## DIETARY RISK ASSESSMENT

### *Long term intake*

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

The International Estimated Daily Intakes in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 0–1% of the maximum ADI of 0.2 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of dimethomorph from uses that have been considered by the JMPR is unlikely to present a public health concern.

### *Short-term intake*

The international estimated short-term intake (IESTI) for dimethomorph was calculated for the food commodities (and their processing fractions) for which maximum residue levels and HRs were estimated and for which consumption data was available. The results are shown in Annex 4.

The IESTI varied from 0–10% of the ARfD (0.6 mg/kg bw) for the general population. The IESTI varied from 0–20% of the ARfD for children 6 years and below. The Meeting concluded that the short-term intake of residues of dimethomorph from uses considered by the Meeting was unlikely to present a public health concern.

## 5.12 FENITROTHION (037)

## TOXICOLOGY

Fenitrothion is the ISO approved name for O,O-dimethyl O-4-nitro-m-tolyl phosphorothioate (IUPAC) (CAS No. 122-14-5), a broad-spectrum organophosphorus pesticide. Its toxicity was first evaluated by the JMPR in 1969, and re-evaluated in 1974, 1977, 1982, 1984, 1986, and 1988. The 2000 JMPR confirmed the ADI of 0–0.005 mg/kg bw based on a NOAEL of 0.5 mg/kg bw per day in a 2-year study of toxicity in rats, that had been established by the 1988 JMPR. Also at the 2000 JMPR, an ARfD of 0.04 mg/kg bw was established based on a NOAEL of 0.36 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in a study in human volunteers.

The 2004 JMPR noted that some estimations of long-term and short-term intake exceeded the ADI or ARfD that had been established by the 2000 JMPR. The 2004 JMPR concluded that a review of the toxicological database of fenitrothion might enable a refinement of the ADI or ARfD, particularly when concepts such as setting of an overall NOAEL or deriving compound-specific adjustment factors, were taken into account. Owing to the intake concerns identified, the CCPR at its 38th Session in 2006[28] asked JMPR to consider possible refinement of the ADI and ARfD for fenitrothion. Since no relevant new toxicological data had been submitted for evaluation, the data from previous evaluations conducted by the JMPR were reconsidered by the present Meeting.

For technical fenitrothion, specifications have been published as *WHO specification and evaluation for public health pesticides: technical fenitrothion* (1999).[29] Specifications have also been established for other formulations of fenitrothion.

### Toxicological evaluation

[28] Codex Alimentarius Commission. *Report of the 38th Session of the Codex Committee on Pesticide Residues, 3–8 April 2006, Fortaleza, Brazil* (ALINORM06/29/24).

[29] Available from: http://www.who.int/whopes/quality/en/Fenitrothion.pdf

The Meeting reviewed the toxicological database for fenitrothion with regard to establishing an overall NOAEL as a basis for the ADI. Inhibition of brain cholinesterase activity was identified as the critical effect after administration of repeated doses to rats. Based on a NOAEL of 0.5 mg/kg bw per day in a 2-year study of toxicity in rats, a NOAEL of 0.6 mg/kg bw per day in a 6-month study of toxicity in rats and a NOAEL of 0.57 mg/kg bw per day in a 3-month study of ocular toxicity in rats, an overall NOAEL of 0.6 mg/kg bw per day was established. The LOAELs for these studies were 1.5, 2.0 and 1.7 mg/kg bw per day, respectively. The NOAEL of 1.3 mg/kg bw per day in a 3-month study of neurotoxicity in rats was considered to be unsuitable as an overall NOAEL, since it was only slightly lower than the lowest LOAEL of 1.5 mg/kg bw per day and was associated with statistically significant inhibition of brain cholinesterase activity by 15%.

