muscles in females at 500 ppm and above were considered to reach statistical significance owing to increased survival at the highest dose compared with the concurrent control group, resulting in a seemingly increased incidence of age-related findings.

In the study of carcinogenicity in mice, the NOAEL for systemic toxicity was 30 ppm (equal to 5.7 and 10.9 mg/kg bw per day in males and females, respectively) on the basis of effects in the liver (increased weight, hepatocellular hypertrophy, fatty change, degeneration) and lymph nodes (vacuolization) in both sexes and in the adrenal cortex (vacuolization in the X-zone) in females at 1250 ppm and above. There was no evidence of oncogenic activity in males. In females, the incidence of benign ovarian luteomas was significantly increased at 1250 ppm and above.

A 13-week mechanistic study on ovarian tumorigenesis in mice showed increased hepatic aromatase activity and vacuolization in the X-zone of the adrenal cortex at 250 ppm and above, while plasma estradiol/progesterone ratio was decreased and plasma progesterone and liver weights were increased at 2500 ppm. Co-treatment with mecamylamine (a nicotine mimic) did not abolish the effects of thiacloprid on the estradiol/progesterone ratio.

The Meeting concluded that the increased incidence of ovarian luteomas in mice was a secondary consequence of liver enzyme (especially aromatase) induction, resulting in increased estradiol synthesis. Increased estradiol levels in mice but not in rats produce a positive feedback response with an increased prolactin release which consequently stimulates ovarian tissues and may explain the increased incidence of ovarian tumours. Based on application of the IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans to the limited available data, the Meeting concluded that the probable mode of action for the luteomas seen in mice is exclusively a high-dose phenomenon that is not relevant for human exposure at the levels of residues found in food.

In the long-term study of toxicity and carcinogenicity in rats, the NOAEL for systemic toxicity was 25 ppm (equal to 1.2 mg/kg bw per day), based on liver toxicity (increased mixed eosinophilic-clear cell foci) and thyroid effects (follicular epithelial hypertrophy) in males at 50 ppm and above. There was also evidence of increased thyroid hyperplasia at 500 ppm and above. The NOAEL for oncogenicity was 50 ppm (equal to 2.5 mg/kg bw per day), based on the increased incidences of thyroid follicular cell adenoma in males and uterine adenocarcinoma in females at 500 ppm and above.

Mechanistic studies on thyroid tumorigenesis in rats showed increased liver weights and increased UDP-glucuronyl transferase activities at 400 ppm and above, with the consequence of a decrease in T4, increase in TSH and thyroid follicular cell hypertrophy. The NOAEL was 100 ppm (equal to 9.0 mg/kg bw per day in males and females, respectively). Thiacloprid or its hydrolysis products had no inhibitory effect on thyroid peroxidase activity in vitro (IC_{50} > 870 µmol/l). Also, plasma extracts from rats treated with thiacloprid had no inhibitory effect on the activity of thyroid peroxidase in vitro.

The Meeting concluded that the increased incidence of thyroid adenoma observed in male rats was a consequence of liver enzyme induction, leading to increased clearance of thyroid hormones and increased levels of TSH. Based on application of the IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans to the available data, the Meeting concluded that the mode of action for the thyroid adenomas seen in rats is exclusively a high-dose phenomenon not relevant for human exposure at the levels of residues found in food.

Mechanistic studies on uterine tumorigenesis in rats showed a dose-related induction of hepatic aromatase at 200 ppm and greater, while liver weights were increased at 500 ppm and greater. Ovarian aromatase activity was similar in control and treated groups.

The Meeting concluded that the increased incidence of uterine tumours in rats was a secondary consequence of hepatic enzyme (especially aromatase) induction, resulting in increased estradiol synthesis. Long-lasting elevations of estradiol levels can lead to an increased incidence of uterine adenocarcinomas especially in older rats, which become acyclic and vulnerable towards the end of their life. Based on application of the IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans to the limited available data, the Meeting concluded that the probable mode of action for the uterine tumours seen in rats is exclusively a high-dose phenomenon not relevant for human exposure at the levels of residues found in food.

On the basis of the above considerations on the likely modes of action for the different tumours observed, the high doses required to induce the tumours and the negative results of studies of genotoxicity, the Meeting concluded that the increased tumour incidences associated with exposure to thiacloprid are threshold phenomena and unlikely to pose a carcinogenic risk to humans at exposure levels relevant to residues found in food.

In studies of reproductive toxicity in rats, difficulties at parturition (dystocia) were observed in some studies, with the possible consequences of increased incidence of stillbirths, decreased live birth index and/or reduced viability of pups at higher doses.

In a two-generation study of reproductive toxicity in rats, the NOAEL for parental toxicity was 50 ppm (equal to 3.5 mg/kg bw) on the basis of thyroid effects (increased weights, thyroid follicular cell hypertrophy) at 300 ppm and above. The NOAEL for reproductive toxicity was 50 ppm (equal to 3.5 mg/kg bw) on the basis of dystocia and decreased pup weights at 300 ppm and above, and decreased live birth index at 600 ppm.

In a supplementary one-generation study in rats, aimed at evaluating the reproducibility of dystocia and stillbirths, four dams at the highest dose of 1000 ppm died during gestation, two died after having begun birth. The incidence of stillbirths was unaffected. Pup survival and body weights were lower and the incidence of 'weak' pups was higher at 1000 ppm than in the controls. The NOAEL for systemic toxicity was 300 ppm (equal to 20 mg/kg bw per day) on the basis of clinical signs (including death), decreased body weight, and increased liver and thyroid weights at 1000 ppm. The NOAEL for reproductive toxicity was 300 ppm (equal to 20 mg/kg bw per day) on the basis of dystocia and decreased pup viability and pup weights at 1000 ppm.

Two modified one-generation studies in rats were conducted to further investigate possible causes of dystocia and stillbirths. In the study using a dose of 800 ppm, lower body weights, increased liver weights including hepatocyte hypertrophy and liver enzyme induction, increased serum steroid hormone (estradiol, progesterone, corticosterone) and luteinizing hormone levels were seen, while there were no effects on follicle-stimulating hormone, oxytocin and prolactin, on uterine and cervical prostaglandin, on liver and uterine glutathione and on uterine estrogen and progesterone levels. Aromatase activity was significantly increased in the liver (at the end of the pre-mating period) and in the ovaries (on day 2 of lactation). In the study using a dose of 1000 ppm, feed consumption, body weights and litter size were reduced, while there were no effects on cervical extensibility and uterine structure and function.

In a further study aimed at investigating possible dystocia, mated female rats were given thiacloprid at doses of 17.5 to 60 mg/kg bw per day by oral gavage on days 18–22 of gestation. Lower body-weight gain and feed consumption were observed in all treated groups, while clinical signs (including hypoactivity, chromorhinorrhea, clear vaginal discharge) and deaths were seen at 35 mg/kg bw per day and above. Dystocia was not observed, but stillbirths were higher at 35 mg/kg bw per day and above.

The Meeting concluded that there was no evidence for a specific effect of thiacloprid on parturition. Changes in metabolism and hormonal balance were considered to be the primary cause of dystocia and stillbirths at clearly maternally toxic doses.

In a study of prenatal developmental toxicity in rats, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of decreased body weights and feed intake at 50 mg/kg bw per day. The NOAEL for developmental toxicity was 10 mg/kg bw per day on the basis of increased resorptions, reduced fetal weights, and an increase in skeletal variations at 50 mg/kg bw per day.

In a study of prenatal developmental toxicity in rabbits, the NOAEL for maternal toxicity was 2 mg/kg bw per day on the basis of decreased body weights and feed intake at 10 mg/kg bw per day and above. The NOAEL for developmental toxicity was 2 mg/kg bw per day on the basis of reduced fetal weights at 10 mg/kg bw per day and above, and a higher incidence of postimplantation losses, supernumerary thirteenth ribs and incomplete ossification at 45 mg/kg bw per day.

The Meeting concluded that thiacloprid was not selectively toxic to embryo or fetal development and was not teratogenic.

In studies of acute neurotoxicity in rats, clinical signs (e.g. tremors, decreased activity, ataxia, dilated pupils, ptosis) were evident at 109 mg/kg bw, the highest dose tested, while effects on FOB observations and on motor and locomotor activity were seen at doses of 22 mg/kg bw and above in males and 11 mg/kg bw and above in females. All effects were generally apparent only on the day of dosing. The microscopic examinations did not reveal any lesions in the nervous system, eyes or skeletal muscle. The NOAEL for neurotoxicity was 11 mg/kg bw in males on the basis of FOB observations (slight tremors, ptosis) at 22 mg/kg bw and above, and 3.1 mg/kg bw in females on the basis of decreased motor and locomotor activity at 11 mg/kg bw and above.

In a 13-week study of neurotoxicity in rats, no compound-related clinical signs were observed at 1600 ppm, the highest dose tested. The FOB, the motor and locomotor activity recordings and the macroscopic and microscopic examinations did not reveal any compound-induced changes. Thus, the NOAEL for neurotoxicity was 1600 ppm (equal to 101 and 115 mg/kg bw per day in males and females, respectively). The NOAEL for systemic toxicity was 50 ppm (equal to 2.9 and 3.4 mg/kg bw per day in males and females, respectively) on the basis of reduced feed intake at 400 ppm and above.

In a study of developmental neurotoxicity in rats, thiacloprid did not cause any specific neurobehavioural or neuropathological effects in the offspring when administered to the dams during gestation and lactation at dietary concentrations of up to 500 ppm. Non-specific signs of general toxicity, including decreased body weights and body-weight gains and delayed sexual maturation, were observed in the offspring at dietary concentrations of 300 ppm and above. The NOAEL for maternal toxicity was 50 ppm (equal to 4.4 mg/kg bw per day) on the basis of reduced body weights and feed consumption at 300 ppm and above. The NOAEL for toxicity to offspring was 50 ppm (equal to 4.4 mg/kg bw per day) on the basis of reduced body weights in both sexes and delayed sexual maturation (preputial separation) in males at 300 ppm and above, and delayed sexual maturation (vaginal patency) in females at 500 ppm.

The environmental metabolites thiacloprid-amide (KKO 2254), thiacloprid-sulfonic acid sodium salt (WAK 6999), and thiacloprid-sulfonic acid amide were of low acute oral toxicity in rats (LD_{50} > 2000 mg/kg bw) and were not mutagenic in assays for reverse mutation in bacteria, in tests for gene mutation or chromosome aberration in mammalian cells.

