Italy, 0.02 kg ai/hl, 0.2 kg ai/ha, three applications, 7-day PHI; Spain, 0.025 kg ai/hl, three applications, 7-day PHI; Switzerland, 0.25 kg ai/ha, two applications, 3-day PHI. GAPs were not available for Greece or the United Kingdom. As three applications were used in all trials, the GAPs of Italy and Spain were used (7-day PHI). The residue levels in the 14 glasshouse trials at this GAP in ranked order were: 0.05, 0.08, 0.09 (two), 0.10 (two), 0.13 (two), 0.14 (two), 0.16, 0.21, 0.28 and 0.32 mg/kg. The levels in the outside trials in Switzerland were: 0.04 and 0.07 mg/kg. The two groups were statistically the same population, and the combined levels from the 16 trials were: 0.04, 0.05, 0.07, 0.08, 0.09 (two), 0.10 (two), 0.13 (two), 0.14 (two), 0.16, 0.21, 0.28 and 0.32 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.12 mg/kg.

*Bell pepper*

Fludioxonil (25% water-dispersible granules) was applied as a foliar spray to bell (sweet) peppers in eight glasshouse trials and two field trials in Spain and Switzerland. The relevant GAPs are: Austria, 0.025 kg ai/hl, 0.25 kg ai/ha, three applications, 7-day PHI; Italy, 0.02 kg ai/hl, 0.2 kg ai/ha, three applications, 7-day PHI; Spain, 0.25 kg ai/ha, three applications, 7-day PHI. The GAP of Austria and Italy was used. The ranked order of residue levels in the eight glasshouse trials ( six in Spain, two in Switzerland) at GAP was: 0.08, 0.10, 0.14, 0.22, 0.29, 0.46, 0.56 and 0.60 mg/kg. The ranked order in field trials at GAP (one in Italy, one in Spain) was: 0.06 and 0.13 mg/kg. As the two groups are from the same population, they were combined to give levels of: 0.06, 0.08, 0.10, 0.13, 0.14, 0.22, 0.29, 0.46, 0.56 and 0.60 mg/kg. The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.18 mg/kg.

*Eggplant*

Fludioxonil formulated as 25% water-dispersible granule was applied to eggplant as a foliar spray three times in glasshouse trials in Italy and Spain. The relevant GAPs are: Italy, 0.02 kg ai/hl, 0.2 kg ai/ha, three applications, 7-day PHI; Spain, 0.025 kg ai/hl, three applications, 7-day PHI. The results at GAP in ranked order were: 0.03, 0.06, 0.06 and 0.08 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.06 mg/kg.

*Sweet corn (corn-on-the-cob)*

Fludioxonil (flowable concentrate) was applied to sweet corn seed in the USA before planting. The relevant GAP is 5 g ai/1000 kg seed. The residue levels were < 0.01 in three trials at three to five times GAP. The Meeting recognized the similarity of sweet corn and maize (see below) and decided to translate the field trial data for seed treatment of maize (same GAP as sweet corn) to sweet corn seed treatment. The residue levels in the eight trials were all < 0.01 mg/kg. The Meeting estimated a maximum residue level of 0.01 (*) mg/kg and an STMR 0.01 mg/kg.

*Leafy vegetables*

*Lettuce, head*

Fludioxonil (25% water-dispersible granules) was applied as a foliar spray to lettuce in 11 glasshouse and 17 field trials in France, Germany, Italy, Spain and Switzerland. The relevant GAPs are: France, 0.15 kg ai/ha, four applications, 14-day PHI; Italy, 0.018 kg ai/hl, 0.18 kg ai/ha, three applications, 14-day PHI; Spain, 0.15 kg ai/ha, three applications, 14-day PHI; Switzerland, 0.12 kg ai/ha, two applications, early season. No GAP was available for Germany. The GAP of Italy was used to evaluate the trials. The ranked order of residue levels in the glasshouse trials was: 0.72, 0.98, 1.1, 2.4, 2.5, 2.7 (two), 3.4 (two), 4.7 and 6.0 mg/kg. The ranked order of residue levels in the field trials was: < 0.02 (six), 0.02 (two), 0.04 (three), 0.07, 0.11, 0.17, 0.29, 1.2 and 1.2 mg/kg. The two sets are not from the same population. In the basis of the indoor trials, the Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 2.7 mg/kg.

*Watercress*

Watercress was treated with fludioxonil (25% water-dispersible granules) as a foliar spray in the USA. The relevant GAP is: 0.25 kg ai/ha, four applications, 0-day PHI. In the two trials at GAP, the residue levels were 4.2 and 4.5 mg/kg. The OECD York Workshop recommended a minimum of three trials for commodities that are not significant in trade or in the diet. (See mustard greens.)

*Mustard greens*

Supervised trials were conducted on mustard greens in the USA. The relevant GAP is: 0.24 kg ai/ha, water-dispersible granules, four applications, 7-day PHI. The ranked order of residue levels in the seven trials at GAP was: 0.06, 0.49, 0.54, 0.76, 1.2, 6.6 and 7.1 mg/kg. The Meeting decided to combine the results of the trials on watercress and mustard greens (same GAP) for mutual support. The ranked order of levels in the nine trials was 0.06, 0.49, 0.54, 0.76, 1.2, 4.2. 4.5, 6.6 and 7.1 mg/kg. The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 1.2 mg/kg for both watercress and mustard greens.

*Legume vegetables and pulses*

*Bean pod with seed (common bean, French bean, edible podded bean)*

Fludioxonil (water-dispersible granules) was applied as a foliar spray to beans in pod in 22 field and glasshouse trials in France, Spain and Switzerland. The relevant GAPs are: France, 0.083 kg ai/hl, 0.25 kg ai/ha, number of applications not specified, 14-day PHI; Spain, 0.025 kg ai/hl, three applications, 14-day PHI. No GAP was available for Switzerland, and the GAP of France was applied. The ranked order of residue levels from the 15 field trials was: < 0.02, 0.02 (two), 0.03 (five), 0.04 (two), 0.06 (three), 0.09 and 0.13 mg/kg. The ranked order in the seven glasshouse trials was: 0.03, 0.04 (two), 0.06, 0.09, 0.17 and 0.20 mg/kg. The two groups are not from different populations and were therefore combined to give residue levels of: < 0.02, 0.02 (two), 0.03 (six), 0.04 (four), 0.06 (four), 0.09 (two), 0.13, 0.17 and 0.20 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.04 mg/kg for beans (pods and/or immature seeds). This maximum residue level and STMR are extended to peas with pod.

Trials were also conducted on the seed treatment of broad bean and French bean seeds (flowable concentrate) at 5 g ai/100 kg seed in Denmark and Germany. The residue levels were < 0.02 mg/kg on bean seed in all six trials, but no GAP was available.

*Peas (succulent)*

Fludioxonil (25% water-dispersible granules) was applied as a foliar spray to pea vines in France and Switzerland. The relevant GAP is that of France for legume vegetables: 0.083 kg ai/hl, 0.25 kg ai/ha, number of applications not specified, 14-day PHI. No GAP was available for Switzerland, and the GAP of France was applied. The ranked order of residue levels in the trials at GAP was: ≤ 0.02 (10) and 0.02 mg/kg.

Trials were also conducted of seed treatment of peas with a flowable concentrate or water-dispersible granule formulation in France and the United Kingdom. The residue levels were < 0.02 mg/kg in the six trials conducted at the GAP of the United Kingdom (5% water-dispersible granules, 10 g ai/100 kg seed).

The Meeting estimated a maximum residue level of 0.03 mg/kg and an STMR of 0.02 mg/kg for peas, shelled (succulent seeds) on the basis of the trials with foliar application. Nevertheless, the maximum residue level and STMR also accommodate seed treatment use and are extended to succulent beans without pod.

*Pulses (dry bean and dry pea)*

A water-dispersible granule formulation of fludioxonil was applied as a foliar spray to pea and bean (kidney) vines in France. The relevant GAP is: Austria and Spain, water-dispersible granules, 0.25 kg ai/ha, two applications, 14-day PHI. No GAP was available for France, and the GAP of Spain was applied. The ranked order of residue levels in dry pea and bean was: < 0.02 (two), 0.04 (two) and 0.05 mg/kg.

Supervised trials on the seed treatment of pea seed in France were also considered. GAP in the United Kingdom is application of a 5% water-dispersible granule formulation of fludioxonil (w/w) at a rate of 10 g ai/100 kg pea seed. The residue levels in the seven trials at this GAP were < 0.02 mg/kg in dry seed at harvest.

The Meeting estimated a maximum residue level of 0.07 mg/kg and an STMR of 0.02 mg/kg for dry peas and for dry beans after foliar application of fludioxonil. The Meeting noted that this also accommodates use of fludioxonil for seed treatment.

*Root and tuber vegetables*

*Potato*

Fludioxonil (flowable concentrate, dustable powder) was applied to potato pieces as seed treatment in six trials in Australia, three in South Africa and 13 in the USA. The available GAPs are: Australia, flowable concentrate, 10%, 2.5 g ai/100 kg seed; USA, flowable concentrate, 2.5 g ai/100 kg seed. The ranked order of residue levels on mature potatoes in trials at GAP in Australia and the USA was: < 0.01 (16) and 0.01 (17) mg/kg. The Meeting estimated a maximum residue level of 0.02 mg/kg and an STMR of 0.01 mg/kg.

*Yam*

A 50% wettable powder formulation of fludioxonil was applied as post-harvest treatment to yams at 0.06 kg ai/hl in the USA. GAP specifies application of a 50% wettable powder formulation as a single dip application at a rate of 0.06 kg ai/hl for about 30 s. Two trials were conducted at GAP, and in each trial both whole tubers and tuber pieces (cut yams) were tested. The ranked order of residue levels was: 4.6 and 5.0 mg/kg. The Meeting regarded two independent trials as insufficient for estimating a maximum residue level or an STMR.

*Carrot*

Nine trials were conducted in the USA in which carrot plots were given four foliar applications of fludioxonil at 0.24 kg ai/ha. The relevant GAP is: water-dispersible granules, 0.25 kg ai/ha, four applications, 7-day PHI. The residue levels in seven trials at GAP were: 0.04, 0.16, 0.18, <u>0.20</u>, 0.20, 0.25 and 0.42 mg/kg. The Meeting estimated a maximum residue level of 0.7 mg/kg and an STMR of 0.20 mg/kg.

*Asparagus*

In two trials in Germany, asparagus plants were treated with a water-dispersible granule formulation after harvest. This gives a PHI of about 240 days. No GAP was available for Germany. GAP for Austria specifies use of a 25% water-dispersible granule formulation three times with a 14–21-day interval at 0.042 kg ai/hl or 0.25 kg ai/ha per application. No PHI is specified, but treatments are to be made at transplantation from the glasshouse to the field. The residue levels in the two German trials were < 0.02 mg/kg. The Meeting considered two trials insufficient for estimating a maximum residue level or an STMR.

*Cereal grains*

Fludioxonil formulations were applied to wheat in France, Germany and Switzerland as seed treatment. The relevant GAPs are: Austria, Belgium, United Kingdom, flowable concentrate formulation, 5 g ai/100 kg seed, one application. In the 48 trials conducted at or above GAP, the residue levels in ranked order were: < 0.02 (36) and < 0.04 (12) mg/kg.

One trial was reported from Denmark in which rye seed was treated. The relevant GAP is: Austria, flowable concentrate, 5 g ai/100 kg seed. No GAP is available for Denmark. The residue level was < 0.02 mg/kg.

Fludioxonil was applied as seed treatment to barley in 30 trials in France, Germany and Switzerland. The relevant GAPs are: Austria, Belgium, United Kingdom, flowable concentrate formulation, 5 g ai/100 kg seed. No GAP was available for France, Germany or Switzerland. The residue levels in six trials conducted at or above GAP were < 0.02 mg/kg.

Fludioxonil was applied as a seed treatment to maize (field corn) in 27 trials in France, Germany, Greece, Hungary, Italy and Spain, three trials in South Africa and five trials in the USA. The relevant GAP is: USA, flowable concentrate formulation, 5 g ai/100 kg seed. No GAPs were available for Europe or South Africa, and the GAP of the USA was applied. The ranked order of residue values in trials conducted at GAP and at three and five times the GAP rate were < 0.01 (five) and < 0.02 (seven) mg/kg.

Fludioxonil was applied as seed treatment to sorghum in four trials in the USA. The relevant GAP is flowable concentrate formulation, 5 g ai/100 kg seed. The residue level at three to five times the GAP rate was < 0.05 mg/kg.

All residue levels resulting from seed treatment of the five different cereal grains were below the LOQ. The combined results from all the trials, in ranked order, were: < 0.01 (five), <u>< 0.02</u> (50), < 0.04 (12) and < 0.05 (four) mg/kg. The Meeting estimated a maximum residue level of 0.05 (*) mg/kg and an STMR of 0.02 mg/kg for cereal grains.

*Pistachio nut*

Fludioxonil was applied as a water-dispersible granule formulation to pistachio trees in the USA. The relevant GAP is: 0.25 kg ai/ha, four applications, 7-day PHI. The residue levels, in ranked order, were: 0.04, 0.05 and 0.08 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR 0.05 mg/kg.

*Rape-seed*

Fludioxonil was applied to rape as seed treatment in trials in France, Germany, Sweden and the United Kingdom. GAP in Germany is treatment of seed with a flowable concentrate formulation at 12 g fludioxonil per 100 kg seed. The residue levels in the 15 trials at this GAP were < 0.02 mg/kg. The Meeting estimated a maximum residue level of 0.02 (*) mg/kg and an STMR of 0.02 mg/kg.

*Cotton-seed*

Fludioxonil was applied as seed treatment (flowable concentrate and emulsion formulations) to cotton in Greece and the USA. The relevant GAP is: USA, flowable concentrate, 5 g ai/100 kg seed. No GAP was available for Greece (or any other European country), and the GAP of the USA was applied. The ranked order of residue levels in the trials was: < 0.02 (two) and <u>< 0.05</u> (six) mg/kg. The Meeting estimated a maximum residue level of 0.05 (*) mg/kg and an STMR of 0.05 mg/kg for cotton-seed.

*Herbs*

Fludioxonil was applied as a foliar spray (water-dispersible granules) to chives and basil in the USA. The relevant GAP is 0.25 kg ai/ha, four applications, 7-day PHI. The residue levels were: 1.8 and 3.9 mg/kg on chives and 1.9 and <u>3.0</u> mg/kg on basil. The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 2.4 mg/kg for fresh basil and a maximum residue level of 10 mg/kg and an STMR of 2.8 mg/kg for fresh chives.

For each herb, one trial included drying. The drying factor for chives is 8 (31/3.9), and that for basil is also 8 (23/3). Application of this factor to the data from field trials with chives yielded a revised ranked order of residue levels: 14 and 31 mg/kg. Therefore, the Meeting estimated a maximum residue level of 50 mg/kg and an STMR of 22 mg/kg for dried chives. Application of the drying factor for basil yield a revised ranked order of 15 and 24 mg/kg. Therefore, the Meeting estimated a maximum residue level of 50 mg/kg and an STMR of 20 mg/kg for dried basil.

*Animal feedstuffs*

*Straw, fodder and forage of cereal grains and grasses*

Trials of residue levels in forage, fodder and straw after application of fludioxonil as seed treatment were conducted with wheat, rye, barley, maize, sweet corn and sorghum. Trials on wheat were conducted in

Europe according to the following relevant GAP: Austria, Belgium, United Kingdom, flowable concentrate formulation, 5 g ai/100 kg seed, one application. In the 45 trials conducted at or above GAP, the ranked order of residue levels in straw was: < 0.02 (eight), < 0.04 (14) and < 0.05 (23) mg/kg. The ranked order of residue levels in forage was: < 0.02 (seven) and < 0.04 (11) mg/kg.

A trial on rye was conducted in Denmark according to the GAP for Austria: flowable concentrate, 5 g ai/100 kg seed. The residue level was < 0.05 mg/kg in straw and < 0.05 mg/kg in forage.

Trials on barley were conducted in Europe according to the GAP for Austria, Belgium and the United Kingdom: flowable concentrate formulation, 5 g ai/100 kg seed. In five trials conducted at or above GAP, the ranked order of residue levels were: < 0.02 and < 0.05 (four) mg/kg in straw and < 0.05 (three) mg/kg in forage.

Trials on maize and sweet corn were conducted Europe (maize only) and in the USA. The relevant GAP was: USA, flowable concentrate formulation, 5 g ai/100 kg seed, as no GAP was available for any country in Europe. There were no detectable residues in fodder (< 0.01 (five) mg/kg) or forage (< 0.01 (seven) mg/kg). Using the default moisture content value of 40% for maize forage (*FAO Manual*, Appendix IX), the Meeting estimated a maximum residue level of 0.03 (*) mg/kg (0.01/0.40) and an STMR of 0 mg/kg (0.00/0.40) for maize forage (dry).

Field trials were conducted on sorghum in the USA, the relevant GAP being flowable concentrate formulation, 5 g ai/100 kg seed. The residue levels after exaggerated application rates were < 0.01 (four) mg/kg on fodder and < 0.01 (four) mg/kg on forage.

The combined values for fodder and straw in ranked order were: < 0.01 (nine), < 0.02 (nine), < 0.04 (four) and < 0.05 (28). As no data were available on the moisture content, the default value of 83% for maize fodder was used (*FAO Manual*, Appendix IX). The Meeting estimated an STMR of 0 mg/kg (0.00/0.83) and a maximum residue level of 0.06 (*) mg/kg (0.05/0.83) for fodder (dry) and straw of cereal grains.

*Rape forage and straw*

Fludioxonil was applied to rape as seed treatment in trials in France, Germany, Sweden and the United Kingdom. The GAP in Germany is treatment of seed with an flowable concentrate formulation at 12 g fludioxonil per 100 kg seed. The residue levels were < 0.05 mg/kg in forage (12) and straw (six).

### *Fate of residues during processing*

A study of hydrolysis with [pyrrole-4-$^{14}$C]fludioxonil showed that fludioxonil is stable under the typical conditions of pasteurization, baking, brewing, boiling and sterilization.

The processing (transfer) factors through commercial-type processes for plums, strawberries, grapes, citrus and tomato are summarized in the table below. Factors could not be calculated for cereal grains, cottonseed or potatoes because there were no quantifiable residues in the raw agricultural commodities, even in trials with exaggerated treatment rates.

*Processing factors and STMR-P values for various commodities*

| Raw agricultural commodity | | | | Processed commodity | | | |
|---|---|---|---|---|---|---|---|
| Commodity | MRL (mg/kg) | STMR (mg/kg) | HR (mg/kg) | Commodity | Processing factor | STMR-P (mg/kg) | HR-P (mg/kg) |
| Plum[1] | 5 | 0.80 | 3.6 | Prunes (dried plums) | 1.91[2] | 0.96 | 4.3 |
| | | | | Juice | 0.10 | 0.080 | |
| | | | | Preserves | 0.50 | 0.40 | |

| Raw agricultural commodity | | | | Processed commodity | | | |
|---|---|---|---|---|---|---|---|
| Commodity | MRL (mg/kg) | STMR (mg/kg) | HR (mg/kg) | Commodity | Processing factor | STMR-P (mg/kg) | HR-P (mg/kg) |
| | | | | Puree | 0.80 | 0.64 | |
| Strawberry | 3 | 0.38 | 2.2 | Juice | 0.16 | 0.061 | |
| | | | | Preserves | 0.62 | 0.24 | |
| | | | | Jam | 0.34 | 0.13 | |
| Grapes | 2 | 0.28 | 1.6 | Raisins (dried grapes) | 1.1[3] | 0.31 | 1.8 |
| | | | | Juice | 0.92[4] | 0.26 | |
| | | | | Wine<br>(< 100 days) | 0.30[5] | 0.08 | |
| | | | | Wine<br>(>100 days | 0.036[6] | 0.010 | |
| Lemons | | | | Juice | 0.031 | | |
| | | | | Oil | 61 | | |
| | | | | Pulp | 2.1 | | |
| Tomato | 0.5 | 0.12 | 0.32 | Juice | 0.22[7] | 0.026 | |
| | | | | Paste | 1.4[8] | 0.17 | |
| | | | | Pomace (wet) | 3.3[9] | | |

[1] Stone fruit, includes field trial data for cherries and peaches
[2] Four trials, range 1.8–2.7, mean 1.91, median 1.6
[3] 15 trials, range 0.58–1.7, mean 1.1, median 1.1
[4] 12 trials, range 0.58–1.0, mean 0.92, median 0.86
[5] 17 trials, range 0.012–0.86, mean 0.30, median 0.24
[6] 11 trials, range 0.0086–0.11, mean 0.036, median 0.029
[7] Four trials for pasteurized juice, range 0.20–0.24, average 0.22, median 0.22
[8] Four trials for pasteurized paste, range 1.1–1.6, average 1.4, median 1.35
[9] Two trials for wet pomace, 3.0 and 3.6

### *Residues in animal commodities*

A feeding study was conducted in which three groups of three dairy cows received 0.55 ppm, 1.6 ppm or 5.5 ppm fludioxonil in the diet for 28–30 days. Residues of fludioxonil and metabolites, determined as CGA-192155 (2,2-difluorobenzo[1,1]dioxole-4-carboxylic acid), were quantifiable only at the highest feeding level (5.5 ppm). Residues were found in the milk of two of three cows, with maximum values of 0.019 mg/kg and 0.014 mg/kg on days 14 and 21, respectively. At the lowest feeding level, residues were detected in milk on days 3–21 at levels of 0.001–0.004 mg/kg, with maximum detection on day 3.

Only tissue samples from cows fed the 5.5 ppm diet were analysed. No residues of fludioxonil or metabolites were found. The LOQ was 0.01 mg/kg in muscle and 0.05 mg/kg in liver, kidney and fat (perirenal and omental).

The dietary intake of ruminants and poultry can be calculated from the recommended STMRs or HRs and consideration of possible animal feed items. The table below shows the bases for the dietary intake calculation.

| Commodity | Group | Maximum or highest residue level (mg/kg) | STMR or STMR-P (mg/kg) | Dry matter (%) | Dietary content (%) | | | Residue contribution (mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Beef cattle | Dairy cows | Poultry | Beef cattle | Dairy cows | Poultry |
| Barley grain | GC | 0.05 | | 88 | 50 | 40 | 75 | | | |
| Barley straw (dry) | AS | 0.06 | | | 10 | 60 | | | | |
| Cotton-seed | SO | 0.05 | | 88 | 25 | 25 | | | | |
| Cotton-seed meal | | 0.05 | | 89 | 15 | 15 | 20 | | | |
| Maize grain | GC | 0.05 | | 88 | 80 | 40 | **80** | 0.02 | 0.03 | 0.05 |
| | | | | | **25** | **40** | | | | |
| Maize forage (dry) | AF | 0.03 | | | 40 | 50 | | | | |
| Maize fodder (dry) | AS | 0.06 | | | 25 | 15 | | | | |
| Oat grain | GC | 0.05 | | 89 | 50 | 40 | 80 | | | |
| Oat straw (dry) | AS | 0.06 | | 90 | 10 | 10 | | | | |
| Potato waste | AB | | 0.01 | 15 | **75** | **40** | | 0.05 | 0.03 | |
| Rape meal | | 0.02 | | 88 | 15 | 15 | 15 | | | |
| Rape forage | AM | 0.05 | | 30 | 30 | 30 | | | | |
| | | | | | | **20** | | | | |
| Rye grain | GC | 0.05 | | | 40 | 40 | 50 | | | |
| Rye straw (dry) | AS | 0.06 | | 88 | 10 | 10 | | | | |
| Wheat grain | GC | 0.05 | | 89 | 50 | 40 | 80 | | | |
| Wheat forage | AF | 0.05 | | 25 | | | | | | |
| Wheat straw (dry) | AS | 0.06 | | 88 | 10 | 10 | | | | |
| Pea seed | VD | 0.07 | | 90 | 20 | 20 | **20** | | | 0.02 |
| **Total** | | | | | **100** | **100** | **100** | **0.07** | **0.06** | **0.07** |

The calculated dietary intakes of beef cattle, dairy cows and poultry are 0.07, 0.06 and 0.07 mg/kg, respectively.

No quantifiable residue was found in the tissues of ruminants at levels 60 times (cows) and 80 times (beef cattle) the calculated dietary burden. Fludioxonil and metabolites were detected in liver and kidney at concentrations of 0.014–0.017 mg/kg and 0.022–0.025 mg/kg, respectively, at the 5.5 ppm feeding level. None was detected in fat or muscle. The Meeting concluded that the maximum residue level is the LOQ, 0.05 (*) mg/kg, for offal and 0.01 (*) mg/kg for muscle and that the STMR values for edible offal and muscle are both 0 mg/kg.

In milk, the highest residue level found was 0.019 mg/kg with the 5.5 ppm diet (60 times). The Meeting concluded that the maximum residue level is the LOQ, 0.01 (*) mg/kg, and that the STMR value for milk is 0 mg/kg.

No feeding study was available with poultry. The dietary intake calculation shows a possible burden of 0.07 ppm. The study of the nature of the residue in poultry was conducted at 89 ppm (1300 times) for 8 consecutive days. While short of the normal 30-day feeding study, the extreme exaggeration provides some idea of the likelihood of residues of fludioxonil and metabolites occurring in poultry commodities. The identified residue levels in eggs, liver, kidney, muscle and skin with fat were 0.26, 0.046, 0.020, 0.036 and 0.036 mg/kg, respectively. This strongly suggests that residues will not be quantifiable in these commodities at a feeding level of 0.07 mg/kg. Therefore, the Meeting estimated MRLs at the LOQ of 0.05 (*) mg/kg for eggs, 0.01 (*) mg/kg for poultry meat and 0.05 (*) mg/kg for poultry offal and STMRs of 0 mg/kg for eggs, poultry meat and poultry offal.

## DIETARY RISK ASSESSMENT

***Long-term intake***

The IEDIs of fludioxonil based on the STMRs estimated for 45 commodities for the five GEMS/Food regional diets were 0–1% of the ADI (Annex 3). The Meeting concluded that the long-term dietary intake of residues of fludioxonil is unlikely to present a public health concern.

***Short-term intake***

The 2004 JMPR decided that an ARfD for fludioxinil is unnecessary. The Meeting therefore concluded that the short-term dietary intake of fludioxonil residues is unlikely to present a public health concern.

## 4.12 FOLPET (041)

## TOXICOLOGY

***Evaluation for an acute reference dose***

Folpet is a fungicide used for the control of fungal diseases in crops. The Meeting prepared toxicological monographs on folpet in 1969 and 1995, and addenda to the monographs were prepared in 1973, 1984, 1986 and 1990. In 1995, an ADI of 0–0.1 mg/kg bw was established on the basis of a NOAEL of 10 mg/kg bw per day in a 2-year study of toxicity and carcinogenicity in rats, a 1-year study of toxicity in dogs, and studies of reproductive toxicity in rats and rabbits, and using a safety factor of 100. The present Meeting considered the requirement for an ARfD for folpet, based on data from the previous evaluations for JMPR and from new studies.

In rodents treated orally, folpet is rapidly degraded to phthalimide and thiophosgene (via thiocarbonyl chloride). Studies of metabolism in vitro with human blood revealed that folpet is rapidly degraded to phthalimide, with a calculated half-life of 4.9 s. Thiophosgene is rapidly detoxified by reaction with cysteine or glutathione, for example, and is ultimately rapidly excreted.

The acute oral toxicity of folpet in rats is low ($LD_{50}$, > 2000 mg/kg bw). In a study in pregnant hamsters, mortality occurred after a single dose of 400 mg/kg bw. In groups of pregnant New Zealand white rabbits treated for 3 days with folpet at a dose of 60 mg/kg bw per day, mortality was observed that may have been related to treatment.

Mice fed diets containing folpet at 5000 ppm, equal to 845 or 1060 mg/kg bw, for 24 h showed a reduction in food consumption of 10–20%. Immediately after the 24 h of treatment, minimal to moderate epithelial erosions and degeneration of the proximal duodenum were observed in some of these animals. Microscopy revealed moderate loss of villi and slight mucosal congestion in some animals. Microscopy was not performed at later time-points.

Studies of developmental toxicity with folpet have been carried out in hamsters, rats and rabbits.

In a study from the published literature, the teratogenic effects of a number of phthalimide derivatives, including folpet, were tested in pregnant golden hamsters. The Meeting noted that this study has major limitations (e.g. small number of animals per dose, limited reporting of the data) and is therefore of limited value. It does, however, suggest that developmental effects may occur after a single exposure to folpet, albeit at maternally toxic doses.

Folpet has been tested in a number of studies of developmental toxicity in rats. In a study in Sprague-Dawley rats treated by gavage, the NOAEL for maternal toxicity was 60 mg/kg bw per day on the basis of reduced body-weight gain and food consumption and increased incidence of clinical signs at 360 mg/kg bw per day. The NOAEL for embryo- and fetotoxicity was 360 mg/kg bw per day, the highest dose tested. In another study in Sprague-Dawley rats treated by gavage, pregnant females received folpet at a dose of 0, 150, 550, or 2000 mg/kg bw on days 6–15 of gestation. On the basis of effects on body weight and food consumption, the NOAEL for maternal toxicity was 150 mg/kg bw per day. There was a slightly increased incidence of angulated ribs and the reduction in ossification of the interparietal bone at 150 mg/kg bw per day. The maternal toxicity and the associated fetal effects are likely to be caused by high local concentrations of folpet and are not considered to be relevant to dietary exposure. In a third study in Sprague-Dawley rats treated by gavage, the NOAEL for maternal toxicity was 100 mg/kg bw per day on the basis of a reduced body-weight gain in the group receiving the highest dose. As treatment had no effect on fetal growth and development, the NOAEL for developmental toxicity was 800 mg/kg bw per day, the highest dose tested. Therefore, in these three studies of developmental toxicity in rats, the overall NOAEL for maternal toxicity was 150 mg/kg bw per day on the basis of reduction of body-weight gain and food consumption. In two out of three studies, no fetal developmental anomalies were found at doses of up to 800 mg/kg bw per day. In one study, however, a possible slight increase in developmental anomalies was reported at 150 mg/kg bw per day.

Folpet has been tested in a number of studies of developmental toxicity in rabbits treated by gavage. In a study in which New Zealand white rabbits were given folpet at a dose of 0, 10, 20, or 60 mg/kg bw per day on days 6–28 of gestation, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reduced body-weight gain and food consumption. The NOAEL for fetal toxicity was 10 mg/kg bw per day on the basis of reduced fetal body weights. The maternal toxicity and the associated reduction in fetal body weight are likely to be caused by high local concentrations of folpet and are not considered to be relevant to dietary exposure. At 60 mg/kg bw per day, there was a significant increase in the incidence of hydrocephaly in four fetuses out of three litters. In these same fetuses, skull, gastric, and pulmonary abnormalities were also observed. As the observation of hydrocephaly and cleft palate in one fetus at the intermediate dose was considered to be within the historical control range, the NOAEL for these effects was 20 mg/kg bw per day.

In a second study, HY/CR New Zealand white rabbits were given folpet at a dose of 0, 10, 40, or 160 mg/kg bw per day on days 7–19 of gestation. The NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reductions in body-weight gain and in gravid uterine weight. The NOAEL for fetal toxicity was 10 mg/kg bw per day on the basis of an increased incidence of bilateral lumbar ribs and delayed skeletal maturation.

In a pulse-dose study, pregnant D1A Hra*:* (New Zealand white) rabbits were given folpet at a dose of 60 mg/kg bw per day by gavage on days 7–9, 10–12, 13–15, or 16–18 of gestation. There were occasional occurrences of abortion, but it was not clear whether these abortions were related to treatment with folpet. Maternal body weight and food consumption were significantly reduced in all treated animals. Two fetuses with hydrocephalus were observed, one in the group treated on days 10–12 of gestation and one in the group treated on days 16–18 of gestation. These incidences were considered to be within the historical control range. A significantly increased incidence (12.1%) of fetuses with an irregularly shaped fontanelle was observed in the group treated on days 13–15 of gestation; the incidence in controls was 4.5%. The significance of these effects was not clear.

### ***Toxicological evaluation***

Other than developmental effects, folpet produced no toxicological effects that might be considered to be a consequence of acute exposure. The Meeting concluded that it was not necessary to establish an ARfD for the general population, including children aged 1–6 years for whom separate data on dietary intake are available. The Meeting concluded that it might be necessary to establish an ARfD to protect the embryo or fetus from possible effects in utero. Such an ARfD would apply to women of childbearing age.

The maternal toxicity and the associated reductions in fetal body weight, delayed ossification and increased incidences in skeletal variations observed in studies of developmental toxicity in rabbits are likely to be caused by high local concentrations of folpet and are not considered to be relevant to dietary exposure. However, the increased incidence of hydrocephalus observed could not be attributed with confidence to maternal toxicity.

The Meeting concluded that the database was insufficient (in particular, with regard to the absence of studies on the developmental effects of phthalimide) to establish the mode of action by which the increased incidence of hydrocephalus, observed in rabbits at 60 mg/kg bw per day (NOAEL, 20 mg/kg bw per day) was induced, and as a consequence, their relevance for deriving an ARfD could not be dismissed. Therefore the Meeting established an ARfD of 0.2 mg/kg bw based on a NOAEL of 20 mg/kg bw per day for the increased incidence of hydrocephalus at 60 mg/kg bw per day in rabbits and a safety factor of 100. The use of a safety factor of 100 was considered to be conservative; although the mode of action by which the developmental effects are induced was uncertain, they are possibly secondary to maternal toxicity. The Meeting noted that it might be possible to refine this ARfD using the results of an appropriately designed study.

An addendum to the toxicological monograph was prepared.

*Estimate of acute reference dose*

0.2 mg/kg bw for women of childbearing age

Unnecessary for the general population

## DIETARY RISK ASSESSMENT

### *Short-term intake*

The Meeting set an ARfD of 0.2 mg/kg bw for folpet for women of childbearing age and decided that an ARfD was unnecessary for the general population, including children aged 1–6 years. Women of childbearing age are also part of the general population.

In the absence of relevant studies on the developmental effects of phthalimide (metabolite of folpet), the Meeting was unable to determine whether phthalimide should be excluded from the residue definition for dietary risk assessment. The Meeting was not able to finalize the risk assessment before an evaluation of the residue definition for risk assessment and associated residue values for dietary intake estimation had been completed.

## 4.13 GLYPHOSATE (158)

## TOXICOLOGY

Glyphosate (*N*-(phosphonomethyl)glycine) is a non-selective systemic herbicide that was last evaluated by the JMPR in 1986, when an ADI of 0–0.3 mg/kg bw was established on the basis of a NOAEL of 31 mg/kg bw per day, the highest dose tested in a 26-month study of toxicity in rats. In 1997, JMPR evaluated aminomethylphosphonic acid (AMPA), the main metabolite of glyphosate, and concluded that AMPA was of no greater toxicological concern than its parent compound. A group ADI of 0–0.3 mg/kg bw was established for AMPA alone or in combination with glyphosate. Glyphosate was re-evaluated by the present Meeting within the periodic review programme of the CCPR. The Meeting reviewed new data on glyphosate that had not been reviewed previously and relevant data from the previous evaluations.

After oral administration to rats, [$^{14}$C]glyphosate was only partially absorbed (about 30–36%) from the gastrointestinal tract. Absorption was not significantly dose-dependent over the range of 10 to 1000 mg/kg bw. Peak plasma concentrations of radiolabel were observed at 0.5–1 h after dosing in rats and hens, respectively, and at 6–8 h after dosing in goats. The highest tissue concentrations were found in bone, with lower concentrations being found in bone marrow, kidney and liver. After oral administration, about 60–70% was eliminated in the faeces. Of the glyphosate that was absorbed, most was excreted in the urine and < 0.2% in expired air. After intravenous application, faecal excretion via bile was only about 2–8% of the administered dose. Whole body clearance (about 99% of an orally administered dose) occurred within approximately 168 h. The estimated half-life for whole-body elimination of the radiolabel was 2.1–7.5 h for the alpha phase and 69–337 h for the beta phase. Repeated dosing did not alter absorption, distribution and excretion. There was very little biotransformation of glyphosate; the only metabolite, AMPA, accounted for ≤ 0.7% of the administered dose in excreta; the rest was unchanged glyphosate.

Glyphosate has low acute oral toxicity in mice ($LD_{50}$, > 2000 mg/kg bw; no deaths at this dose) and rats ($LD_{50}$, > 5000,mg/kg bw), low acute dermal toxicity in rats ($LD_{50}$, > 2000 mg/kg bw) and rabbits ($LD_{50}$, > 5000 mg/kg bw), and low acute inhalation toxicity in rats ($LC_{50}$, > 4.43 mg/l of air). Clinical signs after acute oral exposure included reduced activity, ataxia and convulsions.

Glyphosate was not irritating to the skin, but produced moderate to severe eye irritation with irreversible corneal opacity in one study. Glyphosate salts were slightly irritating to the eye, with minimal to moderate conjunctival irritation and slight iritis that usually disappeared within 48 h after exposure. Glyphosate was not a skin sensitizer in guinea-pigs.

In short-term studies of toxicity in different species, the most important effects were clinical signs related to gastrointestinal irritation, salivary gland changes (hypertrophy and increase in basophilia of cytoplasm of acinar cells) and hepatotoxicity. In mice, reduced body-weight gain was seen at dietary concentrations of 25 000 ppm. Alterations of the salivary glands were present in mice in one of two short-term studies at dietary concentrations of ≥ 6250 ppm; the NOAEL for this finding was 3125 ppm (equal to 507 mg/kg bw per day). In rats, findings included soft faeces, diarrhoea, reduced body-weight gain, decreased food utilization and slightly increased plasma enzyme activities (alkaline phosphatase, alanine aminotransferase) at dietary concentrations of ≥ 20 000 ppm. Additionally, in two out of four 90-day studies in rats, increased incidences of alterations of the salivary glands were observed. At the lower doses, the severity and incidence of these changes were only minimal. The overall NOAEL was 300 mg/kg bw per day.

In dogs, the NOAEL in a 90-day feeding study was 10 000 ppm (equal to 323 mg/kg bw per day) on the basis of reduced body-weight gain, marginal reductions in albumin and calcium concentrations, and increased plasma alkaline phosphatase activities at 50 000 ppm. In a 1-year study in dogs given capsules containing glyphosate, the NOAEL was 30 mg/kg bw per day, on the basis of clinical signs (soft faeces, diarrhoea) and reduced body-weight gain at ≥ 300 mg/kg bw per day. In a 1-year feeding study, the NOAEL was 15 000 ppm (equal to 440 mg/kg bw per day) on the basis of reduced body-weight gain at 30 000 ppm.

Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. In the study of carcinogenicity in mice, no toxic effects were observed at up to the highest dose tested (1000 mg/kg bw per day), and there was no evidence of carcinogenicity.

In a 1-year study of toxicity in rats, the NOAEL was 2000 ppm (equal to 141 mg/kg bw per day) on the basis of a reduction in body weight and clinical chemistry findings at 8000 ppm. Three new long-term studies in rats were evaluated. In the first study, the NOAEL was 8000 ppm (equal to 362 mg/kg bw per day) on the basis of a reduction in body weight in females and an increased incidence of cataracts and lens abnormalities in males at 20 000 ppm. In the second study, the NOAEL was 100 mg/kg bw per day on the basis of more pronounced alterations of the parotid and submaxillary salivary glands at ≥ 300 mg/kg bw per day. In the most recent 2-year study in rats, the NOAEL was 6000 ppm (equal to 361 mg/kg bw per day) on the basis of a reduction in body weight and food consumption and indications of kidney, prostate and liver toxicity at 20 000 ppm. There was no evidence of a carcinogenic response to treatment in rats.

The genotoxic potential of glyphosate has been extensively tested in a wide range of assays both in vitro and in vivo, including end-points for gene mutation, chromosomal damage and DNA repair. Negative results were obtained in studies performed in compliance with current test guidelines. The Meeting concluded that glyphosate is unlikely to be genotoxic.

In view of the absence of a carcinogenic potential in animals and the lack of genotoxicity in standard tests, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans.

Glyphosate had no effect on fertility in either two-generation study of reproductive toxicity in rats. The overall NOAEL for parental and offspring toxicity was 3000 ppm (equal to 197 mg/kg bw per day) on the basis of increased food and water consumption and reduced body-weight gain in $F_1$ animals, and increased incidences of alterations of parotid and submaxillary salivary glands in parental and $F_1$ animals at 10 000 ppm.

In studies of developmental toxicity in rats, the NOAEL for maternal and developmental toxicity was 300 mg/kg bw per day, on the basis of clinical signs and reduced body-weight gain in the dams and increased incidences of fetuses with delayed ossification and skeletal anomalies.

In studies of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 100 mg/kg bw per day on the basis of clinical signs and reduced food consumption and body-weight gain. The NOAEL for developmental toxicity was 175 mg/kg bw per day on the basis of reduced fetal weight and delayed ossification and an increased incidence of postimplantation loss. The Meeting concluded that glyphosate is not teratogenic. The Meeting concluded that the existing database on glyphosate was adequate to characterize the potential hazard to fetuses, infants and children.

Hypertrophy and cytoplasmic alterations of the salivary glands (parotid and/or mandibular) was a common and sensitive end-point in six studies: in three 90-day studies (one in mice, two in rats), a 1-year study in rats, a 2-year study in rats and a two-generation study of reproductive toxicity in rats. Mechanistic studies available to the Meeting hypothesized that the mechanism was adrenergic. However, the inability of a β-blocker to significantly inhibit these effects indicates that glyphosate does not act as a β-agonist. Other proposed mechanisms for the salivary gland alterations include oral irritation caused by dietary administration of glyphosate, a strong organic acid. Although the mechanism of the cytoplasmic alterations in the salivary glands was unclear, the Meeting concluded that this treatment-related effect is of unknown toxicological significance.

In a study of acute neurotoxicity in rats, 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 neurotoxicity was 20 000 ppm, equal to 1547 mg/kg bw per day, the highest dose tested. In a study of acute delayed peripheral neuropathy in hens, clinical and histopathological examination found no evidence for acute delayed peripheral neuropathy at a dose of 2000 mg/kg bw.

New toxicological data on AMPA (the primary degradation product of glyphosate in plants, soil and water, and the only metabolite of glyphosate found in animals) was submitted to the present Meeting for evaluation. AMPA was of low acute oral and dermal toxicity in rats ($LD_{50}$, > 5000 and > 2000 mg/kg bw, respectively), and was not a skin sensitizer in guinea-pigs. In a 90-day study of toxicity in rats, the NOAEL was 1000 mg/kg bw per day, the highest dose tested. AMPA had no genotoxic potential in vitro or in vivo. In a study of developmental toxicity in rats, no evidence for embryo- or fetotoxicity was found and the NOAEL for maternal and developmental toxicity was 1000 mg/kg bw per day, the highest dose tested.