The Meeting also reviewed the toxicological database for fenitrothion with regard to deriving a chemical-specific assessment factor (CSAF). The available information was considered to be insufficient for the assessment of toxicokinetic and toxicodynamic differences between rodents and humans. Neither reliable data on concentrations in the general circulation (such as clearance or AUC) nor data on the concentration–effect relationship in target tissues were available for rats. Also, the Meeting considered that the use of a CSAF for human variability was inappropriate. The available data on plasma toxicokinetics were derived from 12 individuals only, which is an adequate sample to define the central tendency, but inadequate to define the potential variability in the human population. With regard to the acute toxicity of fenitrothion, the Meeting concluded that critical effects (inhibition of brain and/or erythrocyte cholinesterase activity) may not be related to the $C_{max}$ but to AUC, on the basis of the slow recovery of the inhibition of cholinesterase activity and the evidence of slow clearance. Consequently, no modification of the standard safety factor for establishing the ARfD was considered to be justified.

The Meeting refined the ADI to 0–0.006 mg/kg bw based on the overall NOAEL of 0.6 mg/kg bw per day for inhibition of brain cholinesterase activity in repeat-dose studies of toxicity in rats and a safety factor of 100. The 4-day study in human volunteers was not considered suitable for establishing an ADI because of its short duration and the associated absence of steady-state kinetics.

The Meeting identified the 4-day study in human volunteers to be the most suitable basis for setting the ARfD. The Meeting confirmed the ARfD of 0.04 mg/kg bw that was established by the 2000 JMPR, based on a NOAEL of 0.36 mg/kg bw for inhibition of erythrocyte cholinesterase activity in humans and a safety factor of 10.

A toxicological monograph was not prepared.

***Levels relevant to risk assessment***

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Rat | Six-month study of toxicity[a] | Toxicity (inhibition of brain acetylcholinesterase activity) | 10 ppm, equal to 0.6 mg/kg bw per day | 30 ppm, equal to 2.0 mg/kg bw per day |
| | Two-year study of toxicity and carcinogenicity[a] | Toxicity (inhibition of brain acetylcholinesterase activity) | 10 ppm, equal to 0.5 mg/kg bw per day | 30 ppm, equal to 1.5 mg/kg bw per day |
| | Thirteen-week study of neurotoxicity[a] | Toxicity (inhibition of brain acetylcholinesterase activity) | 20 ppm, equal to 1.3 mg/kg bw per day | 60 ppm, equal to 4.0 mg/kg bw per day |
| | Thirteen-week study of ocular toxicity[a] | Toxicity (inhibition of brain acetylcholinesterase activity) | 10 ppm, equal to 0.57 mg/kg bw per day | 30 ppm, equal to 1.7 mg/kg bw per day |

| | | | | |
|---|---|---|---|---|
| Human | Four-day study of toxicity[c] | Toxicity (inhibition of erythrocyte acetylcholinesterase activity) | 0.36 mg/kg bw per day[b] | — |

[a] Dietary administration.

[b] Highest dose tested.

[c] Capsule administration.

*Estimate of acceptable daily intake for humans*

0–0.006 mg/kg bw

*Estimate of acute reference dose*

0.04 mg/kg bw

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

Additional toxicokinetic data in rats

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

## RESIDUE AND ANALYTICAL ASPECTS

Fenitrothion was evaluated for residues by the 2003 JMPR in the Periodic Re-evaluation Programme of the CCPR. The 2003 Meeting recommended an MRL of 10 mg/kg for cereals (post-harvest use only) and identified some data gaps. Additional data were provided to the 2004 JMPR, together with results of supervised trials on apples, pears, beans, peas, and soya beans. The 2004 JMPR confirmed the cereal MRL also for pre-harvest uses and recommended MRLs for apple and for animal commodities. Due to an insufficient number of trials corresponding to GAP, MRLs could not be recommended for pears, beans, peas, and soya beans.

The present Meeting received new labels covering uses on soya bean and cereals, a method of analysis, and additional residue trials on soya beans. Dietary intakes calculated by the 2004 JMPR exceeded the ADI and ARfD. As a consequence CCPR has returned the MRL for cereals to Step 6 several times. To resolve the issue the submission of alternative GAP data for cereals was requested.