In a short-term feeding study in rats given thiacloprid at 1000 ppm for 7 days had increased liver weights and a strong induction of liver enzymes including aromatase. Rats given the metabolites thiacloprid-sulfonic acid sodium salt (WAK 6999) and thiacloprid-sulfonic acid amide at a dose of 1000 ppm did not show these effects.

There were no reports of adverse health effects in manufacturing plant personnel or in operators and workers exposed to thiacloprid formulations during field trials. Also, there were no reports of poisonings with thiacloprid.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.01 mg/kg bw based on the NOAEL of 1.2 mg/kg bw per day in a 2-year dietary study in rats, and a safety factor of 100. Effects at the LOAEL of 2.5 mg/kg bw per day included liver toxicity and thyroid changes (follicular epithelial hypertrophy) secondary to liver enzyme induction.

The Meeting established an ARfD of 0.03 mg/kg bw based on the NOAEL of 3.1 mg/kg bw in a study of acute neurotoxicity in rats, and a safety factor of 100. It was not possible to determine a chemical-specific adjustment factor since it was not confirmed by appropriate toxicokinetic data that

the critical effect (decrease in motor and locomotor activity) at the LOAEL of 11 mg/kg bw is dependent on the C_{max}.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	14-week study of toxicity[a]	Toxicity	50 ppm, equal to 19.9 mg/kg bw per day	250 ppm, equal to 102.6 mg/kg bw per day
	2-year study of carcinogenicity[a]	Toxicity	30 ppm, equal to 5.7 mg/kg bw per day	1250 ppm, equal to 234.1 mg/kg bw per day
		Carcinogenicity	Females: 30 ppm, equal to 10.9 mg/kg bw per day	Females: 1250 ppm, equal to 475.3 mg/kg bw per day
Rat	13-week study of toxicity[a]	Toxicity	400 ppm, equal to 28.6 mg/kg bw per day	1600 ppm, equal to 123.2 mg/kg bw per day
	2-year study of toxicity and carcinogenicity[a]	Toxicity	25 ppm, equal to 1.2 mg/kg bw per day	50 ppm, equal to 2.5 mg/kg bw per day
		Carcinogenicity	50 ppm, equal to 2.5 mg/kg bw per day	500 ppm, equal to 25.2 mg/kg bw per day
	Multigeneration reproductive toxicity[a]	Fertility	600 ppm, equal to 43.9 mg/kg bw per day[c]	—
		Parental toxicity	50 ppm, equal to 3.5 mg/kg bw per day	300 ppm, equal to 21.7 mg/kg bw per day
		Offspring toxicity	50 ppm, equal to 3.5 mg/kg bw per day	300 ppm, equal to 21.7 mg/kg bw per day
	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	50 mg/kg bw per day
		Embryo- and fetotoxicity	10 mg/kg bw per day	50 mg/kg bw per day
	Acute neurotoxicity[b]	Neurotoxicity	3.1 mg/kg bw per day	11 mg/kg bw per day
	Subchronic neurotoxicity[a]	Neurotoxicity	1600 ppm, equal to 101 mg/kg bw per day[c]	—
	Developmental neurotoxicity[a]	Maternal toxicity	50 ppm, equal to 4.4 mg/kg bw per day	300 ppm, equal to 25.6 mg/kg bw per day
		Offspring toxicity	50 ppm, equal to 4.4 mg/kg bw per day	300 ppm, equal to 25.6 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal toxicity	2 mg/kg bw per day	10 mg/kg bw per day
		Embryo- and fetotoxicity	2 mg/kg bw per day	10 mg/kg bw per day
Dog	1-year study of toxicity[a]	Toxicity	250 ppm, equal to 8.3 mg/kg bw per day	1000 ppm, equal to 33.8 mg/kg bw per day

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.03 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 exposures

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

Absorption, distribution, excretion and metabolism in animals	
Rate and extent of oral absorption	Rapid and almost complete, based on oral and intravenous administration of low dose
Dermal absorption	No data
Distribution	Widely; highest concentrations in liver, kidneys, lung, adrenals and thyroid
Rate and extent of excretion	Rapid, >90% within 48 h; 60–83% in urine, up to 34% in faeces (largely due to biliary excretion)
Potential for accumulation	No evidence of accumulation
Metabolism in mammals	Extensive; *C*- and *N*-hydroxylation, *S*-oxidation and methylation, oxidative-ring cleavage and methylene-bridge cleavage, conjugation
Toxicologically significant compounds (animals, plants and the environment)	Parent compound
Acute toxicity	
Rat, LD_{50}, oral	396–836 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50} inhalation	1.233 to > 2.535 mg/L air (4-h, nose-only exposure)
Rabbit, skin irritation	Not irritant
Rabbit, eye irritation	Slightly irritant
Guinea-pig, skin sensitization (test method)	Not sensitizing (maximization)
Short-term studies of toxicity	
Target/critical effect	Liver (histopathological changes), thyroid (hormonal and histopathological changes), adrenals (X-zone: histopathological changes)
Lowest relevant oral NOAEL	8.3 mg/kg bw per day (1-year study in dogs)

Lowest relevant dermal NOAEL	300 mg/kg bw per day (4-week study in rats)
Lowest relevant inhalation NOAEC	0.002 mg/L air (4-week study in rats)
Genotoxicity	
	Not genotoxic in vitro or in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver (histopathological changes), thyroid (hormonal and histopathological changes), adrenals (X-zone: histopathological changes)
Lowest relevant NOAEL	1.2 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Thyroid adenomas in male rats, uterine adenocarcinoma in rats, ovarian luteomas in mice
Reproductive toxicity	
Reproductive target/critical effect	Dystocia; increased incidence of stillbirths, decreased live birth index, decreased pup viability and pup weights at maternally toxic doses
Lowest relevant reproductive NOAEL	43.9 mg/kg bw per day (effects on fertility at highest dose tested in a two-generation study in rats)
	3.5 mg/kg bw per day (systemic toxicity in offspring and parents)
Developmental target/critical effect	Increased resorptions, increased skeletal retardations and variations, decreased fetal weights at maternally toxic doses
Lowest relevant developmental NOAEL	2 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity	Clinical signs, effects in FOB observations, decreased motor and locomotor activity; NOAEL: 3.1 mg/kg bw
Subchronic neurotoxicity	No evidence of neurotoxicity; NOAEL: 101 mg/kg bw per day at highest dose tested
Developmental neurotoxicity	No evidence of developmental neurotoxicity; decreased body weight and delayed sexual maturation at maternally toxic doses; NOAEL: 4.4 mg/kg bw per day
Other toxicological studies	
Studies on metabolites	Thiacloprid-amide (KKO 2254), thiacloprid-sulfonic acid Na-salt (WAK 6999), and thiacloprid-sulfonic acid amide were of low acute oral toxicity in rats (LD_{50} > 2000 mg/kg bw) and not mutagenic in vitro
	No induction of rat liver enzymes by thiacloprid-sulfonic acid sodium salt and thiacloprid-sulfonic acid amide
Enzyme induction	Induction of hepatic cytochrome P450s, UDP-glucuronyl transferase and aromatase
Medical data	Limited data; no adverse health effects reported in manufacturing plant personnel or in operators and workers exposed during field trials

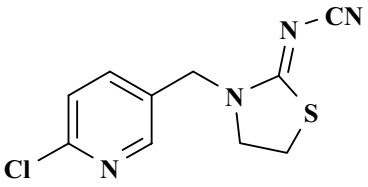
Summary

	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Rat; 2-year study	100

ARfD	0.03 mg/kg bw	Rat; study of acute neurotoxicity	100

RESIDUE AND ANALYTICAL ASPECTS

N-{3-[(6-Chloro-3-pyridinyl)methyl]-1,3-thiazolan-2-yliden}cyanamide



Residues and analytical aspects of thiacloprid were considered for the first time by the present Meeting.

Thiacloprid is a non-systemic insecticide with registered uses in many countries. Thiacloprid causes disruption of the insect nervous system by acting as an inhibitor at nicotinic acetylcholine receptors.

The following abbreviations are used for the metabolites discussed below:

thiacloprid-amide	{3-[(6-chloro-3-pyridinyl)methyl]-2-thiazolidinylidene}urea (M02)
6-CNA	6-chloro-3-pyridinecarboxylic acid (M03)
thiacloprid-sulfoxide	N-[(6-chloro-3-pyridinyl)methyl]-N'-cyano-N-[2-(methylsulfinyl)-ethyl]urea (M08)
M09	N-{[6-(methylthio)-3-pyridinyl]-carbonyl}glycine
M12	Glucuronic acid conjugate of {3-[(6-chloro-3-pyridinyl)methyl]-4(or 5)-hydroxy-2-thiazolidinylidene}=
thiacloprid sulfonic acid	Sodium 2-[[[(aminocarbonyl)amino]-carbonyl][(6-chloro-3-pyridinyl)-methyl]amino]ethanesulfonate (M30)

Animal metabolism

The Meeting received results of animal metabolism studies in lactating goats and laying hens.

Goats

One lactating goat was dosed with [methylene-^{14}C]-thiacloprid at a rate of 10 mg/kg body weight for three consecutive days. Approximately 53.7% of the total radioactivity administered was excreted until sacrifice. A portion of about 48.3% was eliminated with urine and 4.5% with faeces. Due to the short period between the last dose and sacrifice, 40% of the dose was not recovered in the excreta. A low amount (0.93%) was secreted with the milk. At sacrifice 6 hours after the last dose, the total radioactive residues (TRR) in the edible tissues and organs accounted for 5.6% of the administered radioactivity. The major portion and the highest equivalent concentration were observed in the kidney and the liver.

The metabolism of thiacloprid in goats is comparable to the metabolism in rats.

The unchanged parent compound was found in all goat tissues and ranged from 28% of the TRR (equiv. to 7 mg/kg) in kidney, 61% (equiv. to 1.5 mg/kg) in milk, 83% (equiv. to 14.5 mg/kg) in liver, 90% (equiv. to 1.6 mg/kg) in fat to 92% (equiv. to 3.5 mg/kg) in muscle.