On the basis of the new toxicological data, the present Meeting concluded that AMPA is of no greater toxicological concern than its parent compound, thus confirming the conclusion of the 1997 JMPR.

Routine medical surveillance of workers in production and formulation plants revealed no adverse health effects attributable to glyphosate. In operators applying glyphosate products, cases of eye, skin and/or respiratory tract irritation have been reported. Acute intoxication was reported in humans after accidental or intentional ingestion of concentrated glyphosate formulations, resulting in gastrointestinal, cardiovascular, pulmonary and renal effects and occasionally death. The acute toxicity of glyphosate formulations was likely to be caused by the surfactant in these products.

### *Toxicological evaluation*

The Meeting established a group ADI for glyphosate and AMPA of 0–1.0 mg/kg bw on the basis of the NOAEL of 100 mg/kg bw per day for salivary gland alterations in a long-term study of toxicity and carcinogenicity in rats and a safety factor of 100. The ADI is supported by NOAELs of 141 and 197 mg/kg bw per day from the 1-year study and the two-generation study of reproductive toxicity in rats, respectively.

The Meeting concluded that it was not necessary to establish an ARfD for glyphosate in view of its low acute toxicity, the absence of relevant developmental toxicity in rats or rabbits as a consequence of acute exposure and the absence of any other toxicological effect that would be elicited by a single dose.

The NOAEL of 30 mg/kg bw per day in a 1-year study in dogs was not considered relevant for establishing either the ADI or ARfD, since the gastrointestinal effects seen in this study at 300 and 1000 mg/kg bw per day were related to high local concentrations of test substance resulting from the administration of glyphosate in capsules.

An addendum to the toxicological monograph was prepared.

*Levels relevant to risk assessment*

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | 3-month study of toxicity[a,e] | Toxicity | 3125 ppm, equal to 507 mg/kg bw per day | 6250 ppm, equal to 1065 mg/kg bw per day |
| | 2-year study of carcinogenicity[a] | Toxicity | 1000 mg/kg bw per day[d] | — |
| | | Carcinogenicity | 1000 mg/kg bw per day[d] | — |
| Rat | 3-month study of toxicity[a,e] | Toxicity | 300 mg/kg bw per day | 12 500 ppm, equal to 811 mg/kg bw per day |
| | 1-year study of toxicity[a] | Toxicity | 2000 ppm, equal to 141 mg/kg bw per day | 8000 ppm, equal to 560 mg/kg bw per day |
| | 2-year study of toxicity and carcinogenicity[a,e] | Toxicity | 100 mg/kg bw per day | 300 mg/kg bw per day |
| | | Carcinogenicity[d] | 20 000 ppm, equal to 1214 mg/kg bw per day[d] | — |
| | Multigeneration reproductive toxicity[a,e] | Parental toxicity | 3000 ppm, equal to 197 mg/kg bw per day | 10 000 ppm, equal to 668 mg/kg bw per day |
| | | Offspring toxicity | 3000 ppm, equal to 197 mg/kg bw per day | 10 000 ppm, equal to 668 mg/kg bw per day |
| | Developmental toxicity[b,e] | Maternal toxicity | 300 mg/kg bw per day | 1000 mg/kg bw per day |
| | | Embryo- and fetotoxicity | 300 mg/kg bw per day | 1000 mg/kg bw per day |
| Rabbit | Developmental toxicity[b,e] | Maternal toxicity | 100 mg/kg bw per day | 150 mg/kg bw per day |
| | | Embryo- and fetotoxicity | 175 mg/kg bw per day | 300 mg/kg bw per day |
| Dog | 3-month study of toxicity[a] | Toxicity | 10 000 ppm, equal to 323 mg/kg bw per day | 50 000 ppm, equal to 1680 mg/kg bw per day |
| | 1-year study of toxicity[a,c,e] | Toxicity | 30 mg/kg bw per day[c,f] | 300 mg/kg bw per day[c] |

[a] Diet
[b] Gavage
[c] Capsules
[d] Highest dose tested
[e] Two or more studies combined
[f] Not used for establishing the ADI (or ARfD) since the NOAEL is based on an effect induced by high local concentrations

*Estimate of acceptable daily intake for humans*

0–1.0 mg/kg bw

*Estimate of acute reference dose*

Unnecessary

*Studies that would provide information useful for continued evaluation of the compound*

- Additional information on the mechanism of the changes in the salivary glands
- Further observations in humans

### *Critical end-points for setting guidance values for exposure to glyphosate*

| | |
|---|---|
| *Absorption, distribution, excretion and metabolism in animals* | |
| Rate and extent of oral absorption | Rapid, approximately 30–36% |
| Dermal absorption | No information |
| Distribution | Widely distributed |
| Rate and extent of excretion | Largely complete within 48 h; approximately 30% in urine and 70% in faeces |
| Potential for accumulation | No evidence of accumulation (< 1% after 7 days) |
| Metabolism in mammals | Very limited (< 0.7%), hydrolysis leading to AMPA |
| Toxicologically significant compounds (animals, plants and the environment) | Parent compound, AMPA |
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | > 5000 mg/kg bw |
| Rat, $LD_{50}$, dermal | > 2000 mg/kg bw |
| Rat, $LC_{50}$, inhalation | > 4.43 mg/l (4-h, nose-only exposure) |
| Rabbit, dermal irritation | Non-irritant |
| Rabbit, eye irritation | Moderately to severely irritant |
| Skin sensitization | Not sensitizing (Magnusson and Kligman test, Buehler test) |
| *Short-term toxicity* | |
| Target/critical effect | Clinical signs (soft faeces, diarrhoea), reduced body-weight gain; liver (toxicity), salivary glands (hypertrophy) |
| Lowest relevant oral NOAEL | 300 mg/kg bw per day (90-day study in rats) |
| Lowest relevant dermal NOAEL | — |
| Lowest relevant inhalation NOAEC | — |
| *Genotoxicity* | No genotoxic potential |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Reduced body-weight gain; liver (toxicity), salivary glands (hypertrophy), eye (cataract, lens fibre degeneration) |
| Lowest relevant NOAEL | 100 mg/kg bw per day (2-year study in rats) |

| | |
|---|---|
| Carcinogenicity | No evidence of carcinogenicity in rats or mice |
| *Reproductive toxicity* | |
| Reproductive target/critical effect | Reduced pup weight at parentally toxic doses |
| Lowest relevant reproductive NOAEL | 197 mg/kg bw per day (two-generation study in rats) |
| Developmental target/critical effect | Embryo- and fetotoxicity at maternally toxic doses (rat, rabbit) |
| Lowest relevant developmental NOAEL | 175 mg/kg bw per day (rabbit) |
| *Neurotoxicity/delayed neurotoxicity* | No evidence of neurotoxcity in any study conducted |
| *Medical data* | Medical surveillance of workers in plants producing and formulating glyphosate plants did not reveal any adverse health effects. In operators applying glyphosate products, cases of eye, skin and/or respiratory irritation have been reported. Cases of acute intoxication have been observed after accidental or intentional ingestion of glyphosate formulations. |

| *Summary* | *Value* | *Study* | *Safety factor* |
|---|---|---|---|
| ADI[a] | 0–1.0 mg/kg bw | 2-year study in rats (salivary gland effects) | 100 |
| ARfD | Unnecessary | — | — |

[a] For the sum of glyphosate and AMPA

## DIETARY RISK ASSESSMENT

### *Long-term intake*

Estimated theoretical maximum daily intakes for the five GEMS/Food regional diets, based on recommended MRLs, were 1% of the ADI (Annex 3). The Meeting concluded that the long-term intake of residues of glyphosate resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

### *Short-term intake*

The 2004 JMPR decided that an ARfD for glyphosate is unnecessary. The Meeting therefore concluded that the short-term intake of glyphosate residues is unlikely to present a public health concern.

## 4.14 MALATHION (049)

## RESIDUE AND ANALYTICAL ASPECTS

Malathion has been evaluated many times since 1965. The company asked the CCPR at its Thirty-third Session in 2001 to reconsider withdrawal of the existing Codex MRLs recommended during the periodic review of the compound by the 1999 JMPR. The CCPR at its Thirty-sixth Session decided to retain the current CXL for apple, broccoli, cabbage (head), cereal grains, citrus fruit and grape, awaiting the review of the new residue data by the 2004 JMPR. The company submitted data on mandarin, orange, apple, peach, grape, strawberry, tomato, alfalfa fodder and forage (green) to the present Meeting.

### *Results of supervised trials on crops*

*Citrus fruit*

Sixteen trials were conducted with mandarin and orange in Greece (GAP for citrus, 0.044–0.088 kg ai/hl, 7-day PHI), Italy (GAP, 0.053 kg ai/hl, 20-day PHI) and Spain (GAP for foliar application, 0.11–0.15 kg ai/hl, 7-day PHI) between 2000 and 2002. Malaoxon was analysed in all trials, and the maximum residue level found in fruit was 0.09 mg/kg on the day of the last application.

Ten trials conducted at 0.18 kg ai/hl and five trials performed at 0.30 kg ai/hl were evaluated against Spanish and Portuguese GAP for citrus (0.05–0.30 kg ai/hl, 7-day PHI), respectively. Decline studies conducted in both crops indicated that residue levels decreased slowly within 3 days of the last application, and samples harvested from 7 up to 10–11 days could be considered at GAP.

The residue levels in *mandarin* fruit were, in ranked order: 0.75, 1.8 (three), 2.4 (two), 2.9, 3.1 and 4.7 mg/kg. In mandarin pulp, the levels were: < 0.01, 0.01, 0.02, 0.03, 0.12, 0.15, 0.21 and 0.22 mg/kg.

The residue levels in *orange* fruit were, in ranked order: 0.58, 0.75, 0.89, 1.1, 1.4, 1.6, 1.7 and 2.1 mg/kg. The levels in orange pulp were: < 0.01 (three), 0.01 (two), 0.03 and 0.07 (two) mg/kg. One trial conducted at 0.4 kg ai/hl gave residue levels within the same range.

The Meeting agreed that the levels of residues of malathion in mandarin and orange from trials conducted at GAP could be combined to represent a residue population for citrus. In fruit, the levels were, in ranked order: 0.58, 0.75 (two), 0.89, 1.1, 1.4, 1.6, 1.7, 1.8 (three), 2.1, 2.4 (two), 2.9, 3.1 and 4.7 mg/kg. In citrus pulp, the levels were: < 0.01 (four), 0.01 (three), 0.02, 0.03, 0.07 (two), 0.12, 0.15, 0.21 and 0.22 mg/kg.

The Meeting recommended a maximum residue level of 7 mg/kg, a STMR of 0.02 mg/kg and a highest residue levl of 0.22 mg/kg for malathion in citrus.

*Apple*

Twelve trials were conducted on apples in northern France in 2000 and 2001, with three applications at 0.18 kg ai/hl. There is no GAP for malathion in France; however, the results can be evaluated against Spanish or Italian GAP (up to 0.16 kg ai/hl). The PHI is 7 days in Spain and 20 days in Italy. The residue levels in apple fruit at the most critical PHI (7 days) were, in ranked order: 0.02, 0.05 (two), 0.07, 0.08, 0.09, 0.13, 0.14, 0.19, 0.24, 0.25 and 0.37 mg/kg. The levels of malaoxon were < 0.01–0.02 mg/kg.

The Meeting recommended a maximum residue level of 0.5 mg/kg, an STMR of 0.11 mg/kg and an HR of 0.37 mg/kg for malathion in apple.

*Peach*

Four trials were conducted in Italy in 1997 on peaches, with three applications of 0.16 kg ai/hl, corresponding to GAP. The residue levels of malathion in the fruit at 20 days' PHI were < 0.01 (three) and 0.01 mg/kg. No malaoxon was found in the fruit after the last application (0–20 days).

The Meeting agreed that four trials is not enough to recommend a maximum residue level for malathion in peaches. The Meeting confirmed the previous recommendation of 1999 JMPR to withdraw the CXs for malathion in peaches

*Grape*

Six trials were conducted in grapes in southern and northern France (no GAP) in 2000–01, with three applications at 0.27 kg ai/hl. The residue levels of malathion 7 days after the last application were 0.26–1.3 mg/kg.

In four trials conducted in northern Spain in 2000–01 within maximum GAP (0.11–0.15 kg ai/hl, 7-day PHI), the residue levels of malathion at 7 days' PHI were: 1.1, 1.5 (two) and 2.6 mg/kg. The levels of malaoxon were 0.02–0.13 mg/kg. Four trials conducted in Italy at GAP (0.05–0.16 kg ai/hl, 20-day PHI), evaluated against Spanish GAP, showed levels of 0.01, 0.03 and 0.21 (two) mg/kg.

The residue levels in trials conducted in Italy and Spain according to GAP were 0.01, 0.03, 0.21 (two), 1.1, 1.5 (two) and 2.6 mg/kg.

The Meeting recommended a maximum residue level of 5 mg/kg, a STMR of 0.16 mg/kg and a highest residue level of 2.6 mg/kg for malathion grapes.

*Strawberry*

GAPs for malathion on strawberry in Europe are: Denmark, three times 1.1 kg ai/ha, 7-day PHI; Italy, up to 0.16 kg ai/hl, 20-day PHI; Portugal, 0.10 kg ai/hl, 1-day PHI; and Spain, up to 0.15 kg ai/hl, 7-day PHI. In three trials conducted in France, two in Italy and three in Spain with four or six applications at 0.15–0.18 kg ai/hl, the residue levels at 7 days' PHI were < 0.01–0.14 mg/kg.

The Meeting confirmed the currently recommended maximum residue level of 1 mg/kg of malathion in strawberry, which was set by the 1999 JMPR on the basis of trials conducted in the USA according to GAP with a 1-day PHI.

*Tomato*

GAP for malathion in tomato is up to 0.088 kg ai/hl with a 7-day PHI in Greece, up to 0.16 kg ai/hl with a 20-day PHI in Italy and up to 0.10 kg ai/hl with a 1-day PHI in Portugal. In five trials conducted in Italy and one in Spain in 1997–2001 according to Greek GAP, the residue levels were < 0.01 (three), 0.01 and 0.02 (two) mg/kg. Four other trials were conducted in these countries at higher or lower rates than GAP.

The Meeting confirmed the currently recommended maximum residue level of 0.5 mg/kg for malathion in tomato, which was set by the 1999 JMPR on the basis of trials conducted in the USA according to GAP with a 1-day PHI.

*Alfalfa*

Two trials were conducted in Italy in 2000–01 (no GAP) and two in Spain (GAP, 0.12–0.25 kg ai/hl or 1.5–2.8 kg ai/ha) with one application at 0.15 kg ai/hl (1.5 kg ai/ha). The Italian trials, evaluated against Spanish GAP, gave residue levels of malathion of 0.67 and 0.41 mg/kg on a dry weight basis in alfalfa forage (green) at 7 days' PHI, and 0.12 mg/kg in hay harvested at 7 days' PHI and allowed to dry on the field for 3 days. In the Spanish trials, the residue levels were 1.2 and 3.5 mg/kg in forage and 3.3 mg/kg in hay.

The Meeting confirmed the currently recommended maximum residue levels for malathion on alfalfa forage (green) and alfalfa hay of 500 and 200 mg/kg, respectively, which were set by the 1999 JMPR on the basis of trials conducted in USA according to GAP at 1 day PHI.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The current ADI for malathion is 0.3 mg/kg bw. IEDIs were calculated for commodities for human consumption for which STMRs were estimated by the 1999 JMPR and by the present Meeting (Annex 3). The IEDI for the five GEMS/Food regional diets was 0% of the maximum ADI. The Meeting concluded that long-term intake of residues of malathion resulting from uses considered by the JMPR is unlikely to present a public heath concern.

### *Short-term intake*

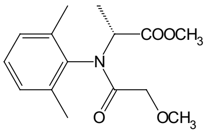
An ARfD for malathion of 2 mg/kg bw was established by the 2003 JMPR. The IESTIs of malathion by the general population and by children were calculated for commodities for which STMR and highest residue values were estimated by the current Meeting (Annex 4). The IESTI was 0–4% of the ARfD for the general population and 0–10% of the ARfD for children. The Meeting concluded that short-term intake of residues of malathion from its use in citrus, apples and grapes is unlikely to present a public health concern.

## 4.15 METALAXYL M (212)

### RESIDUE AND ANALYTICAL ASPECTS

The toxicology of metalaxyl-M was evaluated by the 2002 JMPR, which established a group ADI of 0–0.08 mg/kg bw for metalaxyl and metalaxyl-M. Residue and analytical aspects were considered for the first time by the present Meeting. Metalaxyl-M is the biologically active enantiomer (R-enantiomer) of the racemic compound metalaxyl. Metalaxyl was first evaluated by the JMPR in 1982, and Codex MRLs for metalaxyl were established.

Metalaxyl-M is registered for use on fruit, nut and vegetable crops for the control of various fungal diseases such as those caused by *Phytophthora* and *Pythium* spp. It is applied to foliage, soil or seed and also as a post-harvest fruit treatment.



| | |
|---|---|
| IUPAC name | (R)-2-[(2,6-dimethylphenyl)-methoxyacetylamino]-propionic acid methyl ester |
| Chemical Abstracts name | *N*-(2,6-dimethylphenyl)-*N*-(methoxyacetyl)-D-alanine methyl ester |

The Meeting received information on the metabolism and environmental fate of metalaxyl-M and on methods of residue analysis, stability in freezer storage, national registered use patterns, the results of supervised trials and farm animal feeding studies, the fate of residues in processing and national MRLs.

As metalaxyl-M constitutes 50% of metalaxyl, investigations into the metabolism and fate of metalaxyl can legitimately be accepted as supporting the metabolism and fate of metalaxyl-M. When the metabolism of metalaxyl and metalaxyl-M was compared directly, it was found to be similar.

In the studies of animal and plant metabolism and environmental fate, metalaxyl or metalaxyl-M uniformly $^{14}C$ labelled in the aromatic ring was used.

***Metabolism***

In the list below, the numbering is preserved from the 2002 JMPR toxicology evaluation.

Metabolite 1: *N*-(2,6-dimethylphenyl)-*N*-(methoxyacetyl)alanine

Metabolite 3: *N*-(2,6-dimethylphenyl)-*N*-(hydroxyacetyl)alanine methyl ester

Metabolite 6: *N*-(2,6-dimethylphenyl)-*N*-(hydroxyacetyl)alanine

Metabolite 7: *N*-(2,6-dimethyl-5-hydroxyphenyl)-*N*-(methoxyacetyl)alanine methyl ester

Metabolite 8: *N*-(2-hydroxymethyl-6-methylphenyl)-*N*-(methoxyacetyl)alanine methyl ester (occurs as two isomers)

Metabolite P: *N*-[(2-hydroxymethyl)-6-methylphenyl]-*N*-(hydroxyacetyl)alanine (occurs as two isomers)

*Animals*

The Meeting received the results of studies on metabolism in rats, lactating goats and laying hens. When animals were dosed orally with radiolabelled metalaxyl, most of the radiolabel was excreted in the urine within a short time, with a small amount in the faeces. Numerous metabolites resulting from hydrolysis, oxidation and demethylation of metalaxyl and subsequent conjugate formation were identified. In a study in goats, metalaxyl itself was not detected as a component of the residue in tissues or milk. In a study in laying hens, low levels of metalaxyl were present in liver and eggs. The metabolic pathway for metalaxyl was similar in rats, goats and hens.

The absorption, distribution, metabolism and excretion of radiolabel were similar in *rats* dosed orally with $^{14}$C-metalaxyl or $^{14}$C-metalaxyl-M. Detailed information on metabolism in this species is reported in the 2002 JMPR toxicological evaluations.

Very little radiolabel was found in milk (0.003 mg/kg) or tissues (0.057 mg/kg in liver) from a *goat* dosed with $^{14}$C-metalaxyl at the equivalent of 7 ppm in the feed for 10 days.

When two lactating dairy goats were dosed orally once daily for 4 consecutive days by gelatin capsule with $^{14}$C-metalaxyl, equivalent to 77 ppm in the diet, the radiolabel was excreted rapidly: within 24 h of administration, 67% of the daily dose appeared in urine, 9% in faeces and 0.1% in milk. Metalaxyl was not detected as a component of the residue. Metabolite 6 was the main component of the residue in liver (0.19 mg/kg), leg muscle (0.014 mg/kg) and perirenal fat (0.065 mg/kg); metabolite 8 was the main residue component in kidney. The main metabolites in milk were C-10 and C-8 fatty acid conjugates of metabolite 3 (0.058 mg/kg). These fatty acids are conjugated through the hydroxyacetyl group of metabolite 3.

When five laying *hens* were dosed orally once daily for 4 consecutive days by gelatin capsule with $^{14}$C-metalaxyl, equivalent to approximately 100 ppm metalaxyl in the diet, radiolabel recovered in edible tissues and eggs represented 0.97% of the administered dose; the remainder was recovered in excreta. Metabolite P (consisting of P1 and P2, steric isomers) was the main metabolite in egg white (0.056 mg/kg), egg yolk (0.072 mg/kg) and thigh muscle (0.31 mg/kg). Metalaxyl parent was identified in egg white (0.013 mg/kg), egg yolk (0.010 mg/kg) and liver (0.018 mg/kg), but not in thigh muscle or fat (< 0.001 mg/kg).

*Plants*

The Meeting received the results of studies on the metabolism of metalaxyl in grape, lettuce and potato and of metalaxyl-M in lettuce. No metabolites were identified in plants which had not already been identified in animals. Parent metalaxyl was the main component of the residue in grapes and in juice produced from the grapes when metalaxyl was used on grape vines. In treated lettuce, parent metalaxyl and metabolite 8 were each present at approximately 20% of the total residue. Metabolite 8 was the main residue component in lettuce in both cases in which metalaxyl and metalaxyl-M were compared. When metalaxyl was used on potato plants, some residue reached the tubers, where parent metalaxyl was the main residue component.

Grapevines in Switzerland were sprayed to runoff seven times at 14-day intervals with a $^{14}$C-metalaxyl spray at a concentration of 0.050 kg ai/hl and were harvested 52 days after the final application. Parent metalaxyl (2.0 mg/kg) constituted 64% of the total residues in *grapes*.

When two grapevines in Switzerland were sprayed to runoff six times at approximately 14-day intervals with a $^{14}$C-metalaxyl spray at a concentration of 0.030 kg ai/hl and harvested 68 days after the final application, parent metalaxyl (0.83 mg/kg) comprised 64% of total residues in the grapes. Metabolite 8 accounted for 20% of the residue, and metabolites 1, 6 and 7 were minor components (1.8–4.3%). When the grapes were separated into juice and presscake, metalaxyl was still the main part of the residue (62% and 57%, respectively).

Metalaxyl was the main identified component of the residue in *lettuce* (18.6% of the total $^{14}C$ residue) after seedlings in a greenhouse were sprayed twice, 2 weeks apart, with $^{14}C$-metalaxyl at a rate equivalent to 0.25 kg ai/ha and harvested 2 weeks later. The identified metabolites (including glucose conjugates) were metabolite 8 (22% of the total $^{14}C$ residue), metabolite 6 (10%), metabolite 3 (8.9%), metabolite 7 (6.2%) and metabolite 1 (6.0%).

The metabolic pathways of metalaxyl-M and metalaxyl were compared in lettuce in a field in Switzerland treated three times at 10-day intervals with labelled compounds. The levels of total applied residue and parent compounds in the residue were generally comparable. Metabolite 8 (free and conjugated) was the main identified component of the residue in samples taken 14 and 21 days after treatment. Enantiomeric ratio measurements suggested similar disappearance rates for the two enantiomers and little interconversion.

*Potato* plants in the field in Switzerland received five foliar treatments of $^{14}C$-metalaxyl at 0.2 kg ai/ha at 10-day intervals and were harvested at maturity 5 weeks after the final treatment. Little residue reached the tubers (0.02 mg/kg $^{14}C$ as metalaxyl). No parent metalaxyl was detected in tubers. In a second experiment, the level of $^{14}C$ as metalaxyl in tubers was < 0.0001 mg/kg after $^{14}C$-metalaxyl was applied to the soil (residues in soil, approximately 0.5 mg/kg), indicating that metalaxyl is not taken up by the tubers directly from the soil.

Potato plants in the field in the USA received six foliar treatments, about 2 weeks apart, of $^{14}C$-metalaxyl at 1.3 kg ai/ha. Tubers harvested at maturity, 1 week after the final treatment, contained 0.5 mg/kg $^{14}C$ as metalaxyl, of which 50–60% was parent metalaxyl. A number of metabolites were identified, but only the concentration of metabolite 8 exceeded 5% of the residue.

### *Environmental fate*

#### *Soil*

The Meeting received information on the behaviour and fate of metalaxyl and metalaxyl-M during aerobic metabolism in a number of soils. The rate of degradation is strongly influenced by the properties of the soil, including its biological activity and the conditions of temperature, moisture and concentration of the residue, with recorded half-lives in the range of 5–180 days. In direct comparisons of metalaxyl and metalaxyl-M under aerobic conditions, metalaxyl-M was the more persistent in one case and less persistent in two others. The main soil metabolite is metabolite 1 or, in the case of metalaxyl-M, the specific enantiomer of metabolite 1.

Field dissipation studies for metalaxyl-M were provided from France, Italy, Spain and Switzerland. Metalaxyl-M residues disappeared from the soil with half-lives ranging from 5 to 35 days. The residues occurred mostly in the top 10 cm of soil, but some reached lower levels. The enantiomer of metabolite 1 was produced in all cases, and its level sometimes exceeded that of the parent metalaxyl-M. A comparison of enantiomeric ratios in metalaxyl residues in soil suggested that the R-enantiomer (i.e. the metalaxyl-M enantiomer) disappeared more quickly than the S-enantiomer. This resulted in a preponderance of S-enantiomer in the metalaxyl residue and a preponderance of R-enantiomer in metabolite 1.

The studies of dissipation in the field suggest that, after use of metalaxyl-M for seed treatment or at the time of sowing, little or none will remain as a soil residue when the crop is harvested.

#### *Rotational crops*

Information on the fate of radiolabelled metalaxyl in confined crop rotational studies and of unlabelled metalaxyl-M in field rotational crops was made available to the Meeting. The studies with radiolabel showed that parent metalaxyl was usually a minor part of the residue that reached the rotational crop. The identifiable metabolites were also usually minor, but metabolite 8 as glucose conjugates was detected in spring wheat stalks at 2.3 mg/kg. Metalaxyl-M residues were not detected in unconfined field rotational crops in Switzerland or the United Kingdom, but levels of 0.11 mg/kg were present in broccoli and 0.03 mg/kg in lettuce leaves from crops sown 29 days after treatment of the first crop in a study in Italy. The short interval was used in order to simulate the ploughing-in of a failed crop and the sowing of a new one.

### *Methods of analysis*

The Meeting received descriptions and validation data for analytical methods for residues of metalaxyl in plant material, animal tissues, milk and eggs.

Common moiety methods rely on the 2,6-dimethylaniline moiety of metalaxyl and many of its metabolites, and these methods have been used to identify metalaxyl residues in animal commodities. The typical LOQs are 0.05 mg/kg for tissues and 0.01 mg/kg for milk. Metabolite 8, containing the 2-hydroxymethyl-6-methylaniline moiety, is apparently partially converted to 2,6-dimethylaniline, resulting in low and variable recoveries.

With gas–liquid chromatography and nitrogen–phosphorus detection and HPLC with mass spectrometry detection procedures for identifying metalaxyl or metalaxyl-M after a simple extraction and limited clean-up, the LOQs are 0.02–0.04 mg/kg for many crop substrates. A modification to the method (method REM 181.06), with the introduction of an HPLC chiral separation step before determination, allows for the analysis of specific enantiomers.

A multi-residue regulatory method (DFG S19) is available for metalaxyl.

Method REM 181.06 (gas–liquid chromatography with mass spectrometry detection) is not a multi-residue method, but it is enantioselective and suitable as a regulatory method for metalaxyl-M.

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

The Meeting received information on the stability of residues of metalaxyl-M in crops (orange, potato, rape-seed, tomato, wheat) and animal commodities (beef muscle, beef liver, milk, eggs) during storage of analytical samples. Metalaxyl-M residues were stable in these substrates and under the conditions and intervals of storage (2 years). There was no evidence of epimerization during freezer storage. As a common moiety method was used for the animal commodity samples, storage stability refers to the total residue rather than to parent metalaxyl-M. As the common moiety method, which relies on the 2,6-dimethylaniline moiety, is less suitable for metabolite 8, the freezer stability of this metabolite during storage is not demonstrated.

### *Definition of the residue*

Parent metalaxyl is the main identifiable component of the residue in crops resulting from use of metalaxyl, although metabolite 8 can occur at approximately the same levels. Metabolite 8 was not considered to be toxicologically significant.

The current residue definition of metalaxyl is metalaxyl. As metalaxyl-M is one enantiomer of metalaxyl, it is covered by the current residue definition. Non-enantioselective methods cannot distinguish metalaxyl-M from metalaxyl, but an enantioselective method is available. While metalaxyl-M and metalaxyl are both registered for crop uses, it is preferable, for enforcement purposes, to maintain a single residue definition. As the 2002 JMPR recommended a group ADI for metalaxyl and metalaxyl-M, the inclusive residue definition is also suitable for risk assessment purposes. The Meeting recommended that metalaxyl-M be contained within the metalaxyl residue definition and recommended amendment of the metalaxyl residue definition to provide definitions for enforcement and risk assessment purposes.

*For plant commodities*: Metalaxyl, including metalaxyl-M. Definition of the residue (for compliance with MRL and for estimation of dietary intake): metalaxyl. Note: Metalaxyl is a racemic mixture of an R-enantiomer and an S-enantiomer. Metalaxyl-M is the R-enantiomer.

In animals dosed with metalaxyl, parent metalaxyl was either a minor part of the residue or was not detected. Analytical methods for metalaxyl are based on a common moiety method, and residues in the farm animal feeding studies were measured by this method. Common moiety residues are acceptable for estimation of dietary intake when the parent compound is a minor part of the residue. The log $P_{OW}$ for metalaxyl-M is 1.7, and the studies of animal metabolism confirm that metalaxyl is not fat-soluble.

*For animal commodities*: Metalaxyl including metalaxyl-M. Definition of the residue (for compliance with MRL and for estimation of dietary intake): metalaxyl and metabolites containing the 2,6-dimethylaniline moiety, expressed as metalaxyl.

### *Results of supervised trials on crops*

The Meeting received data from supervised trials with metalaxyl-M used on citrus fruit, apple, grape, onion, tomato, pepper, lettuce, spinach, potato, sunflower and cacao. In some trials, residues were measured on samples taken just before and just after ('zero-day' residue) the final application. The residue level measured just before the final application, expressed as a percentage of zero-day residue, provides a measure of the contribution of previous applications to the final residue in the use pattern used in the trial. For grapes, the average carryover of residue was 32% in 12 trials in Australia, 57% in three trials in Germany and 46% in three trials in Italy. In lettuce, the average carryover was 1.7% in six trials in France, Germany and Italy. In spinach, the average carryover was 1.1% in eight trials in France.

Residue data were evaluated only when labels (or translations of labels) describing the relevant GAP were available to the Meeting.

*Citrus fruit*

Metalaxyl-M is registered for use as a post-harvest treatment on citrus in Israel. It is applied as a 0.1 kg ai/hl spray.

In the trials, the formulation of metalaxyl-M was mixed with a commercial wax to produce a spray solution, which was applied at a rate of 200 l /90 t of fruit (theoretical concentration of residue, 2.1 g/t). The residue levels in three trials on *oranges* were 1.2, 1.3 and 1.6 mg/kg in whole fruit and < 0.02 mg/kg in pulp. This method of post-harvest application includes control of the application rate in terms of the amount of metalaxyl-M per unit weight of fruit. The residue levels agreed substantially with expectations.

The Meeting noted that three supervised trials is generally an insufficient number for a major commodity such as oranges.

The residue levels of metalaxyl-M in the trials conducted in line with Israeli GAP did not exceed the current metalaxyl MRL of 5 mg/kg for citrus fruit.

*Apple*

Metalaxyl-M is registered in Spain for soil treatment around apple trees at 0.5–1.0 g ai/tree and in Italy at 0.5–4 g ai/tree. In two trials each in France, Italy and Spain at application rates of 0.78–10 kg ai/ha, no residues were detected in apples (< 0.02 mg/kg). For an assumed 500–1000 trees per ha, the rate of 10 kg ai/ha appears to be exaggerated.

The Meeting estimated a maximum residue level for metalaxyl-M in apples of 0.02* and an STMR value of 0 mg/kg.

Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.02* mg/kg would not exceed the current metalaxyl MRL of 1 mg/kg for pome fruits.

*Grape*

In Australia, metalaxyl-M is registered for a maximum four applications on grapes at 0.11 kg ai/ha, with a PHI of 7 days. The residue levels in grapes in five Australian trials matching GAP, but with six applications instead of four, were: < 0.02, 0.03, 0.06, 0.14 and 0.52 mg/kg. As the final residue level should not be influenced by earlier applications, residue levels after six applications are acceptable as equivalent to residues levels in GAP trials.

No GAP was available to evaluate the data for grapes treated in Germany and Switzerland.

In Greece, grapes may be treated four times with metalaxyl-M at 0.1 kg ai/ha, with harvest 15 days after the final application. The residue levels in grapes in six trials in Italy and Portugal, conducted substantially according to Greek GAP, were: 0.04, 0.06, 0.18, 0.19, 0.21 and 0.55 mg/kg.

The residue levels in the Australian and European trials appear to be similar and can be combined. In summary, the residue levels in the 11 trials, in ranked order, were: < 0.02, 0.03, 0.04, 0.06, 0.06, 0.14, 0.18, 0.19, 0.21, 0.52 and 0.55 mg/kg

The Meeting estimated a maximum residue level for metalaxyl-M in grapes of 1 mg/kg and an STMR value of 0.14 mg/kg.

Metalaxyl-M residue levels complying with the estimated maximum residue level of 1 mg/kg would not exceed the current metalaxyl MRL of 1 mg/kg for grapes.

*Onion*

In Ecuador and Uruguay, metalaxyl-M is registered for a maximum of three applications on onions at 0.1 and 0.12 kg ai/ha, with a PHI of 7 days. Metalaxyl-M residue levels in bulb onions in three Brazilian trials matching Uruguayan GAP, but with four applications instead of three, were < 0.02 (two) and 0.02 mg/kg.

Metalaxyl-M is registered in Germany for a maximum of three applications on onions at 0.097 kg ai/ha, with a PHI of 21 days. In four trials in Switzerland with conditions matching German GAP, the residue levels were all below the LOQ (0.02 mg/kg).

Data on residues in trials in onions in Italy and Spain could not be evaluated because no relevant GAP was available.

In summary, the residue levels in the seven trials, in ranked order, were < 0.02 (six) and 0.02 mg/kg.

The Meeting estimated a maximum residue level for metalaxyl-M in onions of 0.03 mg/kg and an STMR value of 0.02 mg/kg.

Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.02 mg/kg would not exceed the current metalaxyl MRL of 2 mg/kg for bulb onions.

*Tomato*

Metalaxyl-M is registered for foliar application on tomatoes in Algeria, Chile, Ecuador, Greece, Israel and Morocco at 0.10–-0.14 kg ai/ha, with a PHI of 3 days and a maximum of three or four treatments.

Residue levels in tomatoes in six greenhouse trials in France, two in Spain and four in Switzerland at 0.15 kg ai/ha, with harvest 3 days after treatment (equivalent to the stated GAP) were: 0.02 (two), 0.02, 0.03, 0.04, 0.04, 0.05, 0.05, 0.08, 0.09, 0.12 and 0.18 mg/kg.

The Meeting estimated a maximum residue level for metalaxyl-M in tomatoes of 0.2 mg/kg and an STMR value of 0.045 mg/kg.

Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.2 mg/kg would not exceed the current metalaxyl MRL of 0.5 mg/kg for tomatoes.

*Pepper*

GAP for use of metalaxyl-M in Italy allows three soil applications of 1 kg ai/ha with a 15-day PHI. Data on residues from Italian and Spanish trials approximating Italian GAP were provided. In some of the trials, residues were measured 10 and 20 days after the final application instead of 15 days, but these trials were considered valid because the residue levels were relatively unchanged. The residue levels in the seven greenhouse trials were: < 0.02 (two), 0.02, 0.03, 0.08, 0.10 and 0.36 mg/kg; and those in the three outdoor trials in Italy were: < 0.02 (two) and 0.02 mg/kg.

The Meeting decided to use the data from the greenhouse trials: < 0.02 (two), 0.02, 0.03, 0.08, 0.10 and 0.36 mg/kg.

The Meeting estimated a maximum residue level for metalaxyl-M in sweet peppers of 0.5 mg/kg and an STMR value of 0.03 mg/kg.

Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.5 mg/kg would not exceed the current metalaxyl MRL of 1 mg/kg for peppers.

*Lettuce*

Metalaxyl-M is registered in Spain for use on lettuce at 0.10 kg ai/ha with a PHI of 14 days. The residue levels in lettuce were < 0.02 mg/kg in an Italian trial matching Spanish GAP. The residue levels in lettuce in four French trials matching Spanish GAP were: < 0.02 (two), 0.02 and 0.03 mg/kg.

Metalaxyl-M is registered in Germany for a maximum of two applications on lettuce at 0.097 kg ai/ha, with a PHI of 21 days. In six trials on head lettuce in Germany under conditions matching GAP, but with three applications instead of two, the residue levels were: < 0.02 (four), 0.02 and 0.03 mg/kg. In two German greenhouse trials at 0.10 kg ai/ha with harvest 21 days after the second application, the residue levels were < 0.02 and 0.41 mg/kg.

In two trials in The Netherlands matching German GAP, the residue levels were < 0.02 mg/kg.

Trials in Spain and Switzerland could not be evaluated because there was no matching GAP.

In summary, the residue levels in lettuce in the 15 trials, in ranked order, were: < 0.02 (10), 0.02 (two), 0.03 (two) and 0.41 mg/kg.

The Meeting estimated a maximum residue level for metalaxyl-M in head lettuce of 0.5 mg/kg and an STMR value of 0.02 mg/kg.

Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.5 mg/kg would not exceed the current metalaxyl MRL of 2 mg/kg for head lettuce.

*Spinach*

Metalaxyl-M is registered in Switzerland for a maximum of six applications on spinach at 0.10 kg ai/ha with a PHI of 14 days. In three trials on spinach in Switzerland at 0.10 kg ai/ha and three at 0.14 kg ai/ha, with intervals before harvest of 10 or 14 days, the residue levels were all < 0.02 kg/ha. The levels were also < 0.02 mg/kg in two trials in Germany matching the conditions of GAP in Switzerland.

In a number of trials in France in which the application rate was 0.10 or 0.14 kg ai/ha, spinach was sampled for analysis 10 and 20 days after treatment. The Meeting noted that the residue levels generally changed slowly between 10 and 20 days post-treatment and decided to accept the residue levels at 10 days as sufficiently close to those expected at 14 days. The residue levels in the 10 French trials were: < 0.02 (two), 0.02 (four), 0.03, 0.04 (two) and 0.05 mg/kg.

In summary, metalaxyl-M residue levels in the 18 trials were < 0.02 (10), 0.02 (four), 0.03, 0.04 (two) and 0.05 mg/kg.

The Meeting estimated a maximum residue level for metalaxyl-M in spinach of 0.1 mg/kg and an STMR value of 0.02 mg/kg.

Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.1 mg/kg would not exceed the current metalaxyl MRL of 2 mg/kg for spinach.

*Potato*

Labels were available from Algeria, Australia, Austria, Chile, Ecuador, Greece, Israel and Morocco from formulations for foliar application of metalaxyl-M to potatoes at 0.1–0.12 kg ai/ha. The information on GAP suggests that the recommended foliar application rate on potatoes is 0.1 kg ai/ha in many situations.

The results of supervised trials were available from Brazil (three at 0.1 kg ai/ha and three at 0.2 kg ai/ha), Germany (six at 0.1 kg ai/ha), Switzerland (three at 0.075 kg ai/ha) and the United Kingdom (four at 0.1 kg ai/ha). The residue levels in all 19 trials, measured at intervals of 0–28 days after the final treatment, were below the LOQ (0.02 mg/kg).

As residues were found in potato tubers in the metabolism studies after high application rates, the median residue values cannot be assumed to be nil. The Meeting estimated a maximum residue level for metalaxyl-M in potato of 0.02* mg/kg and an STMR value of 0.02 mg/kg. Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.02* mg/kg would not exceed the current metalaxyl MRL of 0.05* mg/kg for potato.

*Sunflower seed*

Metalaxyl-M is registered in China and Serbia and Montenegro for use as a seed treatment at 0.105 kg ai/100 kg sunflower seed. The Meeting agreed that the results of trials from other countries could be evaluated with respect to this seed treatment GAP.

In six trials in France and two in Spain, metalaxyl-M was used as seed treatment at a nominal rate of 105 g ai/100 kg seed (measured, 61–80 g ai/100 kg seed). The residue levels in harvested sunflower seed 125–151 days after sowing were all below the LOQ (0.01 and 0.02 mg/kg). Because of the long interval between sowing and harvest and the solubility of metalaxyl-M, residues would not be expected in harvested sunflower seed.

The Meeting estimated a maximum residue level for metalaxyl-M in sunflower seed of 0.02* mg/kg and an STMR value of 0 mg/kg. Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.02* mg/kg would not exceed the current metalaxyl MRL of 0.05* mg/kg for sunflower seed.

*Cacao beans*

Metalaxyl-M is registered in Côte d'Ivoire for use on cacao at 0.012 kg ai/ha. In eight trials in Côte d'Ivoire in which metalaxyl-M was applied as foliar treatment four times at 0.09 kg ai/ha (an exaggerated rate), with harvest 29–30 days after the final treatment, the residue levels in the cacao beans were: < 0.02 (four) and 0.02 (four) mg/kg. The cacao beans were fermented and dried before analysis. The Meeting agreed that the residue levels after application at the label rate would not exceed 0.02 mg/kg.

The Meeting estimated a maximum residue level for metalaxyl-M in cacao beans of 0.02 mg/kg and an STMR value of 0.02 mg/kg.

Metalaxyl-M residue levels complying with the estimated maximum residue level of 0.02 mg/kg would not exceed the current metalaxyl MRL of 0.2 mg/kg for cacao beans.

### *Fate of residues during processing*

The Meeting received information on the fate of metalaxyl-M residues during the production of fruit juices and vinification. The Meeting also received information that metalaxyl-M is hydrolytically stable under hydrolysis conditions that simulate those occurring during food processing.