### *Methods of analysis*

The Meeting received descriptions and validation data for an analytical method for the determination of residues of fenitrothion in soya bean. The analytical method used in the Brazilian trials involves extraction of fenitrothion with ethyl acetate in the presence of sodium sulphate, partitioning by a mixture of cyclohexane and ethyl acetate, and cleaning by gel permeation chromatography. The analyte is determined quantitatively by pulsing flame photometric detection (FPD).

Although the method performed satisfactorily, it was only validated in the range of 0.1–1.0 mg/kg.

### *Results of supervised trials on crops*

*Pulses*

The Meeting received information on supervised trials on soya beans from Brazil, and considered this information together with Japanese trials previously found to be matching GAP in 2004. In 2004, four trials were found to comply with Japanese GAP (foliar application, 4 times 0.025–0.050 kg ai/hL, PHI 21 days). Residues found were 0.004 (2), < 0.01 (2) mg/kg. The 2004 Meeting decided that four trials (of which two showed finite residues) were not sufficient to estimate a MRL for soya bean, dry.

The present Meeting received six additional soya bean trials from Brazil. The analytical method used in these trials was not validated below 0.1 mg/kg, but the chromatograms showed well-defined peaks below that level. Two of the six trials were decline trials, in which fenitrothion peaks could be observed at day 0 indicating that the use of fenitrothion on soya beans does not result in a nil-residue situation. However, in both of the decline trials (one at GAP rate, one at double rate) no peaks were observed later than 3 days after treatment. One of the trials was according to Brazilian GAP (foliar spray treatment together with esfenvalerate, 2 treatments at 0.1–0.2 kg/hL, interval 7–10 days, PHI 7 days). Residues were < 0.1 mg/kg. At the double rate, residues found were < 0.1 mg/kg. In the remaining four trials residues were only measured 14 days after the final treatment, residues < 0.1 mg/kg.

Based on the Japanese trials (residues in rank order: 0.004 (2), < 0.01 (2)) and using the Brazilian trials to support on the basis that current uses would not lead to detectable residues at harvest, the Meeting estimated a maximum residue level of 0.01 mg/kg, and an STMR of 0.01 mg/kg to replace the previous recommendations for soya bean.

*Cereal grains*

Five trials on stored wheat were performed in Australia and Argentina and reported by the 2003 JMPR. The Argentinean trials complied with the GAP of Argentina for post-harvest use on cereals: 6 g ai/t with a waiting period of 1 day. The residues found were: 3.1, 3.5, 5.0, 5.6 mg/kg. The Australian trial complied with the GAP of Australia for post-harvest use on wheat: 12 g ai/t with a waiting period of 3 months. The residue found was 7.6 mg/kg. The previous recommendation of the JMPR of 10 mg/kg (Po) was based upon the Australian trial result. In response to a request examine alternative GAP, the Meeting evaluated the available trials against Argentinean GAP.

The Meeting decided to estimate a maximum residue level for cereals based on the post-harvest use at 6 g ai/t. Residues were 3.1, 3.5, 5.0, 5.6 mg/kg. The Meeting decided to withdraw the previous recommendation for cereal grain of 10 mg/kg (Po). Taking into account the results of the dietary risk assessment (see below) the Meeting recommended a new maximum residue level of 6 mg/kg (Po) for cereal grain, excluding maize and estimated an HR of 5.6 mg/kg and a STMR of 4.25 mg/kg.

***Fate of residues during processing***

In the table below (taken from the 2004 JMPR evaluation), processing factors for wheat, barley and rice commodities are summarized. STMR-P and HR-P values were updated as the cereal grain MRL recommendation had changed.