Further main metabolites were identified in kidney. Thiacloprid-sulfoxide was found at levels of 12.3% of the TRR (equiv. to 3.1 mg/kg) and M12 at 10% of the TRR (equiv. to 2.5 mg/kg). Except for thiacloprid-sulfoxide in milk (8.7% of the TRR) no other relevant metabolites in concentrations above 8% of the TRR were identified.

Hens

A group of six laying hens were fed with [methylene-^{14}C]-thiacloprid for three consecutive days at a dose rate of 10 mg/kg body weight each. Until sacrifice the excretion amounted on average to 75.4% of the total radioactivity administered. About 29.4% and 29.6% of the radioactivity eliminated during the test period was excreted within 24 hours of the first and the second doses, respectively. Another 16.4% was excreted between the final dose and sacrifice. On average, only 0.06% (equiv. to 0.4 mg/kg) of the total dose was determined in the eggs. Residue levels in liver, kidney, muscle (leg), muscle (breast) and skin (without fat) were 3.1, 2.4, 0.15, 0.13 and 0.30 mg/kg TRR, respectively.

The metabolism of thiacloprid in laying hens is comparable to the metabolism in rats.

The unchanged parent compound was found in all hen tissues and ranged from 17% of the TRR (equiv. to 0.54 mg/kg) in liver, 19% (equiv. to 0.03 mg/kg) in muscle, 48% (equiv. to 0.06 mg/kg) in eggs to 72% (equiv. to 0.08 mg/kg) in fat.

Further main metabolites were identified in muscle only. M9 was found at levels of 10.9% of the TRR (equiv. to 0.016 mg/kg). Except for thiacloprid-sulfoxide in fat (8.9% of the TRR) no other relevant metabolites in concentrations above 8% of the TRR were identified.

Thiacloprid is only moderately metabolized by goats and hens with 5.6% (goats) and 0.7% (hens) of the applied dose remaining in tissues after three days. The proposed metabolic pathway was via hydroxylation and the formation of glucoronide and cysteine conjugates, resulting in a large variety of metabolites in small amounts.

Plant metabolism

The Meeting received plant metabolism studies for thiacloprid on apples, tomatoes, cotton and wheat. In all studies [methylene-^{14}C]-thiacloprid was applied as a spray.

All plant metabolism studies demonstrated that the metabolic pathway of thiacloprid is comparable in all crops investigated. The main metabolic reactions are:

the hydroxylation of the parent compound at the thiazolidine ring

the oxidative cleavage at the methylene bridge leading to the partially and fully oxidized products 6-chloropicolyl alcohol (M36), 6-chloronicotinic acid (M03)

conjugation of these two aglycones with sugars, phosphate/sulfate and endogenous plant components.

Uptake of soil metabolites followed by further metabolisation also took place. However, these metabolic reactions occurred only to a limited extent, the majority of residue remained on the surface of the fruits as unchanged parent compound exceeding 90% of the total residue. The major metabolites identified were the monohydroxylated derivative of thiacloprid (M01; apples) and the oxidation product 6-chloronicotinic acid (M03; cotton seed, wheat) as well as various conjugates thereof or of its precursor 6-chloropicolyl alcohol (M36; cotton, tomatoes, wheat).

In translocation experiments with tomatoes it was shown that less than 0.1% of the radioactivity in the soil was transported into the fruits after uptake via the roots.

In cotton seeds a different metabolic pattern with 6-chloronicotinic acid (M03), being the main residue (46%), was observed, which might be the result of partitioning and selective transport effects. In treated cotton leaves the metabolism followed the same steps found in the other plants investigated:

Hydroxylation of the parent compound at the thiazolidine ring;

cleavage at the methylene bridge leading to the partially and fully oxidized products 6-chloropicolyl alcohol (M36) and 6-chloronicotinic acid (M03);

conjugation of these two aglycones with sugars, phosphate/sulfate and endogenous plant components.

In each crop tested except cotton seeds, unchanged thiacloprid was found to be relevant residue with amount > 80% of the TRR.

Environmental fate

The Meeting received information on the environmental fate of thiacloprid in soil, including aerobic soil metabolism, field dissipation and crop rotational studies.

The soil photolysis study conducted with [methylene-^{14}C]-thiacloprid gave evidence that no accelerated degradation occurs under irradiation. Thiacloprid-amide could be identified as the main degradation byproduct. The calculated environmental half-life for thiacloprid was 74 days during midday and midsummer at 40° of latitude. No additional metabolites were identified in the samples.

In confined rotational crops studies, soil was treated with [pyridinyl-^{14}C-methyl]-thiacloprid. Turnips, lettuce and wheat were sown into the treated soil at intervals of 30, 170 and 354 days after treatment and were grown to maturity and harvested for analysis. In all matrices radioactivity above 0.01 mg/kg was found. After 354 days the residues measured ranged from 0.005 mg/kg in turnip bulbs up to 0.322 mg/kg in wheat straw. Thiacloprid-amide and thiacloprid sulfonic acid could be identified as relevant metabolites accounting for 15 – 35% of the TRR each. No parent thiacloprid was found.

The Meeting concluded that thiacloprid residues from the use of thiacloprid do not occur in concentrations above 0.01 mg/kg.

Methods of Analysis

The Meeting received descriptions and validation data for analytical methods for thiacloprid in plant and animal matrices. The method for enforcement purposes is based on extraction with acetone/water (3:1; v:v) and a subsequent clean-up by column chromatography on Florisil and elution with acetonitrile. The residues of thiacloprid parent compound are quantified by reversed phase HPLC with UV detection at 242 nm. Validation data for apples, tomatoes, cucumbers, peaches, citrus fruits, cotton seed, potatoes and tobacco was presented. In general a LOQ of 0.02 – 0.05 mg/kg was achieved, the recoveries were in the range of 72% to 105%.

Animal matrices were extracted with a mixture of acetonitrile/water or methanol. For milk samples, partitioning of the extracts against n-hexane was performed to remove fat. The aqueous remainder is partitioned against cyclohexane/ethyl acetate using a ChemElut column. Further clean-up is performed by column chromatography on Florisil and elution with acetonitrile. The residues are quantified by reversed phase HPLC with UV-detection at 242 nm. The method was validated by conducting recovery tests with muscle, milk and eggs. An LOQ of 0.01 mg/kg in milk and 0.02 mg/kg in muscle and egg was achieved, the recoveries were in the range of 75% to 104%

In addition the meeting received information on various specialized methods, mainly based on HPLC-MS/MS techniques with modification in the extraction and clean-up procedure. These methods for plant and animal matrices detect thiacloprid and possible metabolites with LOQs ranging from

0.01 mg/kg to 0.5 mg/kg (rice), depending on the matrix. In general an LOQ of 0.02 mg/kg could be achieved for all matrices except rice.

For thiacloprid, additional methods for the determination of all moieties containing 6-CNA were available. Thiacloprid and its metabolites were extracted from plant matrices with an acidic methanol / water mixture. After the clean-up thiacloprid and all metabolites containing the 6-chloropicolyl moiety were oxidized with alkaline potassium permanganate solution to yield 6-chloronicotinic acid. This was followed by acidification and reduction of the excess permanganate and the developed manganese dioxide with sodium bisulfite. The 6-CNA was converted to the corresponding trimethylsilyl ester with MSTFA (N-methyl-trimethylsilyltrifluoroacetamide) prior to quantitation by gas chromatography with mass selective detection in the single-ion monitoring mode (GC-MS). Validation data for pome fruits, tomatoes, cotton seed, rape seed, sunflower seed, milk, muscle, liver, kidney and fat was presented. In general a LOQ of 0.05 mg/kg for plant matrices and 0.01 – 0.02 mg/kg for animal matrices was achieved, the recoveries were in the range of 66% to 102%.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of thiacloprid in apples, currants, tomatoes, melons, peas, potatoes, cotton seed, rape seed, wheat and tobacco. All samples were fortified at 0.2 mg/kg (except tobacco with 2 mg/kg) and stored at –20°C for between 540 and 730 days. In all matrices the remaining thiacloprid residues levels were above 80% of the initial fortification concentrations.

No stability study was submitted to the Meeting on animal matrices.

Residue definition

The results of the radiolabeled thiacloprid plant metabolism studies on apples, tomatoes, cotton and wheat indicate that thiacloprid metabolizes or degrades slowly under typical foliar application conditions. Greater than 80% of the TRR is recovered as thiacloprid and no significant metabolites or degradates were found in crops treated directly.

In rotational crop studies significant total radioactive residues were found in lettuce and wheat. Most of the residue consisted of the metabolites thiacloprid amide (M02) and thiacloprid sulfonic acid (M30). Unchanged thiacloprid was not identified. These metabolites are not considered toxicologically significant and need not be considered for the residue definition.

In ruminants, orally administered radiolabeled thiacloprid undergoes limited metabolism to glucoronide and cysteine conjugates after hydroxylation. The major component in all matrices was unchanged thiacloprid (> 80% TRR in liver, fat and muscle, 61% TRR in milk and 28% TRR in kidney). Further metabolites were identified in kidney at levels below 12% of the TRR. In poultry orally administered (dosed at 10 mg/kg body weight) thiacloprid was moderately metabolized. In all matrices thiacloprid was identified as the major component (17% TRR liver, 19% TRR muscle, 48% TRR in eggs, 72% TRR in fat). Further metabolite found in muscle, was only M9 which accounted for 10.9% of the TRR.

The log P_{ow} of thiacloprid is 1.26. As no accumulation in fat was observed in animal metabolism studies the Meeting concluded that thiacloprid is not fat-soluble.

The analytical methods determine thiacloprid, possible metabolites or the total residue determined as 6-CNA.

Based on the results of the metabolism studies the Meeting concluded that the residue definition for enforcement and dietary intake calculations in plant and animal commodities is thiacloprid. The residue is not fat-soluble.

Results of supervised trials on crops

Citrus fruit

The Meeting received information on supervised residue trials on lemons and oranges from Brazil, New Zealand and South Africa.

In Brazil thiacloprid can be applied to citrus at 0.0048 kg ai/hL with a PHI of 21 days. In two Brazilian trials on lemons three applications were made at a rate of 0.0048 kg ai/hL and 0.0096 kg ai/hL with a PHI of 21 days. No whole fruit residue data was submitted.

One trial on lemons was submitted from New Zealand where a single spray application of 0.0096 kg ai/hL was made. Residues on whole lemon fruit were found to decline from 0.19 mg/kg 1 day after treatment to 0.07 mg/kg by day 14. A GAP for New Zealand was not submitted.