The following processing factors were calculated from the data from the trials. The factors are mean values, excluding those calculated in cases of undetectable residues.

| Commodity | Processed product | Processing factor | No. of trials |
|---|---|---|---|
| Orange | Washed fruit | 0.97 | 2 |
| | Juice, pasteurized | 0.060 | 4 |
| | Oil | 9.0 | 4 |
| | Pomace, wet | 1.1 | 4 |
| | Pomace, dry | 4.1 | 4 |
| | Peel | 2.5 | 3 |
| | Pulp | 0.091 | 1 |
| | Marmalade | 0.39 | 4 |
| Grapes | Juice | 0.36 | 6 |
| | Young wine | 0.87 | 8 |
| | Wine | 0.66 | 13 |

The Meeting used the processing factors to estimate STMR-Ps for processed commodities. The processing factor for wine (0.66) was applied to the grape STMR (0.14 mg/kg) to calculate an STMR-P of 0.092 mg/kg for wine. The processing factor for grape juice (0.36) was applied to the grape STMR (0.14 mg/kg) to calculate an STMR-P of 0.050 mg/kg for grape juice

### ***Residues in animal commodities***

#### *Feeding studies*

The Meeting received the results of studies of feeding metalaxyl to lactating dairy cows and laying hens, which provided information on probable residue levels in tissues, milk and eggs from residues in animal feeds.

A group of three lactating dairy cows were dosed daily with metalaxyl, equivalent to 75 ppm in their diet, and were slaughtered for tissue collection on days 14, 21 and 28. Liver, kidney, fat and muscle were analysed by a dimethylaniline common moiety method. The residues were transitory and did not accumulate, and the interval between final dose and slaughter (4 and 23.5 h) influenced the residue levels more than the duration of dosing. The level of residue in milk was 0.02 mg/kg. The residue levels in the tissues collected on day 28 from the animal slaughtered 23.5 h after the final dose were 0.11 mg/kg in kidney, 0.12 mg/kg in liver, < 0.05 mg/kg in fat and 0.06–0.08 mg/kg in muscle.

Groups of 15 laying hens were dosed daily for 28 days with metalaxyl at levels equivalent to 10, 30 and 100 ppm in the feed. Tissue and egg samples were analysed by a dimethylaniline common moiety method. No residues appeared in the eggs (< 0.05 mg/kg) at any dose. The residue levels in the tissues of hens fed 10 ppm were generally below the LOQ (< 0.05 mg/kg) or, in a few cases, just above the LOQ.

#### *Maximum residue levels*

The farm animal feeding studies suggest that residues would generally be undetected or transitory in meat, milk and eggs if metalaxyl was present in animal feeds.

Farm animals are therefore not exposed to residues in their feed from commodities in this evaluation, and no MRLs have been established for metalaxyl in animal commodities. Consequently, the Meeting agreed not to recommend animal commodity maximum residue levels.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on recommended MRLs for metalaxyl, were in the range of 2-10% of the ADI (Annex 3). The Meeting concluded that the long-term intake of residues of metalaxyl and metalaxyl-M resulting from their uses that have been considered by JMPR is unlikely to present a public health concern.

### *Short-term intake*

The 2002 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of metalaxyl and metalaxyl-M residues is unlikely to present a public health concern.

# 4.16 METHAMIDOPHOS

## RESIDUE AND ANALYTICAL ASPECTS

The 2003 JMPR evaluated supporting information on cucumbers and concluded that the residue data were insufficient to estimate maximum residue limits for acephate or for methamidophos arising from use of acephate. The Meeting noted that the report of the 2003 JMPR, while stating that the number of trials was inadequate for the purposes of estimating a maximum residue level for acephate on cucumber, made no recommendation with respect to the existing recommended maximum residue level for methamidophos arising from the use of acephate.

### *Recommendation*

The Meeting recommended that the MRL of 1 mg/kg for cucumber (CCN: VC0424) be withdrawn.

# 4.17 METHOMYL (094)

## RESIDUE AND ANALYTICAL ASPECTS

Data on methomyl residues were reviewed in 1975, and data from supervised field trials with various crops and related data were considered in 1976, 1978, 1986, 1991 and 2001. At its Thirty-sixth Session, the CCPR noted that new data on mint hay and pepper had been reported and decided to maintain the CXLs for these commodities for 4 years under the periodic review procedure. The evaluation was scheduled for 2004 (ALINORM 04/27/24, para. 124, p 15).

The 2004 Meeting received data on residues from supervised field trials on pepper and mint hay from the manufacturer. Information on labels and current GAP was also provided.

### *Methods of analysis*

The gas chromatographic method for measuring residues of methomyl in many plant commodities, evaluated by the 2001 JMPR, was validated for pepper and mint hay. This method consists of extraction with an organic solvent, liquid–liquid partition and hydrolysis with sodium hydroxide. The latter converts methomyl to methomyl oxime. The final extract is analysed by gas chromatography, usually with a flame photometric detector in the sulfur mode.

A more recent method is based on HPLC. The plant matrix is extracted with solvent, cleaned up on a Florisil column and analysed by HPLC with post-column reaction to convert methomyl to methylamine. Methylamine is derivatized (on-line) and detected by fluorescence.

The gas chromatographic method has been validated for numerous plant commodities at an LOQ of 0.02 mg/kg. The HPLC method and its modifications have been validated at an LOQ of 0.02 mg/kg for methomyl.

The Meeting concluded that adequate methods exist for the determination of methomyl in pepper and mint hay.

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

As described by the 2001 JMPR, the stability of methomyl under frozen conditions has been demonstrated in a number crop samples, including broccoli, orange, apple and grape, for up to 24 months.

Data were presented on the stability of methomyl under frozen storage (–10 °C) in mint hay. Adequate stability (> 90% remaining) was demonstrated after 6 months' storage.

The Meeting concluded that methomyl is stable under frozen conditions on mint hay and pepper.

### *Results of supervised trials on crops*

*Peppers*

Supervised trials were conducted on peppers in Canada (no GAP) and the USA (GAP: 1.0 kg ai/ha, 3-day PHI). Fifteen trials (one in Canada, 14 in the USA) were conducted at US GAP, with residue concentrations of 0.02, 0.03, 0.04 (two), 0.08 (two), 0.10 (two), 0.11 (two), 0.12, 0.18, 0.24, 0.26, 0.39 and 0.44 mg/kg.

Supervised trials on peppers were conducted in France (no GAP), Greece (GAP: 0.45 kg ai/ha, 15-day PHI), Italy (GAP: 0.04 kg ai/hl, 10-day PHI), Portugal (no GAP) and Spain (no GAP). In nine trials (two in France, three in Italy, one in Portugal and three in Spain) conducted at about Italian GAP, the ranked order of concentrations was: < 0.02 (five), 0.02 (two), 0.03 and 0.04 mg/kg. The data from southern Europe and the USA were considered to represent different populations. Using only the data from the USA (higher values), the Meeting estimated an STMR value of 0.105 mg/kg, a highest residue of 0.44 mg/kg and a maximum residue level of 0.7 mg/kg, which replaces the previous estimate (1 mg/kg).

*Mint hay*

Supervised trials were conducted on fresh mint hay in the USA (GAP: 1.0 kg ai/ha, 14-day PHI, maximum of four applications). In the six trials conducted at GAP, the ranked order of concentrations of residues in fresh and spent mint hay was: 0.02 (three), 0.07 (two), 0.13, 0.16, 0.17, and 0.28 mg/kg. The dry matter in fresh and spent mint is 88%. The Meeting estimated an STMR value of 0.08 mg/kg, a highest residue value of 0.32 mg/kg and a maximum residue level of 0.5 mg/kg for mint hay on a dry weight basis. The Meeting agreed to withdraw the previous recommendation (2 mg/kg) and to replace it with the recommendation for mint hay (0.5 mg/kg, dry weight).

### *Residues in animal commodities*

As mint hay is not considered to be a significant feed item, establishment of an MRL for mint hay would not significantly change the dietary exposure of animals. The Meeting therefore decided not to revise the previous MRL recommendations for animal commodities (edible offal, meat, milk) on the basis of the addition of mint hay (fresh and spent).

## 4.18 OXYDEMETON METHYL (166)

## RESIDUE AND ANALYTICAL ASPECTS

Oxydemeton methyl was evaluated for residues by the 1998 JMPR within the CCPR periodic review programme and then for residues and toxicology by the JMPR in 1999 and 2002, respectively.

At its Thirty-first Session, the CCPR asked the JMPR to clarify whether demeton-*S*-methyl and demeton-*S*-methylsulfon should remain in the residue definition of oxydemeton methyl, as it was believed that registration of these compounds would not be retained. At its Thirty-second Session, the CCPR withdrew the draft MRLs for several commodities, as there was no existing GAP for them. The Committee advanced the proposed draft MRLs to Step 5 and returned the draft MRLs to Step 6 because of intake concerns, which would be considered at its next session. The Committee requested detailed information on oxydemeton methyl. The Committee discussed the residue definition that had been confirmed by the 1999 JMPR. It stated that, as demeton-*S*-methyl was no longer supported and there was no GAP, its use should be prevented by removing this compound from the residue definition. It was pointed out, however, that demeton-*S*-methyl could not be distinguished from oxydemeton methyl in analysis and that it could be generated from oxydemeton methyl during analysis. As no agreement was reached, the Committee agreed as a compromise to maintain the present residue definition but to specify that the residue definition and MRLs apply only to residues resulting from use of oxydemeton methyl. Those conditions would be met by adding a note to the residue definition, reading: “The residue definition and MRLs are based on the use of oxydemeton methyl only.”

At its Thirty-third Session, the CCPR noted a written comment from the European Commission stating a general reservation (lack of an acute RfD) and a specific reservation on the MRLs for grape, lemon and oranges, sweet, sour (acute risk) and decided to return the draft MRLs to Step 6. The CCPR decided to return all the MRLs to Step 6 until calculations of short-term intake had been obtained from the JMPR. The Committee was informed by the manufacturer that data would be submitted to the 2004 JMPR for a review of the residue definition.

The Meeting received new data on physical and chemical properties (partially updated), analytical methods, fate of residues in processing, plant metabolism (apple), residue data (apples, pears, grapes, cabbage, Brussels sprouts, cauliflower, field peas, potatoes, sugar-beet, fodder beet, wheat, barley, rape and sunflower), GAP and national MRLs.

### *Metabolism*

#### *Plants*

The metabolism of [ethylene-1-$^{14}$C]oxydemeton methyl in *apple* was investigated in the field. Apple trees were sprayed on two separate occasions about 4 months before harvest (pink bud stage, BBCH 57) and then about 3 months before harvest (flowers fading, BBCH 67). The formulated material was prepared at a nominal concentration of 1.4 g ai/l and applied at a nominal rate of 350 g ai/ha. Samples of fruit and leaves were taken for analysis 2 h after the first application (leaves only), 2 h after the second application (leaves only), about 60 days before harvest (first intermediate sample; fruit and leaves), about 30 days before harvest (second intermediate sample; fruit and leaves) and at harvest (fruit and leaves).

Analysis of fruit samples (flesh and peel) from the two intermediate samples showed the presence of oxydemeton methyl, but none was found at harvest. The two intermediate samples did, however, contain desmethyl-oxydemeton methyl sulfone (metabolite 7) and two polar materials (P2 and P3). In the first intermediate sample, polar radioactivity in the flesh accounted for 17% of the radioactivity in the fruit (0.2 mg/kg). In the second intermediate sample, polar radioactivity in the flesh had decreased to 10% of that in fruit (0.05 mg/kg), and by harvest no components were detected.

In the peel extracts, polar metabolites accounted for 3% of the radioactivity in the fruit (0.023 mg/kg) at the first intermediate sampling, and this had increased to 4% (0.026 mg/kg) by the second intermediate sampling. No components were detected at harvest.

The main metabolites detected at the first intermediate sampling time in both flesh and peel were oxydemeton methyl (26.6% fruit radioactivity, 0.245 mg/kg) and demeton-*S*-methylsulfone (2.9% fruit radioactivity, 0.026 mg/kg). In the second intermediate sample, oxydemeton methyl (1.7% fruit radioactivity, 0.012 mg/kg) and demeton-*S*-methylsulfone (0.2% fruit radioactivity, 0.001 mg/kg) were detected only in peel extracts. The main component detected in flesh extracts was an unidentified polar compound (14.1% radioactivity, 0.072 mg/kg). No components were detected at harvest in either flesh or peel extracts owing to the low levels of radioactivity in the extract samples (< 0.001 mg/kg). The results of this study do not change the conclusions reached in the 1998 evaluation.

## *Environmental fate*

### *Soil*

The aerobic degradation of oxydemeton methyl was studied in three soils for a maximum of 11 days under aerobic conditions in the dark at 20 °C. [ethylene-1-$^{14}$C]Oxydemeton methyl was applied at a nominal rate of 0.67 mg/kg dry soil, equivalent to the proposed single maximum annual use rate of 250 g ai/ha calculated for 2.5 cm depth of soil.

During the study, the total recovery of radioactivity in individual test vessels ranged from 90.8% to 100%, and the times to 50% and 90% decomposition ($DT_{50}$ and $DT_{90}$) in the three soils ranged from 0.17 to 0.22 and from 0.58 to 0.74 days, respectively. The results also indicate that the main metabolites were continuously degraded, that no metabolite accumulated towards the end of the study and that the bound residues participated in the natural carbon cycle of soil.

Analysis of soil extracts showed two major and one semi-major degradation product, representing 10% or more of the applied radioactivity at any time during the study. The concentration of the 2-ethylsulfinyl ethane sulfonic acid metabolite reached a maximum on day 1 and then declined gradually until day 11. Its concentration was below the LOQ towards the end of the study in soils with higher microbial activity. The 2-ethylsulfonyl ethane sulfonic acid metabolite is an oxidation product of 2-ethylsulfinyl ethane sulfonic acid, and its concentration reached a maximum on day 3 in all soils; it ranked highest, at 16.8% of the applied radioactivity. The level declined towards the end of the study in all soils, and in the most active soil to below the LOQ by day 11. Significant formation of bound residues occurred during overall metabolism of parent compound. The concentration of bound residues reached a maximum on day 11 at about 50% of the applied radioactivity. Soils showed high mineralization capacity, yielding values for $^{14}CO_2$ of > 30% by day 11. The results of study demonstrate that oxydemeton methyl is quickly degraded in aerobic soils.

### *Water–sediment systems*

The hydrolysis of oxydemeton methyl was studied in sterile 0.01 mol/l buffer solutions, which were adjusted to pH4, 7 or 9, for a maximum of 31 days in the dark at two temperatures. The experiment was carried out in compliance with good laboratory practice (GLP) and in accordance with guidelines of the US Environmental Protection Agency, the Society of Environmental Toxicology and Chemistry, the OECD and the European Commission. The test solutions were prepared with [ethylene-1-$^{14}$C]oxydemeton methyl at a concentration of about 5 mg/l. The pre-test solutions were incubated for 7 days under sterile conditions in the dark at 50 °C. The solutions at pH 4 and pH 7 in the main test were incubated for a maximum of 31 days under sterile conditions in the dark at 25 °C.

In the pre-test at 50 °C and in the main test at 25 °C, oxydemeton methyl was not stable at pH 4, 7 or 9, and considerable degradation occurred. Especially at higher pH values, the compound was thoroughly hydrolysed to desmethyl-oxydemeton methyl and 2-ethylsulfinyl-ethyl mercaptan by cleavage of the P–S bound. Furthermore, 2-ethylsulfonyl ethane sulfonic acid was observed as an oxidized P–S cleavage product at low percentages (maximum of 2.2% of the applied radioactivity), although it was identified only tentatively.

By calculation from the data obtained at 50 °C, orienting $DT_{50}$ values (first order) for the hydrolysis of oxydemeton methyl were estimated to be 4.9, 3.5 and 0.2 days at pH 4, 7 and 9, respectively. Using the data obtained at 25 °C, the $DT_{50}$ values (first order) were estimated to be 91, 42 and 2.5 days at pH 4, 7 and 9, respectively. At 20 °C, the $DT_{50}$ values calculated from Arrhenius plots (1/T versus ln(k)) were 174, 73 and 4.5 days at pH 4, 7 and 9, respectively. The results indicate that hydrolytic processes contribute to the degradation of oxydemeton methyl in the environment.

The quantum yield from direct photodegradation of oxydemeton methyl in water was determined according to the European Centre for Ecotoxicilogy and Toxicology of Chemicals method in polychromatic light. The quantum yield calculated from the ultraviolet absorption data and the kinetics of photodegradation was 0.00078. The resulting quantum yield and data on ultraviolet absorption in aqueous solution were used to estimate the environmental half-life of oxydemeton methyl after direct photodegradation in water in two simulation models. The calculated half-lives were 112 days in summer and 274 days in winter at 30° latitude and 200 days in May) and 790 days in October at 50° latitude.

### *Methods of analysis*

A number of methods have been developed for the analysis of residues of oxydemeton methyl in various matrices, many of which were reviewed by the 1998 Meeting as part of the periodic review of this compound. The Meeting was provided with additional methods based on the same principle as those evaluated earlier, i.e. use of the oxidation process to produce demeton-*S*-methylsulfone as the analyte. The LOQs were 0.005 mg/kg for potato; 0.005–0.01 mg/kg for apples and grapes; 0.01 mg/kg for pear, Brussels sprouts, cauliflower, cabbage, corn, sunflower, rape-seed and rape (green plant material); 0.02 mg/kg for wheat grain and 0.05 mg/kg for wheat straw.

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

The stability of oxydemeton methyl in stored cabbage, maize, lettuce and papaya was evaluated by the 1998 JMPR, which concluded that data on the stability of stored analytical samples of raw agricultural commodities containing quantifiable residues of oxydemeton methyl were highly desirable. The available information was not representative of the various crop groups, did not cover extended storage intervals and suggested variable storage stability. The manufacture submitted new study data on the storage stability of oxydemeton methyl in several crops.

A study was conducted to determine the stability of oxydemeton methyl in spiked samples of stored apple, dried peas, potato and oil-seed rape (meal and oil at – 20 °C). Samples for the study were obtained from a commercial source. The samples of apple and potato were prepared for use by fine chopping in an industrial food processor; the preparation of samples of dried peas was not recorded in the report. For each crop, 20 g of prepared sample were spiked with formulated oxydemeton methyl at a nominal concentration of 0.1, 1.0 or 10 mg/kg and placed in storage at – 20 °C. Two samples of each were removed for analysis after 0, 3, 6, 12 and 24 months of storage. The analytical method was validated for each crop at each sampling time.

There was no substantial loss of residue during 24 months' storage from apple, potato or oil; however, the residues in dried peas and rape meal apparently decreased to half the initial values after 3 or 6 months of storage. The control samples (un-spiked samples) also showed residues of oxydemeton methyl, with < 0.005–0.022 mg/kg in apple, < 0.005–0.016 mg/kg in dried peas, < 0.01–0.016 mg/kg in potatoes, 0.013–0.03 mg/kg in rape meal and < 0.005–0.011 mg/kg in rape oil. The Meeting concluded that the data submitted on storage stability were insufficient or inadequate, and the former requirement was maintained.

### *Definition of the residue*

The Meeting received the results of new studies of plant metabolism and supplementary information on the analytical method. The new data did not, however, provide a basis for changing the current residue definition. The Meeting confirmed its previous recommendation.

### *Results of supervised trials on crops*

The results of supervised field trials on apples, pears, grapes, cabbage, Brussels sprouts, cauliflower, field peas, potatoes, sugar-beet, fodder beet, wheat, barley, rape and sunflower were submitted to the Meeting. The new data were evaluated against current GAPs, and highest residue levels were estimated for commodities evaluated by the 1998 JMPR, as the 1998 JMPR did not do so. When no residues were found in any sample in older trials in which the analytical methods used had higher LOQs than current methods, the Meeting decided to use only data from the newly submitted trials in order to avoid unnecessarily high maximum residue levels.

*Citrus fruit*

No data from new supervised trials were submitted. From 11 trials on *orange* and *lemon*, the 1998 JMPR estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.01 mg/kg.

In the 1998 evaluations, the reported residues in pulp, in ranked order, were < 0.01 (seven), 0.01, 0.02 (two) and 0.04 mg/kg. The Meeting estimated a highest residue level of 0.04 mg/kg for orange and lemon.

*Pome fruit*

The results of 15 new supervised trials on apples and two on pears were submitted to the Meeting

One supervised trial on *apples* in northern France in 1998 involved higher doses than used in German GAP (0.13 kg ai/ha once, immediately after flowering). Nevertheless, the residue data could be used, since the residue levels were below the LOQ. Three supervised trials on apples in southern France in 1997 and 1998, three on apples in Italy in 1997 and 1998 and four on apples in Spain in 1997 and 1998 were conducted according to Italian GAP (0.023–0.028 kg ai/hl, 90-day PHI). As two of the four Spanish trials (conducted in 1997) were carried out in the same location under almost identical trial conditions, one residue level was taken from each. The residue levels of oxydemeton methyl in apples were < 0.01 (nine) and 0.01 mg/kg.

One supervised trial on *pears* in southern France in 1998 was conducted according to Italian GAP (0.023–0.028kg ai/hl, 90-day PHI), and one trial on pears in Germany in 1998 was conducted according to Austrian GAP (0.024 kg ai/hl once, up to 2 weeks after flowering). The residue level of oxydemeton methyl in pears was < 0.01 (two) mg/kg.

The 1998 JMPR evaluated 10 supervised trials on apples and pears and estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.01 mg/kg for apple and pear, based on residue levels, in ranked order, of < 0.01 (seven), 0.03 and < 0.04 (two) mg/kg.

The Meeting confirmed that the residue levels found in the newly submitted trials did not exceed the formerly estimated maximum and highest residue values of 0.04 mg/kg for apple and pear in the 1998 JMPR evaluations.

*Grape*

Three new supervised trials from Germany were conducted within German GAP (0.027 kg ai/hl, up to fully developed inflorescence). The residue levels were < 0.01 (three).

The 1998 JMPR evaluated the results of five supervised trails and estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.04 mg/kg.

The Meeting confirmed that the residue levels found in the newly submitted trials did not exceed the formerly estimated maximum and highest residue values of 0.06 mg/kg for grapes in the 1998 JMPR evaluations. The residue levels, in ranked order, were < 0.04 (four) and 0.06 mg/kg.

*Brassica vegetables*

*Cabbage (head)*

The results of four new supervised trials were submitted to the Meeting.

Two supervised trials on red and white cabbage in northern France in 1996 and two supervised trials on Savoy cabbage in Germany were conducted according to German GAP (0.16 kg ai/ha (< 50 cm) once, 21-day PHI). The residue levels were < 0.01 (four) mg/kg.

The 1998 JMPR evaluated 16 supervised trials and estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.03 mg/kg. The highest value of < 0.06 mg/kg was disregarded because of the high LOQ in the older trials (1976).

The Meeting confirmed that the residue levels in the submitted trials did not exceed the formerly estimated maximum and highest residue values of 0.05 mg/kg in the 1998 JMPR evaluations. The residue levels, in ranked order, were < 0.01 (six), 0.02, < 0.03 (three), < 0.04 and < 0.05 (four) mg/kg.

*Kale*

No data from new supervised trials were submitted to the Meeting. Four supervised trials were evaluated by the 1998 JMPR, which estimated a maximum residue level of 0.01* mg/kg and an STMR of 0.01 mg/kg.

On the basis of the reported residue level, < 0.01 (four) mg/kg, the Meeting estimated a highest residue level of 0.01mg/kg.

*Kohlrabi*

No data from new supervised trials were submitted to the Meeting. Four supervised trials were evaluated by the 1998 JMPR, which recommended a maximum residue level of 0.05 mg/kg and an STMR of 0.02 mg/kg. The reported residue levels, in ranked order, were < 0.01 (two), 0.03 and < 0.06 mg/kg. The highest value was disregarded because of the high LOQ associated with the older trials (1979).

The Meeting estimated a highest residue level of 0.05 mg/kg, at the same level as the maximum residue level recommended by the 1998 JMPR.

*Brussels sprouts*

Five supervised trials conducted in Germany in 1997 and 1998, two conducted in Belgium in 1997 and 1998, one conducted in the United Kingdom in 1998 and one conducted in northern France in 1998 were submitted to the Meeting; however, no comparable GAP was submitted. The Meeting could not therefore estimate a maximum residue level, an STMR or a highest residue level.

*Cauliflower*

The results of eight new supervised trials were submitted to the Meeting. Two trials in Germany in 1996 were conducted according to German GAP (0.16 kg ai/ha (< 50 cm) once, 21-day PHI) and also according to Belgian GAP (0.15 kg ai/ ha once, 28-day PHI).

Four supervised trials in southern France in 1996 and 1997 and one in the United Kingdom in 1996 were conducted according to German GAP. One of the trials in France in 1996 involved higher doses than in German GAP, but the residue data could be used for evaluation as the level was below the LOQ.

In all the trials the residue level was $\leq 0.01$ (eight) mg/kg. The Meeting estimated a maximum residue level of 0.01* mg/kg and STMR and highest residue values of 0.01 mg/kg for cauliflower.

*Field peas (dry)*

Data from two supervised trials on field peas were submitted to the Meeting, but no information on GAP was provided. The Meeting could therefore not estimate a maximum residue level, an STMR or a highest residue level.

*Potatoes*

The results of 20 supervised trials were submitted to the Meeting.

Two supervised trials in Germany in 1996 and one in the United Kingdom in 1996 were not matched by comparable GAP. Nine supervised trials in France in 1996 and 1998, one in Greece in 1998, three in Italy in 1997 and 1998 and four in Spain in 1997 and 1998 were conducted according to Greek GAP (0.05kg ai/hl three times, 28-day PHI). As two of four Spanish trials conducted in 1997 were carried out in the same location under similar trial conditions, one residue level was taken from each. The residue levels, in ranked order, were < 0.005 (five) and <u>< 0.01</u> (11) mg/kg.

The 1998 JMPR evaluated the results of 16 supervised trials and estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.02 mg/kg. The reported residue levels, in ranked order, were < 0.01 (seven), < 0.02 (nine) and < 0.05 (two) mg/kg.

The Meeting decided to use the data from the newly submitted trials and estimated a maximum residue level of 0.01*mg/kg and STMR and highest residue values of 0.01 mg/kg to replace the former recommendations.

*Sugar-beet (root)*

The results of seven supervised trials on sugar-beet and two on fodder beet were submitted to the Meeting.

Three supervised trials on sugar-beet in Spain in 1997 and 1998 and four in Italy in 1997 and 1998 involved higher doses than in Spanish GAP (0.025 kg ai/hl, 30-day PHI) or Italian GAP (0.023–0.028 kg ai/hl, 30-day PHI); however, the residue data could be used for evaluation as all the levels in leaf and root were below the LOQ. As two of the three Spanish trials were conducted at the same location under the same trial conditions, one residue level was taken from each.

Two supervised trials on fodder beet in southern France in 1998 involved higher doses than in Spanish GAP (0.025 kg ai/hl, 30-day PHI), but the residue data could be used for evaluation as all the levels in leaf and root were below the LOQ. Six trials on sugar-beet and two on fodder beet could be evaluated together, as all the residue levels were <u>< 0.01</u> (eight) mg/kg.

The 1998 JMPR evaluated seven supervised trials on sugar-beet and two on fodder beet in Germany, and estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.04 mg/kg. The reported residue levels, in ranked order, were < 0.01 (four) and < 0.04 (five) mg/kg.

The Meeting decided to use the data from the newly submitted trials and estimated a maximum residue level of 0.01*mg/kg and an STMR of 0.01 mg/kg, to replace the former recommendations.

*Wheat, barley and rye*

Eleven supervised trials on wheat and two on barley were submitted to the Meeting.

Four supervised trials on wheat in Italy in 1997 and 1998, six in southern France in 1997 and 1998 and one in Spain in 1998 involved higher doses than in Italian GAP (0.023–0.028 kg ai/hl, 30-day PHI), but the data on residues on wheat grain could be used for evaluation as all the levels were below the LOQ. The residue levels, in ranked order, were < 0.01 (six) and < 0.02 (five) mg/kg.

Two supervised trials on barley in southern France in 1997 and 1998 involved slightly higher doses than in the Italian GAP for wheat. The Meeting concluded that this GAP could be applied to trials on barley, as the two crops are cultivated similarly. The residue levels were < 0.01 (two) mg/kg.

The 1998 JMPR evaluated seven supervised trials on wheat and three on barley and estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.04 mg/kg. The reported residue levels, in ranked order, were < 0.04 (seven) and < 0.05 (three) mg/kg.

The Meeting decided to use the data from the newly submitted trials to estimate the maximum residue level. The combined residue levels, in ranked order, were < 0.01 (eight) and < 0.02 (five) mg/kg. The Meeting estimated a maximum residue level of 0.02*mg/kg and an STMR of 0.01 mg/kg, to replace the former recommendations.

*Rape-seed*

One supervised trial on rape was submitted to the Meeting; however, no information on GAP was provided. The Meeting could therefore not estimate a maximum residue level, an STMR or a highest residue level.

*Sunflower seed*

Six supervised trial data on sunflower were submitted to the Meeting; however, no information on GAP was provided. The Meeting could therefore not estimate a maximum residue level, an STMR or a highest residue level.

*Sugar-beet (tops)*

The residue levels in the leaves of sugar-beets and fodder beets treated according to GAP, in ranked order, were < 0.01 (five) and < 0.04 (three) mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg, an STMR of 0.01 mg/kg and a highest residue level of 0.04 mg/kg, to replace the former recommendations.

*Wheat, barley and rye straw and fodder*

The residue levels in straw and fodder from wheat and barley, in ranked order, were < 0.04 (eight), < 0.05 (three) and 0.06 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg, an STMR of 0.04 mg/kg and a highest residue level of 0.06 mg/kg, to replace the former recommendations.

### *Fate of residues during processing*

The results of studies on residues in processed peas were provided to the Meeting. The samples were fortified with diluted oxydemeton methyl formulation by soaking because the levels of residue in samples produced under GAP conditions were expected to be too low. The reported processing factors were 0.034 for processed marrowfat peas (canning), 0.024 for vining peas (canning), 0.43 for vining peas (freezing) and 0.43 for vining peas (freezing and domestic cooking).

### *Residues in animal commodities*

The 1998 JMPR, estimated the dietary burden of farm animals and concluded that quantifiable residues of demeton-*S*-methyl, oxydemeton methyl or demeton-*S*-methylsulfone are unlikely to occur in commodities of animal origin (meat, milk, poultry and egg). Therefore, MRLs could be set at the practical LOQ of 0.05* mg/kg for all commodities except milk and at 0.01* mg/kg for milk. The current Meeting did not recommend the addition of further feed items or an increase in the recommended residue levels. It therefore confirmed the previous maximum residue levels and STMRs for commodities of animal origin and estimated a highest residue level of 0 mg/kg for cattle fat, eggs, meat of cattle, pigs and sheep, pig fat, poultry fats, poultry meat and sheep fat.

### *Further work or information*

*Desirable*

Data on the stability of stored analytical samples of raw agricultural commodities containing quantifiable residues of oxydemeton methyl are highly desirable, as the information provided was not representative of the various crop groups, did not cover extended storage and suggested variable storage stability.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

STMR or STMR-P values were estimated by the 1998 JMPR and by the present Meeting for 27 commodities. When data on consumption were available, these values were used in the estimates of dietary intake.

The dietary intake from the five GEMS/Food regional diets, on the basis of the STMR values, represented 3–30% of ADI (Annex 3). The Meeting concluded that the intake of residues of oxydemeton methyl resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

### *Short-term intake*

The IESTI for oxydemeton methyl was calculated for the commodities for which maximum residue levels, STMR values and highest residue levels were established and for which data on consumption (of large portions and unit weight) were available. The results are shown in Annex 4.

The ARfD for oxydemeton methyl is 0.002 mg/kg bw. The IESTI represented 0–220% of the ARfD for children and 0–90% of that for the general population. For children, 100% of the ARfD was exceeded in apple (130%), cabbage (120%), grape (220%) and orange (120%).

The Meeting concluded that the short-term intake of residues of oxydemeton methyl from uses on commodities other than apples, cabbages, grapes and oranges that have been considered by the JMPR is unlikely to present a public health concern.

## 4.19 PARAQUAT (057)

## RESIDUE AND ANALYTICAL ASPECTS

Paraquat, a non-selective contact herbicide, was first evaluated by the JMPR for toxicology and residues in 1970. Subsequently, it was reviewed for toxicology in 1972, 1976, 1982, 1985 and 1986 and for residues in 1972, 1976, 1978 and 1981. The Meeting reviewed paraquat toxicologically within the periodic review programme in 2003 and established an ADI of 0–0.005 mg/kg bw and an ARfD of 0.006 mg/kg bw as paraquat cation. Currently, there are 22 Codex MRLs for plant commodities, their derived products and animal commodities.

The CCPR at its Thirty-second Session identified paraquat as a priority for periodic review by the 2002 JMPR, but residue evaluation was postponed to the present Meeting.

Paraquat is usually available in the form of paraquat dichloride or paraquat bis(methylsulfate). The Meeting received data on metabolism, environmental fate, analytical methods, storage stability, supervised field trials, processing and use patterns.

### *Metabolism*

#### *Animals*

The WHO Expert Group of the 2003 JMPR reviewed studies on the the excretion balance of paraquat in *rats* given a single dose of 1 or 50 mg/kg bw [1,1′-$^{14}$C-dimethyl]paraquat dichloride or 14 daily doses of 1 mg/kg bw unlabelled paraquat dichloride followed by 1 mg/kg bw of the labelled compound. They also evaluated studies of the biotransformation of paraquat in rats given the same doses of radiolabelled paraquat and other studies of metabolism and toxicity in rats. They concluded that orally administered paraquat is not well absorbed. Excretion was rapid, with 60–70% in faeces and 10–20% in urine; 90% was excreted within 72 h. Paraquat was eliminated largely unchanged: 90–95% of radiolabelled paraquat in urine was identified as the parent compound.

When 23 mg/kg [1,1′-$^{14}$C-dimethyl]paraquat dichloride were administered through a rumen fistula to one *sheep*, all the administered radiolabel was excreted within 10 days in urine (4%) and faeces (96%), indicating that residues of orally administered paraquat would not remain or accumulate in sheep tissues. Most of the radiolabel in urine and faeces was attributed to unchanged paraquat and 2–3% to paraquat monopyridone. Less than 1% 4-carboxy-1-methylpyridinium ion, paraquat dipyridone and monoquat were found.

When 0.92 mg/kg [1,1′-$^{14}$C-dimethyl]paraquat dichloride was administered subcutaneously to a sheep, paraquat was again excreted rapidly. Over 80% of the administered radioactivity was excreted in urine, 69% 1 day after treatment. Unchanged paraquat accounted for most of the radiolabel. The monopyridone was present at 2–3% and monoquat as a trace metabolite. The excretion patterns in the two sheep were virtually identical, regardless of the route of administration.

A *pig* weighing about 40 kg was fed twice daily with a diet containing [1,1′-$^{14}$C-dimethyl]paraquat ion at a rate equivalent to 50 mg/kg for 7 days. At sacrifice, 69% of the administered radiolabel had been excreted in faeces and 3.4% in urine; 13% was present in the stomach contents and viscera. All the radiolabel found in tissues, except in liver, was attributed to paraquat. About 70% of the radiolabel in the liver was identified as paraquat, with 7% as monoquat ion and about 0.6% as monopyridone ion. This result indicates that there is no significant metabolism of paraquat in pigs.

In a similar study, a pig was fed a diet containing [2,2′,6,6′-$^{14}$C]paraquat ion at a rate equivalent to 50 mg/kg for 7 days. At sacrifice, 72.5% of the administered radiolabel had been excreted in faeces and 2.8% in urine. In the liver, about 70% of the radiolabel was identified as paraquat and 4% as monoquat ion.

A Fresian *cow* weighing 475 kg given a single dose of about 8 mg/kg [1,1′-$^{14}$C-dimethyl]paraquat dichloride from a balling gun excreted 95.6% of the administered radioactivity in faeces within 9 days; 89% was excreted within the first 3 days. Analysis indicated that 97–99% of the radioactivity in 1–4-day faeces and 100% of that in 5–6-day faeces co-chromatographed with paraquat. A total of 0.7% of the administered dose was excreted in urine, 80% of which was excreted within the first 2 days. Paraquat accounted for 90% of the radiolabel in urine on day 1, 70% on day 3 and 62% on day 5. The remaining activity was attributed to paraquat monopyridone and monoquat. Only 0.0032% of the administered radiolabel was recovered from milk within 9 days. The traces of radioactivity in milk (a maximum of 0.005 mg/l as paraquat ion equivalent milk taken in the morning of day 2) were attributed mainly to paraquat and its monopyridone and to a naturally occurring compound which appeared to be lactose. The residue level of any one compound in milk was ≤ 0.002 mg/kg.

When a lactating *goat* was dosed with [2,2′,6,6′-$^{14}$C]paraquat dichloride twice daily at each milking for 7 days at a total daily rate equivalent to approximately 100 mg/kg in the diet, 50.3% of the administered radioactivity was excreted in faeces, 2.4% in urine and 33.2% in stomach contents by the time of sacrifice. The total radioactivity, expressed in paraquat ion equivalents, in milk increased during the experimental period, reaching a maximum of 0.0092 mg/kg (equivalent to 0.003% of the daily dose) 4 h before slaughter. Of this radioactivity, 75.7% was attributed to paraquat, and 15.8% did not show a cationic character. There appeared to be no significant metabolism of paraquat in any tissue, except liver and peritoneal fat, where about half the radiolabel was attributed to paraquat, < 5% as monopyridone ion and 5% as monoquat ion.

Warren laying *hens* given [2,2′,6,6′-$^{14}$C]paraquat ion in gelatin capsules at a rate equivalent to 30 mg/kg normal diet for 10 days had excreted 99% of the administered radiolabel in faeces at the time of sacrifice; 96.6% of the radiolabel was attributed to unchanged paraquat. The amount of radiolabel in egg albumen did not exceed 0.0014 mg/kg in paraquat ion equivalents throughout the experimental period, while that in the yolk was < 0.001 mg/kg on day 1 and increased gradually to 0.18 mg/kg (in one bird) on day 8. All the radiolabel in yolk was identified as paraquat.

The studies on the fate of orally administered paraquat show that most is excreted unchanged, mainly in faeces and to a much smaller extent in urine. Excretion of paraquat was rapid in all the species studied, hens showing the most efficient excretion. Little paraquat was absorbed from the gastrointestinal tract, and the small amount absorbed was not significantly metabolized. Less than 0.05 mg/kg of paraquat was found in muscle, milk and eggs, even at the high dose rates used in these studies. These findings indicate that no significant bioaccumulation of paraquat is expected to occur in these species.

The metabolism of paraquat in these species was similar. Four metabolites were identified: monoquat, paraquat monopyridone, 4-carboxy-1-methylpyridinium ion and paraquat dipyridone. In all tissues except liver of all the species tested and in goat peritoneal fat, 80–100% of the total radiolabel was attributable to the parent compound, paraquat. In liver and goat peritoneal fat, 50–80% of the radiolabel was associated with paraquat, and absorbed paraquat was metabolized to monoquat and paraquat monopyridone and to a much smaller extent to 4-carboxy-1-methylpyridinium ion. The metabolism of paraquat involves oxygenation of one pyridine ring to form paraquat monopyridone and desmethylation of one pyridine ring to form monoquat. Cleavage of the pyridine–pyridine linkage produces 4-carboxy-1-methylpyridinium ion. The other *N*-methylpyridine moiety would produce carbon dioxide and methylamine.

*Plants*

When paraquat is used as a directed spray before sowing, before planting, before emergence and after emergence, it is present in soil as residues, but no direct contact occurs with crops. Sandy loam soil in pots in which *lettuce* and *carrots* were sown was sprayed with [U-$^{14}$C-bipyridyl]paraquat ion immediately after sowing at rates equivalent to 14.3 kg ai/ha for lettuce and 14.7 kg ai/ha for carrots, which are 13 times the highest current application rates for those crops, and maintained in a greenhouse. The radiolabel in mature lettuce and carrots harvested 65 and 96 days after treatment represented 0.0034 and 0.0048 mg/kg in paraquat ion equivalents, respectively. This result confirms the lack of significant translocation of residues of paraquat from treated soil to lettuce leaves or carrot roots.

Paraquat is also used as a crop desiccant and harvest aid, when it is in direct contact with crops. The foliage of *potatoes* and *soya beans* growing in pots in a greenhouse was treated with $^{14}$C-paraquat at rates equivalent to 8.7 or 8.8 kg ai/ha (potato) and 8.2 kg ai/ha (soya beans), 14–16 times the highest current use for desiccation on potato and soya beans. The average TRR, expressed in paraquat ion equivalents, in soya and potato plants harvested 4 days after treatment were 638 mg/kg in soya foliage, 0.747 mg/kg in soya beans and 0.082 mg/kg in potato tuber. In all the samples, 89–94% of the TRR was identified as paraquat. The rest of the radioactive residue consisted of two or three fractions, none of which exceeded 10% of the respective

TRR. In soya foliage extracts, small amounts of 4-carboxy-1-methylpyridinium ion (0.3% TRR) and monoquat (0.3 % TRR) were found. The latter is a known photodegradation product of paraquat.

As paraquat is strongly adsorbed by soil (see above), its uptake by plants after pre-emergence or post-emergence directed use is insignificant, even at exaggerated application rates. When paraquat was applied as a desiccant to potato and soya bean at a rate > 10 times the highest recommended application rate, with a 4-day PHI, the main component in potato tuber, soya beans and soya foliage was paraquat. In soya foliage, monoquat and 4-carboxy-1-methylpyridinium ion were also found. Although the latter is a known photodegradation product and was not found in soya beans or potato tuber, biotransformation cannot be excluded because the TRR was too low for reliable identification. As the fate of paraquat in soya foliage appears to involve photodegradation, its fate is considered to be common among plants.

The metabolism of paraquat involves desmethylation of one pyridine ring to form monoquat. 4-Carboxy-1-methylpyridinium ion appears to be produced by photolysis of monoquat, with breakdown of the pyridine–pyridine linkage, but involvement of biotransformation cannot be excluded. Paraquat monopyridone and dipyridone, which are found in animals, were not found in plants even at much higher than normal application rates. The transformation of paraquat in plants is similar to its metabolism in animals.

### *Environmental fate*

#### *Soil*

Paraquat was applied to slurries of loam, loamy sand, silty clay loam or coarse sand in 0.01 mol/l aqueous calcium chloride at rates higher than normal, to give 0.01 mg/l in the equilibrium solution after a 16-h equilibration. The calculated adsorption coefficients ranged from 480 in the coarse sand to 50 000 in the loam. At normal application rates, the concentration of paraquat in the equilibrium solution could not be determined (< 0.0075 mg/l). No significant desorption was observed.