| commodity | Processing factor, range (no. of trials) | Processing factor (mean or best estimate) | STMR-P | HR-P/highest residue |
|---|---|---|---|---|
| Wheat bran | 3.9-4.0 (2) | 3.95 | 16.79 | 22.12 |
| Wheat flour | 0.21-0.26 (2) | 0.235 | 1.00 | |
| White bread | 0.089-0.11 (2) | 0.10 | 0.425 | |
| Wholemeal bread | 0.33-0.43 (2) | 0.38 | 1.615 | |
| Barley malt | 0.16-0.24 (2) | 0.20 | 0.85 | |
| Husked rice | 0.031-0.64 (22) | 0.64 | 2.72 | |
| Polished rice | < 0.002-0.15 (26) | 0.15 | 0.638 | |
| Rice hulls | 0.12-10 (21) | 10 | 42.5 | 56 |
| Rice bran | 0.018-7.2 (23) | 7.2 | 30.6 | 40.3 |
| Cooked husked rice | 0.11 (1) | 0.11 | 0.468 | |
| Cooked polished rice | 0.04 (1) | 0.04 | 0.17 | |
| Washed polished rice | 0.041-0.049 (4) | 0.046 | 0.196 | |
| Cooked washed polished rice | 0.0060-0.033 (13) | 0.020 | 0.085 | |

Using the HR for cereal grains (5.6 mg/kg) and the processing factors as indicated above, the Meeting estimated a maximum residue level of 25 mg/kg in wheat bran, and 40 mg/kg in rice bran. The Meeting maintained its decision to withdraw the current recommendations for polished rice,

wheat flour, white bread and wholemeal bread of 1, 2, 1 and 3 mg/kg (PoP) respectively, as the MRLs would be lower than that of the raw agricultural commodity.

Using the HR for cereal grains (5.6 mg/kg) the Meeting estimated HR-P/highest residues for wheat bran, rice hulls, rice bran, as shown in the table above.

Furthermore, using the STMR for cereal grains (4.25 mg/kg) the Meeting estimated STMR-Ps for wheat bran, wheat flour, white bread, wholemeal bread, barley malt, husked rice, polished rice, rice hulls, rice bran, cooked husked rice, cooked polished rice, washed polished rice and cooked washed polished rice, as shown in the table above.

For the purpose of undertaking a dietary risk assessment, the Meeting decided to extrapolate the processing factor for wheat flour to all other cereal flours (except maize flour as processing was considered to be different) and estimated STMR-Ps of 1 for all cereal flours except maize flour. The Meeting extrapolated the processing factor for wheat bran to buckwheat bran estimating an STMR-P of 16.79 for buckwheat bran. Since fenitrothion is used post-harvest, and the residue is a surface residue, the Meeting considered that removal of the hull and further polishing would reduce the residue in a similar way for all cereals. The Meeting therefore decided to extrapolate the processing factor for husked rice to pot barley[30], estimating an STMR-P of 2.72 for pot barley, and the processing factor for polished rice to pearled barley, estimating an STMR-P of 0.638 for pearled barley. Furthermore the processing factor from wholemeal bread was extrapolated to wheat bulgur[31] wholemeal, yielding an STMR-P of 1.615 and the processing factor from white bread was extrapolated to wheat macaroni and wheat pastry, yielding STMR-Ps of 0.425.

The Meeting decided to use the STMR-Ps for cooked husked rice and cooked polished rice in the dietary intake calculations for rice.

Data were only available for the transfer of fenitrothion residues into malt rather than beer (see JMPR 2004 Evaluation). The Meeting received, at a very late stage, two new studies on the processing of barley to malt. However, upon consideration of these studies the Meeting decided to maintain the existing processing factor as the results of the new studies would not have resulted in an amended estimate. As a consequence the Meeting decided not to include the new data and to extrapolate the existing processing factor for malt to barley beer, millet beer, and sorghum beer yielding a STMR-P of 0.85 for barley beer, millet beer, and sorghum beer.

***Farm animal dietary burden***

The Meeting estimated the dietary burden of fenitrothion in farm animals on the basis of the diets listed in Annex 6 of the 2006 JMPR Report (OECD Feedstuffs Derived from Field Crops). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

*Estimated maximum and mean dietary burdens of farm animals*

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the animal diets from US-Canada, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report).

| | | Animal dietary burden, fenitrothion, ppm of dry matter diet | | |
|---|---|---|---|---|
| | | US-Canada | EU | Australia |
| Beef cattle | max | 14.9 | 7.0 | 24.5 [1] |
| | mean | 14.3 | 6.7 | 22.2 [2] |

[30] Pot barley = hulled or husked barley; pearled barley = hulled barley with the ends of the kernel removed forming a round shape.