In South Africa thiacloprid can be applied to citrus at a rate of 0.0067 kg ai/hL. Corresponding number of applications or PHI was not stated. In two residue trials on oranges one treatment was conducted with spray concentrations of 0.014 kg ai/hL to 0.029 kg ai/hL with the PHI ranging from 44 to 190 days. No residues above the LOQ of 0.02 mg/kg were found in all samples.

The Meeting concluded that there was insufficient data available to support a recommendation for citrus fruit.

Pome fruit

The Meeting received information on supervised residue trials on apples from Australia, Belgium, France, Germany, Italy, Japan, the Netherlands, South Africa, Spain, United Kingdom and the USA.

Thiacloprid is registered for use on apples or pome fruits in some European countries as a pre-harvest foliar spray treatment. Residue trials were carried out in Belgium, France, Germany, Italy, the Netherlands, Spain and the United Kingdom. The GAPs from Austria, Belgium, Cyprus, Czech Republic, Greece, Hungary, Italy, the Netherlands, Russia and the United Kingdom consisted of two to three spray applications at 0.012 – 0.014 kg ai/hL with a PHI of 14 days. The residues matching this GAP in the whole fruits were: 0.04, 0.05, 0.1 (2), 0.11, 0.13, 0.14, 0.16, 0.21 and 0.36 mg/kg.

In Croatia, Germany, Latvia, Lithuania, Portugal, Romania, Slovakia, Slovenia and Spain the GAP consists of two to three spray application at a rate of 0.0096 kg ai/hL with a PHI of 14 days. The residues matching this GAP in the whole fruits were: 0.02, 0.04, 0.07, 0.08, 0.1, 0.11 and 0.12 mg/kg.

GAP in USA for apples consists of up to six applications at 0.01 kg ai/hL and a PHI of 30 days. The residues from 14 supervised trials in the USA, matching the US GAP (± 30%), were: 0.02, 0.04, 0.05, 0.06 (3), 0.07 (2), 0.09 (2), 0.1, 0.11, 0.14 and 0.28 mg/kg.

GAP in South Africa for apples consists of up to four applications at 0.0072 kg ai/hL and a PHI of 14 days. Of the four supervised trials provided from South Africa none matching South African GAP.

GAP in Japan for apples consists of up to three applications at 0.015 kg ai/hL and a PHI of seven days. The residues from two supervised trials in Japan matching GAP were 0.11 and 0.30 mg/kg.

GAP in Australia for apples consists of up to three applications at 0.018 kg ai/hL and a PHI of 14 days. The residue from one trial in Australia, matching GAP (± 30%), was 0.37 mg/kg.

The Meeting decided to pool the data from Australia, Europe, Japan and the USA. The combined results (n = 34) for apples were: 0.02 (2), 0.04 (3), 0.05 (2), 0.06 (3), 0.07 (3), 0.08, 0.09 (2), 0.1 (4), 0.11 (4), 0.12, 0.13, 0.14, 0.14, 0.16, 0.21, 0.28, 0.30, 0.36 and 0.37 mg/kg.

Field trials involving thiacloprid on pears were provided from Australia, South Africa and USA.

GAP in USA for pears consists of up to six applications at 0.01 kg ai/hL and a PHI of 30 days. The residues from 14 supervised trials in the USA, matching GAP (± 30%), in ranked order were :0.05, 0.06, 0.1, 0.14, 0.14, 0.23, 0.24 and 0.27 mg/kg.

GAP in South Africa for pears consists of up to four applications at 0.0072 kg ai/hL and a PHI of 14 days. Of the four supervised trials provided from South Africa none matched GAP.

GAP in Japan for pears consists of up to three applications at 0.015 kg ai/hL and a PHI of seven days. The residues from two supervised trials in Japan matching GAP were: 0.61 and 0.87 mg/kg.

GAP in Australia for pears is up to three applications with 0.018 kg ai/hL each and a PHI of 14 days. The residues from two supervised trials in Australia, matching the GAP, were 0.37 and 0.38 mg/kg.

The Mann-Whitney-U test indicated that the medians of the residues from the Japanese and the combined Australian and US data set for pears were not similar. The Meeting decided to pool only the data from Australia and the USA. The combined results (n = 10) for pears were 0.05, 0.06, 0.1, 0.14, 0.14, 0.23, 0.24, 0.27, 0.37 and 0.38 mg/kg.

The Meeting decided to make a recommendation for the crop group of pome fruits based on the combined data for apples and pears.

For apples and pears the combined results were 0.02, 0.02, 0.04(3), 0.05(3), 0.06(4), 0.07(3), 0.08, 0.09, 0.09, 0.1(5), 0.11(4), 0.12, 0.13, 0.14(4), 0.16, 0.21, 0.23, 0.24, 0.27, 0.28, 0.30, 0.36, 0.37, 0.37 and 0.38 mg/kg.

Based on residue data for apples and pears the Meeting decided to recommend a maximum residue level of 0.7 mg/kg, a STMR of 0.11 mg/kg and a HR of 0.38 mg/kg for pome fruits.

Stone fruits

The Meeting received information on supervised residue trials on Japanese apricots from Japan.

GAP in Japan for Japanese apricots consists of up to two applications at 0.0075 kg ai/hL with a PHI of seven days. The residue trials from Japan were conducted with an application rate of 0.015 kg ai/hL, which did not correspond to the submitted GAP.

Field trials on peaches were available from France, Italy, Japan and Spain.

GAP in Cyprus, Greece, Italy and Slovenia for peaches/nectarines consists of up to two applications at 0.0096 to 0.012 kg ai/hL and a PHI of 14 days. The residues in whole fruits from nine supervised trials in Europe matching the GAP were: 0.03(3), 0.06, 0.08, 0.09, 0.13, 0.13 and 0.19 mg/kg.

GAP in Japan for peaches is up to three applications at 0.015 kg ai/hL and a PHI of 7 days. The residues from two supervised trials from Japan matching the GAP ± 30% were 0.27 and 0.40 mg/kg.

The Mann-Whitney-U test for the data from Japan and the residue data from Europe suggested a similar median for both distributions. The combined residue data was 0.03(3), 0.06, 0.08, 0.09, 0.13, 0.13, 0.19, 0.27 and 0.40 mg/kg.

Field trials on cherries were provided from Belgium, France, Germany, Italy, Japan, Spain and USA.

GAP in Croatia, Cyprus, Czech Republic, the Netherlands, Romania, Slovenia and the United Kingdom for cherries is up to two applications with 0.0096 to 0.015 kg ai/hL each and a PHI of 14 days. The residues in whole fruits from 12 supervised trials in Europe matching the GAP were for sour cherries < 0.02, 0.02, 0.03, 0.04 mg/kg and for sweet cherries 0.02, 0.06, 0.06, 0.07, 0.08, 0.1, 0.11 and 0.15 mg/kg.

GAP in Japan for cherries is up to two applications with 0.015 kg ai/hL each and a PHI of one day. The residues from two supervised trials in Japan matching the GAP were 1.4 and 2.4 mg/kg. The Mann-Whitney-U test indicated that the medians of residues, resulting from applications according to the Japanese and European GAP for cherries, were not similar. Therefore only the data from the European trials were considered for further evaluation.

The Mann-Whitney-U test gave evidence that a similar distribution for sweet and sour cherries were not similar. Therefore only the data for sweet cherries were used for further evaluation.

In Northern America thiacloprid is not registered for use in cherries. Therefore the available supervised residue trials from USA were not considered.

Field trials on plums were provided from France, Germany, Spain and USA.

GAP in the Czech Republic, the Netherlands and Romania for plums is up to two applications at 0.0096 to 0.012 kg ai/hL and a PHI of 14 days. The residues in whole fruits from 14 supervised trials in Europe matching the GAP were: < 0.02(6), 0.02(5), 0.03, 0.03 and 0.05 mg/kg.

GAP in Japan for plums is up to three applications with 0.0075 kg ai/hL each and a PHI of seven days. The residue trials from Japan were conducted with an application rate of 0.015 kg ai/hL, which does not correspond to the submitted GAP.

In Northern America thiacloprid is not registered for use in plums. Therefore the available supervised residue trials from USA are not considered for evaluation.

The Meeting decided to make a recommendation for the stone fruits crop group, based on the combined data for peaches and sweet cherries.

For peaches and sweet cherries the combined results were 0.02, 0.03(3), 0.06(3), 0.07, 0.08, 0.08, 0.09, 0.1, 0.11, 0.13, 0.13, 0.15, 0.19, 0.27 and 0.40 mg/kg.

Based on residue data for peaches and sweet cherries the Meeting recommends a maximum residue level of 0.5 mg/kg, a STMR of 0.08 mg/kg and a HR of 0.4 mg/kg for for thiacloprid in stone fruits.

Grapes

Field trials on grapes were provided from Japan.

GAP in Japan for grapes consists of up to two applications at 0.53 kg ai/ha each and a PHI of 21 days. The residues from 4 supervised trials in Japan matching the GAP (± 30%) were: 0.12, 0.44, 0.80 and 1.6 mg/kg. The Meeting decided that four residue trials were not sufficient for a recommendation for grapes.

Berries and other small fruits except grapes

Field and glasshouse trials on strawberries were provided from Belgium, France, Germany, Japan, the Netherlands, Italy, Spain and the United Kingdom.

The GAP for field use in the Netherlands and the United Kingdom for strawberries consists of up to two applications at 0.12 kg ai/ha each and a PHI of three days. The residues from eight supervised trials in Europe matching the GAP were: 0.02, 0.03, 0.04, 0.07, 0.07, 0.08, 0.08 and 0.09 mg/kg.

GAP for glasshouse use in the Netherlands and the United Kingdom for strawberries is up to two applications at 0.12 to 0.14 kg ai/ha each and a PHI of one day. The residues from eight supervised trials in Europe matching the GAP (± 30%) were 0.04, 0.05, 0.13, 0.22, 0.31(3) and 0.33 mg/kg.

GAP in Japan for protected strawberries is up to three applications with 0.23 kg ai/ha each and a PHI of one day. The residue trials from Japan were conducted with an application rate of 0.15 kg ai/ha, which does not correspond to the submitted GAP.

Field trials on currants were provided from Belgium, Germany and the United Kingdom.