A field survey of 242 agricultural soils in Denmark, Germany, Greece, Italy, The Netherlands and the United Kingdom showed that paraquat was strongly adsorbed to all the soil types studied. The adsorption coefficients calculated at application rates much higher than normal ranged from 980 to 400 000, and those adjusted for the organic carbon content of soil were 8400–40 000 000. Adsorption coefficients could not be calculated at normal application rates because the concentration in equilibrium solution was below the limit of determination (0.01 mg/l). On the McCall scale, paraquat was classified as ‘immobile’ in all these soils, without leaching.

[2,6-$^{14}$C]Paraquat was applied to sandy loam soil in pots at a nominal rate of 1.05 kg/ha and incubated in the dark at 20 ± 2 °C under aerobic conditions in order to study the aerobic degradation of paraquat. After 180 days of incubation, paraquat accounted for > 93% of the applied radiocarbon, with no detected degradation products. Less than 0.1% of the applied radioactivity evolved as $^{14}CO_2$ over the 180-day incubation period. The half-life of paraquat in soil under aerobic conditions could not be estimated, although a long half-life in soil was implied by the results of the study.

In long-term field dissipation studies conducted on cropped plots in Australia, Malaysia, The Netherlands, Thailand, the United Kingdom and the USA, the location had no major effect on the field dissipation rate. Generally, paraquat residue levels had declined to about 50% 10–20 years after the start of the studies. This implies a $DT_{50}$ of 10–20 years after application of single, large doses of paraquat to soil. The $DT_{90}$ could not be estimated in these studies, however, as the experimental periods were too short.

Conventional laboratory studies could not provide useful information on the route or rate of degradation of paraquat in soil because of its strong adsorption to soil minerals and organic matter. In order to obtain information, microbiological degradation studies were conducted with microorganisms isolated from soil. The most effective soil organism for decomposing paraquat was a yeast species, *Lipomyces starkeyi*. When incubated with radiolabelled paraquat, the yeast culture or cultures originating from two sandy loam soils decomposed most of the paraquat, released $CO_2$ and formed oxalic acid at 24–25 °C.

An unidentified bacterium isolated from soil metabolized [1,1′-$^{14}$C]paraquat to monoquat and 4-carboxy-1-methylpyridinium ion. Extracts of *Achromobacter* D were found to produce $CO_2$, methylamine, succinate and formate as metabolites of 4-carboxy-1-methylpyridinium ion. The results showed that the $CO_2$ originated from a carboxyl group, methylamine from the *N*-methyl group and the carbon skeletons of formate and succinate from the C-2 and C-3–C-6 atoms of the pyridine ring, respectively. These results indicate that the pyridine ring is split between C-2 and C-3.

The degradation rate of paraquat in soil was determined by cultivating 10 mg/kg [U-$^{14}$C-dipyridyl]paraquat with *Lipomyces* and mixed cultures derived from two soils. The degradation of paraquat was rapid, with a $DT_{50}$ between 0.02 and 1.3 days after a lag phase of about 2 days, accompanied by rapid mineralization to $CO_2$ and the formation of several unidentified minor polar metabolites.

The photolysis of [2,2′,6,6′-$^{14}$C]-paraquat was studied by applying it to the surface of a highly sandy soil which was exposed to natural sunlight. The proportion of paraquat in samples declined during 85 weeks, at which time paraquat represented 86.6–89.5% of the total radiolabel found in unmixed and mixed soil samples. Thin-layer chromatographic analysis of the 6 mol/l HCl extracts of mixed and unmixed soils contained monoquat ion, paraquat monopyridone ion and an uncharacterized compound, which accounted for 1.4–2.4%, 1.2–1.3% and 1.8–2.4%, respectively, of the total radioactivity after 85 weeks. Photodegradation on the soil surface is not considered to be a major environmental degradation process for paraquat.

*Water–sediment systems*

Aqueous photolysis of paraquat was examined by maintaining ring-labelled paraquat in sterilized 0.01 mol/l phosphate buffer solution (28 mg/l) at 25 °C under light. After 36 days of irradiation simulating summer sunlight in Florida (USA), most of the recovered radioactivity was attributed to paraquat, with 0.13% as $CO_2$ and no photodegradation products. When solutions of radiolabelled paraquat were exposed to unfiltered ultraviolet light, no paraquat remained after 3 days, with formation of $CO_2$, methylamine and 4-carboxy-1-methylpyridinium ion; the last metabolite further degraded to $CO_2$ and methylamine. These results indicate that, while paraquat appears to be stable to photolysis at pH 7, it readily degrades into $CO_2$ and methylamine when exposed to unfiltered ultraviolet light.

[U-$^{14}$C-dipyridyl]Paraquat in deionized water was applied to the water surface of two continuously aerated sediment–water systems at a rate equivalent to 1.1 kg ai/ha. Paraquat was strongly adsorbed to the sediment in both systems, even immediately after treatment. After 100 days of incubation, 0.1–0.2% of the applied radioactivity was found in the aqueous phase, 92.9–94.9% in extracts from sediment fractions and 4.2–4.5% in unextracted sediment fractions. Most of the radiolabel recovered from the aqueous phase and sediment extract was attributed to paraquat, while no degradation products were detected. The $DT_{50}$ or the $DT_{90}$ could not be estimated as no significant degradation of paraquat was observed during the experimental period.

*Residues in succeeding crops*

Seeds of wheat, lettuce and carrot were sown into individual pots containing a sandy loam soil 0, 30, 120 and 360 days after treatment of the soil with [2,2′,6,6′-$^{14}$C]paraquat at an application rate equivalent to 1.05 kg ai/ha, and were maintained in a glasshouse until maturity. Over the course of the study, the TRR in soil represented an average of 99.2% of the applied radioactivity. $^{14}$C-Paraquat accounted for 72.7–99.3% of the TRR in soil extracts and no other radioactive compounds were detected in any soil sample. Radioactive residues, expressed in paraquat ion equivalents per kilogram, were below the LOQ in most crop samples sown 0, 30 and 120 days after treatment. The highest radioactive residue level, 0.009 mg/kg in paraquat ion equivalents, was found in wheat straw sown 30 days after treatment.

Seeds of lettuce and carrot were sown in pots containing sandy loam soil, and the soil was treated immediately afterwards with [U-$^{14}$C-dipyridyl]paraquat at exaggerated rates of 14.3 and 14.7 kg/ha respectively, corresponding to approximately 13 times the highest current application rate. The lettuce was harvested 65 days after treatment and the carrots 96 days after treatment. The levels of radioactive residues in lettuce leaf and carrot root at harvest were 0.0034 and 0.0048 mg/kg in paraquat ion equivalents, respectively. There is therefore no significant uptake of paraquat into rotational crops, even when the soil is treated at exaggerated rates.

### *Methods of analysis*

With the long history of registration of paraquat in many countries, many analytical methods have been developed and used for measuring residues in plant and animal commodities. All the methods provided to the Meeting were for analysis of paraquat only. Some analytical methods allow separate determination of paraquat and diquat in a sample.

#### *Samples of plant origin*

Six analytical methods for the determination of paraquat in plant commodities and oil and oil cake were submitted.

Three of the methods involve extraction of paraquat by refluxing homogenized or comminuted samples in 0.5 mol/l sulfuric acid for 5 h; filtration, cation-exchange chromatography from which paraquat is eluted with saturated ammonium chloride, conversion of paraquat to its coloured free radical with 0.2% (w/v) sodium dithionite in 0.3 mol/l NaOH and spectrophotometric measurement. The methods differ only in the spectrophotometric measures used: absorption of the free radical in the range 360–430 nm measured against a control solution or absorption in the range of 380–430 nm measured in second derivative mode against a paraquat standard.

In the most recent method, the eluate from cation-exchange chromatography is further cleaned up on a C18 SepPak solid phase extraction cartridge, and the second 5-ml eluate is analysed by reverse-phase ion-pair HPLC with ultraviolet detection at 258 nm.

Two other methods developed for the determination of paraquat in liquid samples, such as oil, also involve second derivative spectrophotometry (360–430 nm), but they do not involve extraction with sulfuric acid. Reverse-phase ion-pair HPLC is also used as the confirmatory method.

All these methods were validated in one or several laboratories for vegetables and fruits, cereal grains and seed, grass and straw, sugar-cane juice, oil seeds, oil and oil cake. The LOQ of these methods ranged from 0.01 to 0.05 mg/kg, except for oil cake, for which the LOQ was 0.5 mg/kg. The mean procedural recoveries were 61–107% at fortification rates reflecting both the LOQ and the actual levels of incurred residues. In general, lower recoveries were made from oil and oil cake. The mean recovery from rape-seed oil cake and olive oil was 67% and that from coffee beans was 61%; those from other commodities were > 70%. The relative standard deviation of recoveries ranged from 2% to 19%.

#### *Samples of animal origin*

Three analytical methods for the determination of paraquat in animal products were submitted.

Two methods, including the most recent, for determining paraquat in milk, eggs and animal tissues involve extraction of paraquat by homogenizing samples in 10% trichloroacetic acid, centrifugation, dilution with water, application to a cation-exchange column, sequential washing, elution of paraquat with saturated ammonium chloride, determination by reverse-phase ion-pair HPLC with ultraviolet detection at 258 nm. Fat in milk, skin with subcutaneous fat and fat samples must be removed by hexane extraction before cation exchange.

A method for analysing liquid samples, including milk, does not involve acid extraction or defatting, and milk is mixed directly with cation exchange resin before packing. Otherwise, this method is the same as those described above.

The LOQs were reported to be 0.005 mg/kg for milk, eggs and bovine, ovine and chicken tissues. The mean procedural recoveries were 75–105%, with a relative standard deviation of 2–13%.

The currently used methods for plant and animal samples were found to be suitable for quantification of paraquat in plant and animal commodities for enforcement purposes. The methods are fully validated and include confirmatory techniques. The earlier methods for quantification of paraquat in plant and animal samples were also found to be suitable in validation; however, a mean recovery < 70% was seen for rape-seed cake, olive oil and coffee beans analysed by one of the methods.

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

Investigations were reported of the stability of residues in ground samples of prunes, banana, cabbage, potato, carrot, tomato, maize (grain, forage, fodder and silage), wheat grain, coffee beans, birdsfoot trefoil (forage and hay), meat, milk and eggs stored in a deep freezer at a temperature < –15 °C for 1–4 years.

No decrease in residue levels of paraquat, whether fortified or incurred, was observed in any of the crop matrices during the test period, the longest being 46 months. The exception was a slight decrease in birdsfoot trefoil forage that had been treated at a rate equivalent to 0.54 kg ai/ha and contained incurred residues at 57 mg/kg.

No decrease in the levels of residues of paraquat in animal commodity matrices over time was observed under storage for up to 28 months. The test matrices represented a diverse selection of animal tissues, and the studies demonstrate the stability of paraquat under various storage conditions.

### *Definition of the residue*

Paraquat is usually available as the dichloride salt or the bis(methylsulfate) salt but is determined as paraquat ion in analysis. Paraquat is known to adsorb strongly to soil, and most of the small amount incorporated into plant remains as paraquat (90%). Its metabolites were not found when paraquat was applied at normal rates. When it was applied post-emergence, most of the applied compound remained, with minimal amounts of photodegradation products, indicating the involvement of photolysis in the transformation of paraquat. The residue of concern in plants is paraquat ion.

In studies of metabolism in rats, cattle, goats, pigs and hens, the metabolic pathway was similar, producing minor levels of oxidized metabolites. The metabolic pathways in animals and plants are similar. In animals, the residue of concern is also paraquat ion.

The definition of the residue in all countries that provided national MRLs to the Meeting was paraquat ion.

All the identified metabolites have been covered by toxicological evaluations, owing either to their occurrence in rats or in independent studies. The ADI recommended by the JMPR is for paraquat cation.

The Meeting therefore agreed that the definition of residues for plant and animal commodities should be: Paraquat cation (for both compliance with MRLs and estimation of dietary intake).

### *Results of supervised trials on crops*

When used for weed control, paraquat is not sprayed directly onto crops and is strongly adsorbed to soil. Therefore, little paraquat is expected to be found in harvested crops. After pre-emergence application, no residues were expected to be detected in the harvested crops, although some samples contained residues. After use as a harvest aid desiccant, however, paraquat is in direct contact with crops, and the residue levels tend to be much higher than when it is used for weed control.

The Meeting agreed that data from trials of pre-plant and pre-emergence application should be evaluated against any GAP available to the Meeting, regardless of the country or region; while data on trials of post-emergence application and harvest aid desiccation should be evaluated against GAP of the country in which the trials were conducted or of a neighbouring country.

As degradation of paraquat on the surface of crops appears to involve photolysis, residue levels are expected to be similar in all crops, justifying estimation of group MRLs for paraquat.

For estimating STMR from the results of two or more sets of trials with different LOQs in which no residues exceeding the LOQs are reported, the lowest LOQ should be used, as stated in the 2002 *FAO Manual*, unless the residue level can be assumed to be essentially zero. The size of the trial database supporting the lowest LOQ was taken into account in making decisions in these cases.

Since maximum residue levels were estimated for a number of vegetable groups in which the levels were below the LOQ, the Meeting decided to withdraw the previous recommendation for vegetables (except as otherwise listed) of 0.05 * mg/kg.

In Germany, information is required on the possible contamination of fruits that have fallen onto ground treated with pesticides. Therefore, tests were carried out on apples, stone fruits, grapes and olives to simulate the residue situation in fruit used for juice and other processed products. Nevertheless, direct consumption of fruit picked up from the ground is regarded as inappropriate.

*Citrus fruit*

Numerous supervised residue trials have been carried out over several seasons and in several locations on orange in Italy and in California and Florida, USA, and on lime, lemon and grapefruit in Florida.

Paraquat is registered for the control of weeds around the base of citrus fruit trees at a maximum rate of 1 kg ai/ha as an inter-row spray, with no PHI, in Italy and at a maximum rate of 1.14 kg ai/ha as a directed spray, with no PHI, in the USA. The residue levels of paraquat in whole mature *oranges* in trials in Italy and the USA were below the LOQs of 0.01, 0.02 or 0.05 mg/kg, even when paraquat was applied at twice or 30 times the maximum application rate, except in two trials. In one trial with an application rate of 2.44 kg ai/ha, mature fruit from one plot contained paraquat residues at a level of 0.01 mg/kg. In a trial with an application rate of 1.12 kg ai/ha, residue levels of 0.06 and 0.08 mg/kg were found in whole fruit. In this trial, however, the lower fruit-bearing branches were deliberately sprayed, the fruit fell onto sprayed weeds, and they were picked up from the ground within 3 days of spraying for analysis. Even though this represents the worst-case scenario, it does not reflect GAP in any country and is therefore inappropriate for use in estimating a maximum residue level. The residue levels in whole mature oranges in valid trials were, in ranked order: < 0.01 (15), 0.01, < 0.02 (two) and < 0.05 mg/kg (one).

In one trial in the USA, both juice and pulp were analysed for paraquat residues. Although the levels were below the LOQ of 0.01 mg/kg, the procedural recovery was too low for the results to be regarded as reliable.

In trials in the USA on *grapefruit*, *lemon* and *lime* in 1970 and 1972, with application rates reflecting GAP in the USA, the paraquat residue levels were < 0.01 (one) and < 0.05 mg/kg (three).

As the residue situation in oranges and other citrus fruits is similar and GAP is recommended for citrus fruits as a group in Italy and the USA, the Meeting considered it appropriate to establish a group maximum residue level for citrus fruits. The combined residue levels, in ranked order, were: < 0.01 (16), 0.01, < 0.02 (two) and < 0.05 (four) mg/kg. The Meeting estimated a maximum residue level of 0.02 mg/kg, an STMR of 0.01 mg/kg and a highest residue level of 0.02 mg/kg for paraquat in citrus fruits. The value of 0.02 mg/kg covers only the finite residue level found at 0.01 mg/kg.

*Pome fruit*

Trials were carried out on apples in Canada, Germany and the United Kingdom and on pears in Canada and Germany.

Paraquat is registered for use to control weeds around the base of pome fruit trees at a maximum rate of 0.66 kg ai/ha with one application and no PHI in the United Kingdom and at a maximum rate of 1.14 kg ai/ha with no PHI in the USA. No information on GAP was available for Canada or Germany, but the results of trials conducted in those countries were reviewed against the GAP of the USA and United Kingdom, respectively.

Trials on *apple* were conducted at rates of 1.12–4.48 kg ai/ha, and in one trial in the United Kingdom at a highly exaggerated rate of 12.3 kg ai/ha, about 20 times the maximum rate permitted in that country. In the latter trial, paraquat was applied directly to the bark of the trees to simulate worst-case conditions. In some cases, two applications were made, in the same or subsequent years. Apples were harvested 0–780 days after the last application. In trials on *pear*, paraquat was applied at rates of 1.0–4.48 kg ai/ha once or twice, and pears were harvested 0–77 days after the last application. Paraquat residue levels were below the LOQ of 0.01 mg/kg in all apples and pears taken from trees, even after treatment at rates as high as 20 times the maximum GAP rate.

In the trials in Germany, apples and pears taken from the trees were placed on the ground 6–7 days after application and collected about 7 days later for analysis. Residue levels of paraquat of 0.02–0.19 mg/kg were found in the apples, which could be attributed to the transfer of paraquat from the sprayed weed. The Meeting concluded that these data are not appropriate for use in estimating a maximum residue level.

As the residue situations in apples and pears are similar, and GAP is recommended for pome fruits or orchard fruits as a whole in all the countries that provided information on GAP, the Meeting considered it appropriate to establish a group maximum residue level for pome fruits. As the paraquat residue levels in all the valid trials were below the LOQ, even after application at exaggerated rates, the Meeting estimated a maximum residue level for pome fruits of 0.01* mg/kg, an STMR of 0 mg/kg and a highest residue level of 0 mg/kg.

*Stone fruit*

Trials were carried out on peaches, plums, apricots and cherries in Canada, Germany, the United Kingdom and the USA.

Paraquat is registered for use to control weeds around the base of stone fruit trees at a maximum rate of 0.66 kg ai/ha, with one application and no PHI for stone fruits in the United Kingdom and at a maximum rate of 1.14 kg ai/ha, with three applications and a 28-day PHI for stone fruits other than peaches in the USA; the PHI for use on peach trees in the USA is 14 days. No information on GAP was available from Canada or Germany, and the results of trials conducted in those countries were reviewed against the GAP of the USA and the United Kingdom, respectively.

The application rates in the supervised trials ranged from 0.22 to 4.48 kg ai/ha, applied to the base of the fruit trees up to three times in a season; the fruit was harvested from the trees 0–103 days after the last application. No residues of paraquat above the LOQ of 0.01 or 0.05 mg/kg were found in fruit harvested directly from the trees in any trial, even after spraying three times at a rate four times the maximum permitted rate. In most of the US trials, paraquat was applied one or two times instead of the maximum of three, but because of the higher application rates, the total amount applied was higher than the maximum allowed by GAP.

In trials on plums in the United Kingdom, paraquat was applied directly to suckers at rates of 0.22–1.34 kg ai/ha. No residues were found above the LOQ of 0.01 mg/kg in fruit harvested 21 or 55 days later.

In the trials in Germany, fruit were placed on sprayed weeds and collected for analysis about 1 week later. Small amounts of paraquat residues were found (0.02 and 0.04 mg/kg on peach, < 0.01 mg/kg on plum and 0.07 mg/kg on cherry) in the fruit samples, due to transfer from the sprayed weeds. As stone fruit intended for juice production is usually grown in orchards in which herbicides are rarely used, these data were not used for estimating a maximum residue level.

As the residue situations in stone fruits are similar and GAP is recommended for stone fruits or similar GAPs are established for peach and stone fruits excluding peach, the Meeting considered it appropriate to establish a group maximum residue level for stone fruits. As the paraquat residue levels were below the LOQ, even when applied at exaggerated rates and the methods of analysis in most of the trials had a LOQ of 0.01 mg/kg, the Meeting estimated a maximum residue level for stone fruits of 0.01* mg/kg and STMR and highest residue values of 0 mg/kg.

*Berries and small fruit*

*Grape*

Trials on residues in grapes have been conducted in Canada, Japan, Switzerland and the USA at rates of 0.3–4.4 kg ai/ha applied one to five times. Grapes were harvested from the vines at maturity 0–196 days after the last application. Four trials were conducted in Germany in which paraquat was applied between the rows of established vines at a rate of 1.0 kg ai/ha and grapes were sampled from the vines 0–14 days after application.

Paraquat is registered for weed control around grape vines at a maximum rate of 0.72 kg ai/ha, with five applications and a 30-day PHI in Japan and a maximum rate of 1.14 kg ai/ha, with the number of applications and the PHI unspecified in the USA. No information on GAP was available from Canada, Germany or Switzerland, but the results of trials in Canada were reviewed against US GAP.

In all trials in Canada, Japan and the USA reviewed against respective GAP, grapes obtained directly from the vine did not contain paraquat residues at levels above the LOQ of 0.01 or 0.02 mg/kg, even when applied at five times the recommended rate or with a shorter PHI.

In the German trials, bunches of grapes were also placed on the sprayed weed a few days after application and collected 7 days later for analysis. Small amounts of paraquat residues (0.04, 0.07, 0.09, 0.10, 0.13 and 0.17 mg/kg) were found in the grapes due to transfer from the sprayed weeds. When the fruits were sampled directly from the vine, the levels of residues were always below the LOQ of 0.01 mg/kg (six trials), which supports the results of the trials conducted in Canada, Japan and the USA.

The residue levels of paraquat in grapes in the trials that met the respective GAP or were conducted at higher rates were: < 0.01 (16), < 0.02 (three) and < 0.05 (two) mg/kg.

*Cane fruit*

Trials on residues were conducted in Canada on red and blackcurrants, blueberries, loganberries, gooseberries and raspberries at rates of application of paraquat of 0.56–2.24 kg ai/ha. Paraquat was applied once and the fruit was harvested 20–111 days after application.

GAP for cane fruit in the USA is a maximum rate of 1.14 kg ai/ha, with the number of applications and PHI unspecified.

Even at double the application rate, cane fruit did not contain paraquat residues at levels above the LOQ of 0.01 mg/kg. The residue levels in 25 trials following GAP or conducted at higher rates were < 0.01 mg/kg.

*Strawberry*

Supervised trials were conducted in France, Germany and the United Kingdom in which paraquat was used to control runners of strawberry plants at rates of 0.42–1.32 kg ai/ha once or twice. Berries were harvested 47–226 days after the last application. Three trials in Germany were conducted in plastic greenhouses.

GAP in the United Kingdom for strawberries is a maximum rate of 0.66 kg ai/ha, with one application and PHI unspecified.

The residue levels of paraquat in strawberries in trials following GAP or conducted at higher application rates were < 0.01 (six) and < 0.05 mg/kg.

As the samples analysed in all the trials except that in which grapes were kept and taken from the ground did not contain paraquat residues at levels above the LOQs and the application rate in the respective GAP is similar, the Meeting decided to propose a group maximum residue level for small fruits and berries. The residue levels in these fruits, in ranked order, were: <u>< 0.01</u> (47), < 0.02 (three) and < 0.05 mg/kg (three). The Meeting, considering that use of modern analytical methods would enable lower LOQs, agreed to disregard residue levels of < 0.05 mg/kg and < 0.02 mg/kg and estimated a maximum residue level of 0.01* mg/kg and STMR and highest residue values of 0 mg/kg.

*Olive*

Trials on residues in olives have been carried out in Greece, Italy, Spain and the USA (California).

Paraquat is registered for controlling weeds around the base of olive trees at a maximum rate of 1 kg ai/ha, with the number of applications unspecified and a 40-day PHI in Italy and at a maximum rate of 1.14 kg ai/ha, with four applications and a 13-day PHI in the USA. The results of trials conducted in Greece and Spain were reviewed against GAP in Italy.

In trials in Italy, paraquat was applied at rates of 0.54–1.8 kg ai/ha to the base of trees, and olives were harvested from the ground or trees 7–21 days after application. Although the delay was shorter than the recommended PHI of 40 days, the residue levels in the olives were < 0.05 and < 0.1 (two) mg/kg, indicating that at a PHI of 40 days the levels are likely to be < 0.1 mg/kg. No residues (< 0.05 mg/kg) of paraquat were detected in the oil from these fruits.

In one trial in the USA, paraquat was applied four times at an exaggerated rate (5.6 kg ai/ha; 22.4 kg/ha total) and the fruit was harvested from the trees 13 days later for analysis. The residue levels of paraquat were below the LOQ of 0.05 mg/kg, as were the levels in oil and cake prepared from the olives.

In six trials in Spain, olives were harvested from the ground 0, 1 and 7 days after application of paraquat at 0.60 kg ai/ha, simulating the worse-case scenario of collecting olives intended for oil production. In these trials, the application rate was 60% of the maximum allowed in Italy, but the olive fruit were harvested much earlier than the PHI of 40 days. The residue levels in whole fruit were 0.64–10 mg/kg, indicating that there had been transfer of paraquat from the sprayed weeds to the olives. In all the oil produced from these samples, however, the maximum residue levels of paraquat were 0.06 mg/kg, indicating that paraquat is not extracted into oil, as might be expected from its chemical nature.

In other trials in Spain, mature olives were sprayed directly on the ground with paraquat at rates of 0.36–1.3 kg/ha, and the fruit was analysed 3–17 days after application. The residue levels of paraquat in the olives were 0.08–4.4 mg/kg. Residues of paraquat did not transfer to extracted oil, and washing appeared to reduce the levels on the fruit.

In one trial in Greece, mature olives were sprayed directly with paraquat at a rate of 1.0 kg ai/ha to simulate direct spraying on fallen fruit in collection nets during weed control. No residues were found at levels above the LOQ (0.05 mg/kg) in oil extracted from treated fruit harvested 5 days after application.

Olives for oil production are often harvested from the ground and paraquat used for weed control may occasionally be applied directly to the fallen fruit on the ground. The whole fruit will contain some paraquat residue, either through transfer from treated vegetation or through direct spraying. Although the olives may contain relatively high levels of paraquat, no transfer of paraquat to oil occurs. This practice is not in compliance with GAP for olives.

The residue levels in olives taken directly from trees were: < 0.05 and < 0.10 mg/kg (two). In another trial, the level was < 0.05 mg/kg in olives taken from ground that had not been directly sprayed. The residue levels in one US trial conducted at five times the usual rate were below the LOQ of 0.05 mg/kg, indicating that when paraquat is applied in accordance with GAP no residues are expected to occur in olive fruit. The Meeting estimated a maximum residue level of 0.1 mg/kg to replace the previous recommendation for olive at 1 mg/kg. The Meeting also estimated an STMR of 0.05 mg/kg and a highest residue level of 0.1 mg/kg.

*Assorted tropical fruits minus inedible peel*

Trials on residues were carried out on *passion fruit* in Hawaii, USA, at an application rate of 1.12–4.48 kg ai/ha, to control weeds. Fruit was harvested 1–28 days after application. GAP in the USA for use on passion fruit is a maximum rate of 1.05 kg ai/ha, with an unspecified number of applications and PHI. The residue level in whole fruit in a trial complying with the maximum GAP was 0.13 mg/kg. After application at a rate higher than the maximum GAP, residue levels of up to 0.19 mg/kg were found in whole fruit. The levels in the edible pulp of all passion fruits analysed in the trials, regardless of PHI, ranged from < 0.01 to 0.02 mg/kg at 1.12 kg ai/ha and from < 0.01 to 0.06 mg/kg at higher rates. Higher levels were found in peel than in the edible portion.

Trials on residues were carried out on *kiwifruit* in California, USA, at an application rate of 0.56–2.24 kg ai/ha, three times, to control weeds. Fruit was harvested 7–14 days after the last application. The US GAP for kiwifruit is a maximum rate of 1.14 kg ai/ha, with the number of applications unspecified and a 14-day PHI. The residue level in kiwifruit in one trial conducted in accordance with the maximum US GAP was < 0.01 mg/kg. Even at a higher application rate or a shorter PHI, the levels were below the LOQ of 0.01 mg/kg.

Trials on *guava* were carried out in two locations in Hawaii, USA, with three different application rates of 1.12–4.48 kg ai/ha at each location. Fruit was harvested 1–28 days after application. The US GAP for guava is identical to that for passion fruit. The residue levels of paraquat in all edible pulp and peel analysed were below the LOQ of 0.01 mg/kg at the maximum GAP rate and at rates up to four times the maximum GAP. No residue was found at levels above the LOQ of 0.01 or 0.02 mg/kg in juice, discarded skin or seed obtained from guava treated at 1.12 or 4.48 kg/ha with a 6-day PHI. Although no information was available on residues in whole fruit, levels above the LOQ were not expected in whole fruit in view of the residue situation in pulp, peel and other fractions.

Trials were carried out on *banana* in Honduras, with three applications of paraquat at 1.4 kg ai/ha or a single application at double this rate, to control weeds in established plantations. Fruit was harvested 0–90 days after the last application. As no information was available on GAP in Honduras, the data were reviewed against GAP of the USA (maximum rate of 1.14 kg ai/ha). The residue levels of paraquat in flesh (0- and 3-day PHI) and whole fruit (≥ 7-day PHI) were below the LOQ (0.01 mg/kg) in three trials, except in skin from fruit harvested immediately after application.

Except in the trials on passion fruit, the residue levels in tropical fruits in 10 trials conducted according to the respective GAP were all below the LOQ (< 0.01 mg/kg). The Meeting estimated a maximum residue level for paraquat in assorted tropical fruits with inedible peel, excluding passion fruit, of 0.01* mg/kg. The Meeting decided to withdraw the previous recommendation for passion fruit.

The residue levels in edible portions of these fruit were below the LOQ: < 0.01 (11) mg/kg. The Meeting estimated STMR and highest residue values for paraquat in assorted tropical fruits minus inedible peel, excluding passion fruit, of 0.01mg/kg.

*Bulb vegetables*

Trials on residues were conducted on *onion* in Canada, Germany and the United Kingdom in the 1960s. Paraquat is registered in the USA for pre-plant or pre-emergence application to onion in a limited number of states at a maximum rate of 1.14 kg ai/ha, with one application and a 60-day PHI (200 days in California). Uses on bulb vegetables are not included in the label in the United Kingdom.

In one Canadian trial at twice the GAP rate and with a shorter PHI (36 days), the residue levels were below the LOQ of 0.01 mg/kg. In another Canadian trial at an application rate of 1.12 mg/kg, the levels were also < 0.01 mg/kg, but the PHI was 143 days.

Trials were conducted in Germany for post-emergence directed application and for harvest aid uses, but there was no related GAP.

In one trial conducted in the United Kingdom of pre-emergence application on spring onion, the residue level was 0.02 mg/kg, but the application rate was > 30% higher than the maximum rate allowed in the USA. A further trial on spring onion involved directed post-emergence application, for which no information on GAP was available.

The Meeting concluded that there were insufficient data to recommend a maximum residue level for paraquat in onion bulb or bulb vegetables.

*Brassica vegetables*

Residue trials were carried out on *broccoli* in Canada; *Brussels sprouts* in The Netherlands (harvest aid); *cabbage* in Canada, Japan, Spain and the USA; and *cauliflower* in Canada. Paraquat was applied once or twice at 0.67–2.2 kg ai/ha for inter-row weed control, and the crop was harvested 5–52 days after the last application.

Paraquat is registered for use in the cultivation of *Brassica* vegetables during seed-bed preparation as a pre-plant or pre-emergence treatment, or applied as a post-emergence directed or guarded spray for inter-row weed control. GAP in Japan is a maximum rate of 0.36 kg ai/ha, with three applications and a 30-day PHI, for broccoli, cabbage, cauliflower and Chinese cabbage as pre-plant inter-row applications. GAP in the USA is a maximum rate of 1.14 kg ai/ha, with the number of applications and PHI unspecified, for *Brassica* vegetables as pre-plant, pre-emergence treatment.

In trials conducted on broccoli, cabbage and cauliflower in Canada, the residue levels were below the LOQ of 0.01 mg/kg, even when applied at double the rate. The exception was one trial in Canada in which cabbage harvested 51 days after treatment at twice the rate contained a residue level of 0.06 mg/kg. The residue levels were < 0.01 (two) and 0.06 mg/kg.

In two trials conducted on cabbage in Japan, the residue levels were below the LOQ of 0.03 mg/kg even after application at a higher rate of 0.96 kg ai/ha and a shorter PHI of 5 days. At a highly exaggerated rate of 19.2 kg ai/ha but with only one application and a longer PHI of 52 days, the residue levels were also < 0.03 mg/kg.

No information was available on GAP that would allow evaluation of trials conducted in Spain.

Trials on Chinese cabbage were conducted in the USA in which paraquat was applied once as pre-emergence treatment at 1.05 kg ai/ha, followed by three post-emergence directed applications at 0.56 kg ai/ha. The residue levels were < 0.05 and 0.07 mg/kg. The US label allows only pre-plant and pre-emergence applications.

Trials on Brussels sprouts in The Netherlands involved a direct harvest aid application to the vegetable. In these trials, the unwashed vegetable contained a residue level of 7.3 mg/kg after 31 days, while washed vegetable had a reduced level of 1.6 after 31 days. Harvest aid desiccation was not, however, included in the labels provided to the Meeting.

The residue levels in these crops in trials that followed GAP and in trials that showed residue levels below the LOQ were, in ranked order: < 0.01 (two), $\underline{<0.03}$ (two) and 0.06 mg/kg. The Meeting concluded that there were insufficient data for estimating a maximum residue level for *Brassica* vegetables.

*Fruiting vegetables*

Numerous residue trials were carried out on tomatoes in Canada and the USA, on cucumbers, melons and summer squash in the USA and on peppers in Canada and the USA.

Paraquat is registered in the USA for use on tomatoes for pre-plant or pre-emergence application at a maximum rate of 1.14 kg ai/ha, with an unspecified number of applications and a 30-day PHI; on tomatoes for post-emergence directed spray at a maximum rate of 0.55 kg ai/ha, with an unspecified number of applications and a 30-day PHI; on peppers by directed spray application at a maximum rate of 0.55 kg ai/ha, with three applications and no PHI; and on other fruiting vegetables for pre-plant or pre-emergence application at a maximum rate of 1.14 kg ai/ha, with unspecified number of applications and PHI.

The trials in Canada on *tomatoes* were for pre-emergence or pre-planting weed control, in which paraquat was used at a low rate of 0.11 kg ai/ha. Trials on tomatoes in the USA involved post-emergence directed application at 0.56–2.24 kg/ha and an exaggerated single high pre-emergence application at a rate of 11.2 kg ai/ha or pre-emergence application of 1.12 kg ai/ha followed by three inter-row directed applications at 2.8 kg ai/ha. Although samples were harvested 21 days after treatment, 30% shorter than the PHI in US GAP of 30 days, the residue levels in tomatoes were below the LOQ of 0.01 mg/kg after application at 0.56 kg ai/ha for post-emergence directed application, except in one trial in which levels up to 0.04 mg/kg were found. After application at exaggerated rates, the residue levels were still below the LOQ of 0.005 or 0.01 mg/kg or at a maximum of 0.02 mg/kg.

The residue levels in trials following GAP or conducted at higher application rates were, in ranked order: < 0.005 (two), <u>< 0.01</u> (seven) and 0.04 mg/kg.

The trials on *sweet peppers* were for use of paraquat in inter-row weed control at 0.56–2.2 kg ai/ha. The residue levels in trials at maximum GAP were < 0.01 and 0.01 mg/kg. The levels after exaggerated application rates were either below the LOQ of 0.01 mg/kg, 0.03 mg/kg (once at 1.12 kg ai/ha pre- emergence and four times at 1.12 or 2.24 kg ai/ha post-emergence applications) or 0.02 mg/kg (one trial).

The Meeting considered it appropriate to evaluate residues in tomato and peppers together for estimating the maximum residue level for fruiting vegetables, other than cucurbits. The combined levels were: < 0.005 (two), <u>< 0.01</u> (eight), 0.01 and 0.04 mg/kg. The Meeting estimated a maximum residue level for fruiting vegetables, other than cucurbits, of 0.05 mg/kg, an STMR of 0.01 mg/kg and a highest residue level of 0.04 mg/kg.

In trials on *cucumbers*, *melons* and *summer squash* in California (USA), paraquat was applied at 1.12 kg ai/ha pre-emergence, followed by three inter-row applications at 0.56 kg ai/ha. While US GAP allows pre-emergence application at a maximum of 1.12 kg ai/ha, the residue levels of paraquat in all 12 trials were below the LOQ of 0.025 mg/kg. The Meeting estimated a maximum residue level for cucurbits of 0.02 mg/kg and STMR and highest residue values of 0 mg/kg.

### *Leafy vegetables*

Trials for residues were conducted on lettuce in Canada, Germany, Spain, the United Kingdom and the USA, on kale in France, Italy and the United Kingdom and on turnip greens in the USA.

Paraquat is registered for pre-emergence application on collard and lettuce in the USA at a maximum rate of 1.14 kg ai/ha, with the number of applications and PHI unspecified. Uses on leafy vegetables are not included on labels in Italy or the United Kingdom.

Trials on residues on *lettuce* were conducted in Canada, Germany, Spain, the United Kingdom and the USA at application rates of 0.42–2.24 kg/ha; lettuce was sampled 0–147 days after application. In trials conducted in Canada and the USA following US GAP, the residue levels in untrimmed head or bunch were 0.01, 0.04 and 0.05 mg/kg.

The results of trials in the United Kingdom were evaluated against US GAP, as the uses were similar in trials in the two countries. The residue levels in unwashed lettuce head in trials following US GAP were < 0.01, 0.01 and 0.02 mg/kg.

Residue levels up to 1.4 mg/kg were found in German trials on lettuce harvested immediately after one or two applications of paraquat for post-emergence inter-row weed control. The residues were believed to have derived from spray drift onto the outer leaves. In most of these trials, the whole lettuce head was analysed without removal of outer wrapper leaves that were yellow and withered. The residue levels had declined to close to the LOQ (< 0.01 mg/kg) by 21 days after harvest. The results of trials in Germany and Spain could not be evaluated as no information on GAP in Europe was available.

Residue trials on *kale* were carried out in France, Italy and the United Kingdom at rates of 1.0–2.24 kg/ha, and kale was sampled 0–147 days after application. As no information was available on GAP in Europe, these data were not evaluated.

Six trials on *turnip greens* were carried out in the USA at a rate of 1.12 kg/ha, with sampling 55–128 days after application. The levels of paraquat residue were < 0.025 (three), 0.03, 0.04 and 0.05 mg/kg.

As the US GAPs for collard and lettuce are identical and the residue situations for these crops were similar, the Meeting considered it appropriate to combine the results for estimating a maximum residue level for leafy vegetables. The combined residue results, in ranked order were: < 0.01, 0.01 (two), 0.02, <u>< 0.025</u> (three), 0.03, 0.04 (two) and 0.05 (two) mg/kg. The Meeting estimated a maximum residue level for paraquat in leafy vegetables of 0.07 mg/kg, an STMR of 0.025 mg/kg and a highest residue level of 0.05 mg/kg.

*Legume vegetables and pulses*

Residue trials were conducted on beans (with pod and dry) in Canada, Germany, Italy, The Netherlands and Spain, on broad beans in Spain, on peas in Australia, Canada and the USA, and on soya beans in Brazil and the USA.

Paraquat is registered for weed control and harvest aid on legume vegetables and pulses in Australia, Brazil and the USA as follows:

| Country | Maximum rate (kg ai/ha) | No. of applications | PHI (days) | Crop | Type of application |
|---|---|---|---|---|---|
| Australia | 0.2 | | 14 | Chickpea | Over-the-top spray |
| | 0.2 | | 14 | Field pea | Over-the-top spray |
| | 0.43 | | | Soya bean | Pre-plant |
| Brazil | 0.6 | 1 | 7 | Soya bean | Pre-plant |
| | 0.5 | 1 | 7 | Soya bean | Desiccation |
| USA | 1.14 | | – | Beans (lima, snap) | Pre-plant, pre-emergence |
| | 1.14 | | – | Pea | Pre-plant, pre-emergence |
| | 0.55 | 2 | 7 | Pulses | Harvest aid |
| | 1.14 | | – | Soya bean | Pre-plant or pre-emergence<br>Should not exceed 1.9 l per season |
| | 0.14 | 2 | – | Soya bean | Post-emgence directed spray<br>Second and final application 7–14 days later if needed |
| | 0.28 | | 15 | Soya bean | Harvest aid |

Uses on legumes and pulses were not included in the European labels provided to the current Meeting.

Residue trials were carried out on *dry beans* (genus *Phaseolus*) in Germany, Italy, The Netherlands and Spain, in which paraquat was used for pre-emergence weed control at single application of 0.56 or 2.24 kg ai/ha or post-emergence directed inter-row weeding at rates of 0.28–1.12 kg ai/ha. In trials in Europe, young pods were harvested 0–7 days after treatment and analysed. The residue levels in beans in pods were < 0.05–0.10 mg/kg (five trials). As no related GAP was available, these results were not used in estimating a maximum residue level. The Meeting concluded that there were insufficient data to estimate a maximum residue level for legume vegetables.

The residue levels of paraquat in dry beans in Canadian trials after pre-emergence application following GAP were < 0.01 (two), < 0.05 and 0.07 mg/kg.

Residue trials were conducted on *broad beans* in Spain after post-emergence directed spray. The residue levels in seeds harvested on the day of application were < 0.05 mg/kg (two); however, no information was available on related GAP.

Residue trials were carried out on *peas* in Canada and the United Kingdom with paraquat used for pre-emergence weed control at single applications or post-emergence directed inter-row weeding at rates of 0.14–1.68 kg ai/ha and harvesting 55–152 days after application. The residue levels of paraquat in seeds were below the LOQ of 0.01 or 0.05 mg/kg in trials with post-emergence application; however, no GAP was available for post-emergence application on peas.

Paraquat was applied at 0.20 or 1.12 kg ai/ha to field peas and chick peas as a harvest aid desiccant in Australia and the USA, with samples taken 1–38 days after application. The resulting residues of paraquat in seed in trials following GAP were found at levels of: 0.05, 0.15, 0.23, 0.25, 0.31 and 0.41 mg/kg.

A number of trials were conducted on *soya beans* in Brazil between 1981 and 1983 with a harvest aid desiccation application of paraquat at 0.25–0.80 kg/ha and sampling 2–21 days after application. The residue levels of paraquat in seed in trials following GAP in Brazil were: < 0.02, 0.03 (two), < 0.05 (two), 0.07, 0.08, 0.09, 0.10, 0.11 (two), 0.13, 0.16 (two) and 0.28 (three) mg/kg.

In trials conducted in the USA with pre-emergence application with or without a post-emergence directed application at 0.14–1.4 kg/ha, the residue levels of paraquat in soya beans harvested 3–147 days after the last application in trials following GAP were < 0.025 (nine) and 0.03 mg/kg.

Other trials were conduced in the USA on harvest aid desiccation application at 0.28 or 0.56 kg/ha and sampling 6–36 days after application. The residue levels of paraquat in seeds in trials following GAP were: < 0.01, 0.02 (four), 0.03 (two), 0.04 (two), 0.05, 0.06, 0.07, 0.08 (two), 0.09, 0.12 and 0.13 mg/kg. The hulls of treated soya beans contained higher residues than seeds.