[31] Bulgur (wheat) = wheat that has been cooked, dried, and coarsely ground.

| | | | | |
|---|---|---|---|---|
| Dairy cattle | max | 14.0 | 15.0 | 22.5 |
| | mean | 13.7 | 14.5 | 22.2 [3] |
| Poultry - broiler | max | 19.6 | 11.6 | 14.4 |
| | mean | 19.2 | 10.6 | 13.5 |
| Poultry - layer | max | 19.6 [4] | 9.9 | 14.1 |
| | mean | 19.2 [5] | 8.9 | 13.2 |

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

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

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

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

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

### *Animal commodity maximum residue levels*

The calculated maximum dietary burden for dairy and beef cattle is 24 ppm. In the cattle feeding study described in 2004, no residues were found above the LOQ (0.05 mg/kg) in muscle, fat, liver or kidney at feeding levels of 10, 30 and 100 ppm. Therefore, no residues above the LOQ are to be expected at the calculated dietary burden. Residues of fenitrothion in milk were below the LOQ of 0.01 mg/kg for all dose groups.

The calculated dietary burden for poultry is 20 ppm. In the poultry feeding study no residues were detected in muscle, liver, fat and eggs (< 0.05 mg/kg) at feeding levels of 10, 30 and 100 ppm.

The Meeting confirmed its previous recommendation of maximum residue levels of 0.05* mg/kg in meat (from mammals other than marine mammals), in edible offal (mammalian), in poultry meat, and eggs. Further the Meeting recommended a maximum residue level of 0.01 mg/kg in milks. The HRs for muscle, fat, liver, kidney, poultry meat and fat are estimated to be 0 mg/kg, and the STMRs are all estimated to be 0 mg/kg.

## DIETARY RISK ASSESSMENT

In previous evaluations (JMPR 2003, 2004) the Meeting identified both long-term and short-term intake exceedances of the ADI and ARfD. The Meeting noted at the time that the intake calculations were conservative, as they did not take into account any reduction in residue obtained by processing of cereal grains, except the processing of wheat, barley and rice. Processing information on maize was identified as necessary allow a refinement of intake calculations. The present Meeting did not receive processing information on maize, as a result intake problems arising for clusters B, C and M (long-term intake) as well as for the short-term intake remain. The Meeting considered that the group MRL for cereal grains would not go forward as processing data on one of the members of that group, with significant consumption, was lacking. The Meeting therefore decided to recommend a maximum residue level for cereal grains, *excluding maize.*

### *Long term intake*

The evaluation of fenitrothion has resulted in recommendations for MRLs and STMRs for raw and processed commodities. Consumption data were available for 37 food commodities and was used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 30–80% of the maximum ADI of 0.006 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of fenitrothion from uses that have been considered by the JMPR is unlikely to present a public health concern.

***Short-term intake***

The international estimated short-term intake (IESTI) for fenitrothion was calculated for the food commodities (and their processing fractions) for which maximum residue levels, STMRs and HRs were estimated and for which consumption data was available. The results are shown in Annex 4. The IESTI varied from 0–80 % of the ARfD (0.04 mg/kg bw) for the general population. The IESTI varied from 0–110% of the ARfD for children 6 years and below. The intake of 110% was for unprocessed wheat bran. Since this is not the edible commodity and further processing is likely to reduce the level of residues, the Meeting assumed that the intake of fenitrothion from processed wheat bran would be below the ARfD. The Meeting concluded that the short-term intake of residues of fenitrothion from uses considered by the Meeting was unlikely to present a public health concern.