GAP in Germany, Latvia, the Netherlands and the United Kingdom for currants is up to three applications with 0.072 to 0.14 kg ai/ha each and a PHI of three days. The residues from eight supervised trials in Europe matching the GAP (± 30%) were: 0.08, 0.16, 0.21, 0.21, 0.28, 0.35, 0.37 and 0.59 mg/kg.

Field trials on raspberries were provided from Germany and the United Kingdom.

GAP in Germany, the Netherlands and the United Kingdom for raspberries is up to three applications with 0.096 to 0.14 kg ai/ha each and a PHI of three days. The residues from eight supervised trials in Europe matching the GAP (± 30%) were: 0.1, 0.15, 0.15, 0.27, 0.31, 0.34, 0.34 and 0.62 mg/kg.

Various GAPs in Germany, Latvia, the Netherlands, Poland, Switzerland and the United Kingdom for small fruits and berries is up to three applications with 0.12 to 0.14 kg ai/ha each and a PHI of three days. The Meeting decided to make a recommendation for the whole group of berries and other small fruits except grapes based on the combined data for protected strawberries, currants and raspberries.

For protected strawberries, currants and raspberries the combined results were 0.04, 0.05, 0.08, 0.1, 0.13, 0.15, 0.15, 0.16, 0.21, 0.21, 0.22, 0.27, 0.28, 0.31(4), 0.33, 0.34, 0.34, 0.35, 0.37, 0.59 and 0.62 mg/kg.

Based on residue data for protected strawberries, currants and raspberries the Meeting recommends a maximum residue level of 1 mg/kg, a STMR of 0.275 mg/kg and a HR of 0.62 mg/kg for thiacloprid in berries and other small fruits except grapes.

Kiwi fruits

The Meeting received information on supervised residue trials on kiwi fruits from New Zealand.

GAP in New Zealand for kiwi fruit is up to two applications with 0.0096 kg ai/hL each before the flowering. The residues from nine supervised trials in New Zealand matching the GAP (± 30%) were: < 0.02 (5), 0.03, 0.04, 0.06 and 0.1 mg/kg.

The Meeting recommended a maximum residue level of 0.2 mg/kg, an STMR value of 0.02 mg/kg and a HR of 0.1 mg/kg for thiacloprid in kiwi fruits.

Onions

The Meeting received information on supervised residue trials on onions from Brazil and Germany.

GAP in Belize, Brazil, Costa Rica, Dominican Republic, El Salvador, Guatemala. Honduras, Nicaragua and Panama for onions is up to 0.1 kg ai/ha and a PHI of 21 days. Only one supervised residue trial from Brazil matched this GAP. The corresponding residue was < 0.02 mg/kg in bulb onion. From Germany two additional trials were provided with residues of < 0.01 and < 0.01 mg/kg.

The Meeting concluded that the data available for onions was not sufficient to support an STMR or MRL recommendation.

Garlic

The Meeting received information on supervised residue trials on garlic from Brazil.

GAP in Belize, Brazil, Costa Rica, Dominican Republic, El Salvador, Guatemala. Honduras, Nicaragua and Panama for garlic is up to 0.1 kg ai/ha and a PHI of 21 days. Neither of the two supervised residues trials matched the GAP for garlic within ± 30%.

The Meeting concluded that the data available for garlic was not sufficient to support a recommendation.

Cucumbers

The Meeting received information on supervised residue trials on field and glasshouse grown cucumbers from Belgium, France, Germany, Greece, the Netherlands, Italy and Spain.

The GAP for field use in Croatia, Cyprus, Georgia, Greece, Italy, the Netherlands and Spain for cucumbers is up to four applications at 0.12 to 0.15 kg ai/ha each and a PHI of one to three days. The residues from eight supervised trials in Europe matching the GAP (± 30%) were: 0.02, 0.03(3), 0.04, 0.1, 0.11 and 0.14 mg/kg.

The GAP for glasshouse use in the United Kingdom for cucumbers, which reflects the critical GAP, is up to three applications at 0.21 kg ai/ha each and a PHI of three days. The residues from 12 supervised trials in Europe matching the GAP (± 30%) were 0.04, 0.04, 0.07, 0.07, 0.08(4), 0.12, 0.15, 0.15 and 0.18 mg/kg.

The Meeting decided to pool the data from outdoor and indoor residues trials for a recommendation on cucumbers. The combined results are 0.02, 0.03(3), 0.04(3), 0.07, 0.07, 0.08(4), 0.1, 0.11, 0.12, 0.14, 0.15, 0.15 and 0.18 mg/kg.

For gherkins, GAPs from Greece and the Netherlands were available, which correspond to the GAPs for cucumber. The Meeting concluded that an extrapolation of the data from cucumbers to gherkins is not possible, because of the different surface area-to-mass ratio for gherkins, from higher residues can be expected than in cucumbers.

Based on the combined data for cucumbers the Meeting recommended a maximum residue level of 0.3 mg/kg, an STMR value of 0.08 mg/kg and a HR of 0.18 mg/kg for cucumbers.

Squash, summer

The Meeting received GAPs for courgettes and squash corresponding to the uses in cucumbers and gherkins. The treatment methods cover foliar spraying as well as drip application. The Meeting concluded that the residue data for cucumber can be extrapolated to summer squash.

Based on an extrapolation from cucumbers the Meeting recommended a maximum residue level of 0.3 mg/kg, an STMR value of 0.08 mg/kg and a HR of 0.18 mg/kg for thiacloprid in summer squash.

Melons and watermelons

The Meeting received information on supervised residue trials on melons from France, Greece and Italy. Data on protected melons was also received from Japan.

GAP in Croatia, Italy and Spain for melons and watermelons is up to three applications at 0.14 kg ai/ha each and a PHI of three to four days. The residues for whole melon fruits from six supervised trials in Europe matching the GAP (± 30%) were < 0.02, 0.02, 0.03, 0.05, 0.06 and 0.06 mg/kg. In melon pulp all residues were < 0.02(6) mg/kg.

GAP in Japan for protected melons is up to three applications at 0.45 kg ai/ha each and a PHI of one day. The residues from two supervised trials in Japan matching the GAP (±30%) were < 0.005 and < 0.005 mg/kg in the pulp.

Field trials on watermelons were available from Greece and Spain. Data on protected watermelons was also available from Japan.

GAP in Croatia, Italy and Spain for watermelons is up to three applications at 0.14 kg ai/ha each and a PHI of three to four days. The residues for whole watermelon from four supervised trials in Europe matching the GAP (± 30%) were < 0.02(3) and 0.06 mg/kg. In watermelon pulp all residues were < 0.02(4) mg/kg.

GAP in Japan for protected watermelons is up to three applications at 0.45 kg ai/ha each and a PHI of one day. The residue trials from Japan were conducted with an application rate of 0.3 kg ai/ha, which did not correspond to the submitted GAP.

The Mann-Whitney-U test for melons and watermelons indicated that a similar distribution for melons and watermelons can be assumed. The combined residues for whole melons and watermelons were < 0.02(4), 0.02, 0.03, 0.05, 0.06, 0.06 mg/kg.

The Meeting decided to pool the data for melons and watermelons for mutual support and recommended a maximum residue level of 0.2 mg/kg for thiacloprid in melons and watermelons and an STMR of 0.02 mg/kg and HR value of 0.02 mg/kg for melon and watermelon pulp.

Squash, winter

GAP in Cyprus and the Netherlands for squash, field and glasshouse grown, is up to four applications at 0.014 kg ai/hL and a PHI of one to three days. This use corresponds to the GAP available for melons and watermelons in field. The Meeting concluded that the residue data for melon and watermelon can be extrapolated for use in winter squash.

Based on an extrapolation from melon and watermelon the Meeting recommends a maximum residue level of 0.2 mg/kg for thiacloprid in winter squash and an STMR of 0.02 mg/kg and HR value of 0.02 mg/kg for winter squash pulp.

Tomatoes

The Meeting received information on supervised residue trials on field and glasshouse grown tomatoes. Supervised trials were provided for field use from France and Italy and for glasshouse use from Germany, France, Japan and Spain. In addition, residue trials with drip application in glasshouse were conducted in Belgium and the Netherlands.

Supervised residue trials of field were conducted with two applications of 0.14 up to 0.22 kg ai/ha each and PHIs from zero to eight days. Corresponding GAPs from Greece and Slovenia were available with a PHI of three days. The residues for tomatoes from seven trials in Europe, matching the GAP (± 30%), in ranked order were: 0.02, 0.03, 0.03, 0.04, 0.05, 0.09 and 0.16 mg/kg.

For foliar use in glasshouses, data from eight supervised residue trials were provided corresponding to the GAP of the United Kingdom (three applications at 0.22 kg ai/ha each and a PHI of three days). The residues from protected tomatoes from eight trials in Europe matching the UK GAP (± 30%) in ranked order were: 0.07, 0.12, 0.12, 0.15, 0.18, 0.19, 0.25 and 0.29 mg/kg.

GAP in Japan for protected tomatoes is up to three applications with 0.23 kg ai/ha each and a PHI of one day. The residue trials from Japan were conducted with an application rate of 0.38 kg ai/ha, which does not correspond to the submitted GAP.

In the Netherlands drip application to glasshouse tomatoes is registered at an application rate of 0.0096 kg ai per 1000 plants and a PHI of three days. The corresponding residues from eight trials on protected tomatoes in Europe matching the GAP (± 30%) were: < 0.02(3), 0.02(3), 0.03 and 0.03 mg/kg.

Based on the glasshouse foliar spray GAP for tomatoes the Meeting recommended a maximum residue level of 0.5 mg/kg, an STMR value of 0.165 mg/kg and a HR value of 0.29 mg/kg for thiacloprid in tomatoes.

Peppers, sweet

Supervised residue field trials were provided from France, Italy and Spain. Data for glasshouse use as foliar spray was generated in France, the Netherlands and Spain. In addition, residue trials with drip application in glasshouse were conducted in Belgium and the Netherlands.

Supervised residue trials in field use with thiacloprid were conducted with two applications of 0.14 up to 0.22 kg ai/ha each and PHIs from zero to seven days. Corresponding GAPs from Greece and Slovenia are available with a PHI of three days. The residues for peppers from seven trials in Europe matching the GAP (± 30%) in ranked order were: 0.05, 0.06, 0.08, 0.1, 0.11, 0.21 and 0.45 mg/kg.