The results of these trials clearly indicate that the levels of residues arising from harvest desiccant uses are higher than those from pre-emergence or post-emergence application.

The Meeting considered it appropriate to combine the results of trials on field peas and chick peas in Australia and on soya beans in Brazil and the USA in which paraquat was used as a harvest aid desiccant to estimate a group maximum residue level for pulses. The combined residue levels in seeds were, in ranked order: < 0.01 (two), < 0.02, 0.02 (four), 0.03 (four), 0.04 (two), < 0.05 (two), 0.05 (two), 0.06, 0.07 (two), 0.08 (three), 0.09 (two), <u>0.10</u>, 0.11 (two), 0.12, 0.13 (two), 0.15, 0.16 (two), 0.23, 0.25, 0.28 (three), 0.31 and 0.41 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg to replace the previous recommendation for soya bean and an STMR of 0.08 mg/kg and a highest residue level for pulses of 0.41 mg/kg.

*Root and tuber vegetables*

Paraquat is registered for use at a maximum rate of 0.36 kg ai/ha with three applications and a 30-day PHI in Japan for pre-plant, inter-row application on carrot and in the USA at a maximum rate of 1.14 kg ai/ha for pre-emergence treatment of root and tuber vegetables excluding potatoes.

Two residue trials carried out on *beetroot* in Canada and the United Kingdom for pre-emergence application in compliance with US GAP resulted in residue levels of < 0.01 and 0.03 mg/kg.

Residue trials were conducted in the United Kingdom on beetroot and *sugar-beet* in which paraquat was used pre-sowing or pre-emergence at 1.68 kg ai/ha, followed by two directed inter-row applications at

2.24 kg ai/ha after crop emergence. No information was available, however, on GAP for post-emergence application from Europe.

In trials conducted in four states of the USA with pre-emergence application at 1.12 kg ai/ha, the residue levels in sugar-beet roots harvested 136–178 days after application were < 0.05 mg/kg (six) after a single pre-emergence application at 1.12 kg ai/ha. After application at an exaggerated rate of 5.6 kg ai/ha, the residue levels in unwashed root were < 0.05 mg/kg.

Residue trials on *carrots* with use of paraquat for pre-emergence or inter-row weed control have been carried out in Canada, Japan, Germany and the United Kingdom. The residue levels of paraquat in carrot in the Japanese trials after both pre-emergence and inter-row applications were all below the LOQ of 0.03 mg/kg, despite a shorter PHI or use of a highly exaggerated rate of 19.2 kg ai/ha. The residue levels in carrot in four trials following GAP or conducted at higher rates or shorter PHI were < 0.03 mg/kg. In Canadian trials, the residue levels were below the LOQ of 0.01 mg/kg, even in one trial in which the rate was doubled and the PHI shorter.

As no information was available on GAP in Europe, the data from German trials with post-emergence application were not considered in estimating the maximum residue level.

Residue trials were carried out on *parsnips* and *swedes* in the United Kingdom and on *turnips* in Canada and United Kingdom with use of paraquat for pre-emergence weed control (Canada) or pre-emergence followed by inter-row weed control (United Kingdom). The rates of application were 0.56–2.24 kg ai/ha. Turnip, swede and parsnip roots were harvested 49–122 days after application. The residue levels of paraquat in turnips in two Canadian trials that followed US GAP were < 0.01 mg/kg. No information on GAP was available for post-emergence application in Europe.

One trial was conducted in France on *black salsify*, in which paraquat was applied as an inter-row treatment at 0.5 and 0.8 kg ai/ha. There were no residues (< 0.02 mg/kg) in salsify roots harvested 8 and 80 days after treatment; however, no information on GAP was available.

The combined residue levels in beetroot, sugar-beet, carrots and turnips were, in ranked order: < 0.01 (four), < 0.03 (four), 0.03 (two) and < 0.05 (six) mg/kg.

*Potato*

Trials were carried out on potatoes in Canada, Germany, the United Kingdom and the USA for pre-emergence, post-emergence and harvest aid applications of paraquat.

Paraquat is registered in the United Kingdom for pre-emergence use at a maximum rate of 0.66 kg ai/ha with one application. It is registered in the USA for pre-plant and pre-emergence broadcast application at a maximum rate of 0.55 kg ai/ha and for broadcast application for pre-harvest vine killing and weed dessication at a maximum rate of 0.42 kg ai/ha with a 3-day PHI. The latter application is restricted to fresh market produce, with a restriction of 2.3 l/ha per season; split applications must be applied a minimum of 5 days apart.

Trials were carried out in Germany with post-emergence directed application. The residue levels were below the LOQ of 0.01 mg/kg.

Several residue trials were carried out in Canada and the USA in which paraquat was applied for weed control by pre-emergence or post-crop emergence application at a rate of 0.20–1.12 kg ai/ha. The residue levels in the tubers in trials following US GAP were < 0.01 (eight) and 0.02 mg/kg. At double the application rate, the residue levels were below the LOQ of 0.01 mg/kg.

Trials were also carried out on harvest aid desiccant use in Canada, the United Kingdom and the USA. The US label allows use of paraquat for vine killing and weed desiccation at a maximum of 0.42 kg ai/ha, with a PHI of 3 days, but in these trials rates equivalent to or higher than twice the maximum rate or a much longer PHI were used. Harvest aid use is not included in the United Kingdom label.

The residue levels in trials of pre- and post-emergence application were < 0.01 (eight) and 0.02 mg/kg. The levels in trials with double the application rate in the USA and in trials conducted in Germany were all below the LOQ.

The Meeting decided to combine the results from trials on beetroot, sugar-beet, carrot, turnip and potato. The combined residue levels, in ranked order, were: < 0.01 (12), 0.02, < 0.03 (four), 0.03 (two) and < 0.05 (six) mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg, an STMR of 0.02 mg/kg and a highest residue level of 0.05 mg/kg for root and tuber vegetables. The maximum residue level replaces the previous recommendation for potato.

*Stem vegetables*

Residue trials have been carried out on asparagus, celery and globe artichokes in Canada and the USA with use of paraquat for post-emergence directed inter-row weeding at rates of 1.12–3.25 kg ai/ha in a single application. Three applications of 1.12 or 1.35 kg/ha on artichokes were also tested.

Paraquat is registered in the USA for *asparagus* at a maximum rate of 1.14 kg ai/ha for pre-plant and pre-emergence broadcast or banded over-row application and at the same maximum rate with a 6-day PHI for asparagus more than 2 years old by broadcast or banded over-row application. The residue levels were < 0.02 (two) and < 0.05 mg/kg.

Although trials were conducted on *celery* in Canada and on *artichoke* in the USA, no information on GAP for these crops was available. The Meeting concluded that the data were insufficient for estimating a maximum residue level for asparagus.

*Cereal grains*

*Maize*

Residue trials were conducted on maize in Canada, Italy, the United Kingdom and the USA with pre- and post-emergence applications and harvest aid uses.

Paraquat is registered for use in the USA at a maximum rate of 1.14 kg ai/ha for pre-plant or pre-emergence broadcast of banded over-row applications and at a maximum rate of 0.55 kg ai/ha for post-emergence directed spray. Residue trials were conducted with use of paraquat for pre-emergence weed control or for post-emergence directed spray in Canada and the USA at rates of 0.28–1.12 kg ai/ha.

In a series of trials in the USA in 1987, one pre-emergence application at 1.12 kg ai/ha and two post-emergence applications at 0.31 kg ai/ha were made. Although the post-emergence application rate was not as high as the maximum rate, the pre-emergence application rate was the maximum allowed for pre-emergence application. The Meeting considered that these trials were conducted in accordance with US GAP. The residue levels in trials in Canada and the USA conducted in accordance with US GAP were: < 0.01 (eight) and < 0.025 mg/kg (16). In trials with higher application rates (up to four times), the residue levels were below the LOQ. The levels in maize cobs were also below the LOQ of 0.01 mg/kg (two trials).

In two residue trials in Italy, paraquat was applied pre-emergence at 0.92 kg ai/ha. The residue levels in cob were < 0.05 mg/kg; however, no analysis of kernels or grain was reported.

Trials were conducted in South Africa and the United Kingdom with post-emergence application; however, owing to the lack of relevant GAP for South Africa and the fact that post-emergence application is not included on the label in the United Kingdom, the results of these trials could not be evaluated by the Meeting.

Several trials were conducted in the USA on use of paraquat as a harvest aid desiccator at rates of 0.56–1.12 kg/ha. This use is not included in US GAP, although it is allowed in Argentina, Brazil and Uruguay.

On the basis of the residue levels in maize grain in trials with paraquat applied pre- or post-emergence in Canada and the USA, < 0.01 (eight) and < 0.025 mg/kg (16), the Meeting estimated a maximum residue level of 0.03 mg/kg to replace the previous recommendation for maize and STMR and highest residue values of 0.025 mg/kg.

*Sorghum*

A number of residue trials were conducted in the USA, where paraquat is registered for use on sorghum at a maximum rate of 1.14 kg ai/ha, with a PHI of 48 days for grain and 20 days for forage, for pre-plant or pre-emergence broadcast application, and at a maximum rate of 0.55 kg ai/ha in two applications with the same PHIs for post-emergence directed spray. In the latter application, the applications must not exceed 2.5 l per season.

Several residue trials were carried out in the USA in several years and locations, in which paraquat was applied for weed control, either pre-emergence, post-crop emergence directed or as a harvest aid, at rates of 0.21–7.8 kg ai/ha. Samples were taken 20–131 days after pre-emergence or post-emergence directed application. The residue levels in grain in 12 trials conducted in accordance with maximum GAP for pre-emergence or post-emergence applications were all ≤ 0.025 mg/kg. When both pre- and post-emergence applications were made, if the post-application rate was in compliance with GAP, the residue results were taken into consideration in estimating the maximum residue level. In one trial with one pre-emergence application at 0.56 kg ai/ha followed by a post-emergence application at 0.56 kg ai/ha, a residue level of 0.01 mg/kg was found.

In harvest aid desiccation applications, paraquat was applied at a rate of 0.21–2.8 kg/ha, and sorghum was sampled 7–49 days after application. Harvest aid desiccant use is not included on the US label.

The Meeting estimated a maximum residue level of 0.03 mg/kg to replace the previous recommendation and STMR and highest residue values of 0.025 mg/kg for sorghum.

*Rice*

Trials on residues of paraquat on rice were conducted in Guatemala, Italy and the USA. Paraquat is registered for use on rice in the USA by pre-plant or pre-emergence broadcast at a maximum rate of 1.14 kg ai/ha, with no PHI specified.

Two trials were conducted in Italy in 1993, in which paraquat was applied at a rate of 0.92 kg ai/ha to the seed bed 5 days before rice was sown. Rice grain and straw samples taken at harvest did not contain residues of paraquat at levels above the LOQ of 0.05 mg/kg.

Three residue trials were conducted in Guatemala in 1983 in which paraquat was applied as a pre-emergence treatment at rates of 0.30 and 1.0 kg ai/ha to rice. Rice grain and straw samples were taken at harvest. The residues in de-husked rice in one trial conducted in compliance with the maximum rate in US GAP were < 0.05 mg/kg, but residues in rice grain were not analysed.

Residue trials were conducted in the USA in 1978 and 1982 in which paraquat was applied as a pre-emergence treatment at rates of 0.56 and 1.12 kg ai/ha to rice. In trials conducted at the maximum GAP, the residue levels in rice grain were below the LOQ of 0.01 (two) or 0.02 mg/kg. No trials were conducted at rates higher than the maximum allowed in US GAP for rice.

The Meeting concluded that there were insufficient data to estimate a maximum residue level and withdrew the previous recommendation for rice and rice, polished.

*Tree nuts*

It is common practice to harvest nuts from the ground, and this may result in residues of paraquat in the nuts.

Supervised residue trials were carried out over a number of years in Italy on *hazelnuts* and in the USA on *almonds* (California), *macadamia nuts* (Hawaii), *pecans* (Alabama and Texas), *pistachio nuts* (California) and *walnuts* (California).

Paraquat is registered for use on hazelnuts in Italy at a maximum rate of 1 kg ai/ha with a 40-day PHI and on walnuts at the same maximum rate but with no PHI specified. In the USA, paraquat is registered for use on pistachio nuts at a maximum rate of 1.14 kg ai/ha with a 7-day PHI, with the proviso that no more than two applications should be made after the nuts have split. It is registered for use in the USA on other tree nuts at the same maximum rate with no specification of the number of applications or PHI.

Two trials were conducted in Italy in which hazelnuts were harvested from the ground 1–10 days after treatment around the base of the trees at rates of 0.54–1.8 kg ai/ha. Although the PHI was shorter than 40 days, the residue levels in shelled nuts were below the LOQ of 0.05 mg/kg in one trial. At almost twice the maximum application rate and with a shorter PHI of 10 days, the levels were still below the LOQ.

In a trial in the USA, paraquat was applied at rates of 0.56–4.5 kg ai/ha one to eight times, to control weeds under mature nut trees. In some cases, applications were made over 2 years. Nuts were harvested, in some cases immature, 1–171 days after the last application. The residue levels in shelled nuts in trials following GAP were: < 0.01 (seven), 0.01, 0.02 and < 0.05 (three) mg/kg.

The combined results of all the trials, in ranked order, were: <u>< 0.01</u> (seven), 0.01, 0.02 and < 0.05 (four) mg/kg. The Meeting estimated a maximum residue level for paraquat in tree nuts of 0.05 mg/kg, an STMR of 0.01 mg/kg and a highest residue level of 0.05 mg/kg.

*Oil seeds*

*Cotton-seed*

Paraquat is registered for use on cotton in the USA at a maximum rate of 1.14 kg ai/ha, with no specification of the number of applications of PHI, for pre-plant or pre-emergence treatment, and at a maximum rate of 0.55 kg ai/ha, with repeated application if necessary and a 3-day PHI as a harvest aid, with the proviso that a total of 1.5 l should not be exceeded in this use.

Residue trials were conducted in the USA over several years and locations, involving pre-emergence applications at 1.12 kg/ha and harvesting 4–176 days after application. The residue levels in fuzzy seed in trials at the maximum GAP were < 0.01 (four) and 0.04 mg/kg.

In numerous trials with pre-emergence application followed by harvest aid desiccation application or a single application as harvest aid desiccant, the residue levels of paraquat in fuzzy seed in trials following maximum GAP were: 0.07, 0.09, 0.15, 0.16 (two), 0.18, 0.21, 0.23, 0.30, <u>0.34</u>, 0.35, 0.38, 0.44, 0.46, 0.49, 0.50, 0.58 and 2.0 mg/kg. On the basis of residue levels arising from harvest aid uses, the Meeting estimated a maximum residue level for cotton-seed of 2 mg/kg, to replace the previous recommendation, an STMR of 0.34 mg/kg and a highest residue level of 2 mg/kg.

*Sunflower seed*

In the USA, paraquat is registered for use on sunflower at a maximum rate of 1.14 kg ai/ha with no PHI specified for pre-plant or pre-emergence broadcast or banded over-row application and at a maximum rate of 0.55 kg ai/ha with a 7-day PHI for dessication use.

Trials were conducted with pre-emergence application to sunflowers at 1.12 or 5.6 kg/ha and sampling 41–131 days after application. The residue levels in seeds in four trials conducted in compliance with maximum GAP were < 0.05 mg/kg. When paraquat was applied at five times the maximum recommended rate, the levels were still below the LOQ of 0.05 mg/kg.

In further trials, paraquat was applied as a harvest aid desiccator at 0.28–1.12 kg/ha, and sunflower seeds were harvested 7–21 days after application. The residue levels of paraquat in seeds in trials conducted at maximum GAP were: 0.09, 0.14, 0.15, 0.16 (three), 0.19, <u>0.22</u>, 0.24, 0.32, 0.35, 0.51, 0.60, 0.74, 0.81

(two) and 0.93 mg/kg. The Meeting used the residue levels arising from harvest aid uses to estimate a maximum residue level for sunflower seed of 2 mg/kg, an STMR of 0.22 mg/kg and a highest residue level of 0.81 mg/kg.

*Hops*

Residue trials were conducted in Canada and the USA. Paraquat was registered in the USA for use as a directed spray or for suckering and stripping on hops at a maximum rate of 0.55 kg ai/ha in three applications with a 14-day PHI; no more than two applications or applications at no more than 1.5 l/ha were recommended.

In a trial in Canada, a single post-emergence directed application of 1.12 kg ai/ha, which is double the maximum recommended dose, resulted in residue levels of < 0.01 mg/kg in green hops harvested 53 days after application.

In the USA, trials were conducted in the states of Idaho, Oregon and Washington with three post-emergence directed applications of paraquat at 2.8 kg ai/ha. The residue levels of paraquat in dried hops prepared from hops harvested 14 days after the last of three directed application at the maximum GAP rate were 0.05 mg/kg in two trials. At double this rate, the levels in dried hops prepared from green hops harvested 13 or 14 days after the last treatment were below the LOQ of 0.1 mg/kg (0.01 and 0.07 mg/kg). Two applications at higher rates than that of maximum GAP resulted in 0.02 and 0.03 mg/kg in dried hops.

The residue levels in dried hops were 0.05 mg/kg (two). In view of the low levels of residues in the other trials, the Meeting estimated a maximum residue level of 0.1 mg/kg, to replace the previous recommendation, and STMR and highest residue values of 0.05 mg/kg for hops, dry.

*Tea, green, black*

Residue trials on tea were conducted in India, where paraquat is registered for use for pre-emergence or post-emergence directed application between rows at a maximum rate of 0.75 kg ai/ha in one application, with no PHI specified.

Six trials were conducted at a total application rate of 0.57–2.0 kg ai/ha over 5–6 months. Green tea leaves were harvested 7 or 21 days after blanket application (after the first or last spot application) and processed into black tea, which was analysed. The residue levels of paraquat in black tea from tea plants treated in accordance with GAP in India or at higher rates were almost always below the LOQ of 0.05 mg/kg. In trials conducted in accordance with GAP, the levels in black tea were: < 0.05 (three), 0.07, 0.09 and 0.12 mg/kg.

In other trials in India, with application rates of 0.05–0.06 kg ai/ha, black tea samples from green tea leaves harvested 5 or 7 days after application contained 0.05 mg/kg (one) or < 0.05 mg/kg. As the application rate was much lower than the maximum, these results were not considered in estimating the maximum residue level.

The Meeting estimated a maximum residue level for teas, green, black of 0.2 mg/kg and an STMR of 0.06 mg/kg.

*Animal feedstuffs*

*Soya forage and hay or fodder*

Paraquat is registered for use in Australia, Brazil and the USA for weed control andas a harvest aid on soya beans. In the USA, it is registered for use at a maximum rate of 1.14 kg ai/ha for pre-plant or pre-emergence treatment, not to exceed 1.9 l per season, at a maximum rate of 0.14 kg ai/ha as a post-emergence directed spray with a second and final application 7–14 days later; it can also be used at a maximum rate of 0.28 kg ai/ha with a 15-day PHI as a harvest aid.

The residue levels in forage in trials conducted in the USA in accordance with US GAP were: < 0.025 (12), <u>< 0.05</u> (13), 0.05, 0.06 (four), 0.07, 0.08, 0.15, 0.28 and 1.8 mg/kg, expressed on a dry weight basis.

The Meeting estimated a maximum residue level for soya bean forage (green) of 2 mg/kg, an STMR of 0.05 mg/kg and a highest residue level of 1.8 mg/kg.

The residue levels in hay or fodder in trials conducted in accordance with US GAP were: < 0.025 (five), 0.04, <u>< 0.05</u> (four), 0.05, 0.1, 0.2 and 0.3 mg/kg, on a dry weight basis. The Meeting estimated a maximum residue level for soya bean fodder of 0.5 mg/kg, an STMR of 0.05 mg/kg and a highest residue level of 0.3 mg/kg.

*Sugar-beet tops*

Trials were conducted on beet and sugar-beet in the United Kingdom and the USA. The residue levels in sugar-beet tops in six trials conducted in accordance with US GAP were < 0.025 mg/kg, on a fresh weight basis. The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.11 mg/kg. On the basis of 23% dry matter and a highest residue level on a fresh weight basis of 0.025 mg/kg, the Meeting calculated the highest residue level on a dry weight basis to be 0.11 mg/kg. As there is no code for sugar-beet tops, the maximum residue level was recommended for fodder beet leaves and tops.

*Maize forage and fodder*

Trials were conducted in Italy and the USA. The residue levels in maize forage in trials in the USA conducted in accordance with US GAP were <u>< 0.025</u> (eight), 0.09, 0.6, 2 (two) and 3 (two) mg/kg on a dry weight basis. The Meeting estimated a maximum residue level for maize forage of 5 mg/kg, an STMR of 0.025 mg/kg and a highest residue level of 3 mg/kg.

The levels of residues in silage were mostly below the LOQ of 0.025 or 0.05 mg/kg, except in one trial in which levels up to 0.04 mg/kg were found.

The residue levels in maize fodder in trials in the USA conducted in accordance with US GAP were: <u>< 0.025</u> (eight), 0.03, 0.05, 0.06, 0.2, 1, 2 and 6 mg/kg on a dry weight basis. The Meeting estimated a maximum residue level for maize fodder of 10 mg/kg, an STMR of 0.025 mg/kg and a highest residue level of 6 mg/kg.

*Sorghum forage (green) and straw and fodder, dry*

In trials conducted in the USA in accordance with GAP, the residue levels in sorghum forage were: <u>< 0.025</u> (six), <u>0.025</u> (three), 0.04, 0.06 and 0.2 mg/kg. The Meeting estimated a maximum residue level for sorghum forage (green) of 0.3 mg/kg, an STMR of 0.025 mg/kg and a highest residue level of 0.2 mg/kg.

The residue levels in sorghum fodder or hay (whichever gave higher levels) in trials conducted in accordance with GAP were: < 0.025 (four), <u>0.03</u>, <u>0.04</u>, 0.05, 0.06 (two), 0.09, 0.1 and 0.2 mg/kg. The Meeting estimated a maximum residue level for sorghum straw and fodder, dry, of 0.3 mg/kg, an STMR of 0.035 mg/kg and a highest residue level of 0.2 mg/kg.

*Rice straw and fodder, dry*

The Meeting concluded that there were insufficient data for estimating a maximum residue level for rice straw and fodder, dry.

*Almond hulls*

In three trials conducted in the USA in accordance with GAP, the residue levels in almond hulls were < 0.01 mg/kg. The Meeting estimated maximum residue, STMR and highest residue values of 0.01 mg/kg.

*Cotton fodder*

The Meeting concluded that there were insufficient data for estimating a maximum residue level for cotton fodder.

***Fate of residues during processing***

Numerous studies of residue levels after processing conducted in conjunction with supervised trials were submitted. Residue levels found after processing of raw agricultural commodities into animal feedstuffs are described in the section above. Some processed commodities for which maximum residue levels and STMR-Ps were estimated are also described in that section.

In this section, processing factors from raw commodities to processed food products and by-products are discussed. Information on processing was provided for orange, plum, grape, olive, tomato, sugar-beet, maize, sorghum, cotton-seed, sunflower seed and hop. Processing factors could not be reliably calculated for the processing of orange, plum, grape, tomato and sugar-beet because the paraquat residue levels in both raw commodities and processed products were all below the respective LOQs.

Processing factors were calculated for olive (oil), potato (crisps and granules), maize (milling fractions and oil), sorghum (milling fractions), cotton-seed (trash, gin products and oil), sunflower seed (oil) and hop (dried hop and beer) and are shown below.

| Commodity | Processing factor | STMR-P (mg/kg) |
|---|---|---|
| Olive | | 0.05 |
| Unwashed olives before processing | 0.57 | |
| Washed olives before processing | < 0.43 | |
| Virgin oil | < 0.35 | 0.018 |
| Refined oil | < 0.35 | 0.018 |
| Potato | | 0.02 |
| Wet peel | > 1.9 | 0.04 |
| Dry peel | > 11 | 0.22 |
| Peeled potato | 0.27[a] | 0.01 |
| Crisps | > 0.95 | 0.02 |
| Granules | > 2.7 | 0.05 |
| Maize | | 0.025 |
| Wet milling | | |
| Coarse starch | < 0.25[a] | 0.006 |
| Starch | < 0.25[a] | 0.006 |
| Crude oil | < 0.25[a] | 0.006 |
| Refined oil | < 0.25[a] | 0.006 |
| Dry milling | | |
| Germ | 0.3[a] | 0.0075 |
| Grits | 0.25–0.5[a] | 0.0006–0.013 |
| Coarse meal | 1[a] | 0.025 |
| Meal | 0.5[a] | 0.013 |
| Flour | 1.5[a] | 0.038 |
| Crude oil | < 0.25[a] | 0.006 |
| Refined oil | < 0.05[a] | 0.001 |
| Sorghum | | 0.025 |

| Commodity | Processing factor | STMR-P (mg/kg) |
|---|---|---|
| Hulled grain | 0.07[a] | 0.002 |
| Dry milled bran | 3.9 | 0.097 |
| Coarse grits | 0.17 | 0.004 |
| Flour | 0.14 | 0.004 |
| Wet milled bran | 2.3 | 0.058 |
| Starch | 0.07 | 0.002 |
| Shorts | 2.6 | 0.065 |
| Germ | 0.52[a] | 0.013 |
| Cotton (from cotton including trash and bolls) | | |
| Fuzzy seed | 0.08 | 0.34 |
| Crude oil | < 0.006 | 0.01[b] |
| Meal | < 0.009 | 0.04 |
| Sunflower seed | | 0.3 |
| Hulls | 2.8[a] | 0.64 |
| Meal | 0.05[a] | 0.01 |
| Oil | < 0.05[a] | 0 [b] |
| Hop | | |
| Dry cones | 1.2 | 0.05 [b] |
| Beer | < 0.28 | 0.0001[c] |

[a] Based on only one trial.
[b] Estimated from supervised trials
[c] Calculated from a factor of 0.0001

The STMR values for processed products from raw commodities with no residues or for which the results of many supervised trials were available were estimated on the basis of supervised trials.

In four trials in the USA, orange fruit was processed into juice, and the paraquat residues were measured; in all cases, the levels were below the LOQ of 0.01 mg/kg. The residue levels in *orange juice*, including those in trials conducted at rates higher than the maximum application rate, were all below the LOQ of 0.01 mg/kg. The Meeting estimated an STMR-P for orange juice of 0 mg/kg.

No residues of paraquat were found at levels above the LOQ of 0.05 mg/kg in *dried prunes* prepared from plums in two trials. The STMR-P for dried prunes was estimated to be 0 mg/kg.

In a number of trials, olives were processed into oil for analysis of residues. *Olive oil* prepared from olive fruits harvested directly from trees did not contain levels above the LOQ of 0.05 mg/kg. Most samples of olive oil prepared from olive fruits picked up from ground or sprayed directly did not contain paraquat residues at levels above the LOQ; however, in some samples, paraquat residues were found at levels up to 0.06 mg/kg, and fruit harvested at the same time contained 6.8 mg/kg of paraquat residues. As paraquat is unlikely to be transferred into oil owing to its chemical and physical characteristics, its STMR-P is calculated from the processing factor to be 0.018 mg/kg.

*Tomato juice* and *ketchup* prepared from tomato in trials conducted at an exaggerated rate did not contain paraquat residues at levels above the respective LOQ (0.005 mg/kg for juice and 0.025 mg/kg for ketchup). The STMR values for these products were estimated to be 0 mg/kg.

The residue levels in oil prepared from soya bean treated with paraquat as a harvest aid desiccant in accordance with GAP were below the LOQ of 0.01 mg/kg in five trials. The Meeting estimated an STMR-P for *soya bean oil* of 0.01 mg/kg.

The residue levels in cotton-seed oil, crude, were below the LOQ of 0.01 mg/kg in two trials. The Meeting estimated an STMR-P for *cotton-seed oil* of 0.01 mg/kg and decided to withdraw the previous recommendation for cotton-seed oil, edible.

The residue levels in *sunflower seed oil* obtained from sunflower seed in eight trials conducted at the maximum GAP were < 0.01 mg/kg. Oil obtained from sunflower seed in a trial at double the rate did not contain residues at levels above the LOQ of 0.01 mg/kg. The Meeting estimated an STMR-P for sunflower seed oil of 0 mg/kg and decided to withdraw the previous recommendation for sunflower seed oil, crude and edible.

The residue levels of paraquat in *cotton gin by-product* in trials for harvest aid uses were (including results for cotton harvested 13–17 days after treatment): 5.2, 5.3, 5.9, 6.2, 7.3, 8.0, 9.4, 11, 12 (two), 18, 23, 32, 34 and 69 mg/kg. The Meeting estimated an STMR-P of 10.2 mg/kg for cotton gin by-products.

As *maize flour* contained a higher concentration of paraquat residues than maize grain in one trial, the Meeting estimated a maximum residue level of 0.05 mg/kg.

### ***Residues in animal commodities***

*Dietary burden of farm animals*

The Meeting estimated the dietary burden of paraquat residues for farm animals on the basis of the diets described in Appendix IX to the *FAO Manual* (FAO, 2002), by summing the contribution of each feed to the residue.

*Estimated maximum dietary burden of farm animals*

| Crop | Residue (mg/kg) | Basis | Group | Dry matter (%) | Residue/ Dry matter (mg/kg) | Dietary content (mg/kg) | | | Residue contribution (mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Beef cattle | Dairy cows | Poultry | Beef cattle | Dairy cows | Poultry |
| Sugar-beet tops | 0.025 | HR | AV | 23 | 0.11 | | | | | | |
| Cotton-seed | 2 | HR | SO | 88 | 2.27 | 25 | 25 | | 0.57 | 0.57 | |
| Cotton gin by-product | 10.2 | STMR-P | | 90 | 11.3 | 20 | 20 | | 2.27 | 2.27 | |
| Maize grain | 0.025 | HR | GC | 88 | 0.03 | | | 80 | | | 0.023 |
| Maize forage | 3 | HR | AF | | 3 | 40 | 50 | | 1.2 | 1.5 | – |
| Potato, wet peel | 0.04 | STMR-P | VR | 15 | 0.27 | | | | | | |
| Sorghum grain | 0.025 | HR | GC | 86 | 0.03 | | | | – | | – |
| Sorgum forage | 0.2 | HR | AF | – | 0.20 | | | | – | | – |
| Soya bean | 0.41 | HR | VD | 89 | 0.46 | | | 20 | | | 0.092 |
| Soya bean, forage | 1.8 | HR | AL | – | 1.8 | 15 | 5 | | 0.27 | 0.09 | – |
| Soya bean, hay | 0.3 | HR | AL | – | 0.3 | | | | – | | – |
| Sunflower meal | 0.011 | STMR-P | AL | 92 | 0.01 | – | – | – | – | – | – |
| Turnip tops | 0.05 | HR | VL | 30 | 0.17 | | | | | | |
| Total | | | | | | | | | 4.30 | 4.43 | 0.11 |

*Estimated maximum dietary burden of farm animals*

| Crop | Residue (mg/kg) | Basis | Group | Dry matter (%) | Residue/ Dry matter (mg/kg) | Dietary content (mg/kg) | | | Residue contribution (mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Beef cattle | Dairy cows | Poultry | Beef cattle | Dairy cows | Poultry |
| Sugar-beet tops | 0.025 | STMR | AV | 23 | 0.11 | | | | | | – |
| Cotton-seed | 0.34 | STMR | SO | 88 | 0.39 | 25 | 25 | | 0.098 | 0.098 | |
| Cotton gin by-product | 10.2 | STMR-P | | 90 | 11.3 | 20 | 20 | | 2.27 | 2.27 | |
| Maize grain | 0.025 | STMR | GC | 88 | 0.028 | | | 80 | | | 0.02 |
| Maize forage | 0.025 | STMR | AF | | 0.03 | 40 | 50 | | 0.010 | 0.013 | – |
| Potato wet peel | 0.55 | STMR-P | VR | 15 | 0.27 | | | | | | |
| Sorghum grain | 0.025 | STMR | GC | 86 | 0.03 | | | | – | | – |
| Sorgum forage | 0.025 | STMR | AF | | 0.03 | | | | – | | – |
| Soya bean | 0.08 | STMR | VD | 89 | 0.09 | | | 20 | | | 0.02 |
| Soya bean, forage | 0.05 | STMR | AL | | 0.05 | 15 | 5 | | 0.008 | 0.003 | – |
| Soya bean, hay | 0.05 | STMR | AL | | 0.05 | | | | – | | – |
| Sunflower meal | 0.011 | STMR-P | AL | 92 | 0.01 | – | – | – | – | | – |
| Turnip tops | 0.025 | STMR | VL | 30 | 0.08 | | | | | | |
| Total | | | | | | | | | 2.39 | 2.38 | 0.04 |

The dietary burdens of paraquat for estimation of MRL and STMR values for animal commodities are: beef cattle, 4.30 and 2.39 ppm; dairy cattle, 4.43 and 2.38 ppm; and poultry, 0.11 and 0.04 ppm.

*Feeding studies*

In a study of metabolism in goats (see above), one goat was dosed at a rate equivalent to 100 mg/kg of total diet. This is considerably higher than the estimated maximum dietary burden for cattle of 4.30 or 4.43 mg/kg. At 100 mg/kg of diet, the maximum TRRs, expressed in paraquat ion equivalents, found in milk and edible goat tissues were 0.009 mg/kg in milk, 0.12 mg/kg in meat, 0.03 mg/kg in fat, 0.56 mg/kg in liver and 0.74 mg/kg in kidney. In milk, 75.9% of the radiolabel was identified with paraquat.

At the estimated maximum animal burden of 4.30 or 4.43 mg/kg, the levels of paraquat residues were calculated to be < 0.005 mg/kg in milk, 0.005 mg/kg in meat, 0.025 mg/kg in liver and 0.033 mg/kg in kidney. The Meeting estimated maximum residue levels of 0.005* mg/kg for milks, 0.005 mg/kg for mammalian meat and 0.05 mg/kg for edible mammalian offal. These levels replace the previous recommendations for related animal commodities. The STMR values were estimated to be 0.00002 mg/kg for milk, 0.0003 mg/kg for meat and 0.0018 mg/kg for edible offal; and the highest residue level values were estimated to be 0.005 mg/kg for meat and 0.033 mg/kg for edible offal.

In the study of metabolism in hens (see above), birds were dosed at a rate equivalent to 30 mg/kg of total diet, which is considerably higher than the estimated maximum dietary burden for poultry of 0.11 mg/kg. At 30 mg/kg diet, the maximum TRRs, expressed in paraquat ion equivalents, found in eggs and edible chicken tissues were 0.18 mg/kg in egg yolk, 0.001 mg/kg in egg albumen, 0.05 mg/kg in meat, 0.05 mg/kg in fat and 0.09 mg/kg in liver.

At the estimated maximum animal burden of 0.11 mg/kg, the maximum residue levels were calculated to be far below the LOQ of 0.005 mg/kg in eggs and other tissues. The Meeting estimated the maximum residue levels to be 0.005* mg/kg for eggs, poultry meat and edible poultry offal. The STMR and highest residue level values were estimated to be 0 for these commodities.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The IEDIs were calculated for the five GEMS/Food regional diets from the STMR values for fruit, vegetables, maize, sorghum, cotton-seed, sunflower, hops, tea and animal commodities and the STMR-P values for their processed products, as estimated by the current Meeting (Annex 3). The ADI is 0–0.005 mg/kg bw, and the calculated IEDIs were 2–5% of the ADI. The Meeting concluded that the intake of residues of paraquat resulting from uses considered by the current JMPR was unlikely to present a public health concern.

### *Short-term intake*

The IESTIs of paraquat by the general population and by children were calculated for commodities for which STMR or STMR-P values had been estimated by the current Meeting when information on consumption was available (Annex 4). The ARfD is 0.006 mg/kg; the calculated IESTIs for children up to 6 years range from 0 to 50% and those for the general population from 0 to 20% of the ARfD. The Meeting concluded that the short-term intake of residues of paraquat from uses considered by the current Meeting was unlikely to present a public health concern.

## 4.20 PHORATE (112)

## TOXICOLOGY

Phorate is the ISO approved name for phosphorothioic acid, *O*-diethyl *S*-(ethyl thio)methyl ester, which is an organophosphate insecticide that inhibits acetylcholinesterase activity and is a systemic and contact insecticide and acaricide. Phorate was first evaluated by the JMPR in 1977. In 1985, an ADI of 0–0.0002 mg/kg bw was established. Phorate was re-evaluated in 1994 when an ADI of 0–0.0005 mg/kg bw was established. In 1994, because it was reported in a limited study of metabolism in rats that < 40% of the administered dose was excreted, the Meeting requested adequate studies on absorption, for review in 1996. Such studies were received and the ADI established previously was confirmed.

Since the 1994 JMPR, a study of acute neurotoxicity and a 13-week study of neurotoxicity in rats have been submitted. The present Meeting re-evaluated phorate within the periodic review programme of the CCPR, using new data that had not been reviewed previously and relevant data from previous evaluations.

After oral administration of radiolabelled phorate to rats, 77% of the administered dose was recovered in the urine within 24 h after dosing. Faecal excretion accounted for approximately 12% of the administered dose. Over the total duration of the study (192 h), essentially the entire administered dose was eliminated by excretion.

Phorate was highly toxic when administered orally, dermally or by inhalation. The oral $LD_{50}$ values for rats were 3.7 mg/kg bw in males and 1.4 mg/kg bw in females. The dermal $LD_{50}$ values for rats were 9.3 mg/kg bw in males and 3.9 mg/kg bw in females. The $LC_{50}$s for rats after exposure for 1 h were 0.06 and 0.011 mg/l of air in males and females respectively. Studies of dermal and eye irritation and of dermal sensitization were not performed owing to the high acute toxicity of phorate by skin contact.

The toxicological effects of phorate are associated with inhibition of acetylcholinesterase activity. Inhibition of acetylcholinesterase activity and clinical signs occurred at similar doses in rats, rabbits and dogs, while mice appeared to be somewhat less sensitive. The NOAELs for toxicologically significant inhibition of brain acetylcholinesterase activity were 0.05–0.07 mg/kg bw per day in 13-week and 2-year studies in rats and in 1-year studies in dogs. The NOAELs for clinical signs were generally higher. The Meeting noted that the dose–response curve for acetylcholinesterase inhibition is steep.

In an 18-month study in mice and in a 24-month study in rats, phorate did not increase the incidence of tumours or cause any non-neoplastic effects other than clinical signs secondary to inhibition of acetylcholinesterase activity.

Phorate was tested for genotoxicity in vitro and in vivo in an adequate battery of assays. In view of the lack of genotoxicity in vitro and in vivo and on the basis of the results of studies of carcinogenicity in rodents, the Meeting concluded that phorate is not likely to pose a carcinogenic risk to humans.

In a multigeneration study of reproductive toxicity in mice, the NOAEL was 1.5 ppm (equal to 0.30 mg/kg bw per day) on the basis of slightly reduced lactation indices in four out of the six litters at 3 ppm (equal to 0.60 mg/kg bw per day).

In a two-generation study of reproductive toxicity in rats, phorate showed effects on pup growth and mortality at maternally toxic doses. The NOAEL was 2 ppm (equal to 0.17 mg/kg bw per day) on the basis of decreased brain acetylcholinesterase activity, decreased parental and pup body weights and decreased pup survival at 4 ppm (equal to 0.35 mg/kg bw per day).

In a study of developmental toxicity in rats, the NOAELs for maternal and developmental toxicity with phorate were 0.3 mg/kg bw per day on the basis of mortality, cholinergic signs of toxicity, significantly decreased body weights and food consumption in the dams, decreased fetal body weights and delays in skeletal ossification at 0.4 mg/kg bw per day. No fetal malformations were produced, even at the lethal dose (0.4 mg/kg bw per day), the highest dose tested. The Meeting concluded that phorate is not teratogenic in rats.

Phorate was not embryotoxic, fetotoxic or teratogenic in rabbits at doses of up to and including 1.2 mg/kg bw per day, a dose that produced severe maternal toxicity. The NOAEL for maternal toxicity with phorate was 0.15 mg/kg bw per day on the basis of mortality observed at 0.5 mg/kg bw per day. The NOAEL for developmental toxicity was 1.2 mg/kg bw per day, the highest dose tested.

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

In a study of acute neurotoxicity in rats treated by gavage, phorate at a dose of 1 mg/kg bw caused miosis in 2 out of 20 males and 5 out of 20 females, tremors in 2 out of 20 females, fasciculations, slightly impaired locomotion and splayed or dragging hindlimbs in one female and significant inhibition of brain and erythrocyte acetylcholinesterase activity in females (65%), but not in males (14–21%). No histopathological signs were observed. At 0.5 mg/kg bw, miosis was observed in 2 out of 20 males and 2 out of 20 females. Although miosis was observed in a small number of animals (and in 1 out of 20 controls) in the absence of inhibition of erythrocyte and brain acetylcholinesterase activity, it could not be dismissed as a compound-related effect. The NOAEL was 0.25 mg/kg bw on the basis of miosis.

Phorate did not cause acute delayed neurotoxicity in hens. Although measurements of neuropathy target esterase were not carried out, the Meeting noted that the dose used (approximately equal to the $LD_{50}$) was sufficiently high to indicate that dietary exposure to phorate would not cause delayed polyneuropathy.

The mammalian and plant metabolites of phorate, phorate sulfone and phorate sulfoxide, had similar toxicity to the parent compound. In rats, the oral $LD_{50}$ values for these metabolites were 1.2–3.5 and 2.2–2.6 mg/kg bw, respectively. The NOAELs for inhibition of brain acetylcholinesterase activity were 0.80 ppm (equal to 0.08 and 0.06 mg/kg bw per day) for phorate sulfone and sulfoxide, respectively, in 90-day studies in rats.

Several cases of occupational and non-occupational poisoning in humans have been reported. The subjects showed typical cholinergic symptoms, including gastrointestinal effects, bradycardia and neurological effects (headache, giddiness, fatigue). Skin and eye irritation were also observed.

### *Toxicological evaluation*

An ADI of 0–0.0007 mg/kg bw was established on the basis of a overall NOAEL of 0.07 mg/kg bw per day for inhibition of brain acetylcholinesterase activity in rats and dogs and a safety factor of 100. This ADI includes the phorate metabolites, phorate sulfone and phorate sulfoxide.

An ARfD of 0.003 mg/kg bw was also established based on the NOAEL of 0.25 mg/kg bw for miosis in the study with single doses in rats. Although inhibition of acetylcholinesterase activity is a $C_{max}$-dependent phenomenon, a safety factor of 100 was used in view of the steep dose–response curve and the slow recovery of brain acetylcholinesterase activity because of irreversibility of its inhibition. This ARfD includes the metabolites of phorate, phorate sulfone and phorate sulfoxide.