## 5.13 FENPYROXIMATE (193)

### TOXICOLOGY

### Evaluation for an acute reference dose

Fenpyroximate is the ISO approved name for the phenoxypyrazole acaricide, *tert*-butyl (*E*)-α-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethylene aminooxy)-*p*-toluate (International Union of Pure and Applied Chemistry, IUPAC), also known as 1,1-dimethylethyl 4-[[[(*E*)-[(1,3-dimethyl-5-phenoxy-1*H*-pyrazol-4-yl)methylene]amino]oxy]methyl] benzoate (CAS; CAS No. 134098-61-6). Fenpyroximate is a contact acaricide with a mode of action involving the inhibition of mitochondrial proton-translocating NADH-quinone oxidoreductase (complex I).[32]

Fenpyroximate was evaluated by the JMPR in 1995, when an ADI of 0–0.01 mg/kg bw was established based on the NOAEL for reduced body-weight gain in a 2-year study in rats. In 2004, the JMPR established an ARfD of 0.01 mg/kg bw based on the LOAEL of 2 mg/kg bw per day for the induction of diarrhoea at the beginning of a 13-week study of toxicity in dogs. It was unclear whether the diarrhoea was the result of a direct irritant or pharmacological effect of fenpyroximate. Since a NOAEL for diarrhoea was not identified, an additional safety factor of 2 was applied to the usual 100 to establish the ARfD. The Meeting concluded that the ARfD was conservative and could be refined if a suitable study became available.

The present Meeting reconsidered the ARfD following submission of a new study of acute toxicity in dogs. The Meeting also reconsidered the existing database on fenpyroximate, as previously evaluated. The submitted study in dogs complied with GLP requirements.

***Toxicological data***

*Previously evaluated study in dogs*

In a 13-week study, groups of four male and four female dogs received capsules containing fenpyroximate (purity, 98.4–98.6%) at a dose of 2, 10 or 50 mg/kg bw per day. Controls (four dogs of each sex per group) received the empty gelatin capsules. Dogs were inspected throughout the working day and daily observation of each animal was carried out. A more detailed weekly examination was also carried out. A detailed veterinary examination was carried out before the start of the study and after 4, 8 and 12 weeks of treatment. Ophthalmoscopic examination of the eyes was undertaken after 4, 8 and 12 weeks of treatment. Debilitated animals were carefully observed and those in extremis were killed, blood samples having been taken ante-mortem. Body weight was measured at the start of the study, and then weekly and before death. Food consumption was measured daily. Water consumption was measured during 3 days in week 6. Electrocardiography was performed before the start of treatment and at weeks 6 and 12; at weeks 6 and 12, electrocardiography was performed 2 h

[32]Nakamaru-Ogiso, E., Sakamoto, K., Matsuno-Yagi, A., Miyoshi, H. & Yagi, T. (2003) The ND5 subunit was labelled by a photoaffinity analogue of fenpyroximate in bovine mitochondrial complex I. *Biochemistry*, **42**, 7.

and 24 h after dosing. Before the start of treatment and after 6 and 12 weeks of dosing, blood was taken for haematological investigations and clinical chemistry studies; during the treatment period, samples were taken before dosing. Urine analysis was carried out before the start of the study and after 11 weeks of treatment. Surviving dogs were killed at 12 weeks and a detailed necropsy undertaken. Selected organs were removed and weighed. Samples of selected organs and any macroscopical abnormalities were processed for histopathological examination.

Two females at the highest dose were killed in extremis during the study, because of severe weight loss and loss of appetite. Dogs in all treated groups had diarrhoea, and in the males this appeared to be dose-related and was apparent from week 1 (see Tables 9 and 10).

Table 9. The mean percentage[a] of dogs having diarrhoea after treatment with capsules containing fenpyroximate for 13 weeks

| Sex | Dogs with diarrhoea (%) | | | |
|---|---|---|---|---|
| | Dose (mg/kg bw per day) | | | |
| | 0 | 2 | 10 | 50 |
| Males | 8.5 | 22.7 | 21.2 | 70.0 |
| Females | 5.0 | 30.8 | 50.0 | 48.0 |

From Broadmeadow (1989)

[a] The percentage of dogs having diarrhoea was recorded each day. The mean percentage of dogs having diarrhoea was calculated by adding the daily percentage for each group and dividing by the number of days on which observations had been carried out.