For the use as a foliar spray in glasshouse eight supervised residue trials were conducted, corresponding to the UK GAP (three applications at 0.22 kg ai/ha and a PHI of three days). The residues for protected peppers from eight trials in Europe matching GAP (± 30%) were: 0.07, 0.08, 0.1, 0.11, 0.33, 0.37, 0.37 and 0.38 mg/kg.

GAP in Japan for protected peppers is up to three applications with 0.23 kg ai/ha each and a PHI of one day. The residues from two supervised trials in Japan matching the GAP ±30% were 1.1 and 2.0 mg/kg. The Meeting compared the data sets for Japan and Europe using the Mann-Whitney-U test and decided that they belonged to different populations and could not be combined. Therefore only data from European trials was used for further evaluation.

In the Netherlands drip application in glasshouses is registered for peppers with an application rate of 0.0096 kg ai per 1000 plants and a PHI of three days. The corresponding residues from eight trials on protected peppers in Europe matching GAP (± 30%) were: 0.04, 0.04, 0.05(4), 0.06, 0.07 mg/kg.

For chili peppers GAPs are available, which correspond to the GAPs for sweet peppers. The Meeting concluded that an extrapolation of the data from sweet peppers to chili pepper is not possible, because of the different surface area to mass ratio for chili peppers, for which higher residues than in sweet peppers can be expected.

Based on the glasshouse foliar spray GAP for peppers the Meeting recommended a maximum residue level of 1 mg/kg, an STMR value of 0.22 mg/kg and a HR value of 0.38 mg/kg for thiacloprid in sweet peppers.

Eggplants

Field trials on protected aubergines were provided from Japan.

GAP in Japan for eggplants consists of up to three applications at 0.23 kg ai/ha each and a PHI of one day. The residues from two supervised trials in Japan matching the GAP (± 30%) were 0.28 and 0.38 mg/kg.

The Meeting received GAPs for eggplants from the Netherlands, Japan, the United Kingdom and various other countries corresponding to the GAO for field and glasshouse tomatoes. The treatment methods cover foliar spraying as well as drip application. The Meeting concluded that the residue data for tomatoes can be extrapolated to support the use in eggplants.

The Meeting compared the data sets eggplant from Japan and for protected tomatoes using the Mann-Whitney-U test and decided that they belonged to the same population and could be combined. The combined eggplant and protected tomato residues were: 0.07, 0.12, 0.12, 0.15, 0.18, 0.19, 0.25, 0.28, 0.29 and 0.38 mg/kg.

Based on an extrapolation from the critical glasshouse foliar spray GAP for tomatoes and residue trials for eggplants from Japan the Meeting recommended a maximum residue level of 0.7 mg/kg, an STMR value of 0.185 mg/kg and a HR value of 0.38 mg/kg for thiacloprid in eggplants.

Potatoes

The Meeting received information on supervised field trials on potatoes from Belgium, Brazil, France, Germany, Italy, Japan, Spain and the United Kingdom.

The 16 supervised trials available from Europe for potatoes were conducted with up to three applications at 0.096 kg ai/ha each and a PHI of 21 days. This corresponds to the GAP from Austria, Cyprus, Greece, Portugal, Romania, Spain and the United Kingdom. The residues in potato tuber were < 0.02(16) mg/kg.

GAP in Japan for potatoes is up to three applications with 0.23 kg ai/ha each and a PHI of seven days. The residues from two supervised trials in Japan matching GAP (± 30%) were: < 0.005 and < 0.005 mg/kg in the tubers.

In addition the Meeting received information from two supervised residue trials on potatoes from Brazil. The application rates were 0.14 and 0.29 kg ai/ha with a PHI of 21 days. No residue above the LOQ of 0.02 mg/kg was found in potato tubers.

The Meeting recommended a maximum residue level of 0.02 (*) mg/kg and an STMR value and HR value of 0 mg/kg for thiacloprid in potatoes.

Wheat

Field trials on wheat were provided from France and Germany.

Thiacloprid is registered for use on wheat in Romania and Lithuania. The application rates are 0.048 kg ai/ha and 0.034 kg ai/ha respectively with a PHI of 21 days for Lithuania and an undefined PHI for Romania. The Meeting received supervised residue trials on wheat with application rates of 0.05 up to 0.062 kg ai/ha, which corresponds to + 29% of the GAP. Residues in wheat grain were < 0.02 (5), 0.03 (3), 0.04 and 0.04 mg/kg.

The Meeting recommended a maximum residue level of 0.1 mg/kg, an STMR value of 0.025 mg/kg and a highest residue value of 0.04 mg/kg for thiacloprid in wheat grain.

Barley

The Meeting received information from supervised residue trials on barley from France and Germany.

Thiacloprid is registered for on barley in Romania. The application rate is 0.048 kg ai/ha with an undefined PHI. The Meeting received supervised residue trials on barley with application rates of 0.062 kg ai/ha, which corresponds to + 29% of the GAP. Residues in barley grain were < 0.02, 0.05, 0.06, 0.11 and 0.12 mg/kg.

The Meeting decided that there was insufficient data from which to recommend a maximum residue level for thiacloprid on barley.

Rice

Field trials on rice were provided from India and Japan.

GAP in India for foliar spraying of rice is 0.12 kg ai/ha each and a PHI of 30 days. All supervised residue trials were performed, with application rates of 0.18 up to 0.36 kg ai/ha which were up to 3 × GAP. In addition, only the limit of detection of 0.001 mg/kg was reported for thiacloprid in rice. Nevertheless no residues above this LOD were detected in rice grain without husks or in the husks in any of the six supervised residue trials.

GAP in Japan for rice consists of up to three applications with 0.15 kg ai/ha without a PHI. In two residue trials with an application rate of 1.5 kg ai/ha no residue above the LOQ of 0.005 mg/kg could be detected in the grain after 117, and up to 152 days.

The Meeting concluded that the LOQ of the monitoring method (0.02 mg/kg) is an appropriate estimate for MRL values in rice.

The Meeting recommended a maximum residue level of 0.02 (*) mg/kg, an STMR value of 0 mg/kg and a highest residue of 0 mg/kg for thiacloprid in rice husks.

Maize

Field trials on maize were provided from France, Germany, Greece and Italy.

In Europe GAP is available from Romania (an application rate of 0.048 kg ai/ha and no PHI). Eight supervised residue trials were conducted with two treatments of 0.075 kg ai/ha each and a PHI of 28 – 31 days. These trials did not match any of the GAPs provided to the Meeting.

The Meeting concluded that the residue data on maize was not sufficient for recommending MRL, STMR or HR values.

Tree nuts

The Meeting received information on supervised field trials on walnuts from Italy.

GAP in Argentina, Chile, Italy and the United Kingdom consists of up to two applications at 0.0096 – 0.018 kg ai/hL and a PHI of 1 to 14 days. The four trials provided were performed at above GAP rate (0.03 kg ai/hL), but no residue could be detected in thenut kernel above the trial specific LOQ of 0.005 mg/kg.

Field trials were provided on almonds from USA.

GAP in Italy and the United Kingdom is up to two applications with 0.012 – 0.018 kg ai/hL and a PHI of 14 days. The residues for almond kernel from 14 trials in the USA matching the GAP (± 30%) were: < 0.01(13), 0.01 mg/kg.

Field trials were provided on pecan from USA.

GAP in Italy is up to 0.018 kg ai/hL and a PHI of 14 days. The residues for pecan kernel from 14 trials in USA matching the GAP (± 30%) were < 0.01(14) mg/kg.

Various GAPs in Germany, Italy and Turkey for tree nuts consist of up to two applications at rates of 0.0096 to 0.012 kg ai/hL each and a PHI of 21 days. The Meeting concluded that an extrapolation from almonds, walnuts and pecan to the whole group of tree nuts is possible. As thiacloprid is non-systemic, it was concluded that residues in nuts were comparable from different areas in the world. The combined thiacloprid residues in nuts were: < 0.01 (31), 0.01 mg/kg.

Because the analytical methods for enforcement are validated with a LOQ of 0.02 mg/kg, this value is used for the maximum residue level proposal for tree nuts.

The Meeting recommended a maximum residue level of 0.02 mg/kg and an STMR and HR value of 0.01 mg/kg for thiacloprid in tree nuts.

Oilseed rape and white mustard

Field trials on oilseed rape were provided from France, Hungary, Germany, Spain and Sweden.

Various GAPs in Czech Republic, Slovakia, Switzerland and the United Kingdom are up to two applications with 0.0096 up to 0.14 kg ai/ha. The residues in rapeseeds from 14 supervised trials matching the GAP ±30% were < 0.02(3), 0.02, 0.03, 0.05, 0.06, 0.07(3), 0.09, 0.1, 0.22, 0.33 mg/kg.

The GAP in Czech Republic for white mustard is up to two applications with 0.096 kg ai/ha each and no PHI reported. The Meeting concluded that residue trials for rapeseed can be extrapolated to white mustard seed.

The Meeting recommended a maximum residue level of 0.5 mg/kg, an STMR value of 0.065 mg/kg and a HR value of 0.33 mg/kg for thiacloprid in rapeseed and white mustard seeds.

Cotton seeds

Field trials on cotton were provided from Greece, Spain and the USA.

For cotton, two sets of supervised residue trials from Europe and USA were made available. The trials conducted in the USA were analyzed using a total residue method measuring 6-CNA. In the European trials total thiacloprid residue, determined as 6-CNA, and thiacloprid only, were analyzed. This data shows clear differences in the residue levels. Therefore the Meeting concluded that the residue data from USA for cotton would not be considered for further evaluation. The residue trials from Europe were conducted with three applications of 0.096 kg ai/ha each and a PHI of 21 days. This use pattern corresponded to GAPs from Greece, Guatemala, Spain and Turkey. The residues in cotton seed from eight supervised trials matching the GAP (± 30%) were < 0.02(8) mg/kg.

The Meeting recommended a maximum residue level of 0.02 (*) mg/kg and an STMR and HR value of 0.02 mg/kg for thiacloprid in cotton seeds.

Sunflower seeds

The Meeting received information from one field trial on sunflowers from Hungary.

Registered uses of thiacloprid on sunflowers are available from Hungary and Slovakia. The application rates are 0.036 – 0.048 kg ai/ha and an undefined PHI and a PHI of 30 days, respectively. The one supervised trial on sunflowers (application rate of 0.097 kg ai/ha) did not correspond to any available GAP.