A toxicological monograph was prepared.

*Levels relevant to risk assessment*

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | 18-month study of toxicity and carcinogenicity[a] | Toxicity | 3 ppm, equivalent to 0.45 mg/kg bw per day | 6 ppm, equivalent to 0.90 mg/kg bw per day |
| | | Carcinogenicity | 6 ppm, equal to 0.90 mg/kg bw per day[d] | — |
| | Multigeneration study of reproductive toxicity[a] | Parental and offspring toxicity | 1.5 ppm, equal to 0.30 mg/kg bw per day | 3 ppm, equal to 0.60 mg/kg bw per day |
| Rat | 2-year study of toxicity and carcinogenicity[a] | Toxicity | 1 ppm, equal to 0.05 mg/kg bw per day | 3 ppm, equal to 0.16 mg/kg bw per day |
| | | Carcinogenicity | 6 ppm, equal to 0.32 mg/kg bw per day[c], [d] | — |
| | Multigeneration reproductive toxicity[a] | Parental and offspring toxicity | 2 ppm, equal to 0.17 mg/kg bw per day | 4 ppm, equal to 0.35 mg/kg bw per day |
| | Developmental toxicity[a] | Embryo- and fetotoxicity and maternal toxicity | 0.3 mg/kg bw per day | 0.40 mg/kg bw per day |
| | Single-dose study[c] | Miosis | 0.25 mg/kg bw | 0.50 mg/kg bw per day |
| | 13-week study of neurotoxicity[a] | Neurotoxicity | 0.07 mg/kg bw per day | 0.3 mg/kg bw per day |
| Rabbit | Developmental toxicity[a] | Maternal toxicity | 0.15 mg/kg bw per day | 0.50 mg/kg bw per day |
| | | Embryo- and fetotoxicity[a] | 1.2 mg/kg bw per day[d] | — |
| Dog | 1-year study of toxicity[b] | Toxicity | 0.05 mg/kg bw per day | 0.25 mg/kg bw per day |

[a] Diet
[b] Capsules
[c] Gavage
[d] Highest dose tested

*Estimate of acceptable daily intake for humans*

0–0.0007 mg/kg bw

*Estimate of acute reference dose*

0.003 mg/kg bw

*Studies that would provide information useful for the continued evaluation of the compound*

Further observation in humans

### *Critical end-points for setting guidance values for exposure to phorate*

| | |
|---|---|
| *Absorption, distribution, excretion and metabolism in animals* | |
| Rate and extent of oral absorption | Rapid, approximately 90% within 24 h |
| Dermal absorption | Extensive based on acute toxicity |
| Distribution | Rapid and extensive |
| Potential for accumulation | None |
| Rate and extent of excretion | 89% within 24 h; urinary excretion predominated (77%); faecal excretion (12%) |
| Metabolism in animals | Major pathway: cleavage of phosphorus–sulfur bond, methylation of the liberated thiol group and oxidation of the resulting divalent moiety to the sulfoxide and sulfone |
| Toxicologically significant compounds (plants, animals and the environment) | Parent, phorate sulfoxide and phorate sulfone |
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | 3.7 mg/kg bw in males, 1.4 mg/kg bw in females |
| Rat, $LD_{50}$, dermal | 9.3 mg/kg bw in males, 3.9 mg/kg bw in females |
| Rat, $LC_{50}$, inhalation | 0.06 mg/l of air in males (1-h), 0.011 mg/l of air (1-h) in females |
| Rabbit, skin irritation | Highly toxic by skin contact — could not be tested |
| Rabbit, eye irritation | Highly toxic by eye contact — could not be tested |
| Skin sensitization | Highly toxic by skin contact — could not be tested |
| *Short-term studies of toxicity* | |
| Target/critical effect | Brain and erythrocyte acetylcholinesterase activity and miosis (rats) |
| Lowest relevant oral NOAEL | 0.07 mg/kg bw per day |
| Lowest relevant dermal NOAEL | No data |
| Lowest relevant inhalation NOAEC | No data |
| *Genotoxicity* | Negative results in vivo and in vitro |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Inhibition of erythrocyte and brain cholinesterase activity |
| Lowest relevant NOAEL | 0.07 mg/kg per day (rat) |
| Carcinogenicity | Not carcinogenic in mice and rats |
| *Reproductive toxicity* | |
| Reproduction target/critical effect | Reduced pup growth at maternally toxic dose |
| Lowest relevant reproductive NOAEL | 2 ppm, equivalent to 0.17 mg/kg bw per day |
| Developmental target/critical effect | Decreased pup weights and delayed ossification at maternally toxic doses (rats) |
| Lowest relevant developmental NOAEL | 0.3 mg/kg bw per day (rats) |
| *Neurotoxicity/delayed neurotoxicity* | |
| Single dose study of neurotoxicity | |
| Target/critical effect | Signs consistent with acetylcholinesterase inhibition; no neuropathological effects |
| Relevant NOAEL | 0.25 mg/kg bw |
| Delayed neuropathy | No delayed neurotoxicity in hens |

| | |
|---|---|
| *Medical data* | Findings consistent with inhibition of acetylcholinesterase activity; no record of permanent sequelae |

| ***Summary*** | ***Value*** | ***Study*** | ***Safety factor*** |
|---|---|---|---|
| ADI | 0–0.0007 mg/kg bw | Rats and dogs, short- and long-term studies, inhibition of brain acetylcholinesterase activity | 100 |
| ARfD | 0–0.003 mg/kg bw | Rats, single-dose study, miosis | 100 |

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The estimated theoretical maximum daily intakes in the five GEMS/Food regional diets, based on recommended MRLs, were in the range of 40–200% of the ADI (Annex 3). Further refinements of dietary intake estimates will be undertaken during the periodic review of phorate residues scheduled for 2005.

### *Short-term intake*

The Meeting established an ARfD for phorate of 0.003 mg/kg bw but was unable to finalize the risk assessment before the residue evaluation, scheduled for 2005, had been completed.

## 4.21 PIRIMICARB (101)

## TOXICOLOGY

Pirimicarb is the ISO approved common name for 2-dimethylamino-5,6-dimethylpyrimidin-4-yl dimethylcarbamate. It is a selective aphicide that is used extensively on a broad range of crops, including vegetable, cereal and orchard crops. The mode of action of pirimicarb is by inhibition of acetylcholinesterase activity.

Pirimicarb was evaluated by the JMPR in 1976, 1978 and 1982; an ADI of 0–0.02 mg.kg bw was established in 1983. Pirimicarb was reviewed by the present Meeting within the periodic review programme of CCPR, using new data not previously reviewed and relevant data from previous evaluations.

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. There were no pronounced sex differences in the routes or rates of excretion. 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.

The acute oral median $LD_{50}$ for pirimicarb was 152 mg/kg bw in male rats and 142 mg/kg bw in female rats, while the acute dermal median $LD_{50}$ of pirimicarb was > 2000 mg/kg in both male and female rats. The 4-h inhalation median $LC_{50}$ of pirimicarb in rats was 0.948 and 0.858 mg/l of air in males and females respectively. Pirimicarb is not irritating to the rabbit eye or skin. It does, however, have skin sensitizing potential under the conditions of the Magnusson & Kligman maximization test.

In a 21-day study of dermal toxicity in rats, there were no signs of irritation and no clinical signs of systemic toxicity, but there was a reduction in brain cholinesterase activity at 1000 mg/kg bw per day. The NOAEL was 200 mg/kg bw per day.

Acetylcholinesterase that has been inhibited by pirimicarb is rapidly reactivated (both in vivo and in vitro). This property hampers the reliable determination of acetylcholinesterase inhibition in erythrocytes and brain in treated animals, and special attention must be given to crucial methodological features (e.g. time between sampling and measurement, sample temperature and dilution). Consequently, the most reliable indicators of an effect are clinical signs, which usually occur when acetylcholinesterase inhibition is > 50% at nerve terminals.

In experiments with multiple doses, common toxicological targets are blood and acetylcholinesterase.

Three dietary studies of up to 90 days in duration have been conducted in rats. In the first study (in which animals were given diets containing pirimicarb at a concentration of 250 or 750 ppm for 90 days) there were no adverse clinical, haematological or other pathological effects. A reduction in plasma cholinesterase activity was seen at 750 ppm, providing evidence for the absorption of the compound from the intestinal tract. In the second study (in which animals were given diets containing pirimicarb at a concentration of 250 or 750 ppm for 8 weeks) a clear reduction in body-weight gain was seen at 750 ppm, with a slight reduction at 250 ppm. These growth reductions were completely reversible after an 8-week recovery period. In the final study (in which animals were given diets containing pirimicarb at a concentration of 100, 175, 250 or 750 ppm for 8 weeks) there were no adverse clinical effects. A reduction in body-weight gain and food consumption was seen at 750 ppm. Owing to the effect on body-weight gain in the second study at 250 ppm, the Meeting concluded that the overall NOAEL in short-term studies in rats was 175 ppm, equivalent to 17.5 mg/kg bw per day.

Reports of three studies of 13–16 weeks in duration in dogs were available. In the first study, beagle dogs were given diets delivering pirimicarb at a dose of 0, 4, 10 or 25 mg/kg bw per day for at least 90 days. Body weight was reduced at the highest dose and plasma cholinesterase activity was reduced at 10 and 25 mg/kg bw per day. Bone-marrow changes, indicative of increased erythropoiesis, were observed in the terminal blood films in all treatment groups. Three out of 32 animals (two receiving 25 mg/kg bw per day and one receiving 10 mg/kg bw per day) developed anaemia. Two dogs of each sex per group were killed after 90 days (one male only in the group receiving 25 mg/kg bw per day, as one had been killed after 10–11 weeks) and the remainder were allowed to recover untreated for 28 days. Partial recovery from the bone-marrow changes was evident at 28 days after cessation of treatment. A NOAEL for this study was not identified, therefore a second study with diets delivering pirimicarb at a dose of 0.4, 1.8 and 4 mg/kg bw per day for at least 90 days was conducted. An additional group received pirimicarb at 4 mg/kg bw per day for 180 days. There were no adverse clinical or pathological effects, but dogs at 4 mg/kg bw per day showed evidence of increased erythropoietic activity in the bone marrow. The NOAEL was 1.8 mg/kg bw per day. In the third study, foxhounds were given diets delivering pirimicarb at a dose of 0, 2 or 25/50 mg/kg bw per day for 16 weeks, followed by a 7-week recovery period. The dose of 25 mg/kg bw per day was increased to 50 mg/kg bw per day from week 8. Anaemia and reticulocytosis developed in dogs receiving a dose of 50 mg/kg bw per day and bone-marrow changes, characterized by an increase in normoblasts and hypoplasia, were observed. Both the anaemia and bone-marrow changes were reversible when the dose was reduced to 25 mg/kg bw per day, or upon cessation of treatment. The NOAEL in this study in dogs was 2 mg/kg bw per day.

In addition, there were two 2-year dietary studies in dogs and a more recent, guideline-compliant, 1-year study in which pirimicarb was administered in capsules. In the first 2-year dietary study, designed to reproduce and characterize the anaemia, two out of four unrelated beagles had an immune haemolytic anaemia when exposed to pirmicarb at a dose of 25 or 50 mg/kg bw per day for at least 3 months. Dogs at ≤ 2 mg/kg bw per day did not show such effects. The anaemia was completely reversible after withdrawal of the compound. Other dogs in the same study showed no haematological changes when exposed to primicarb at a dose of up to 50 mg/kg bw per day for 2 years. In the second dietary study, pirimicarb was administered at a dose of 0.4, 1.8 or 4 mg/kg bw per day for 2 years. There were no adverse changes in growth rate, blood and urine clinical chemistry, organ weights or histopathology. At 4 mg/kg bw per day, there were reductions in haemoglobin concentration and erythrocyte volume fraction in males and a slight increase in the erythroid to myeloid ratio in two females. No adverse changes were detected in the bone marrow. None of the dogs developed overt anaemia. In the most recent study, groups of beagles were dosed orally with gelatine capsules containing pirimicarb delivering a dose of 0, 3.5, 10 or 25/35 mg/kg bw per day for 1 year. The highest dose of 35 mg/kg bw per day could not be sustained owing to adverse clinical signs in week 1, so from week 4 onwards, the dose was reduced to 25 mg/kg bw per day. One female dog receiving 25 mg/kg bw per day was killed humanely in week 36 after significant body-weight loss and the development of anaemia. The haematological changes in this dog were characterized by increased erythropoietic activity in the bone marrow and by histological changes consistent with increased erythrocyte breakdown. No other dog showed any treatment-related haematological changes; however, increased haemosiderin deposition was observed in the liver and spleen of dogs at 25 mg/kg bw per day. The NOAEL in this study was 3.5 mg/kg bw per day; this value is very close to the LOAEL of 4 mg/kg bw identified in three other experiments. The overall NOAEL was 2 mg/kg bw per day in dogs.

The carcinogenic potential of pirimicarb has been assessed in feeding studies of 80 and 96 weeks' duration in mice and 104 weeks in rats. In both species, the highest dose tested induced moderate levels of toxicity. Two studies of carcinogenicity were conducted in Alderley Park Swiss-derived mice and one in C57 black Alderley Park mice; however, one of the studies in Swiss-derived mice, a study that pre-dated the establishment of good laboratory practice (GLP), was not considered adequate for assessing the carcinogenic potential of pirimicarb, owing to a high incidence of respiratory disease. Similarly, three pre-GLP studies in rats were not adequate for carcinogenicity assessment owing to high incidences of respiratory disease.

In Alderley Park Swiss-derived mice given diets containing pirimicarb at a concentration of 0, 0, 200, 400 or 1600 ppm for up to 96 weeks, there was a significant increase in the incidence of liver tumours [classified as type A (hyperplastic nodules and benign neoplasms) and type B nodules (which showed characteristics of malignancy)] at the highest dose (equivalent to approximately 240 mg/kg bw per day), with no evidence of nodule induction at lower doses. The incidence of liver nodules was above the historical control range for the test laboratory. This finding was not confirmed in C57 black Alderley Park mice given diets containing pirimicarb at a concentration of 0, 50, 200 or 700 ppm for at least 80 weeks, where there was no evidence that liver tumours induced by pirimicarb at doses of up to 700 ppm (equal to approximately 94 and 130 mg/kg bw per day in males and females, respectively). Thus, the significant response was only seen at a very high dose and after a prolonged exposure time in a mouse strain with a high and variable background incidence of liver tumours.

Also in Alderley Park Swiss-derived mice, the incidence of pulmonary adenoma was significantly increased in both sexes at the highest dose, but with no significant response at lower doses. Concurrent and historical control data indicate a high and variable spontaneous background incidence of pulmonary adenomas in this strain of mouse. Given the overall variability in the incidence of pulmonary adenoma in these mice, the observation of an increased tumour incidence at the highest dose does not give cause for concern in terms of cancer risk. A small, statistically significant, increase in the incidence of pulmonary adenoma was also observed in female (but not male) C57 black Alderley Park mice at the highest dose tested, with no evidence of pulmonary adenoma induction at lower doses. In contrast to Swiss-derived mice, C57 black mice have a low spontaneous background incidence of pulmonary adenoma. Therefore, the occurrence of these tumours is considered to be treatment-related. The absence of a significant response in male mice could be a chance difference in the incidence of an uncommon tumour type. The Meeting concluded that oral administration of pirimicarb at a dose of up to 700 ppm, equal to 94 and 130 mg/kg bw per day for males and females, respectively, for at least 80 weeks produced a small increase in the incidence of benign lung tumours in females, but not in males. The NOAEL for non-neoplastic effects was 50 ppm, equal to 6.7 mg/kg bw per day, on the basis of slight haematological changes at 200 ppm, equal to 26.6 mg/kg bw per day in the 80-week study.

A 2-year study in rats showed that dietary administration of pirimicarb at 0, 75, 250 or 750 ppm resulted in reduced body-weight gains and food consumption in both sexes at 750 ppm, indicating that a maximum tolerated dose had been achieved. There was also a slight reduction in body-weight gain at 250 ppm in females. There were increases in plasma cholesterol at all observation times at 750 ppm, at weeks 13 and 26 at 250 ppm and (in females only) at week 13 at 75 ppm. Plasma concentrations of triglycerides were increased at 750 ppm in males at weeks 52 and 78 and in females at weeks 13 and 26. Males fed diets containing pirimicarb at 750 ppm showed a small increase in incidence and severity of necrosis in the brain. The significance of this is equivocal, but could not be dismissed as being incidental to treatment with pirimicarb. Females fed diets containing pirimicarb at 750 ppm showed an increased severity of sciatic nerve demyelination and an increased severity and incidence of voluntary muscle degeneration that were considered to be an exacerbation of a spontaneous age-related change. Overall, the findings in the brain, sciatic nerve and voluntary muscle were minor, confined to the highest dose and did not elicit any clinical signs of increased neurological dysfunction. Plasma cholinesterase activity was slightly reduced in females at 250 and 750 ppm, demonstrating the absorption of the test substance, but brain and erythrocyte cholinesterase activities were not affected at any dose. The NOAEL for non-neoplastic effects was 75 ppm, equal to 3.7 mg/kg bw per day, on the basis of reductions in body weights and increases in plasma cholesterol and triglycerides at 250 ppm, equal to 12.3 mg/kg bw per day. There was an overall higher, but non-significant incidence in the number of male rats with tumours at 250 and 750 ppm. This reflected an increased incidence of males with multiple tumours at 250 ppm and of males with single tumours at 750 ppm. There were also small increased incidences of astrocytoma of the brain in all treated groups and in females at 750 ppm, but these were not statistically significant and no dose–response relationship was evident. As there was a decreased incidence of males with multiple tumours at 750 ppm and there were no consistent effects across doses, the Meeting concluded that pirimicarb did not induce a carcinogenic response in any tissue.

The Meeting concluded that pirimicarb had no clear carcinogenic potential in mice or rats. Liver tumours were not consistently found in the two studies in mice, while the benign lung tumours were found only at the highest dose and with clear evidence for a threshold. There were no compound-related increases in the incidences of any tumour type in rats.

Pirimicarb was tested for genotoxicity in an adequate range of studies, both in vitro and in vivo. The results observed were largely negative. A small increase in mutant frequency in the assay for mutation in L5178Y mammalian cells, in the presence of metabolic activation, was considered not to be a significant alert for genotoxicity. Pirimicarb has shown no evidence of genotoxic potential in several test systems in vivo. The Meeting concluded that pirimicarb is unlikely to pose a genotoxic risk to humans.

Because the results of the studies of carcinogenicity in rodents were judged not to provide evidence of carcinogenic potential, an evaluation supported by the lack of genotoxic potential, the Meeting concluded that pirimicarb is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, the NOAEL for adult rats and for their offspring was 200 ppm, equal to 23 mg/kg bw per day in adults, on the basis of systemic toxicity in the parental rats and reduced body-weight gain in the parental rats and the offspring at a dose of 750 ppm, equal to 88 mg/kg bw per day; no other signs of reproductive toxicity were observed at this dose, the highest tested. In studies of developmental toxicity in rats, the NOAEL for foetal toxicity and maternal toxicity was 25 mg/kg bw per day on the basis of reduced fetal weight and maternal body-weight gains at 75 mg/kg bw per day. In studies of developmental toxicity in rabbits, the NOAEL for fetal and developmental toxicity was 60 mg/kg bw per day, the highest dose tested, and the NOAEL for maternal toxicity for 10 mg/kg bw per day, on the basis of reduced food consumption and body-weight gains at 60 mg/kg bw per day. The results from the two studies of developmental toxicity and the study of reproductive toxicity demonstrated that fetuses and pups were not more susceptible than adults to toxicity caused by pirimicarb.

In a study of acute neurotoxicity in rats, a single oral administration of pirimicarb at 110 mg/kg bw per day by gavage resulted in early mortalities, adverse clinical signs and reductions in brain, erythrocyte and plasma cholinesterase activities. These clinical and enzyme activity changes were transient and were not associated with histopathological changes in the nervous system. At a dose of 40 mg/kg bw, there was evidence of toxicity seen as a single mortality, transient adverse clinical signs in a few rats and reduced motor activity on day 1. Plasma cholinesterase activity was reduced, but this observation was not accompanied by biologically significant reductions in brain or erythrocyte cholinesterase activity at this dose. The Meeting concluded that the NOAEL for acute neurotoxic potential was 10 mg/kg bw per day and this value formed the basis for the ARfD. The acute toxic effects of pirimicarb are due to inhibition of acetylcholinesterase activity at nerve terminals. Inhibition of acetylcholinesterase by carbamates (such as pirimicarb) and organophosphates involves the carbamoylation or phosphorylation of the active site on the enzyme. Plasma cholinesterase is inhibited by a similar mechanism; therefore, although this is a toxicologically irrelevant target, its inhibition serves as an indicator of exposure and a surrogate for the response of acetylcholinesterase. The degree of enzyme inhibition is dependent on the concentration of inhibitor, a property that is particularly significant for carbamates because of the short occupation half-life at the active site of the enzyme (a few minutes, both in vitro and in vivo). Consequently, plasma cholinesterase activity was inhibited after a single dose of pirimicarb at 25 mg/kg bw by gavage, but not after dietary exposure corresponding to a daily dose of about 40 mg/kg bw, when the $C_{max}$ would have been lower.

In a 90-day study of neurotoxicity, rats fed diets containing pirimicarb at a concentration of 250 or 1000 ppm resulted in toxicity evident as reduced growth and food consumption or utilization. There were no treatment-related effects on the functional observational battery, motor activity, cholinesterase and neurotoxic esterase activities or neuropathology. The NOAEL for neurotoxicity in this study was 1000 ppm, equal to 77 mg/kg bw per day, the highest dose tested.

Studies of toxicity have been conducted on a number of metabolites of pirimicarb: three carbamate metabolites, three hydroxypyrimidine metabolites and three guanidine metabolites. The acute toxicities of two carbamates (the desmethyl pirimicarb and the desmethylformamido pirimicarb metabolites) were of the same order as that of pirimicarb itself, whereas the $LD_{50}$ values of all the other seven metabolites were less or considerably less than that of pirimicarb itself. In addition, some of these metabolites tested in studies of toxicity with repeated doses and some to assays for genotoxicity. Desmethyl pirimicarb and desmethylformamido pirimicarb had effects on cholinesterase that were similar to those caused by pirimicarb itself and are included in the residue definition, since they occur in plants. In 28- and 90-day studies of toxicity in rats, the hydroxypirimidine metabolite, 2-dimethylamino-5,6-dimethylpyrimidin-4-ol (and, by implication, its mammalian metabolite, 5,6-dimethyl-2-(methylamino)pyrimidin-4-ol) was of low toxicity; the NOAEL was 240 ppm, equal to 19.5 mg/kg bw per day, on the basis of blood chemistry changes at 800 ppm, equal to 65.6 mg/kg bw per day. NOAELs could not be identified because testing was restricted to single doses in the cases of desmethyl pirimicarb (100 mg/kg bw per day for 2 weeks) and desmethylformamido pirimicarb (25 mg/kg bw per day for 2 weeks). Each of these metabolites caused slight hypochromia (reduced haemoglobin concentrations per cell). Genotoxicity tests were conducted with the hydroxypyrimidines, 2-dimethylamino-5,6-dimethylpyrimidin-4-ol and 5,6-dimethyl-2-(methylamino)pyrimidin-4-ol. Both metabolites, like pirimicarb itself, produced some weak evidence of mutagenic effects in the assay in mouse lymphoma cells, but not in other assays. The Meeting concluded that, within the limitations of studies conducted (short-term and only in rats), desmethyl pirimicarb and desmethylformamido pirimicarb have toxicological profiles similar to that of pirimicarb itself.

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

Production workers have been reported to show inhibition of plasma and erythrocyte cholinesterase activity of sufficient severity to result in their movement to other work areas.

### *Toxicological evaluation*

An ADI of 0–0.02 mg/kg bw was established for pirimicarb and its dimethyl carbamate metabolites on the basis of the overall NOAEL of 2 mg/kg bw per day in 90-day and 2-year studies in dogs treated by dietary administration and with a safety factor of 100.

The Meeting established an ARfD of 0.1 mg/kg bw for pirimicarb on the basis of a NOAEL of 10 mg/kg bw in a study of acute neurotoxicity in rats. Although a reduced safety factor would be supported by the reversibility of clinical signs and the $C_{max}$-dependency of the effects, a safety factor of 100 was used in consideration of the steep dose–response curve (indicated by a mortality at the LOAEL) and the lack of reliable measurement of acetylcholinesterase inhibition. Haematotoxicity in dogs was also considered as a possible end-point for an ARfD; however, in one study in dogs haematological parameters were measured during treatment before the onset of anaemia, indicating that this condition did not occur after a single dose.

A toxicological monograph was prepared.

*Levels relevant to risk assessment*

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | 18-month and 21-month studies of toxicity and carcinogenicity[a] | Toxicity | 50 ppm, equal to 6.7 mg/kg bw per day | 200 ppm, equal to 27 mg/kg bw per day |
| | | Carcinogenicity | 200 ppm, equal to 37mg/kg bw per day | 700 ppm, equal to 94 mg/kg bw per day |
| Rat | 24-month study of toxicity and carcinogenicity [a] | Toxicity | 75 ppm, equal to 3.7mg/kg bw per day | 250ppm, equal to 12.3 mg/kg bw per day |
| | | Carcinogenicity | 750 ppm, equal to 37 mg/kg bw per day[c] | — |
| | Two-generation study of reproductive toxicity[a] | Parental toxicity | 200 ppm, equal to 22 mg/kg bw per day | 750 ppm, equal to 88 mg/kg bw per day |
| | | Offspring toxicity | 200 ppm, equal to 23 mg/kg bw per day | 750 ppm, equal to 88 mg/kg bw per day |
| | Developmental toxicity[b] | Maternal toxicity | 25 mg/kg bw per day | 75 mg/kg bw per day |
| | | Embryo- and fetotoxicity | 25 mg/kg bw per day | 75 mg/kg bw per day |
| | Single-dose neurotoxicity[b] | Neurotoxicity | 10 mg/kg bw | 40 mg/kg bw per day |
| | 3-month study of neurotoxicity[a] | Neurotoxicity | 1000 ppm, equal to 81 mg/kg per day[c] | — |
| Rabbit | Developmental toxicity[b] | Maternal toxicity | 10 mg/kg bw per day | 60 mg/kg bw per day |
| | | Embryo and foetal toxicity | 60 mg/kg bw per day[c] | — |
| Dog | 90-day and 2-year studies of toxicity[a] | Toxicity | 2 mg/kg bw per day | 4 mg/kg bw per day |

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

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

0–0.02 mg/kg bw

### *Estimate of acute reference dose*

0.1 mg/kg bw

### *Studies that would provide information useful to the continued evaluation of the compound*

Further observations in humans

## *Critical end-points forsetting guidance values for exposure to pirimicarb*

| | |
|---|---|
| *Absorption, distribution, excretion and metabolism in animals* | |
| Rate and extent of oral absorption | Rapid; > 80% absorbed |
| Dermal absorption | No study of direct dermal absorption available, but brain cholinesterase activity was inhibited after application of pirimicarb to rat skin, indicating absorption by this route |
| Distribution | Distributed throughout the body; highest concentrations in liver and fat |
| Potential for accumulation | Low, owing to rapid excretion |
| Rate and extent of excretion | Rapid, > 80 % excretion within 24 h |
| Metabolism in animals | Extensive |
| Toxicologically significant compounds (animals, plants and environment) | Parent and the metabolites desmethyl pirimicarb and desmethylformamido pirimicarb |
| *Acute toxicity* | |
| Rat, LD$_{50}$, oral | 142 mg/kg bw |
| Rat, LC$_{50}$, inhalation | 0.858 mg/l (4 h) |
| Rabbit, LD$_{50}$, dermal | > 2000 mg/kg bw |
| Rabbit, skin irritation | Not irritiating |
| Rabbit, eye irritation | Not irritating |
| Skin sensitization | Sensitizing (Magnusson and Kligman test) |
| *Short-term studies of toxicity* | |
| Target/critical effect | Body-weight gain decrement, haemolytic anaemia or cholinesterase inhibition |
| Lowest relevant oral NOAEL | 1.8 mg/kg bw per day: (3-month study in dogs) |
| Lowest relevant dermal NOAEL | 2000 mg/kg bw per day (21-day study in rats) |
| Lowest relevant inhalation NOAEC | No data available |
| *Genotoxicity* | No genotoxic potential: negative in vivo, positive results in one study in vitro |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Blood/anaemia, increased plasma lipids |
| Lowest relevant NOAEL | 2 mg/kg bw per day (24-month study in dogs) |
| | 3.7 mg/kg bw per day (24-month study in rats) |
| *Carcinogenicity* | Benign lung tumours in mice induced by a non-genotoxic mode of action; a clear NOAEL was identified; therefore pirimicarb is unlikely to pose a carcinogenic risk to humans |
| *Reproductive toxicity* | |
| Reproductive target/critical effect | Reduced parental and offspring body weight, clinical signs |
| Lowest relevant reproductive NOAEL | 23 mg/kg bw per day |
| Developmental target/critical effect | Not teratogenic; reduced fetal body weight at maternally toxic doses |
| Lowest relevant developmental NOAEL | 25 mg/kg bw per day (rat) |
| *Neurotoxicity/delayed neurotoxicity* | |

| | |
|---|---|
| Target/critical effect | Nervous system/cholinergic signs |
| Lowest relevant NOAEL | 10 mg/kg bw |
| *90-day neurotoxicity* | |
| Target/critical effect | Nervous system/cholinergic signs |
| Lowest relevant NOAEL | 77 mg/kg bw per day |
| *Other toxicological studies* | Desmethyl pirimicarb and desmethylformamido pirimicarb inhibited acetylcholinesterase activity in rats (no studies in dogs) |
| *Medical data* | There have been a few reports of cholinesterase inhibition in workers exposed during manufacture. |

| *Summary* | *Value* | *Study* | *Safety factor* |
|---|---|---|---|
| ADI | 0–0.02 mg/kg bw | Dog; haematological changes in short- and long-term studies | 100 |
| ARfD | 0.1 mg/kg bw | Rat; mortality and clinical signs of neurotoxicity in a study of acute neurotoxicity | 100 |

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The estimated theoretical maximum daily intakes in the five GEMS/Food regional diets, based on recommended MRLs, were in the range of 3–20% of the ADI (Annex 3). The Meeting concluded that the long-term intake of residues of pirimicarb resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

### *Short-term intake*

The Meeting established an ARfD of 0.1 mg/kg bw for pirimicarb but was unable to finalize the risk assessment before the residue evaluation, scheduled for 2006, had been completed.

## 4.22 PIRIMIPHOS-METHYL (086)

## RESIDUE AND ANALYTICAL ASPECTS

Pirimiphos-methyl was evaluated for residues by the 2003 JMPR within the CCPR periodic review programme. As no data were reported on the storage stability in animal tissues or eggs, the JMPR recommended withdrawal of the CXLs for eggs and meat (from mammals other than marine mammals). Data on the storage stability of pirimiphos-methyl in animal tissues, milk and eggs were provided to the present Meeting.

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

Pirimiphos-methyl residues at 0.5 mg/kg were shown to be stable for up to 12 months in beef muscle, liver, kidney, fat and milk and hens’ eggs stored below – 18 °C.

### *Residues in animal commodities*

The 2003 JMPR calculated the dietary burden of pirimiphos-methyl for estimated MRLs and STMR values for animal commodities as 6.4 and 2.1 mg/kg for beef cattle, 5.6 and 2.9 mg/kg for dairy cattle and 6.3 and 2.1 mg/kg for poultry, respectively. In one study submitted to the 2003 Meeting, the residue levels were below the LOQ (0.01 mg/kg) in heart, liver, kidney, fat and pectoral muscle from cows fed diets containing 0, 5, 15 or 50 ppm (dry weight basis) of pirimiphos-methyl for 30 days. Adductor muscle from one of three cows at the highest feeding level contained detectable residues (0.02 mg/kg). In another study submitted to the previous Meeting, eggs from hens receiving 32 ppm pirimiphos-methyl for 7 days contained residues at a maximum of 0.01 mg/kg. No detectable residues were found in leg or breast muscle.

#### *Maximum residue levels*

The Meeting agreed that it is unlikely that pirimiphos-methyl residues would remain in tissues of cows fed commodities treated with the insecticide, and recommended a maximum residue level of 0.01* mg/kg and STMR and highest residue values of 0 mg/kg for pirimiphos-methyl in edible offal (mammalian) and meat (fat) from mammals, other than marine mammals. For calculating dietary intake, the Meeting also recommended an STMR and a highest residue level of 0 mg/kg for pirimiphos-methyl in muscle and fat from mammals other than marine mammals.

The Meeting agreed that it is unlikely that pirimiphos-methyl residues would remain in poultry tissues after birds have been fed commodities treated with the insecticide, and recommended a maximum residue level of 0.01* mg/kg and STMR and highest residue values of 0 mg/kg for pirimiphos-methyl in poultry meat and poultry edible offal. For estimating dietary intake, the Meeting also recommended STMR and highest residue values of 0 for pirimiphos-methyl in poultry muscle and fat.

Pirimiphos-methyl was detected in eggs of hens at the highest feeding level, which corresponded to five times the dietary burden of poultry for MRL estimation. The Meeting recommended maximum and highest residue levels of 0.01 mg/kg for pirimiphos-methyl in eggs. As the dietary burden for STMR corresponds to 15 times the feeding level, the Meeting agreed to recommend an STMR of 0 mg/kg for eggs.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The Meeting agreed that the STMR of 0 mg/kg estimated by the present Meeting for pirimiphos methyl in animal commodities will not affect the IEDIs calculated by the 2003 JMPR, which concluded that the long-term intake of residues of pirimiphos methyl is unlikely to present a public heath concern.

### *Short-term intake*

The IESTIs of pirimiphos-methyl by the general population and by children were calculated for commodities for which highest residue levels were estimated by the current Meeting (Annex 4). For all the commodities, the IESTI was 0–0.08 µg/kg bw. Although it might be necessary, no ARfD has yet been established for pirimiphos methyl, and the short-term risk assessment could not be finalized.

## 4.23 PROCHLORAZ (142)

### RESIDUE AND ANALYTICAL ASPECTS

Prochloraz is a broad-spectrum imidazole fungicide that is active against a range of diseases in field crops, fruit and vegetables and is also used on mushrooms, as a post-harvest treatment of fruit and as a seed treatment on cereals. It was evaluated initially in 1983 for residues and toxicology; six additional reviews of residues were carried out between 1985 and 1992, and a periodic toxicological review in 2001. The CCPR at its Twenty-ninth Session scheduled prochloraz for periodic review with respect to residues, and it was included on the 2004 JMPR agenda. The Meeting received information on the metabolism and environmental fate of prochloraz, methods of residue analysis, freezer storage stability, national registered use patterns, the results of supervised residue trials, farm animal feeding studies, fate of residues in processing and national MRLs. Information on GAP and national MRLs was submitted by Australia and Japan.

The formulations that are available include emulsifiable concentrates, suspo-emulsions and wettable powders. A number of formulations with other fungicides are also available, mainly for use on cereal crops. Wettable powder formulations of a 4:1 complex of prochloraz and manganese chloride are available for use on crops susceptible to phytotoxicity.

In this evaluation, the term ‘total prochloraz’ refers to the parent compound and metabolites containing the common 2,4,6-trichlorphenol moiety, expressed as prochloraz equivalents (using a correction factor of 1.9). The term ‘free prochloraz’ refers to the parent compound only.

The following abbreviations are used for the metabolites:

| | |
|---|---|
| BTS 44595 | *N*-propyl-*N′*-2-(2,4,6-trichlorophenoxy)ethylurea |
| BTS 44596 | *N′*-formyl-*N*-propyl-*N*-[2-(2,4,6-trichlorophenoxy)ethyl]urea |
| BTS 44770 | *N*-2-(2,4,6-trichlorophenoxy)ethylurea |
| BTS 9608 | 2,4,6-trichlorophenoxyacetic acid |
| BTS 45186 | 2,4,6-trichlorophenol |
| BTS 54906 | 2-(2,4,6-trichloro-3-hydroxyphenoxy)ethanol |
| BTS 54908 | *N*-2-(2,4,6-trichloro-3-hydroxyphenoxy)ethyl-*N*-propylurea |

### *Metabolism*

*Animals*

The Meeting received information on the metabolism of prochloraz in rats, lactating goats lactating cows and laying hens.

Prochloraz was extensively metabolized in rats, no unchanged parent compound being detected in urine; it was, however, detected in faeces and was the most abundant component on day 1. Faeces contained significant quantities of the plant metabolites BTS 44595 and BTS 44596, formed by opening of the imidazole ring. The most abundant metabolite in urine was BTS 9608, comprising around 35% of the excreted radioactivity. A more recent study in rats (2003) generally confirmed the results of the earlier studies, although a more complex pattern of metabolism was reported, additional metabolites being detected in urine and faeces. The metabolism of prochloraz in the rat proceeds via cleavage of the imidazole ring, oxidation of the side-chain, phenyl-ring hydroxylation and substitution of chlorine by a hydroxyl group. Other processes were revealed in the latest study in rats, including *N*-dealkylation, *N*-deacetylation and sulfate conjugation of hydroxy groups.

Straw from field plots treated 11 weeks before harvest with $^{14}$C-prochloraz and containing the equivalent of 19 mg/kg was fed to a lactating goat daily for 4 days. Milk and blood samples were taken twice daily, and the animal was killed on the fifth day. The highest residue levels were found in liver (0.05 mg/kg), kidney fat and rumen wall (0.04 mg/kg), expressed as equivalents. All other tissues contained ≤ 0.03 mg/kg, milk contained ≤ 0.006 mg/l; the maximum level in plasma was 0.08 mg/l.

A lactating cow was given gelatin capsules containing $^{14}$C-prochloraz at a rate providing 1.5 mg/kg bw per day twice a day for 3 days, equivalent to 37.5 mg/kg of diet. The radioactivity in plasma reached a plateau at 72 h, and the levels in milk rose to a plateau of 0.14 mg/l after 24 h. Most of the radioactivity was found in the liver (10 mg/kg) and kidney (1.7 mg/kg), with lower levels in other tissues. Parent prochloraz was not found in the gut contents, plasma, milk or tissues. Analysis of the gut contents indicated that prochloraz was rapidly degraded to the imidazole ring-opened metabolites BTS 44596, BTS 44595 and BTS 44770, and these metabolites were also detected in tissues and in early plasma samples. The phenolic metabolites BTS 54906 and BTS 54908 were prevalent in milk, in addition to BTS 4496 (23% TRR).

In laying hens given $^{14}$C-prochloraz in gelatin capsules daily at a rate of 1.5 mg/day for 14 days, equivalent to 10 mg/kg of diet, 85% of the TRR had been excreted within 24 h, and the levels of radioactivity in eggs, mostly in the yolk, reached a plateau of 1.7 mg/kg by day 8. The highest residue levels were found in the liver (0.9 mg/kg) and gastrointestinal tract (0.8 mg/kg), and levels ≤ 0.19 mg/kg were found in skin, ≤ 0.09 mg/kg in fat, 0.05 mg/kg in breast muscle and 0.07 mg/kg in thigh muscle. Parent prochloraz was not found in excreta, eggs or tissues; BTS 9608 and BTS 44596 were the main metabolites in liver, muscle, fat and eggs.

Generally, prochloraz is rapidly absorbed, metabolized and excreted, and it is not detected in milk, eggs or tissues. BTS 44596, the formyl urea metabolite, is the residue component found predominantly in egg yolk, and BTS 54906 and BTS 44596 are the main components in milk. Except in liver and to a lesser extent in kidney, the residue levels in tissues are generally low and consist mainly of BTS 44596, BTS 44595 and BTS 44770.

*Plants*

The Meeting received the results of studies of the metabolism of prochloraz in wheat and oil-seed rape after foliar application, in mushrooms after treatment of the casing and in wheat after seed treatment.

In two studies in which young wheat plants received foliar treatment with radiolabelled prochloraz at 0.25–0.39 kg ai/ha, the residue levels of parent compound were 0.6–1% TRR after 19–20 days. The main metabolites detected were BTS 44596 (32–38%), free and conjugated BTS 44595 (31%) and BTS 45186 (8%). In one of the studies, mature grain harvested 14 weeks after treatment contained < 0.05 mg/kg, representing < 0.2% of the TRR present in straw; the residues in grain were mostly bound in fibre, while the residues in straw consisted mainly of BTS 44596 (26% TRR) and BTS 44595 (8% TRR), with less than 0.1% parent compound.

In two studies on mature wheat harvested 13 weeks after foliar treatment with radiolabelled prochloraz at 1 kg ai/ha, the residues in grain represented 3–8% TRR as free BTS 45186 and 40–54% TRR as stable polar conjugates containing the 2,4,6-trichlorophenol moiety. Of the residues in straw, about 5% TRR was free BTS 45186 and 38–58% was conjugates containing the 2,4,6-trichlorophenol moiety.

In wheat plants grown from seed treated with radiolabelled prochloraz (0.4 g ai/kg of seed), 5.6% TRR was measured in aerial plant portions during the first 6 weeks of growth; no further translocation was seen. At maturity, 58% of the applied radiolabel was found in soil and 15% in the root system; no radioactivity was observed in grain.

The metabolism of prochloraz in oil-seed rape was studied after foliar treatment of young plants. Leaves sampled 19 days after treatment contained < 3% of the TRR, and the main metabolites were BTS 44596 (20%), BTS 44595 (29%) and material of polar origin (30%). A similar distribution was reported in mature plants; about 3% of the TRR was detected in plant parts that had not been treated directly, and the residues in mature seeds accounted for about 0.1% TRR.

In mushrooms treated with the prochloraz–manganese chloride complex at 3 g ai/m$^2$ and analysed 8 and 30 days later, unchanged parent compound accounted for 75% and 83% of the extracted radioactivity, respectively, and BTS 9608 accountedfor a further 9–10%.

In summary, prochloraz is metabolized to BTS 44596 via cleavage of the imidazole ring, followed by ‘deformylation’ to generate BTS 44595. Low levels of conjugates of both these metabolites are formed, which are resistant to the initial extraction solvents, being released only under more exhaustive conditions (e.g. microwave acetonitrile:water extraction). The fact that polar materials could be converted to BTS 45186 by pyridinium hydrochloride hydrolysis indicates that the trichlorophenol moiety is present in this material. The metabolic fate of prochloraz in oil-seed rape is similar to that in wheat. In mushrooms, prochloraz–manganese complex underwent dissociation to free prochloraz and subsequent metabolism to BTS 9608 and conjugates containing the BTS 45186 moiety.

*Rotational crops*

The Meeting received information on the behaviour and fate of prochloraz in soil and in rotational crops.