Table 10. Incidence of diarrhoea in individual dogs before dosing and during week 1 of dosing with fenpyroximate[a]

| Dog | Incidence of diarrhoea (days) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dose (mg/kg bw per day) | | | | | | | | | | | | | | | |
| | Males | | | | | | | | Females | | | | | | | |
| | 0 | | 2 | | 10 | | 50 | | 0 | | 2 | | 10 | | 50 | |
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| 1 | 0 | 3 | 0 | 4 | 0 | 4 | 0 | 7 | 0 | 0 | 0 | 5 | 0 | 5 | 0 | 3 |
| 2 | 0 | 0 | 0 | 2 | 0 | 6 | 0 | 7 | 0 | 0 | 1 | 6 | 0 | 6 | 1 | 7 |
| 3 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 3 | 3 | 0 | 2 | 0 | 0 | 0 | 2 |
| 4 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |

From Broadmeadow (1989)

[a] 'Pre' refers to the number of days during the week before dosing that each beagle had diarrhoea; 'Post' refers to the number of days during the first week of dosing that each beagle had diarrhoea.

Emesis was seen in both sexes at 10 and 50 mg/kg bw per day. Emaciation was seen at 50 mg/kg bw per day (and in one female at 2 mg/kg bw per day). Lethargy (torpor) was seen in some females at 2 and 10 mg/kg bw per day, and in males and females at 50 mg/kg bw per day. Weight loss was seen in week 1, in females receiving fenpyroximate at 10 mg/kg bw per day and in males and females at 50 mg/kg bw per day. Body-weight gain was clearly depressed at 50 mg/kg bw per day in males, and at 50 and 10 mg/kg bw per day in females, compared with that of the controls. Body-weight gain in females was marginally depressed, compared with that of the controls, in the group receiving fenpyroximate at 2 mg/kg bw per day. Food consumption was unaffected by treatment in males, but was reduced by treatment in a dose-related fashion in females.

No treatment-related ocular lesions were noted. Slight bradycardia was seen in all treatment groups in both sexes, but especially in the groups receiving fenpyroximate at 10 and 50 mg/kg bw per day. There was no consistent difference between the measurements made 2 h after dosing and 24 h after dosing, and the bradycardia was not consistently present at 2 mg/kg bw per day. In males at all doses and in females at 2 and 10 mg/kg bw per day, no differences in haematological parameters were seen, compared with those of the concurrent controls. In females at 50 mg/kg bw per day, low total leukocyte counts at 6 weeks and 12 weeks, prolonged activated partial thromboplastin times at 6 weeks and high platelet counts at 12 weeks were recorded relative to these values for the concurrent controls. The two decedents (both females at 50 mg/kg bw per day) had low leukocyte counts. Raised concentrations of blood urea nitrogen were seen in females at 50 mg/kg bw per day at week 6, and at 2 and 50 mg/kg bw per day at week 12; it is unclear whether these effects were treatment-related as there was no clear dose–response relationship. Low concentrations of glucose were seen in males at 10 mg/kg bw per day and in both sexes at 50 mg/kg bw per day at weeks 6 and 12. The two decedents (both females at 50 mg/kg bw per day) had high blood urea concentrations and low plasma butyrylcholinesterase activities, and one of them had a low concentration of blood glucose. No inter-group differences were seen in the results of urine analysis.

Slightly higher absolute and relative weights of the adrenals were observed in males at 50 mg/kg bw per day and slightly higher relative weights of the adrenals in females at that dose. Relative weights of the liver were increased in both sexes at 50 mg/kg bw per day. Macroscopic examination post mortem showed emaciation in one surviving female at 50 mg/kg bw per day. The decedents showed emaciation. There was depleted hepatic glycogen and fine renal medullary cytoplasmic vacuolation in the two decedent females at the highest dose, as well as in one surviving female at 50 mg/kg bw per day. The lowest-observed-adverse-effect level (LOAEL) for the study was 2 mg/kg bw per day on the basis of clinical signs at that dose (diarrhoea in both sexes, and lethargy in females) and reduced body-weight gain in females. This LOAEL was probably close to the NOAEL.[33, 34]