The Meeting concluded that the available residue data on sunflowers was not sufficient for a recommendation of MRL, STMR of HR values.

Green tea

Field trials on green tea were made available from Japan.

GAP in Japan for green tea is one applications at 0.6 kg ai/ha and a PHI of seven days. The residue trials from Japan were conducted with an application rate of 0.3 kg ai/ha, which did not correspond to the submitted GAP. The Meeting concluded that a recommendation of maximum residue levels for green tea was not possible.

Wheat forage

Field trials on wheat were provided from France and Germany.

Registered uses of thiacloprid on wheat are available from Romania and Lithuania. The application rates are 0.048 kg ai/ha and 0.034 kg ai/ha respectively with a PHI of 21 days for Lithuania and an undefined PHI for Romania. The Meeting received supervised residue trials on wheat with application rates of 0.05 up to 0.062 kg ai/ha, which corresponds to + 29% of the GAP. Residues in wheat forage were: 1.2, 1.2, 1.3(3), 1.7, 1.8, 1.8, 1.9 and 2.2 mg/kg.

The Meeting estimated an STMR value of 1.5 mg/kg and a highest residue value of 2.2 mg/kg for thiacloprid in wheat forage.

Wheat straw

Field trials on wheat straw were available from France and Germany.

Registered uses of thiacloprid on wheat straw are available from Romania and Lithuania with application rates of 0.048 kg ai/ha and 0.034 kg ai/ha respectively, with a PHI of 21 days for Lithuania and an undefined PHI for Romania. The Meeting received supervised residue trials on wheat with application rates of 0.05 up to 0.062 kg ai/ha, which corresponded to + 29% of the GAP. Residues in wheat straw were 0.06, 0.07, 0.07, 0.14, 0.53, 0.89, 0.97, 1.2, 1.6 and 1.7 mg/kg.

The Meeting estimated an STMR value of 0.71 mg/kg and a highest residue value of 1.7 mg/kg for thiacloprid in wheat straw.

Based on 88% dry weight matter the residues in wheat straw (dry matter) were 0.07, 0.08, 0.08, 0.16, 0.6, 1.0, 1.1, 1.3, 1.8, 1.9 mg/kg. The Meeting estimated a MRL of 5 mg/kg for wheat straw (dry matter based).

Almond hulls

Field trials on almonds were made available from the USA.

GAP in Italy and the United Kingdom is up to two applications with 0.012 – 0.018 kg ai/hL and a PHI of 1 to 14 days. The residues for almond hulls from 14 trials in the USA matching the European GAP (± 30%) were 0.99, 1.3, 1.4, 1.5, 1.8, 1.8, 2.0, 2.1, 3.2, 3.3, 3.3, 3.4, 4.5, 4.9 mg/kg.

The Meeting estimated an STMR value of 2.05 mg/kg and a highest residue of 4.9 mg/kg for thiacloprid in almond hulls (fresh weight).

Based on 90% dry weight matter the residues in almond hulls were 1.1, 1.4, 1.6, 1.7, 2.0, 2.0, 2.2, 2.3, 3.5, 3.6, 3.6, 3.7, 5.0 and 5.4 mg/kg. The Meeting estimated a MRL of 10 mg/kg for almond hulls (dry matter based).

Rape forage

The Meeting received information on supervised residue trials on oilseed rape from France, Hungary, Germany, Spain and Sweden.

Various GAPs in the Czech Republic, Slovakia, Switzerland and the United Kingdom consist of up to two applications at 0.0096 to 0.14 kg ai/ha with PHI between zero and 30 days. The residues in rape forage from 12 supervised trials matching the GAP (± 30%) were 1.0, 1.1(4), 1.2, 1.4, 1.5, 1.6, 1.7, 1.9 and 2.2 mg/kg.

The Meeting estimated an STMR value of 1.3 mg/kg and a highest residue of 2.2 mg/kg for thiacloprid in rape forage (fresh weight).

Cotton gin by-products

Field trials on cotton gin by-products were provided from Greece, Spain and the USA.

For cotton two sets of supervised residue trials from Europe and USA were made available. The residue trials conducted in the USA were analyzed using a total residue method measuring 6-CNA. In the European trials total thiacloprid residue, determined as 6-CNA, and thiacloprid only, were analyzed. Residues analyzed with the total residue method are much higher than thiacloprid only residues and can not be extrapolated to evaluate the residue situation. In the supervised residue trials according to the residue definition “thiacloprid only” no gin trash samples were analyzed. A recommendation for a STMR or highest residue value for cotton gin by-products was not possible.

Fate of residues during processing

Thiacloprid was generally stable to hydrolysis during pasteurization, baking and boiling conditions.

Information on the fate of thiacloprid residues during food processing was available for melons and watermelons, apples, peaches, cherries and tomatoes.

Calculated processing factors and the mean or best estimate are summarized in the following table.

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factor	Estimate of the processing factor
Apples	Apple, dried	0.3, 0.7	0.5
	Apple, juice	0.2, 0.29	0.25
	Apple, sauce	0.6, 0.86	0.73
	Apple, pomace dry	4.3, 8.7	6.5
Peaches without stone	Peach, preserve	0.22, 0.66, 0.66	0.66
Tomatoes	Tomatoes, peeled	0.25, 0.43	0.34
	Tomato, paste	2, 3.1	2.6
	Tomato, juice	0.42, 0.71	0.615
	Tomato, preserve	0.33, 0.71	0.52

For apples the estimated processing factors are applied to the STMR value of 0.11 mg/kg for pome fruits. The Meeting estimated STMR-P values for dried apple of 0.055 mg/kg, for apple juice of 0.0275 mg/kg, for apple sauce of 0.077 mg/kg and for apple pomace dry of 0.71 mg/kg.

For peaches the estimated processing factors are applied to the STMR value of 0.08 mg/kg for stone fruits. The Meeting estimated STMR-P values of 0.05 mg/kg for preserved peaches.

For cherries it was not possible to calculate processing factors as residues in the RAC were below the limit of quantification.

For tomatoes the estimated processing factors are applied to the STMR value of 0.165 mg/kg. The Meeting estimated STMR-P values for peeled tomatoes of 0.056 mg/kg, for tomato paste of 0.429 mg/kg, for tomato juice of 0.1 mg/kg and for tomato preserve of 0.086 mg/kg.

Farm animal dietary burden

The Meeting estimated the dietary burden of thiacloprid residues for ruminants based on STMR and highest residue values obtained from the submitted supervised residue trials. The diets are described in Appendix IX of the *FAO Manual* (FAO, 2002).

Estimated maximum dietary burden of farm animals

Crop	Residue (mg/kg)	Basis	Group	Dry matter (%)	Residue/ Dry matter (mg/kg)	Dietary content (%)			Residue contribution (mg/kg)		
						Beef cattle	Dairy cows	Poultry	Beef cattle	Dairy cows	Poultry
Apple, dry pomace	0.72	STMR-P	AB	100	0.72	*40*	*20*		0.29	0.14	0
Rape, forage	2.2	HR	AM	30	7.33	*30*	*30*		2.20	2.20	0

Crop	Residue (mg/kg)	Basis	Group	Dry matter (%)	Residue/ Dry matter (mg/kg)	Dietary content (%)			Residue contribution (mg/kg)		
						Beef cattle	Dairy cows	Poultry	Beef cattle	Dairy cows	Poultry
Cottonseed (meal)	0.02	HR	-	89	0.02			*20*	0.00	0.00	0.004
Wheat, forage	2.2	HR	AF	25	8.80	*25*	*50*		2.20	4.40	0
Wheat, grain	0.04	HR	GC	89	0.045	*5*		*80*	0.002	0.000	0.036
Total						*100*	*100*	*100*	4.7	6.7	0.04

Estimated median dietary burden of farm animals

Crop	Residue (mg/kg)	Basis	Group	Dry matter (%)	Residue/ Dry matter (mg/kg)	*Dietary content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Apple, dry pomace	0.72	STMR-P	AB	100	0.65	*40*	*20*		0.29	0.14	0
Rape, forage	1.3	STMR	AM	30	4.33	*30*	*30*		1.3	1.3	0
Cottonseed (meal)	0.02	STMR	-	89	0.02			*20*	0	0	0.004
Wheat, forage	1.5	STMR	AF	25	6.00	*25*	*50*		1.5	3	0
Wheat, grain	0.025	STMR	GC	89	0.03	*5*		*80*	0.001	0	0.022
Total						*100*	*100*	*100*	3.1	4.4	0.03

The dietary burdens of thiacloprid for estimation of MRL and STMR values for animal commodities are for beef cattle 4.7 and 3.1 mg/kg and for dairy cows 6.7 and 4.4 mg/kg respectively. For poultry a dietary burden of 0.04 and 0.03 mg/kg was calculated.

Farm animal feeding studies

The Meeting received animal feeding studies on ruminants. No study on poultry feeding was available.

Three groups of cows were dosed at levels equivalent to 2.1 (0.07 mg/kg bw) (1×), 6.2 (0.213 mg/kg bw) (3×) and 20.6 ppm (0.655 mg/kg bw) (10×) of thiacloprid in the diet together with a control group. On average from the cows treated at the 1× dose level, the liver contained the highest thiacloprid residue levels (0.10 mg/kg) followed by kidney (0.03 mg/kg), milk and muscle (0.02 mg/kg) and fat (0.01 mg/kg). Maximum levels for tissues were 0.02 mg/kg for fat, 0.02 mg/kg for muscle, 0.04 mg/kg for kidney and 0.11 mg/kg for liver.

In the second dose group thiacloprid residue increased to average values of 0.04 mg/kg in milk and fat (highest value 0.04 mg/kg) 0.05 mg/kg in muscle (highest value 0.06 mg/kg), 0.1 mg/kg in kidney (highest value 0.11 mg/kg) and 0.29 mg/kg in liver (highest value 0.32 mg/kg). In the high dose group the residues found were 0.17 mg/kg in milk, 0.12 mg/kg in fat (highest value 0.16 mg/kg), 0.16 mg/kg in muscle (highest value 0.18 mg/kg), 0.27 mg/kg in kidney (highest value 0.32 mg/kg) and 0.94 mg/kg in liver (highest value 1.1 mg/kg).