Under normal agricultural conditions, prochloraz is moderately persistent in soil, with a $DT_{50}$ of < 40 days. The products of biotic and photolytic degradation, BTS 44596 and BTS 44595, have been detected occasionally in soil samples collected in the field but at levels close to the LOQ .

When prochloraz is applied to bare soil, it is metabolized in rotational crops to BTS 44596, BTS 44595, BTS 45186 and BTS 9608. The levels of total residues declined sharply between 30- and 120-day crops and declined further with soil ageing. The metabolites in rotational crops were essentially the same as those reported in the studies of plant metabolism, except that the levels of BTS 9608 were lower. The concentrations of metabolites were low in all crops (< 0.01 mg/kg), exceeding 0.05 mg/kg only in wheat forage and straw.

## *Methods of analysis*

The Meeting received information on methods for analysis for free prochloraz and for total prochloraz (prochloraz plus metabolites containing the common 2,4,6-trichlorophenol moiety), in plant material, animal tissues and soils. Analytical methods for specific metabolites in plant and animal tissues were also provided.

The ‘common moiety’ method, involving hydrolysis of prochloraz and its metabolites to 2,4,6-trichlorophenol, was used in most of the supervised residue trials and for enforcement purposes. In this method (RESID/88/72) and in an earlier, related method (RESID/82/88), samples are Soxhlet-extracted with acetone, concentrated and hydrolysed with pyridine hydrochloride to break down all components to 2,4,6-trichlorophenol. This hydrolysate is then extracted into petroleum ether by steam distillation, with further clean-up by extraction into the aqueous layer with alkali and re-extraction into toluene after acidification. Total 2,4,6-trichlorophenol residues are determined by gas chromatography (with electron capture detection for plant material and soil and MS detection or mass spectrometry for milk and animal tissues), and the results are expressed as prochloraz equivalents, with a correction factor of 1.9.

Methods for measuring free prochloraz in plant materials are based on acetone extraction, acidification with hydrochloric acid, evaporation and extraction under acid conditions with petroleum ether. The aqueous extract is neutralized, further extracted with petroleum ether and evaporated, and the residue is dissolved in ethyl acetate before analysis by gas chromatography with electron capture detection.

An HPLC method for measuring prochloraz and the major metabolites BTS 44596 and BTS 44595 and the hydroxyamide metabolite BTS 54908 has also been reported for milk (liquid chromatography with tandem mass spectrometry), with an LOQ of 0.01 mg/kg for prochloraz and 0.005 mg/kg for each metabolite.

The LOQs of ‘common moiety’ methods for prochloraz equivalent in most substrates are 0.01–0.05 mg/kg, although a higher LOQ of 0.1 mg/kg may be required for some materials (immature cereal plants and straw, sub-tropical citrus fruit peel) in which there are high background levels of residues. Recovery efficiencies of about 90% are common, usually ranging from 75% to 110%.

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

The Meeting received information on the stability of prochloraz in various commodities under freezer storage (–18 to –20 °C). Less than 30% of the residues had degraded during storage in wheat stored for 24 months, in barley at 23 months, in sugar-beet roots and tops at 14 months, in maize plants at 24 months, in rape-seed at 36 months, in muscle at 12 months, in milk at 12 months and in eggs at 12 months.

### *Definition of the residue*

Studies of metabolism in lactating goats and cows and in hens indicate that the parent compound is not found in tissues, milk or eggs; however, a number of metabolites containing the 2,4,6-trichlorophenol moiety occur, BTS 44596, BTS 44595, BTS 44770, BTS 54906, BTS 54908 and BTS 9608 being found in one or more of the above substrates.

In plants, the metabolic pathway is consistent, involving cleavage of the imidazole ring to form the aldehyde BTS 44596, oxidation of the side-chain to form the urea (BTS 44595) and the carboxylic acid (BTS 9608, generally only in conjugated form), with eventual formation of the phenol BTS 45186 and its polar conjugates.

The Meeting therefore considered that the residues of toxicological concern would be those of unchanged parent compound, the non-polar metabolites BTS 44595 and BTS 44596 and low levels of free BTS 45186, which are readily extracted from plant material with acetone. The Meeting noted that these compounds are also found in rats and are therefore covered by the toxicological assessment.

The Meeting confirmed the current prochloraz residue definition, ‘Sum of prochloraz and its metabolites containing the 2,4,6-trichlorphenol moiety, expressed as prochloraz’, for compliance with MRLs and for estimation of dietary intake from both animal and plant commodities.

Taking into account the log $P_{ow}$ of prochloraz of 3.5 and the results of the animal feeding studies, the Meeting decided that residues of prochloraz should be classified as fat-soluble.

### *Results of supervised trials on crops*

The results of supervised trials were available for use of prochloraz on citrus fruit (lemon, mandarin, orange), avocado, banana, mango, papaya, pineapple, onion, melon, mushroom, tomato, lettuce, bean, pea, sugar-beet, rape-seed, sunflower seed, linseed, soya bean, barley, oat, rice, rye, wheat and pepper, black.

The results of trials or relevant GAP were not submitted for coffee beans or stone fruits, for which maximum residue levels are currently recommended. The Meeting agreed to withdraw the previously recommended maximum residue levels for these commodities.

The Meeting noted that a post-treatment interval has not been defined for most approved uses on citrus and sub-tropical fruit (inedible peel), and that in the relevant studies on orange, mandarin, avocado and banana, the residue levels, although variable, were often high in fruit sampled after day 0. As the residues in post-harvest-treated fruit did not appear to degrade appreciably during storage, the Meeting agreed to use the results of analyses up to 21 days after treatment to reflect the residue levels expected in fruit immediately after treatment.

*Citrus fruit*

The results of trials of post-harvest dipping and spraying on lemon, mandarin and orange were available from Argentina, Australia, Greece, Italy, Morocco, Spain and the United Kingdom, and the results of post-harvest brushing trials on oranges were available from South Africa.

*Lemon*

GAP in Argentina for citrus includes a post-harvest spray application of 0.2–0.29 kg ai/hl (no post-treatment interval specified). In trials in Spain reflecting this GAP, the residue levels in lemons sampled 12–16 days after treatment were 3.8 and 4.5 mg/kg. The corresponding residue levels in lemon pulp were 0.16 mg/kg and 0.23 mg/kg

*Orange*

GAP for citrus in Argentina includes a post-harvest spray application of 0.2–0.29 kg ai/hl (no post-treatment interval specified). While no trials in Argentina matched this GAP, one trial in Spain that did showed a residue level of 1.7 mg/kg in oranges (0.07, 0.1, 0.13, 0.14 and 0.17 mg/kg in pulp) sampled 14 days after treatment.

In South Africa, GAP is for a post-harvest brush treatment with 0.15 kg ai/hl (no post-treatment interval specified). In one trial in Argentina reflecting this GAP (± 25–30%), the residue level was 5.3 mg/kg in oranges (0.02 mg/kg in pulp).

In Greece, GAP is for use of prochloraz as a post-harvest dip or spray at up to 0.09 kg ai/hl. Trials in Australia, Morocco and Spain were evaluated against the GAP of Greece. The residue levels in oranges were: 1.3, 1.4, 1.5, 1.7, 2.0, 3.7, 5.9 and 6.8 mg/kg, and those in pulp (edible portion) were: 0.02, 0.06 (two), < 0.1 (two), 0.26, 0.33, 0.56 and 0.92 mg/kg.

The residue levels in oranges, in ranked order, were: 1.3, 1.4, 1.5, 1.7 (two), 2.0, 3.7, 5.3, 5.9 and 6.8 mg/kg, and those in pulp were: 0.02 (two), 0.06 (two), 0.07, < 0.1 (two), 0.1, 0.13, 0.14, 0.17, 0.26, 0.33, 0.56 and 0.92 mg/kg.

*Mandarin*

Two post-harvest trials in Spain matching GAP in Argentina (up to 0.29 kg ai/hl) showed residue levels of 2.1 and 3.5 mg/kg, with corresponding levels of 0.1 and 0.35 mg/kg in pulp.

In Greece, GAP is for use of prochloraz as a dip or spray at up to 0.09 kg ai/hl, while in Spain GAP is for use at up to 0.08 kg ai/hl. The trials in Australia (no GAP), Morocco (no GAP) and Spain were evaluated against the GAP of Greece. The residue levels in mandarins were 2.0, 2.1 (three), 2.3, 3.2, 3.4, 3.5, 3.9, 4.3, 4.6, 5.4 and 5.9 mg/kg, and the corresponding levels in pulp (edible portion) were: 0.07 (two), 0.09 (three), 0.1, 0.12, 0.26 and 0.31 mg/kg.

The residue levels in mandarins, in ranked order, were: 2.0, 2.1 (four), 2.3, 3.2, 3.4, 3.5 (two), 3.9, 4.3, 4.6, 5.4 and 5.9 mg/kg, and the corresponding levels in pulp (edible portion) were: 0.07 (two), 0.09 (three), 0.1 (two), 0.12, 0.26, 0.31 and 0.35 mg/kg.

The Meeting agreed to combine the data for lemon, orange and mandarin, to give a data set for citrus from 27 trials of: 1.3, 1.4, 1.5, 1.7 (two), 2.0 (two), 2.1 (four), 2.3, 3.2, <u>3.4</u>, 3.5 (two), 3.7, 3.8, 3.9, 4.3, 4.5, 4.6, 5.3, 5.4, 5.9 (two) and 6.8 mg/kg, and residue levels in pulp of: 0.02 (two), 0.06 (two), 0.07 (three), 0.09 (three), < 0.1 (two), <u>0.1</u> (three), 0.12, 0.13, 0.14, 0.16, 0.17, 0.23, 0.26 (two), 0.31, 0.33, 0.35, 0.56 and 0.92 mg/kg.

The Meeting estimated a maximum residue level of 10 mg/kg for prochloraz in citrus, replacing the previous recommendation of 5 mg/kg for oranges, sweet and sour. The Meeting also estimated an STMR of 0.1 mg/kg and a highest residue level of 0.92 mg/kg for prochloraz in the edible portion.

*Assorted tropical and sub-tropical fruits minus inedible peel*

*Avocado*

The results of trials on post-harvest dipping and spraying on avocado were made available to the Meeting from Australia, Colombia (no GAP) and South Africa.

GAP in South Africa is for post-harvest spray at 0.05 kg ai/hl (no post-treatment interval specified). The residue levels in trials in Australia and South Africa matching this GAP were: 0.42, 1, 1, 1.3, 2.3 and 3.5 mg/kg in whole fruit with stone and < 0.1 and 0.11 mg/kg in pulp.

The residue levels in post-harvest trials in Australia and South Africa matching Australian GAP (0.025 kg ai/hl, no post-treatment interval specified) were: 0.39, 0.83, 0.87, 0.92, 1, 1.2 (two) and 2.4 mg/kg in whole fruit with stone and < 0.1 (four) and 0.12 mg/kg in the edible portion.

The residue levels in 14 trials in avocados, in ranked order, were: 0.39, 0.42, 0.83, 0.87, 0.92, 1 (three), 1.2 (two), 1.3, 2.3, 2.4 and 3.5 mg/kg in whole fruit with stone and < 0.1 (five), 0.11 and 0.12 mg/kg in the edible portion.

The Meeting noted that, while data for pre-harvest foliar application were available, no matching GAP was provided.

*Banana*

The results of trials of post-harvest dipping on banana were available from Australia, South Africa and the West Indies, and trials of spray or drench application were reported from the Canary Islands and the Philippines.

GAP in the Philippines is for a spray application at 0.09 kg ai/hl, but no trials matched this GAP. In China, GAP is for use of prochloraz as a dip at up to 0.05 kg ai/hl (no post-treatment interval specified). The residue levels in trials of dipping in Australia, the Canary Islands, South Africa and the West Indies matching this GAP were: 1.8, 2.5, 2.6, 2.7, 3.0, 3.3, 3.5 and 5.1 mg/kg in whole fruit and: 0.04, < 0.1, 0.1, 0.11, 0.12 and 0.17 (two) mg/kg in pulp.

In Australia, GAP (0.025 kg ai/hl) is for use of prochloraz as a dip. The residue levels in dipping trials in Australia, the Canary Islands, the Philippines, South Africa and the West Indies matching this GAP were: < 0.1, 0.69, 1.1, 1.3, 1.6, 1.7 (two), 2.3, 2.4, 2.9, 3.0 and 3.4 mg/kg in whole fruit and: 0.03, 0.06, 0.07, 0.08, < 0.1, 0.1 (two), 0.12 (two), 0.13 and 0.21 (two) mg/kg in pulp.

The residue levels in banana, in ranked order, were: < 0.1, 0.69, 1.1, 1.3, 1.6, 1.7, 1.8, 2.3, 2.4, 2.5, 2.6, 2.7, 2.9, 3.0 (two), 3.4, 3.5 and 5.1 mg/kg in whole fruit, and the residue levels in pulp were: 0.03, 0.04, 0.06, 0.07, 0.08, < 0.1 (two), 0.1 (three), 0.11, 0.12 (three), 0.13, 0.17 (two) and 0.21 (two) mg/kg.

The Meeting noted that, while data for pre-harvest foliar applications were available, no matching GAP was provided.

*Mango*

The Meeting was provided with the results of trials on pre-harvest foliar spray in Israel (no GAP), Malaysia (GAP: 0.056 kg ai/hl, 15-day PHI), South Africa (no GAP) and Taiwan (no GAP), and of trials on post-harvest dipping in Australia (post-harvest spray at 0.025 kg ai/hl, no post-treatment interval specified), Colombia (0.025 kg ai/hl, no post-treatment interval specified), Israel (no GAP) and South Africa (maximum of 0.08 kg ai/hl, no post-treatment interval specified).

None of the pre-harvest trials from Malaysia matched Malaysian GAP.

None of the post-harvest treatment trials matched GAP in China (0.1 kg ai/hl) or South Africa (maximum of 0.08 kg ai/hl), but four trials in Australia, Colombia, Israel and South Africa matched GAP in

Brazil (0.05 kg ai/hl) and Peru (0.045 kg ai/hl). In these trials, the residue levels in total fruit were: 1, 1.2, 1.3 and 1.4 mg/kg, while those in the edible portion were: 0.18 and 0.44 mg/kg.

In three trials in Australia and South Africa that matched GAP in Australia and Colombia (0.025 kg ai/hl), the residue levels were 0.48, 0.68 and 1.8 mg/kg in whole fruit without stone and 0.1 and 0.47 mg/kg in pulp.

The residue levels in the post-harvest trials on mango, in ranked order, were: 0.48, 0.68, 1, 1.2, 1.3 and 1.4 (two) mg/kg, and those in pulp were: 0.1, 0.18, 0.44 and 0.47 mg/kg.

*Papaya*

The results of post-harvest dipping trials were provided from Australia (GAP: 0.025 kg ai/hl, no post-treatment interval specified), Brazil (GAP: 0.034 kg ai/hl, 3-day post-treatment interval) and South Africa (no GAP).

In three post-harvest dipping trials in Australia and South Africa that matched the GAP of Australia (0.025 kg ai/hl), the residue levels were: 0.41, 0.61 and 1.4 mg/kg in whole fruit (including pips) and < 0.1 and 0.7 mg/kg in the edible portion.

*Pineapple*

The results of post-harvest dipping trials were made available from Australia (GAP: 0.025 kg ai/hl, no post-treatment interval specified) and Kenya (no GAP). In the one trial matching Australian GAP, the residue level was 1.1 mg/kg in whole fruit and 0.18 mg/kg in the edible portion.

The Meeting considered that the available data on residue levels in avocado, banana, mango, papaya and pineapple were sufficient to mutually support a group maximum residue level for assorted tropical and sub-tropical fruits minus inedible peel. The residue levels, in ranked order, were: < 0.1, 0.39, 0.41, 0.42, 0.48, 0.61, 0.68, 0.69, 0.83, 0.87, 0.92, 1 (four), 1.1 (two), 1.2 (three), 1.3 (three), 1.4 (three), 1.6, 1.7, 1.8, 2.3 (two), 2.4 (two), 2.5, 2.6, 2.7, 2.9, 3.0 (two), 3.4, 3.5 (two) and 5.1 mg/kg in whole fruit in 43 trials, and: 0.03, 0.04, 0.06, 0.07, 0.08, < 0.1 (eight), 0.1 (four), 0.11 (two), 0.12 (four), 0.13, 0.17 (two), 0.18 (two), 0.21 (two), 0.44, 0.47 and 0.7 mg/kg in the edible portion in 33 trials.

The Meeting estimated a maximum residue level of 7 mg/kg for prochloraz in assorted tropical and sub-tropical fruits minus inedible peel, replacing the previous recommendations of 5 mg/kg for avocado and banana, 2 mg/kg for mango and 1 mg/kg for papaya. The Meeting also estimated an STMR of 0.1 mg/kg and a highest residue level of 0.7 mg/kg for prochloraz in the edible portion.

*Onion*

The results of field trials on onions were made available to the Meeting from The Netherlands (no GAP) and from Thailand (no GAP). The results of post-harvest dipping trials were provided from Australia (no GAP).

*Melon*

The results of field trials on melons involving foliar drenching and flood irrigation were made available to the Meeting from Spain. None of the trials matched Spanish GAP (up to four applications at 0.9 kg ai/ha, 15-day PHI). The results of post-harvest dipping trials were provided from Australia and Colombia, but no matching GAP was available.

*Mushroom*

The Meeting noted two distinct patterns of use of prochloraz on mushrooms: one established in the United Kingdom, involving two to three casing sprays of 0.3–0.6 g ai/$m^2$, with a PHI of 2 days, and the other common in a number of other European countries, Australia and New Zealand, involving one or more treatments at 1.5 g ai/$m^2$ and a PHI of 10–14 days.

In seven trials in The Netherlands, Switzerland and the United Kingdom matching GAP in Denmark, Italy, The Netherlands, New Zealand and Poland (one or two treatments at 1.5 g ai/$m^2$, 10-day PHI), the residue levels were: 0.21, 0.25, 0.48, 0.71 and 0.74 mg/kg.

The maximum GAP of two sprays of 0.6 g ai/$m^2$ (2-day PHI) in the United Kingdom is supported by the results of trials in Germany and the United Kingdom, with residue levels of: 0.81, <u>3.6</u>, <u>6.2</u> and 37 mg/kg.

The Meeting noted that these two residue populationsare different and, on the basis of the data supporting the United Kingdom GAP, estimated a maximum residue level of 40 mg/kg for prochloraz in mushrooms, an STMR of 4.9 mg/kg and a highest residue level of 37 mg/kg. The recommended maximum residue level of 40 mg/kg for mushrooms replaces the previous recommendation of 2.0 mg/kg.

*Tomato*

The results of field trials of both foliar application and soil drenching on tomatoes were made available to the Meeting from Israel (no GAP) and the USA (no GAP).

*Lettuce*

The results of field trials on lettuce, head, were made available to the Meeting from Australia (GAP: 0.18 kg ai/ha, 0.023 kg ai/hl, 7-day PHI) and from the United Kingdom (no GAP). Trials on protected lettuce crops were also provided by the United Kingdom (no GAP). Four trials in Australia matching Australian GAP showed residue levels of: 0.06, 0.16, 0.41 and 0.59 mg/kg.

The Meeting agreed that the available data were insufficient to estimate a maximum residue level for lettuce

*Beans, dry*

The results of field trials on beans were made available to the Meeting from Germany, and two trials of seed treatment were provided from Brazil. No matching GAP was available for either use pattern.

*Peas, dry*

The results of field trials on peas were made available to the Meeting from Germany and the United Kingdom; however, no matching GAP was available.

*Sugar-beet*

The results of field trials on sugar-beet were made available to the Meeting from Italy (GAP: one or two applications at 0.48–0.8 kg ai/ha, 20-day PHI). Three of the trials matched Italian GAP (± 30%); however, because the control samples apparently contained high residue levels, the Meeting agreed that the available data were insufficient to estimate a maximum residue level for sugar-beet.

*Oil seeds*

*Rape-seed*

The results of field trials from Canada (no GAP), Denmark (GAP: 0.45–0.7 kg ai/ha, 28-day PHI), France (GAP: 0.45–0.6 kg ai/ha), Germany (GAP: 0.6 kg ai/ha, 56-day PHI), Sweden (no GAP) and the United Kingdom (GAP: 0.2–0.5 kg ai/ha, 42-day PHI, maximum of 1 kg ai/ha per season) were made available to the Meeting.

In trials in Denmark, France and Germany that matched German GAP (0.6 kg ai/ha, 56-day PHI), the residue levels in mature seed were: 0.05, 0.07, 0.08, 0.09 (two), < 0.1 (four), 0.11, 0.12 and 0.15 mg/kg.

In field trials from the United Kingdom matching the corresponding GAP (up to 0.5 kg ai/ha, 42-day PHI), the residue levels in mature rape-seed were < 0.1 (five), 0.1 (three), 0.12, 0.14, 0.17, 0.18, 0.19, < 0.2 (two), 0.22, 0.24, 0.36, 0.39, 0.46 and 0.48 mg/kg.

The residue levels in rape-seed, in ranked order, were: 0.05, 0.07, 0.08, 0.09 (two), < 0.1 (nine), 0.1 (three), 0.11, 0.12 (two), 0.14, 0.15, 0.17, 0.18, 0.19, < 0.2 (two), 0.22, 0.24, 0.36, 0.39, 0.46 and 0.48 mg/kg in 33 trials.

The Meeting estimated a maximum residue level of 0.7 mg/kg for prochloraz in rape-seed, replacing the previous recommendation of 0.5 mg/kg. The Meeting also established an STMR of 0.1 mg/kg and a highest residue level of 0.48 mg/kg.

*Sunflower seed*

The results of field trials in France (GAP: one or two applications at 0.32–0.6 kg ai/ha, no PHI specified) were made available to the Meeting. In view of the similarity between GAP in France and that in Croatia (GAP: up to two applications at 0.6 kg ai/ha, 63-day PHI), the Meeting evaluated the trials in France against GAP in Croatia.

In the 11 trials, the residue levels were: ≤ 0.1 (eight), 0.14, 0.27 and 0.32 mg/kg,

One trial on seed treatment was reported from France, but no matching GAP was available

The Meeting estimated a maximum residue level of 0.5 mg/kg, an STMR of 0.1 mg/kg and a highest residue level of 0.32 mg/kg for sunflower seed.

*Linseed*

The results of six trials of seed treatment were reported from the United Kingdom (GAP: 0.4 g ai/kg seed) in which seed treated with prochloraz according to GAP was grown to maturity and the daughter seeds analysed for residues 149–178 days after planting. In all the trials, the residue levels of total prochloraz were below the LOQ of 0.05 mg/kg. As a residue level of 0.04 mg/kg was reported in the control samples in one trial, the Meeting decided to evaluate the remaining five trials, with residue levels < 0.05 mg/kg.

The Meeting estimated a maximum residue level of 0.05* mg/kg, an STMR of 0.05 mg/kg and a highest residue level of 0.05 mg/kg for linseed.

*Soya beans*

The results of two field trials by foliar application on soya beans were made available to the Meeting from France, but no GAP was available.

*Cereal grains*

*Barley*

The results of field trials on barley were made available to the Meeting from Austria (GAP: one application at 0.45 kg ai/ha, 35-day PHI), Brazil (GAP: 0.45 kg ai/ha, 32-day PHI), Canada (no GAP), Denmark (maximum GAP: one application at 0.45 kg ai/ha, PHI up to Zadoks 39), France (maximum GAP: 0.6 kg ai/ha, PHI up to stem elongation), Germany (maximum GAP: one application at 0.48 kg ai/ha, 35-day PHI), Greece (maximum GAP: 0.19 kg ai/ha, 56-day PHI), The Netherlands (GAP: 0.45 kg ai/ha, 42-day PHI), Italy (maximum: GAP: 0.8 kg ai/ha, 40-day PHI), Portugal (GAP: 0.45 kg ai/ha, 35-day PHI), Spain (maximum GAP: one application at 0.72 kg ai/ha, 60-day PHI), Sweden (one application at 0.45 kg ai/ha, PHI not specified) and the United Kingdom (maximum GAP: 0.45 kg ai/ha, 42-day PHI).

In five trials in Denmark, The Netherlands and the United Kingdom, involving a single application of prochloraz, which matched German GAP (0.48 kg ai/ha, 35-day PHI), the residue levels in grain were: < 0.05, 0.06, 0.08, 0.13 and 0.21 mg/kg.

The residue levels in 34 trials in Belgium, Denmark, France, Germany, Sweden and the United Kingdom with two applications and matching GAP in the United Kingdom (0.45 kg ai/ha, 42-day PHI) were: < 0.02 (two), 0.03, 0.07, 0.08 (three), 0.1 (three), 0.11 (two), 0.12 (two), 0.14, 0.16 (three), 0.23 (two), 0.24, 0.26 (two), 0.3, 0.31, 0.35, 0.38, 0.45, 0.48, 0.5, 0.53, 0.59, 0.65 and 0.68 mg/kg.

In 15 trials in France, Greece, Italy, Portugal and Spain involving two applications of prochloraz according to GAP in Portugal (0.45 kg ai/ha, 35-day PHI), the residue levels were: 0.13, 0.21, 0.22, 0.23, 0.26, 0.3, 0.35, 0.36, 0.41, 0.43, 0.46, 0.47, 0.51, 0.87 and 0.88 mg/kg.

The residue levels in 54 trials in barley, in ranked order, were: < 0.02 (two), 0.03, < 0.05, 0.06, 0.07, 0.08 (four), 0.1 (three), 0.11 (two), 0.12 (two), 0.13 (two), 0.14, 0.16 (three), 0.21 (two), 0.22, <u>0.23</u> (three), 0.24, 0.26 (three), 0.3 (two), 0.31, 0.35 (two), 0.36, 0.38, 0.41, 0.43, 0.45, 0.46, 0.47, 0.48, 0.5, 0.51, 0.53, 0.59, 0.65, 0.68, 0.87 and 0.88 mg/kg.

The Meeting also received data from field trials in Denmark (GAP: 20 g ai/100 kg seed) and Germany (no GAP) on barley grown from seed treated with prochloraz. In the 17 trials matching GAP in Denmark, the residue levels of total prochloraz were < 0.01 (two) and < 0.05 (15) mg/kg..

*Oats*

Prochloraz is registered for use on cereals in Austria, Belgium, Croatia, Denmark and Germany, with a common GAP of one or two foliar applications at 0.45 kg ai/ha, and a 35-day PHI. None of the four trials provided from Denmark matched this GAP.

The Meeting was also provided with the results of trials of seed treatment in Germany (GAP: 20 g ai/kg seed), in which the residue levels in oats grown from seed treated with prochloraz were: < 0.05 (eight) and < 0.1 (two) mg/kg.

*Rice*

Field trials of foliar application on rice were made reported to the Meeting from Japan (no GAP), Spain (GAP: 0.45 kg ai/ha, 15-day PHI) and Taiwan China (no GAP). None of the trials in Spain matched Spanish GAP.

*Rye*

Field trials of foliar application on rye were reported to the Meeting from Denmark (maximum GAP: one application at 0.45 kg ai/ha, 28-day PHI) and Germany (maximum GAP: one to two applications at 0.48 kg ai/ha, 35-day PHI). In three trials in Germany that matched German GAP, the residue levels were: 0.06, 0.09 and < 0.1 mg/kg. The Meeting noted that GAP for rye in the United Kingdom is similar to that in Germany but with a PHI of 42 days. It therefore considered that the trials in Germany supported the United Kingdom GAP. The residue levels in trials matching GAP in the United Kingdom were: < 0.05, 0.05, 0.06 (three), 0.09 and < 0.1 mg/kg.

The Meeting also received the results of field trials of seed treatment in Germany (GAP: 20 g ai/100 kg seed) with regard to residues in rye grown from seed treated with prochloraz. In five trials matching German GAP, the residue levels of total prochloraz were < 0.02 (two) and < 0.05 (three) mg/kg.

*Wheat*

The results of field trials on wheat were made available to the Meeting from Austria (GAP: one application at 0.45 kg ai/ha, 35-day PHI), Brazil (GAP: 0.45 kg ai/ha, 40-day PHI), the former Czechoslovakia (no GAP), Denmark (maximum GAP: one application at 0.45 kg ai/ha, 28-day PHI), France (maximum GAP: 0.6 kg ai/ha, PHI up to stem elongation), Germany (maximum GAP: one application at 0.48 kg ai/ha, 35-day PHI) Italy (GAP: 0.45 kg ai/ha, 42-day PHI), The Netherlands (GAP: 0.45 kg ai/ha, 42-day PHI), Portugal (no GAP), Spain (maximum GAP: one application at 0.72 kg ai/ha, 60-day PHI), Sweden (one application at 0.45 kg ai/ha, PHI not specified), the United Kingdom (maximum GAP: 0.45 kg ai/ha, 42-day PHI) and the USA (no GAP).

None of the trials in Spain trials matched Spanish GAP. One trial in Italy matching Italian GAP (maximum GAP: 0.8 kg ai/ha, 40-day PHI) showed a residue level of 0.12 mg/kg. In six trials in the former Czechoslovakia, The Netherlands and the United Kingdom involving a single application of prochloraz, which matched German GAP (maximum GAP: one application at 0.48 kg ai/ha, 35-day PHI), the residue levels in grain were: < 0.05, 0.09, 0.12, 0.21, 0.23 and 0.24 mg/kg.

The residue levels in trials in southern France, Greece, Italy, Portugal and Spain involving two applications of prochloraz according to GAP in Portugal (0.45 kg ai/ha, 35-day PHI) were: < 0.05 (six), 0.07 (two), 0.09, 0.13, 0.14, 0.15, 0.52 and 1.2 mg/kg. The residue levels in trials involving two applications of prochloraz to wheat in northern France, Germany and the United Kingdom and matching GAP in Belgium and the United Kingdom (maximum GAP: 0.45 kg ai/ha, 42-day PHI) were: 0.03, < 0.05 (10), 0.05 (two), 0.06 (two), 0.07 (two), 0.08, 0.09, < 0.1 (four), 0.11, 0.12 (two), 0.13, 0.15, 0.16, 0.17, 0.2 and 0.31 (two) mg/kg.

The residue levels in 54 trials in wheat, in ranked order, were: 0.03, < 0.05 (17), 0.05 (two), 0.06 (two), 0.07 (four), 0.08, 0.09 (three), < 0.1 (four), 0.11, 0.12 (four), 0.13 (two), 0.14, 0.15 (two), 0.16, 0.17, 0.2, 0.21, 0.23, 0.24, 0.31 (two), 0.52 and 1.2 mg/kg.

The Meeting also received the results of field trials on residues in wheat grown from seed treated with prochloraz in Denmark (no GAP), Germany (GAP: 20 g ai/100 kg seed), Greece (no GAP) and the United Kingdom (GAP: 14 g ai/100 kg seed). In the 26 trials matching GAP in Germany, the residue levels of total prochloraz were: < 0.01 (three), < 0.02 (nine) and < 0.05 (14) mg/kg..

The Meeting considered that the available data on barley, rye and wheat treated by foliar application were sufficient to mutually support a group maximum residue level for cereal grains. The residue levels, in ranked order, in 118 trials were: < 0.02 (two), 0.03 (two), < 0.05 (19), 0.05 (three), 0.06 (seven), 0.07 (five), 0.08 (five), 0.09 (five), < 0.1 (six), 0.1 (three), 0.11 (three), 0.12 (six), 0.13 (four), 0.14 (two), 0.15 (two), 0.16 (four), 0.17, 0.2, 0.21 (three), 0.22, 0.23 (four), 0.24 (two), 0.26 (three), 0.3 (two), 0.31 (three), 0.35 (two), 0.36, 0.38, 0.41, 0.43, 0.45, 0.46, 0.47, 0.48, 0.5, 0.51, 0.52, 0.53, 0.59, 0.65, 0.68, 0.87, 0.88 and 1.2 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg for prochloraz in cereal grains, replacing the previous recommendations of 0.5 mg/kg for barley, oats, rye and wheat. The Meeting also estimated an STMR of 0.11 mg/kg and a highest residue level of 1.2 mg/kg.

The Meeting agreed that the proposed maximum residue level, the STMR and the highest residue level for cereal grains based on foliar application would also accommodate seed treatment use of prochloraz.

*Pepper, black*

The results of trials on foliar application on black pepper were made available to the Meeting from Malaysia (GAP: 0.05 kg ai/hl, 30-day PHI). In trials matching this GAP, the residue levels were 5.0 and 5.1 mg/kg.

The Meeting estimated a maximum residue level of 10 mg/kg, an STMR of 5.1 mg/kg and a highest residue level of 5.1 mg/kg for prochloraz in pepper, black.

*Animal feed commodities*

*Barley straw and fodder, dry*

In four trials on barley in Denmark and The Netherlands involving a single application of prochloraz and which matched the GAP of Germany, the residue levels in barley straw were: 5.0, 6.8, 7.0 and 17 mg/kg.

The residue levels in straw in 34 trials in Belgium, Denmark, France, Germany, Sweden and the United Kingdom with two applications and matching GAP in the United Kingdom were: 0.68, 0.7, 1.1 (two), 1.4, 1.6, 2.1, 2.3, 2.4, 3.3, 3.5, 3.6, 3.7, 4.1 (two), 4.5, 4.8, 5.4, 5.7, 6.0, 6.5, 6.7, 7.6, 9.7 (two), 9.8, 12, 13 (two), 14 (two), 21, 24 and 30 mg/kg.

In 15 trials in France, Greece, Portugal and Spain, involving two applications of prochloraz according to GAP in Portugal, the residue levels in straw were: 4.0, 4.1, 4.6, 5.0, 6.4, 7.0, 7.1, 8.2, 8.4 (two), 8.8, 12 (two), 13 and 20 mg/kg.

The residue levels in barley straw in the 53 trials, in ranked order, were: 0.68, 0.7, 1.1 (two), 1.4, 1.6, 2.1, 2.3, 2.4, 3.3, 3.5, 3.6, 3.7, 4.0, 4.1 (three), 4.5, 4.6, 4.8, 5.0 (two), 5.4, 5.7, 6.0, 6.4, 6.5, 6.7, 6.8, 7.0 (two), 7.1, 7.6, 8.2, 8.4 (two), 8.8, 9.7 (two), 9.8, 12 (three), 13 (three), 14 (two), 17, 20, 21, 24 and 30 mg/kg.

In field trials in Denmark (GAP: 20 g ai/100 kg seed) and Germany (no GAP) on residues in barley grown from seed treated with prochloraz, the residue levels of total prochloraz in straw in 17 trials matching Danish GAP were: < 0.05 (three), < 0.1 (13) and < 0.2 mg/kg.

*Oat straw and fodder, dry*

In 10 field trials of seed treatment in Germany that matched German GAP (20 g ai/kg seed), the residue levels of total prochloraz in oat straw grown from seed treated with prochloraz were: < 0.05 (two), < 0.1 (seven) and < 0.2 mg/kg.

*Rye straw and fodder, dry*

In three trials in Germany matching German GAP, the residue levels in straw were: 1.1, 1.5 and 1.7 mg/kg. The residue levels in additional trials in Germany matching GAP in the United Kingdom were: 0.09, 3.1, 3.4 and 4.7 mg/kg. The residue levels in rye straw, in ranked order, were: 0.09, 1.1, 1.5, 1.7, 3.1, 3.4 and 4.7 mg/kg.

In five trials in Germany matching German GAP on residues in straw from rye grown from seed treated with prochloraz, the residue levels of total prochloraz were: < 0.1 (four) and < 0.2 mg/kg.

*Wheat straw and fodder, dry*

In six trials on wheat conducted in the former Czechoslovakia, The Netherlands and the United Kingdom involving a single application of prochloraz and matching German GAP, the residue levels in straw were: 1.5, 4.6, 5.2, 6.4, 6.8 and 11 mg/kg.

The residue levels in straw in 14 trials on wheat in southern France, Greece, Italy, Portugal and Spain involving two applications of prochloraz according to GAP in Portugal (0.45 kg ai/ha, 35-day PHI), the residue levels were: 3.5, 4.3, 8.0, 8.2 (two), 8.3, 9.6 (two), 10 (two), 11, 13 (two) and 22 mg/kg.

The residue levels in 32 trials involving two applications of prochloraz to wheat in northern France, Germany and the United Kingdom matching GAP in Belgium and the United Kingdom were: 1.7, 1.8, 2.3, 2.4, 2.5, 2.6, 2.7 (two), 2.8, 3.0, 3.7, 4.3, 5.1, 5.2, 5.3, 5.6, 5.8, 6.5, 6.6, 6.9, 8.0, 8.8, 10, 11 (three), 13, 15, 16, 19, 20 and 22 mg/kg.

The residue levels in wheat straw in all 52 trials, in ranked order, were: 1.5, 1.7, 1.8, 2.3, 2.4, 2.5, 2.6, 2.7 (two), 2.8, 3.0, 3.5, 3.7, 4.3 (two), 4.6, 5.1, 5.2 (two), 5.3, 5.6, 5.8, 6.4, 6.5, 6.6, 6.8, 6.9, 8.0 (two), 8.2 (two), 8.3, 8.8, 9.6 (two), 10 (three), 11 (five), 13 (three), 15, 16, 19, 20 and 22 (two) mg/kg.

In 24 trials of seed treatment matching German GAP, the residue levels of total prochloraz in wheat straw were: < 0.05 (four), < 0.06, < 0.1 (17) and < 0.2 (two) mg/kg.

The Meeting considered that the available data on barley, rye and wheat straw and fodder treated by foliar application were sufficient to mutually support a group maximum residue level for straw and fodder, dry, of cereal grains. The residue levels in the 112 trials, in ranked order, were: 0.09, 0.68, 0.7, 1.1 (three), 1.4, 1.5 (two), 1.7 (two), 1.6, 1.8, 2.1, 2.3 (two), 2.4 (two), 2.5, 2.6, 2.7 (two), 2.8, 3.0, 3.1, 3.3, 3.4, 3.5 (two), 3.6, 3.7 (two), 4.0, 4.1 (three), 4.3 (two), 4.5, 4.6 (two), 4.7, 4.8, 5.0 (two), 5.1, 5.2 (two), 5.3, 5.4, 5.6, 5.7, 5.8, 6.0, 6.4 (two), 6.5 (two), 6.6, 6.7, 6.8 (two), 6.9, 7.0 (two), 7.1, 7.6, 8.0 (two), 8.2 (three), 8.3, 8.4 (two), 8.8 (two), 9.6 (two), 9.7 (two), 9.8, 10 (three), 11 (five), 12 (three), 13 (five), 14 (two), 15, 16, 17, 19, 20 (two), 21, 22 (two), 24 and 30 mg/kg.

Allowing for a dry matter content of 90% (*FAO Manual*), the Meeting estimated a maximum residue level of 40 mg/kg for prochloraz in straw and fodder, dry, of cereal grains, replacing the previous recommendations of 15 mg/kg for barley straw and fodder, dry; oats straw and fodder, dry; rye straw and fodder, dry, and wheat straw and fodder, dry. The Meeting also estimated an STMR of 7.2 mg/kg and a highest residue level of 33 mg/kg.

The Meeting agreed that the available data indicated that the proposed maximum residue level, STMR and highest residue level for straw and fodder, dry, after foliar application would also accommodate seed treatment use of prochloraz.

### *Fate of residues during storage*

The Meeting received the results of a study on the fate of prochloraz residues in oranges. Fruit dipped in prochloraz at 0.1–0.2 kg ai/hl and shipped under refrigeration for 44 days were stored at 4 °C or 20 °C for a further 7, 14 or 21 days. No significant degradation of residue was observed during the post-shipping 21-day storage period, as > 87% of the residue remained in the stored fruit. The median retention value was 99% for ambient-stored fruit and 117% for cool-stored fruit.

### *Fate of residues during processing*

The effect of processing on levels of residues of prochloraz was studied in barley, rape-seed and wheat, and the residue levels in oil and press cake were reported in several field trials on sunflower seed; residue levels in green black pepper and in processed white pepper were reported in one trial on pepper. A study on residues in dehydrated and preserved mushrooms was also provided to the Meeting. The processing factors of relevance to estimation of maximum residue levels, the dietary burden of farm animals and dietary risk assessment, shown below, were derived from these studies.

| Raw agricultural commodity | Processed product | No. of samples | Mean processing factor |
|---|---|---|---|
| Barley | Beer | 4 | 0.09 |
| Wheat | Bran (total) | 1 | 4.3 |
| | Flour (unspecified) | 3 | 0.23 |
| | Bread (whole grain) | 1 | 1.3 |
| Rape-seed | Seed cake (meal) | 18 | 0.79 |
| | Refined oil | 4 | < 0.6 |
| Sunflower seed | Seed cake (meal) | 6 | 0.49 |
| Pepper | Black peppercorns | 4 | 0.96 |
| | White peppercorns | 4 | 0.35 |
| Mushrooms | Dehydrated | 3 | 3.7 |
| | Preserved | 2 | 0.4 |
| | Preservation liquor | 2 | 0.65 |

*Wheat* was processed into milled by-products (bran), flour and whole-grain bread, with processing factors of 4.3, 0.23 and 1.3, respectively. On the basis of the STMR value of 0.11 mg/kg for cereal grains, the STMR-Ps were 0.025 mg/kg for wheat flour and 0.14 mg/kg for wholemeal bread.

Wheat milled by-products (bran) is listed as animal feed in the *FAO Manual* (Appendix IX). Allowing for the standard 88% dry matter, the Meeting estimated an STMR-P of 0.54 mg/kg for wheat bran (dry weight).

On the basis of the highest residue level of 1.2 mg/kg, the processing factor of 4.3 and the standard dry matter content of 88%, the Meeting recommended a maximum residue level of 7 mg/kg for wheat bran, unprocessed (dry weight basis).

*Barley* was processed into beer, with a processing factor of 0.09. On the basis of the STMR value of 0.11 mg/kg for cereal grains, the STMR-P for beer was 0.01 mg/kg.

The residue levels in seed cake in trials on rape in Denmark and Germany, matching the GAP of the United Kingdom and Germany, respectively, and used in estimating the maximum residue levels, were: < 0.05, 0.05 (three), 0.07, 0.08 (two) and 0.1 mg/kg. The Meeting established an STMR-P of 0.06 mg/kg for rape-seed meal.

In four processing studies, the residue levels in refined oil from rape-seed containing 0.07–0.12 mg/kg were below the LOQ (< 0.05 mg/kg). Using a processing factor of < 0.6 and an STMR of 0.1 mg/kg for rape-seed, the Meeting established an STMR-P of 0.06 mg/kg for rape-seed oil, edible.

The residue levels in seed cake in three trials on *sunflower seed* in France that were used in estimating the maximum residue level were < 0.1 (two) and 0.15 mg/kg. Taking into account the STMR for sunflower seed (0.1 mg/kg) and the processing factor of 0.49, the Meeting established an STMR-P of 0.05 mg/kg for sunflower seed meal.