A linear relation between the dose levels and the residue concentrations was observed.

In milk, residues reached a plateau level within five days and no accumulation was observed.

For poultry no feeding studies were provided. In the metabolism study based on a feeding level of 10 mg/kg bw (corresponding to 124 ppm in feed, based on dry weight) thiacloprid residues of 0.06 mg/kg in eggs, 0.03 mg/kg in muscle, 0.08 mg/kg in fat and 0.54 mg/kg in liver were found.

Animal commodity maximum residue levels

The dietary burden for beef and diary cattle was estimated at a maximum level 4.7 and 6.7 mg/kg respectively. The maximum residue level to be expected in tissues can be obtained from the results of feeding at a level of 6.2 ppm.

Dietary burden (mg/kg)[1]	Feeding level [ppm][2]	Thiacloprid residue level (mg/kg)[3]				
		Milk (mean)	Fat (high)	Muscle (high)	Liver (high)	Kidney (high)
MRL dairy cattle	(6.7) [6.2]	*(0.04)* *0.04*	*(0.04)* *0.04*	*(0.06)* *0.06*	*(0.32)* *0.34*	*(0.11)* *0.11*
		Milk (mean)	Fat (mean)	Muscle (mean)	Liver (mean)	Kidney (mean)
STMR dairy cattle	(4.4) [2.1,6.2]	*(0.02, 0.04)* *0.03*	*(0.02, 0.04)* *0.03*	*(0.02, 0.05)* *0.035*	*(0.1, 0.29)* *0.21*	*(0.04, 0.1)* *0.07*

1 In parentheses, estimated dietary burden

2 In square brackets, actual feeding level in transfer studies

3 Values in parentheses in italics are derived from the dietary burden, feeding levels and residue levels found in the transfer studies ´. "high" is the highest residue level in an individual tissue in the relevant feeding group. "mean" is the mean residue level in milk in the relevant feeding group.

The median dietary burdens were 3.1 mg/kg for beef cattle and 4.4 mg/kg for dairy cattle. The burden for dairy cows is between the dose levels of 2.1and 6.2 mg/kg of the animal feeding study. Therefore the mean value for each dose group and each commodity is taken for STMR estimation. The values are 0.03 mg/kg for milk, 0.03 mg/kg for mammalian fat, 0.035 mg/kg for mammalian meat and 0.21 mg/kg for edible offal, mammalian. For HR the calculated residues based on the maximum estimated dietary burden were 0.04 mg/kg for mammalian fat, 0.06 mg/kg for mammalian meat and 0.34 for mammalian edible offal.

Based on the highest residues found in the feeding study (3× dose) the Meeting estimated maximum residue levels of 0.1 mg/kg for mammalian meat and 0.5 mg/kg for mammalian edible offal. Based on the mean value the Meeting estimated a maximum residue level of 0.05 mg/kg for milk.

For poultry no feeding studies are available. When the calculated maximum dietary burden for poultry is extrapolated from the results of the poultry metabolism study the resulting residue levels are far below 0.01 mg/kg. The Meeting estimated an STMR value and a highest residue of 0 mg/kg for thiacloprid in poultry products.

The Meeting estimated a MRL of 0.02 (*) mg/kg for poultry meat, poultry edible offal and eggs.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDI) of thiacloprid based on 13 GEMS/Food regional diets were in the range of 1–10% of the maximum ADI of 0.01 mg/kg bw. The Meeting concluded that the long-term intake of residues of thiacloprid 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) of thiacloprid on the basis of the recommendations made by the JMPR represented 0–90% of the ARfD (0.03 mg/kg bw) for children and 0–30% for the general population. The Meeting concluded that the short-term intake of residues of thiacloprid resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

4.30 THIOPHANATE-METHYL (077)

TOXICOLOGY

Evaluation for an acute reference dose

Thiophanate-methyl is the ISO approved common name for dimethyl 4,4'-(*o*-phenylene)bis(3-thioallophanate), a systemically active benzimidazole fungicide that inhibits the synthesis of β-tubulin. Thiophanate-methyl was previously evaluated by the Joint Meeting on Pesticide Residues in 1973, 1975, 1977, 1995, and 1998. In 1998, an ADI of 0–0.08 mg/kg bw was established based on the NOAEL of 8 mg/kg bw per day in a three-generation study of reproductive toxicity in rats and in a 1-year study in dogs (both of these studies having been evaluated at earlier meetings) and a safety factor of 100. The 1998 JMPR also concluded that an ARfD was not required because thiophanate-methyl is of low acute toxicity when administered orally or dermally and that the acute intake of residues is unlikely to present a risk to consumers.

The Meeting was asked by the CCPR to reconsider the need for an ARfD for thiophanate-methyl. The present Joint Meeting therefore evaluated relevant original studies that had been considered by previous Meetings, and newly submitted studies on genotoxicity, reproductive toxicity, developmental toxicity and acute and short-term neurotoxicity.

Toxicological data

Thiophanate-methyl has low acute toxicity: the oral LD_{50} was 6640–7500 mg/kg bw in rats and 3400–3514 mg/kg bw in mice. The clinical signs of toxicity after single high (near-lethal) doses included whole body tremors at 1–2 hours after dosing, which progressed to tonic and clonic convulsions.

In a 1-year study of toxicity in dogs given capsules containing thiophanate-methyl, slight tremors were observed in all eight animals approximately 2–4 hours after administration of the highest dose of 200 mg/kg bw per day on one to five occasions during the initial 17 days of the study. One dog exhibited severe tremors that progressed to tonic convulsions on three occasions. The NOAEL was 8 mg/kg bw per day on the basis of increased thyroid weights and hypertrophy of the thyroid follicular epithelium at 40 mg/kg bw per day and above.

In a 3-month study of toxicity in dogs given capsules containing thiophanate-methyl at doses of up to 800 mg/kg bw per day, dose-related clinical signs including dehydration, thinness and

lethargy were seen in animals at the highest dose and to a lesser extent at the intermediate dose (200 mg/kg bw per day). No tremors were seen up to the highest dose tested. A NOAEL could not be identified in this study because of the presence of follicular-cell hypertrophy in the thyroid of two dogs at 50 mg/kg bw per day, the lowest dose tested.

Thiophanate-methyl has been adequately tested in a range of assays for genotoxicity. Thiophanate-methyl does not cause gene mutations or structural chromosomal aberrations; however, it causes changes in chromosome number (aneuploidy) both in vitro and in vivo. Induction of micronucleus formation in mice was seen after single high doses (500 mg/kg bw and above), but the response was weak when compared with that for the main metabolite of thiophanate-methyl, carbendazim, which is considered to be responsible for the observed effect. The mechanism by which aneuploidy is induced by carbendazim is clearly understood and there is a clear threshold for this effect.

The Meeting concluded that the genotoxic effect of thiophanate-methyl is a threshold phenomenon and is related to the production of carbendazim.

On the basis of evaluations from previous Meetings, there was no adverse effect on fertility and reproductive performance in a recent two-generation study of reproduction toxicity using doses of up to 2000 ppm, equal to 147.1 and 164.3 mg/kg bw per day in males and females, respectively.

The developmental toxicity potential of thiophanate-methyl had been investigated in mice, rats, and rabbits. From evaluations made at previous Meetings, the NOAEL for developmental toxicity in mice was 500 mg/kg bw per day, on the basis of decreased number of live fetuses at 1000 mg/kg bw per day, while no maternal toxicity was observed at this dose. In rats, there was no evidence of developmental toxicity at doses of up to 1000 mg/kg bw per day, but maternal toxicity (reduced body-weight gain) was seen at this dose.

In a study of prenatal developmental toxicity in rabbits, which had not been evaluated previously, the NOAEL for developmental effects was 20 mg/kg bw per day on the basis of increased incidence of supernumerary thoracic ribs and decreased fetal weights at 40 mg/kg bw per day, the highest dose tested. The NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reduced feed consumption and reduced body-weight gain at 20 mg/kg bw per day and above.

Thiophanate-methyl was not selectively toxic to embryo or fetal development in rats and rabbits and was not teratogenic.

In a study of acute neurotoxicity in rats, the NOAEL for general toxicity was 125 mg/kg bw on the basis of transient reductions in body-weight gains (including body-weight losses) and feed consumption at 500 mg/kg bw and above. The NOAEL for neurotoxicity was 2000 mg/kg bw, the highest dose tested.

In a short-term study of neurotoxicity in rats, the NOAEL for general toxicity was 500 ppm (equal to 30.3 and 34.9 mg/kg bw per day in males and females, respectively) on the basis of decreased body weights and feed consumption in females and increased liver and thyroid weights in both sexes at 2500 ppm. No neurohistological changes were seen at 2500 ppm. The NOAEL for neurotoxicity was 2500 ppm (equal to 149.6 and 166.3 mg/kg bw per day in males and females, respectively), the highest dose tested.

Toxicological evaluation

The Meeting considered whether the establishment of an ARfD was necessary. The initial, transient clinical signs (tremors) that were seen in a 1-year study in dogs given thiophanate-methyl at a dose of 200 mg/kg bw per day were not observed in a 3-month study in dogs given thiophanate-methyl at doses of up to 800 mg/kg bw per day. Therefore the Joint Meeting considered that the tremors were not attributable to a toxicological effect of the test substance.

The developmental effects that had been observed in rabbits at 40 mg/kg bw per day were not considered to be elicited by a single exposure.

The Joint Meeting concluded that it was not necessary to establish an ARfD for thiophanate-methyl in view of its low acute toxicity, the absence of relevant developmental toxicity that could be a consequence of acute exposure, the absence of relevant findings in a study of acute neurotoxicity, and the absence of any other toxicological effect that would be likely to be elicited by a single dose.

The Joint Meeting noted that the use of thiophanate-methyl on crops may give rise to residues of carbendazim, although thiophanate-methyl can also be detected as part of the residue to which consumers of treated produce are exposed. Since the toxicity of thiophanate-methyl is qualitatively and quantitatively (when corrected for relative molecular mass) different from that of carbendazim, and since the ARfD for carbendazim is lower than that which would be derived from data on thiophanate-methyl, the Joint Meeting concluded that the intake of residues in food should initially be compared with the ARfD for carbendazim. If further refinement of the risk assessment is necessary, the different components of the residue (carbendazim and thiophanate-methyl) could be considered separately.

A toxicological monograph was prepared.

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 exposures.