The Meeting agreed to use the STMR of 0.1 mg/kg for sunflower seed and the processing factor of < 0.6 derived for refined rape-seed oil to estimate an STMR-P of 0.06 mg/kg for sunflower seed oil (refined).

In a field study in Malaysia on green (fresh) peppercorns, the residues were not concentrated during the sun-drying process used to produce black peppercorns (mean processing factor, 0.96), and the residue levels decreased during husking to produce white peppercorns (mean processing factor, 0.35).

### ***Residues in animal commodities***

#### *Dietary burden of farm animals*

The Meeting estimated the dietary burden of total prochloraz in cows and poultry on the basis of the diets listed in Appendix IX of the *FAO Manua*. Calculations from MRLs and highest residue levels provide the levels in feed suitable for estimating MRLs for animal commodities, while calculations from STMR values for feed are 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 | Dry matter (%) | Residue/Dry matter (mg/kg) | Dietary content (%) | | | Residue contribution (mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Beef cattle | Dairy cattle | Poultry | Beef cattle | Dairy cattle | Poultry |
| Rape meal | – | 0.06 | STMR-P | 88 | 0.07 | | | | | | |
| Sunflower meal | – | 0.05 | STMR-P | 92 | 0.05 | | | | | | |
| Barley straw | AS | 33 | HR | 100 | 33 | **10** | **60** | | 3.3 | 19.8 | |
| Wheat straw | AS | 33 | HR | 100 | 33 | | | | | | |
| Rye straw | AS | 33 | HR | 100 | 33 | | | | | | |
| Oat straw | AS | 33 | HR | 100 | 33 | | | | | | |
| Wheat milled by-products | CF | 0.54 | STMR-P | 100 | 0.54 | **10** | | **20** | 0.05 | | 0.11 |
| Barley grain | GC | 1.2 | HR | 88 | 1.36 | | | | | | |

| Commodity | Group | Residue (mg/kg) | Basis | Dry matter (%) | Residue/Dry matter (mg/kg) | Dietary content (%) | | | Residue contribution (mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Beef cattle | Dairy cattle | Poultry | Beef cattle | Dairy cattle | Poultry |
| Corn grain | GC | 1.2 | HR | 88 | 1.36 | **80** | **40** | **80** | 1.09 | 0.55 | 1.09 |
| Rye grain | GC | 1.2 | HR | 88 | 1.36 | | | | | | |
| Wheat grain | GC | 1.2 | HR | 89 | 1.35 | | | | | | |
| Oat grain | GC | 1.2 | HR | 89 | 1.35 | | | | | | |
| Total | | | | | | 100 | 100 | 100 | **4.4** | **20** | **1.2** |

*Estimated median dietary burden of farm animals*

| Commodity | Group | Residue (mg/kg) | Basis | Dry matter (%) | Residue/Dry matter (mg/kg) | Dietary content (%) | | | Residue contribution (mg/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Beef cattle | Dairy cattle | Poultry | Beef cattle | Dairy cattle | Poultry |
| Rape meal | – | 0.06 | STMR-P | 88 | 0.07 | | | | | | |
| Sunflower meal | – | 0.05 | STMR-P | 92 | 0.05 | | | | | | |
| Barley straw | AS | 7.2 | STMR | 100 | 7.2 | **10** | **60** | | 0.72 | 4.32 | |
| Wheat straw | AS | 7.2 | STMR | 100 | 7.2 | | | | | | |
| Rye straw | AS | 7.2 | STMR | 100 | 7.2 | | | | | | |
| Oat straw | AS | 7.2 | STMR | 100 | 7.2 | | | | | | |
| Wheat milled by-products | CF | 0.54 | STMR-P | 100 | 0.54 | **10** | | **20** | 0.05 | | 0.11 |
| Barley grain | GC | 0.11 | STMR | 88 | 0.13 | | | | | | |
| Corn grain | | 0.11 | STMR | 88 | 0.13 | **80** | **40** | **80** | 0.1 | 0.05 | 0.1 |
| Rye grain | GC | 0.11 | STMR | 88 | 0.13 | | | | | | |
| Wheat grain | GC | 0.11 | STMR | 89 | 0.12 | | | | | | |
| Oat grain | GC | 0.11 | STMR | 89 | 0.12 | | | | | | |
| Total | | | | | | 100 | 100 | 100 | **0.87** | **4.4** | **0.21** |

The total dietary burdens of prochloraz for estimating MRLs for animal commodities (residue levels in animal feeds expressed as dry weight) are 4.4 ppm for beef cattle, 20 ppm for dairy cattle and 1.2 ppm for poultry. The associated median dietary burdens for estimating STMR are 0.87 ppm for beef cattle, 4.4 ppm for dairy cattle and 0.21 ppm for poultry.

*Feeding studies*

The Meeting received information from two studies on the residue levels in tissues and milk from dairy cows dosed with prochloraz for 28 days at an equivalent of 10, 30 and 100 ppm in the diet and from a feeding study in which calves were fed a diet containing prochloraz twice daily, resulting in a rate of 0.263 mg/kg bw (dietary concentration could not be estimated).

In one of the studies in dairy cows, tissues were analysed for total prochloraz residues by gas chromatography with mass spectrometry detection after conversion of the metabolites to 2,4,6-trichlorphenol. The mean recovery efficiency was 89%, and the LOQ was 0.05 mg/kg. At the end of the 28-day treatment period, the mean residue levels in muscle ranged from < 0.05 mg/kg to 0.37 mg/kg in cows at the highest dose. In subcutaneous fat, the mean residue levels ranged from 0.09 mg/kg at the lowest dose to 1.2 mg/kg at the highest dose, and those in peritoneal fat ranged from 0.16 mg/kg to 1 mg/kg for the three groups. The mean residue levels in kidney were 0.52 mg/kg at the lowest dose to 3.2 mg/kg at the highest, and those in liver were 2.8 mg/kg at the lowest dose, 6.4 mg/kg at 30 ppm and 23 mg/kg at 100 ppm.

The results of the study in which calves were dosed at 0.26 mg/kg bw for 28 days were similar to those for cows receiving the lowest dose, with mean residue levels of 2.2 mg/kg in liver, 0.55 mg/kg in kidney, 0.09 mg/kg in fat and 0.06–0.09 mg/kg in muscle.

Residues of free prochloraz and three metabolites were measured in milk from cows dosed twice daily after milking with prochloraz for 28 days at an equivalent of 10, 30 and 100 ppm in the diet. Traces of prochloraz were detected in the group at 100 ppm from day 4 and in the group at 30 ppm after day 28, but all the residue levels were below the reported LOQ of 0.01 mg/kg. No residues of the metabolites BTS 54906 and BTS 54908 were detected in milk from cows at any dose. Trace levels (< 0.01 mg/kg) of BTS 44596 were reported in milk from cows at 30 ppm from day 22, and the average levels in milk from cows at 100 ppm reached a plateau of 0.01 ± 0.003 mg/kg from day 4. Milk sampled and separated on day 24contained average levels of BTS 44596 of 0.005 mg/kg in skim milk and 0.032 mg/kg in cream, suggesting preferential partitioning (six times) into milk fat.

*Maximum residue levels*

As the total dietary burdens of *beef and dairy cattle* are 4.4 and 20 ppm, respectively, the maximum residue levels to be expected in tissues can be obtained by interpolating the results of feeding at a level of 10 or 30 ppm. The maximum residue levels reported were 3.3 mg/kg and 9 mg/kg in liver, 0.24 mg/kg and 0.51 mg/kg in fat, 0.05 mg/kg and 0.14 mg/kg in muscle and 0.59 mg/kg and 1.8 mg/kg in kidney.

The median dietary burdens were 0.87 ppm for beef cattle and 4.4 ppm for dairy cattle. STMR values can be extrapolated from the mean residue levels in tissues of animals at 10 ppm, i.e. 2.8 mg/kg in liver, 0.13 mg/kg in fat, < 0.05 mg/kg in muscle and 0.52 mg/kg in kidney. The mean residue level in milk at both feeding levels was < 0.01 mg/kg,

| Dietary burden (mg/kg)[a]<br>Feeding level [ppm][b] | | Prochloraz residue level (mg/kg)[c] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Milk (mean) | Fat | | Muscle | | Liver | | Kidney | |
| | | | High | Mean | High | Mean | High | Mean | High | Mean |
| MRL beef cattle | (20)<br>[10:30] | | *(0.38)*<br>0.24:0.51 | | *(0.1)*<br>0.05:0.14 | | *(6.2)*<br>3.3:9 | | *(1.2)*<br>0.59:1.8 | |
| MRL dairy cattle | (20)<br>[10:30] | *(< 0.01)*<br>< 0.01:< 0.01 | | | | | | | | |
| STMR beef cattle | (4.4)<br>[5] | | | *(0.057)*<br>0.13 | | *(< 0.022)*<br>< 0.05 | | *(1.23)*<br>2.8 | | *(0.229)*<br>0.52 |
| STMR dairy cattle | (4.4)<br>[5] | *(< 0.0044)*<br>< 0.01 | | | | | | | | |

---

[a] In parentheses, estimated dietary burden

[b] In square brackets, actual feeding levels in transfer studies

[c] 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 tissue (or milk) in the relevant feeding group.

On the basis of the above considerations, the Meeting estimated highest residue levels of 0.1 mg/kg in meat (muscle), 0.38 mg/kg in meat (fat), 6.2 mg/kg in edible offal (mammalian) and 0 mg/kg in milks.

The Meeting estimated maximum residue levels of 0.5 mg/kg (fat) in meat (from mammals other than marine mammals); 10 mg/kg in edible offal, mammalian and 0.05 (*) mg/kg in milks. These recommendations replace the previous recommendations of 0.5 mg/kg for cattle fat, 0.1 (*) mg/kg for cattle meat, 5.0 mg/kg for cattle, edible offal of, and 0.1 (*) mg/kg for milks. The Meeting estimated STMRs of 0.02 mg/kg for meat (muscle), 0.06 mg/kg for meat (fat), 1.2 mg/kg for edible offal (mammalian) and 0 mg/kg for milks.

For poultry, the information provided by the study of metabolism in hens at feeding rates of 5 and 10 ppm in hens was considered by the Meeting to be sufficient for use in estimating maximum residue levels in eggs and poultry tissues. In tissues from birds at 5 ppm, the maximum residue levels were 0.41 mg/kg in liver, 0.029 mg/kg in fat and 0.02 mg/kg in muscle. The average residue level in eggs after a plateau had been reached at day 8 was 0.28 mg/kg. The average residue levels in hens at 5 ppm were 0.34 mg/kg in liver, 0.028 mg/kg in fat, 0.019 mg/kg in muscle and 0.28 mg/kg in eggs (after day 8).

The total dietary burden of poultry is 1.2 mg/kg, and the median dietary burden is 0.21 mg/kg. The Meeting agreed that extrapolation from the results for hens at the 5 ppm feeding level in the metabolism study was appropriate for estimating maximum residue levels, STMRs and highest residue levels

| Dietary burden (mg/kg)[a] Feeding level [ppm][b] | | Prochloraz residue levels (mg/kg)[c] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Eggs (mean) | Fat | | Muscle | | Liver | |
| | | | High | Mean | High | Mean | High | Mean |
| MRL poultry | (1.2) | *(0.0672)* | *(0.007)* | | *(0.0048)* | | *(0.0984)* | |
| | [5] | 0.28 | 0.029 | | 0.02 | | 0.41 | |
| STMR poultry | (0.21) | *(0.0118)* | | *(0.0012)* | | *(0.0008)* | | *(0.0143)* |
| | [5] | 0.28 | | 0.028 | | 0.019 | | 0.34 |

[a] In parentheses, estimated dietary burden

[b] In square brackets, actual feeding levels in transfer studies

[c] 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 tissue in the relevant feeding group.

On the basis of this extrapolation, the Meeting estimated highest residue levels of 0.005 mg/kg for poultry meat, 0.007 mg/kg for poultry fats, 0.1 mg/kg for poultry, edible offal of, and 0.07 mg/kg for eggs.

The Meeting estimated maximum residue levels of 0.05 (*) mg/kg for poultry meat, 0.2 mg/kg for poultry, edible offal of, and 0.1 mg/kg for eggs; it also estimated STMRs of 0.001 mg/kg in poultry meat (muscle), 0.001 mg/kg in poultry meat (fat), 0.015 mg/kg in poultry, edible offal of, and 0.012 mg/kg in eggs.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The evaluation of prochloraz resulted in recommendations for MRLs and STMRs for raw and processed commodities. Data were available on the consumption of 35 food commodities, and these were used in calculating dietary intake. The results are shown in Annex 3.

The IEDIs in the five GEMS/Food regional diets, on the basis of the estimated STMRs, represented 7–10% of the ADI of 0–0.01 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of prochloraz from uses that have been considered by the JMPR is unlikely to present a public health concern.

### *Short-term intake*

The IESTI of prochloraz was calculated for the food commodities (and their processing fractions) for which maximum and highest residue levels had been estimated and for which data on consumption were available. The results are shown in Annex 4.

The IESTI varied from 0 to 130% of the ARfD (0.1 mg/kg bw) for the general population and from 0 to 150% of the ARfD for children ≤ 6 years. The short-term intake of mushrooms, for which the calculation was made, represented 150% of the ARfD for children ≤ 6 years and 130% of the ARfD for the general population. The information provided to the Meeting precluded a conclusion that the short-term dietary intake of mushrooms would result in residue levels below the ARfD.

## 4.24 PROPICONAZOLE (160)

### TOXICOLOGY

Propiconazole is the ISO approved name for 1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl-methyl]-1*H*-1,2,4-triazole, a systemic fungicide that acts by inhibition of ergosterol biosynthesis. Propiconazole was evaluated toxicologically by the JMPR in 1987, when an ADI of 0–0.04 mg/kg bw was established on the basis of the NOAEL of 4 mg/kg bw per day for effects on body weight, clinical chemistry and haematology in a 2-year study in rats, and this was supported by the NOAEL of 7 mg/kg bw per day in a 1-year study in dogs. Propiconazole was considered by the present Meeting within the periodic review programme of the CCPR. The Meeting reviewed new data on propiconazole that had not been reviewed previously and relevant data from the previous evaluation.

After oral administration of radiolabelled propiconazole to rats and mice, the radiolabel is rapidly ($C_{max}$ at 1 h) and extensively (> 80% of the administered dose) absorbed and widely distributed, with the highest concentrations being found in the liver and kidney. Excretion of the radiolabel is rapid (80% in 24 h) with significant amounts being found in the urine (39–81%) and the faeces (20–50%), the proportions varying with dose, species and sex. There is a significant degree of biliary excretion and subsequent enterohepatic recirculation. There was no evidence for bioaccumulation with tissue or carcass residues being typically < 1% of the administered dose 6 days after dosing. Propiconazole is extensively metabolized and < 5% of the dose remains as parent compound; however, many metabolites have not been identified. The primary metabolic steps involve oxidation of the propyl side-chain on the dioxolane ring to give hydroxy or carboxylic acid derivatives. Hydroxylation of the chlorophenyl and triazole rings followed by conjugation with sulfate or glucuronide was also detected. There is evidence for only limited cleavage between the triazole and chlorophenyl rings. The extent of cleavage of the dioxolane ring was significantly different according to species and sex, representing about 60% of urinary radioactivity in male mice, 30% in female mice and 10–30% in male rats. In rats, about 30% propiconazole is absorbed within 10 h of dermal application.

Propiconazole has moderate acute oral toxicity in rats and mice ($LD_{50}$ values, about 1500 mg/kg bw) and low acute dermal ($LD_{50}$ values, > 4000 mg/kg bw) and inhalation toxicity ($LC_{50}$, > 5 mg/l of air). Propiconazole is not an eye irritant in rabbits, but is irritating to rabbit skin and is a skin sensitizer in guinea-pigs in the Magnusson and Kligman test.

Decreased body-weight gain was seen in short- and long-term studies of toxicity and studies of developmental and reproductive toxicity and was often linked with reduced food consumption. In studies of repeated doses, liver was the primary target organ for toxicity attributable to propiconazole. In rats, erythrocyte parameters were reduced and a range of clinical chemistry changes were seen, however, with the exception of reduced chloride and cholesterol concentrations, there was no consistent pattern between sexes and studies, and results were generally within the physiological range.

In two studies, mice given diets containing propiconazole at ≥ 850 ppm for up to 17 weeks had increases in liver weight, reduced concentrations of serum cholesterol and increased hepatocyte hypertrophy, vacuolation and necrosis. The findings were present after 4 weeks and did not progress with increased duration of dosing. The NOAEL was 500 ppm (equal to 65–85 mg/kg bw per day) in both studies.

Rats given propiconazole at 450 mg/kg bw per day for 28 days by gavage exhibited a range of effects. Males had reductions in body-weight gain, while females had clinical signs of toxicity and reductions in erythrocyte parameters. Both sexes had increased liver weights and hepatocyte hypertrophy, with hepatocyte necrosis also being seen in females. Increases in liver weight with hepatocyte hypertrophy were seen at 150 mg/kg bw per day, but these effects were not considered to be adverse and the NOAEL was this dose. In a 13-week dietary study in rats, reductions in body-weight gain, increased relative liver weight and increased γ-glutamyltranspeptidase activity was seen in both sexes at 6000 ppm. In females, erythrocyte parameters were reduced at this dose. The NOAEL was 1200 ppm (equal to 76 mg/kg bw per day).

Dogs appeared to be sensitive to the local effects of propiconazole as manifested by gastrointestinal tract irritation at ≥ 8.4 mg/kg bw per day; the NOAELs were 250 ppm (equal to 6.9 mg/kg bw per day) after 90 days and 1.9 mg/kg bw per day after 1 year. No systemic effects were seen in dogs receiving 8.4 mg/kg bw per day for 1 year or 1250 ppm (equal to 35 mg/kg bw per day) for 90 days, the highest doses tested.

In a 3-week (five applications per week) study of dermal toxicity in rabbits, tremors, dyspnoea and ataxia were increased at ≥ 1000 mg/kg bw per day. The NOAEL was 200 mg/kg bw per day. In a 13-week (5 days per week; 6 h per day) study in rats treated by inhalation, reduced body-weight gain was seen in females at 0.19 mg/l of air; the NOAEC was 0.085 mg/l of air.

The carcinogenic potential of propiconazole was studied in one study in rats and in two studies in mice. In a 2-year dietary study in male and female mice and an 18-month dietary study in male mice, the liver was the only target organ. At ≥ 500 ppm, there were decreases in body-weight gain and serum concentration of cholesterol and increases in liver weight, hepatocellular hypertrophy and hepatocellular vacuolation. The NOAEL for non-neoplastic effects in both studies was 100 ppm (equal to 11 mg/kg bw per day). Propiconazole was a hepatocarcinogen only in male mice, on the basis of significant increases in the incidence of liver tumours at ≥ 850 ppm (equal to 108 mg/kg bw per day), with a NOAEL of 500 ppm (equal to 59 mg/kg bw per day). Assays for hepatocyte proliferation (measured by bromodeoxyuridine incorporation) in mice showed qualitative similarities between propiconazole and phenobarbital. The doses that produced increases in tumour incidences (≥ 850 ppm) also produced cell proliferation, increased liver weight and hepatocyte hypertrophy. Studies of liver enzyme induction in mice showed that propiconazole increased the activity of a number of cytochrome P450s, particularly Cyp2b and exhibited similar characteristics to a phenobarbital-type inducer of xenobiotic metabolizing enzymes. The progression from cytochrome P450 (Cyp2b) induction, initial mitogenic response, hepatocyte hypertrophy and increased liver weight to tumours is consistent with a mode of action similar to that of phenobarbital.

At 2500 ppm (96 mg/kg bw per day) in a 2-year dietary study in rats, there were reductions in body-weight gain in both sexes. Increased incidences of enlarged hepatocytes were present in males and increases in atrophy of the exocrine pancreas and dilatation of the uterine lumen in females. Slight (< 10%), transient reductions in body-weight gain, variations in clinical chemistry and haematology parameters that fell within physiological ranges at 500 ppm (equal to 18 mg/kg bw per day) were not considered to be adverse. Propiconazole was not carcinogenic in rats at doses of up to 2500 ppm (equal to 96 mg/kg bw per day). The NOAEL in the 2-year study in rats was 500 ppm (equal to 18 mg/kg bw per day).

Propiconazole gave negative results in an adequate battery of studies of genotoxicity in vitro and in vivo.

The Meeting concluded that propiconazole was unlikely to be genotoxic.

On the basis of the above consideration of the male mouse liver tumours, the high doses required to induce tumours, the likely mechanism of action, the absence of tumorigenicity in rats and the negative results in studies of genotoxicity, the Meeting concluded that propiconazole was unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, reproductive parameters were not affected by treatment with propiconazole. At 500 ppm (equivalent to 35 mg/kg bw per day) dams had reduced body-weight gains ($p < 0.01$) and both sexes exhibited hepatoxicity, thus the NOAEL for parental toxicity was 100 ppm (equivalent to 7 mg/kg bw per day). The NOAEL for offspring toxicity was 100 ppm (equivalent to

7 mg/kg bw per day) on the basis of decreased pup body weights in the $F_{2b}$ litters ($p < 0.01$). The NOAEL for reproductive effects was 500 ppm (equivalent to 35 mg/kg bw per day) on the basis of reduced pup survival at 2500 ppm (equivalent to 175 mg/kg bw per day).

Three studies of developmental toxicity were conducted in rats and one in rabbits. In the first study in rats, at the highest dose of 300 mg/kg bw per day there was evidence of maternal toxicity and retarded development, but no malformations. In the second study, propiconazole caused developmental delay (incomplete ossification of sternebrae and rudimentary cervical ribs) at a dose of 90 mg/kg bw per day, which also produced a slight, transient reduction in food consumption and body-weight gain at the initiation of dosing. The NOAEL was 90 mg/kg bw per day for maternal effects and 30 mg/kg bw per day for developmental effects. A low incidence of cleft palate was observed at 90 mg/kg bw per day (one fetus, 0.3%) and at 360/300 mg/kg bw per day (two fetuses, 0.7%) in the presence of severe maternal toxicity. The maternal toxicity included lethargy, ataxia, salivation and reductions in food consumption and body-weight gain at the start of the dosing period. The cleft palate finding was also seen at a low incidence in rats in an extensive study that specifically investigated the palate and jaw at a single dose of 300 mg/kg bw per day. Cleft palates were detected in two out of 2064 fetuses of treated animals versus none in the 2122 fetuses of controls, in the presence of severe maternal toxicity. Marked maternal toxicity was observed throughout the treatment period, included reductions in food consumption and body-weight gain, ataxia, coma, lethargy and prostration and three treatment-related deaths among 189 dams. Cleft palate is a very rare but occasional finding in control rats and there were published data that indicated testing compounds at maternally toxic doses is associated in some way with the induction of a number of malformations, including cleft palate.

Propiconazole was not teratogenic in rabbits. The NOAEL for fetal effects was 250 mg/kg bw per day on the basis of an increased incidence of the formation of thirteenth ribs at 400 mg/kg bw per day in the presence of maternal body-weight loss, signs of toxicity and abortions. The NOAEL for maternal toxicity was 100 mg/kg bw per day on the basis of reduced food consumption and body-weight loss at 250 mg/kg bw per day.

No studies of neurotoxicity with propiconazole were available; however, no evidence of neurotoxicity was apparent in any of the available studies.

Humans exposed to formulated products containing propiconazole have shown local irritant reactions. No evidence of sensitization was seen in an epicutaneous test in 20 volunteers.

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

### *Toxicological evaluation*

The Meeting established an ADI of 0–0.07 mg/kg bw based on the NOAEL of 7 mg/kg bw per day in a multigeneration study of reproductive toxicity in rats and a 100-fold safety factor. This value covers all other end-points and is supported by NOAELs of 11 mg/kg bw per day in a 24-month study in mice and 18 mg/kg bw per day in a 2-year study in rats. This ADI is protective against the local effects seen in the gastrointestinal tract in dogs (NOAEL, 1.9 mg/kg bw per day), which were considered to be concentration-dependent and hence would merit a safety factor of 25.

An ARfD of 0.3 mg/kg bw was established based on the NOAEL of 30 mg/kg bw per day in the study of developmental toxicity in rats and a 100-fold safety factor. The NOAEL was identified on the basis of slight increases in rudimentary ribs and unossified sternebrae at 90 mg/kg bw per day, which could not be discounted. This provides an adequate margin over the maternal toxicity and cleft palate seen at 300 mg/kg bw per day. The Meeting noted that the highest dose tested in dogs was 35 mg/kg bw per day and that the proposed ARfD would be protective for any potentially acute effects observed in dogs.

A toxicological monograph was prepared.

*Levels relevant to risk assessment*

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | 24-month study of toxicity and carcinogenicity[a, e] | Toxicity | 100 ppm, equal to 11 mg/kg bw per day | 500 ppm, equal to 59 mg/kg bw per day |
| | | Carcinogenicity | 500 ppm, equal to 59 mg/kg bw per day | 850 ppm, equal to 108 mg/kg bw per day |
| Rat | 2-year study of toxicity and carcinogenicity[a] | Toxicity | 500 ppm, equal to 18 mg/kg bw per day | 2500 ppm, equal to 96 mg/kg bw per day |
| | | Carcinogenicity | 2500 ppm, equal to 96 mg/kg bw per day[c] | — |
| | Two-generation study of reproductive toxicity[a] | Parental toxicity | 100 ppm, equivalent to 7 mg/kg bw per day | 500 ppm, equivalent to 35 mg/kg bw per day |
| | | Offspring toxicity | 100 ppm, equivalent to 7 mg/kg bw per day | 500 ppm, equivalent to 35 mg/kg bw per day |
| | Developmental toxicity[b] | Maternal toxicity, | 90 mg/kg bw per day | 300 mg/kg bw per day |
| | | Embryo- or fetotoxicity | 30 mg/kg bw per day | 90 mg/kg bw per day |
| Rabbit | Developmental toxicity[b] | Maternal toxicity | 100 mg/kg bw per day | 250 mg/kg bw per day |
| | | Embryo- or fetotoxicity | 250 mg/kg bw per day | 400 mg/kg bw per day |
| Dog | 3-month study of toxicity[a] | Systemic effects | 1250 ppm, equal to 35 mg/kg bw per day[c] | — |
| | | Local effects on gastrointestinal tract | 250 ppm, equal to 6.9 mg/kg bw per day | 1250 ppm, equal to 35 mg/kg bw per day [c] |
| | 12-month study of toxicity[d] | Systemic effects | 8.4 mg/kg bw per day[c] | — |
| | | Local effects on gastrointestinal tract | 1.9 mg/kg bw per day | 8.4 mg/kg bw per day[c] |

[a] Diet
[b] Gavage
[c] Highest dose tested
[d] Capsules
[e] Two studies

*Estimate of acceptable daily intake for humans*

0–0.07 mg/kg bw

*Estimate acute reference dose*

0.3 mg/kg bw

*Studies that would provide information useful for continued evaluation of the compound*

Further observations in humans

### ***Critical end-points for setting guidance values for exposure to propiconazole***

| *Absorption, distribution, excretion and metabolism in animals* | |
|---|---|
| Rate and extent of oral absorption: | > 80% in 48 h |
| Dermal absorption | About 30% in 10 h (rat) |
| Distribution: | Widely distributed; highest concentrations in the liver and kidney |
| Potential for accumulation: | Limited |
| Rate and extent of excretion: | > 95% in the faeces and urine in 48 h; extensive enterohepatic recirculation (68% of administered dose in bile) |

| | |
|---|---|
| Metabolism in animals | Extensive; oxidation of propyl side-chain; hydroxylation of phenyl and triazole rings, plus conjugation; cleavage of dioxolane ring |
| Toxicologically significant compounds (animals, plants and the environment) | Propiconazole; triazolyl alanine and triazolyl acetic acid are produced in plants but not animals |
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | 1517 mg/kg bw |
| Rat, $LD_{50}$, dermal | > 4000 mg/kg bw |
| Rat, $LC_{50}$, inhalation | > 5 mg/l of air (4-h; nose only) |
| Rabbit, dermal irritation | Irritating |
| Rabbit, eye irritation | Not irritating |
| Skin sensitization | Sensitizing (Magnusson and Kligman test) |
| *Short-term studies of toxicity* | |
| Target/critical effect | Body weight, liver (mice, rats); erythrocytes (rat); stomach (dog) |
| Lowest relevant oral NOAEL | 50 ppm, equal to 1.9 mg/kg bw per day (1-year study in dogs) |
| Lowest relevant dermal NOAEL | 200 mg/kg bw per day (5 days/week) |
| Lowest relevant inhalation NOAEL | 0.085 mg/l (6 h/day; 5 days/week) |
| *Genotoxicity* | Not genotoxic in vitro or in vivo |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Liver hypertrophy and tumours (mice)<br>Liver, body weight, uterine lumen dilatation (rats) |
| Lowest relevant NOAEL | 100 ppm, equal to 11 mg/kg bw per day (mice) |
| Carcinogenicity | Hepatocellular tumours in male mice (≥ 850 ppm, equal to 108 mg/kg bw per day). Phenobarbital-type mechanism. The NOAEL was 500 ppm (equal to 59 mg/kg bw per day).<br>Unlikely to pose a carcinogenic risk to humans |
| *Reproductive toxicity* | |
| Reproduction target/critical effect | Reduced pup weight at parentally toxic dose |
| Lowest relevant reproductive NOAEL | 100 ppm, equivalent to 7 mg/kg bw per day (rat) |
| Developmental target/critical effect | Skeletal variations |
| Lowest relevant developmental NOAEL | 30 mg/kg bw per day (rat) |
| *Neurotoxicity/delayed neurotoxicity* | No specific studies; no findings in other studies |
| *Other toxicological studies* | |
| Mechanism of induction of liver tumours | Phenobarbital-type mode of action indicated by cell proliferation, liver weight and microsomal enzyme induction patterns |
| *Medical data* | Local irritation associated with exposure to the formulated product |

| *Summary* | *Value* | *Study* | *Safety factor* |
|---|---|---|---|
| ADI | 0–0.07 mg/kg bw | Reproductive toxicity in rats: pup and parental body weight | 100 |
| ARfD | 0.3 mg/kg bw | Developmental toxicity in rats: embryo- or fetoxicity | 100 |

## DIETARY RISK ASSESSMENT

### *Long-term intake*

Theoretical maximum daily intake were estimated for the commodities of human consumption for which Codex (CX) MRLs existed (Annex 3). The intakes in the five GEMS/Food regional diets ranged from 0 to 1% of the maximum ADI. The Meeting concluded that the long-term intake of residues of propiconazole resulting from uses considered by the JMPR is unlikely to present a public health concern.

### *Short-term intake*

An ARfD of 0.3 mg/kg bw was established for propiconazole at this Meeting, but IESTIs could not be calculated, as the residues of the compound were evaluated before procedures for estimating STMRs and highest residue levels in the edible portion of a commodity found in trials used to estimate an MRL had been established. Propiconazole was scheduled for periodic evaluation of residues in 2007, when the risk assessment would be finalized.

## 4.25 PROPINEB (105)

## TOXICOLOGY

At the present Meeting, the FAO Panel of Experts asked the WHO Core Assessment Group to establish an ARfD for propineb on the basis of the data available to the 1993 JMPR. The results of this evaluation are given in section 2.3.1.

## RESIDUE AND ANALYTICAL ASPECTS

Propineb is a broad-spectrum dithiocarbamate fungicide used on many crops. It has been evaluated several times, the initial evaluation being in 1977 and the latest in 1993. It was listed in the periodic review programme of the CCPR at its Thirty-third Session for residue review by the 2003 JMPR (ALINORM 99/24) but was re-scheduled for evaluation in 2004. The Meeting received information on the metabolism and environmental fate of propineb, methods of residue analysis, freezer storage stability, national registered use patterns, the results of supervised residue trials and national MRLs. Information on GAP, national MRLs and residue data were submitted by Australia and Japan.

The 1993 JMPR established an ADI for propineb of 0–0.007 mg/kg bw, and the 1999 JMPR established an ADI of 0–0.0003 and an ARfD of 0.003 mg/kg bw for the metabolite propylenethiourea.

### *Metabolism*

#### *Animals*

The Meeting received the results of studies of the metabolism of propineb in rats and a lactating goat. The biotransformation and degradation pathways in the goat were similar to those established in studies of rat metabolism. The metabolism of $^{14}$C-propineb proceeds mainly via propylenethiourea and propylene diamine.

Once formed, propylenethiourea undergoes further reactions, leading to propylene urea, which can in turn be transformed by methylation to 2-methoxy-4-methylimidazoline. Other metabolites of propylenethiourea include 2-methylthio-4-methylimidazoline and 2-sulfonyl-4-methylimidazoline; the latter can undergo further metabolism to 4-methylimidazoline and *N*-formylpropylene diamine. In the lactating goat, the main metabolites detected were 2-methylthio-4-methylimidazoline in milk (48% TRR), kidney (25% TRR) and muscle (17% TRR), a sulfonyl conjugate of propylenethiourea in liver (23% TRR) and kidney (18% TRR) and propylenethiourea in fat and muscle (23% TRR).

*Plants*

The Meeting received the results of studies on the metabolism of propineb in apples, grapes, potato vines and tomato. The metabolism of $^{14}$C-propineb was similar. It proceeds mainly via propylenethiourea (apple, 15% TRR; grape, 5.3% TRR; tomato, 30% TRR; potato vine, 3.5% TRR), which is itself further metabolized to propylene urea (apple, 5% TRR; tomato, 6.7% TRR; potato vine, 9.7% TRR). Propylenethiourea is also transformed to 4-methylimidazoline (apple, 10% TRR; tomato, 5% TRR; potato vine, 9.4% TRR), which on ring opening and oxidation gives *N*-formyl-propylene diamine (tomato, 6.7% TRR). The main metabolites identified in potato tubers after foliar spray were propylene urea (21% TRR) and a conjugate of its oxidation product 5-methylhydantoin (11% TRR). In a study on grapes harvested 0, 21 and 43 days after the last of one or three foliar applications of [1-propane-$^{14}$C]propineb, 83% of the $^{14}$C was located on the surface of the fruit 43 days after three foliar sprays. Propineb was the main component of the radiolabelled residue at all times sampled (about 42% TRR at 43 days), metabolites each accounting for < 6% of the residues.

In contrast, when two applications of $^{14}$C-propineb were made at the pre-blossom growth stage and grapes harvested about 100 days after the last application, most of the $^{14}$C was associated with small molecules arising from incorporation of $^{14}$C into natural plant products. Only low levels of propineb, propylene urea and *N*-formylpropylene diamine were detected, all at < 2% TRR.

After one or three applications of $^{14}$C-propineb to individual fruit on an apple tree, most (55–59%) of the $^{14}$C residue 14 days after application was located on the surface of the fruit. After 14 days, propineb accounted for 15–22% of the TRR, and no individual metabolite was present at > 10% TRR.

The metabolism of $^{14}$C-propylenethiourea was also studied after application to apples. Propylenethiourea (metabolite 1) undergoes rapid degradation on apples, only 0.7% of the applied $^{14}$C remaining on or in the peel 3 days after application. The main metabolite of propylenethiourea is the main metabolite of propineb, 4-methyl-imidazoline.

In greenhouse tomatoes harvested 7 days after four foliar applications of $^{14}$C-propineb, most of the TRR was located on the surface of the fruit (about 70%), propineb accounting for 11% of the TRR. With the exception of propylenethiourea, which accounted for 30% of the TRR, all other metabolites were present at < 10% of the TRR.

In potato tubers and vines harvested 14 days after four foliar applications of $^{14}$C-propineb, the $^{14}$C residues in vines were mainly propineb (29%), with smaller amounts of propylene urea (10%) and 4-methylimidazoline (6.4%). Propylenethiourea was only a minor metabolite (3.5% TRR). In contrast, propineb and propylenethiourea were not detected in tubers. Propylene urea was the main metabolite (21%), with smaller amounts of a derivative of 5-methylhydantoin (11%). Most of the $^{14}$C in tubers was incorporated into natural products (33%).

### *Environmental fate*

The Meeting received information on the behaviour and fate of propineb during solution photolysis in aerobic soil metabolism. Information was also provided on the soil adsorption properties of propineb and on its behaviour and fate during anaerobic soil metabolism and column leaching of aged residues. Consistent with the policy outlined by the 2003 JMPR, only data on environmental fate relevant to residues of propineb in crops were evaluated.

Crop rotation studies were not provided; however, the aerobic soil metabolism of propineb was rapid, with inferred degradation half-lives of < 1 day. The main degradate formed was propylene urea. In aqueous solution, propineb is readily hydrolysed, the rate of hydrolysis increasing with pH; the $DT_{50}$ values were 1–5 days. The rate of degradation in the field and in aquatic environments is fast, and propineb is not expected to persist in the environment.

### *Methods of analysis*

Propineb residues are measured as $CS_2$ or propylene diamine formed by a common acid hydrolysis step. Samples in the field trials were analysed for propineb as $CS_2$ (spectrophotometry) or propylene diamine (gas chromatography with electron capture or mass spectrometry detection) and for propylenethiourea (HPLC with ultraviolet detection, gas chromatography with flame photometricf detection). LOQs of 0.05–0.1 mg/kg for propineb and 0.01 mg/kg for propylenethiourea were reported to be achievable in numerous commodities.

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

The Meeting received information on the stability of propineb residues during storage of analytical samples at freezer temperatures. The available data indicate that the combined residues of propineb and propylenethiourea are stable under frozen storage conditions (–20 °C) in and on the following commodities (storage interval in parentheses): tomatoes (2 years); tomato juice (2 years); tomato marc (2 years) and potatoes (2 years for propineb, 2 weeks for propylenethiourea).

### *Definition of the residue*

The studies of metabolism in grapes, apples and tomatoes after spraying with propineb demonstrated rapid degradation of the residues on the surface of plant parts. The patterns of metabolites found were similar in different species of plants. The main metabolites found in plants—propylenethiourea, propylene urea, 4-methylimidazoline, 2-sulfonyl-4-methylimidazoline and *N*-formylpropylene diamine—were also detected in animals. The Meeting agreed that propineb and propylenethiourea should be regarded as the residues of toxicological concern.

For estimating dietary intake and to enable comparison of the calculated intakes with the ADI, the residues should be expressed in terms of propineb (propineb = $1.9 \times CS_2$).

Currently, the residue definition for dithiocarbamates including propineb is ‘total dithiocarbamates, determined as $CS_2$, evolved during acid digestion and expressed as mg $CS_2$/kg’. Propineb can be determined by a specific method that measures both $CS_2$ and the amine (propylene diamine) released on acid hydrolysis. Therefore, separate MRLs could be established for propineb. Until specific methods are developed for all dithiocarbamates, however, the listing of one compound under two different residue definitions would be confusing for analysts and enforcement agencies. The *FAO Manual* (page 51) states that no compound, metabolite or analyte should be listed in more than one residue definition. In national systems, the residue definition for propineb is generally in terms of $CS_2$.

The Meeting agreed that the residue definition applicable to propineb should continue to be that for dithiocarbamates in general. For estimation of dietary intake and for the risk assessment component relating to exposure, the metabolite propylenethiourea is considered to be toxicologically relevant and must be accounted for. For an overall risk assessment of ‘thyroid-active’ dithiocarbamates such as propineb, the 1997 JMPR “agreed that it is necessary to combine not only the intake of different parent pesticides but also the intake of [ethylene thiourea] or propylenethiourea” and recommended that an ADI adjustment approach be used. Therefore, in estimating dietary intake, residues of both propineb and propylenethiourea must be accounted for and their relative toxicity taken into account. A conservative approach is to sum the residues after scaling the propylenethiourea residues for 'potency' on the basis of the ratio of the ADIs for propineb and propylenethiourea (2.3), in order to estimate STMRs, and the ratio to ARfDs (3.3) for estimating the highest residue levels. This approach has been used for dimethoate–omethoate and acephate–methamidophos. The ratios are based on mass and do not require correction for relative molecular mass.

For estimation of the STMR for propineb, residue = propineb + (2.3 × propylenethiourea)

For estimation of the highest reside level for propineb, residue = propineb + (3.3 × propylenethiourea)

*Definition of propineb residue for compliance with MRLs*: Total dithiocarbamates, determined as $CS_2$, evolved during acid digestion and expressed as mg $CS_2$/kg

*Definition of propineb residue for estimation of dietary intake*: propineb and propylenethiourea

These definitions apply to plant and animal commodities.

***Results of supervised trials on crops***

The results of supervised trials were available on the use of propineb on apple, asparagus, cabbage, cherry, Chinese cabbage, celery, citrus (orange), cucumber, garlic, grape, leek, lettuce, melon, onion, olive, pear, pepper, potato, tomato and watermelon.

The Meeting decided to use only data from trials in which propineb was determined as $CS_2$ for estimation of maximum residue, STMR and highest reside levels. In some cases, untreated control samples also contained residues of $CS_2$. Trials were considered acceptable if the residue levels in untreated control samples were < 10% of the residue in the treated crop or, when propineb was also determined as propylene diamine, there was satisfactory agreement between the results for propineb determined as $CS_2$ and propylene diamine.

The following relation is useful when considering the data: $CS_2$ residue (mg/kg) = 0.52 × propineb residues (mg/kg).

*Citrus fruit*

Trials on citrus were conducted in Brazil and Japan but were provided only in summary form, which was unsuitable for the purpose of estimating maximum residue levels.

*Pome fruit*

Trials on apple and pear were conducted in Belgium (GAP, 0.49–0.71 kg ai/ha fruit tree leaf wall, equivalent to 0.84–1.6 kg ai/ha for a standard orchard, applied just after flowering), Germany (GAP, 1.58 kg ai/ha, 0.105 kg ai/hl, 28-day PHI), Italy (GAP, 0.105–0.14 kg ai/hl, 28-day PHI) and Spain (GAP for pome fruit, 0.14–0.21 kg ai/hl, 28-day PHI). The trials conducted in Germany, Italy and Spain did not match GAP in the respective countries and were evaluated against the GAP of Belgium.

In two trials in Belgium and one in Germany on *apple*, the residue levels of propineb (measured as $CS_2$) in untreated controls were unacceptable. One trial in Belgium approximated Belgian GAP, with levels of propineb residues < 0.10 mg/kg (propylenethiourea, < 0.01 mg/kg). In a further trial in Germany and one in Spain that approximated Belgian GAP, the residue levels were < 0.10 and < 0.10 mg/kg (propylenethiourea, < 0.01 (two) mg/kg).

Trials on *pear* were conducted in Belgium (GAP, 0.49–0.71 kg ai/ha fruit tree leaf wall, equivalent to 0.84–1.6 kg ai/ha for a standard orchard, applied just after flowering), Germany (GAP, 1.58 kg ai/ha, 0.105 kg ai/hl, 28-day PHI) and Italy (GAP, 0.105–0.14 kg ai/hl, 28-day PHI). One trial in Belgium and one