*Study evaluated for the first time by the present Meeting*

In a study designed to establish the maximum tolerated dose and a NOAEL for acute toxicity, two male and two female beagle dogs (age 34–37 weeks) were given fenpyroximate (purity, 99.8%) at a concentration of 5 ml/kg (suspended in 0.5% w/v methylcellulose) by gavage. In the first phase of the study, the four dogs were given a single dose at 2 mg/kg bw on day 1, followed by 5 mg/kg bw on day 8, and finally 20 mg/kg bw on day 15. In the second phase, the same four dogs were dosed on day 23 at 5 mg/kg bw per day for five consecutive days.

Food consumption was measured daily and the body weight was measured before the day of dosing during the incremental dosing phase and then twice per week for the repeat-dosing phase until necropsy. Clinical monitoring, with an emphasis on neurobehavioural effects, was performed daily. Haematology parameters (erythrocyte volume fraction, haemoglobin, mean cell haemoglobin concentration (MCHC), mean corpuscular volume, erythrocyte count, leukocyte differential count, reticulocyte count, platelet count and prothrombin time) were determined before treatment (day–5) and again on the morning following each incremental change in dose before feeding, and at the end of the fixed-dose phase.

Clinical chemistry was carried out to measure blood glucose, blood urea nitrogen, total serum protein, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sodium, potassium, chloride, calcium, phosphorus, cholesterol, creatinine, albumin, gamma globulins and the

[33] Broadmeadow, A. (1989) NNI-850: toxicity study by oral (capsule) administration to CD beagle dogs for 13 weeks. Unpublished report No. 89/NNH036/1111 (amended from 89/NNH036/614) from Life Sciences Research, Eye, Suffolk, England. Submitted to WHO by Nihon Nohyaki Co. Ltd, Tokyo, Japan. GLP: USA, USEPA (40 CFR 160); UK DHSS; OECD (1981); MAFF, Japan. Guidelines: USEPA/FIFRA, 1982; MAFF Japan, 1985.

[34] Annex 5, reference *101*.

albumin : globulin ratio. Surviving dogs were killed on day 28 and a detailed necropsy was undertaken. Selected organs were removed and weighed. Samples of selected organs and any macroscopic abnormalities were processed for histopathological examination.

There were no treatment-related deaths or changes in body weight at any dose. The only clinical sign observed was soft or liquid faeces in all dogs at 20 mg/kg bw. The diarrhoea started 2–3.5 h after dosing and lasted for up to 6 h. Surprisingly, two out of four dogs (one male, one female) who received fenpyroximate at a dose of 5 mg/kg bw in the second phase of the test on day 23 had diarrhoea 3 h after dosing, but no dogs exposed to the same dose on day 8 had any clinical signs. All four dogs had clinical signs at about 3–6 h after the second consecutive dose at 5 mg/kg bw on day 24. The investigators suggested that this may have been due to pre-exposure to fenpyroximate at a high dose (20 mg/kg bw) 8 days earlier. Although blood had been collected 1, 3, 6 and 24 h after dosing at 5 mg/kg bw (fixed-dose phase) for toxicokinetic purposes, it was not possible to test this assertion owing to the absence of any blood collection before dosing.

The haematological and clinical chemistry analyses revealed values that were well within the range for historical controls. Necropsy revealed no apparent effects on organ weights, but macroscopically there were lesions observed in the gastrointestinal tract of three dogs (two males, one female). In two of the dogs, the mucosa of the ileo-caecal junction was red and dark. In the third dog, the mucosa of the stomach fundus was reported to be pale. The NOAEL was 2 mg/kg bw on the basis of clinical signs (diarrhoea in both sexes) at the next higher dose of 5 mg/kg bw.[35]

## Toxicological evaluation

An examination of the existing toxicological database indicated that the toxic effects of fenpyroximate are diarrhoea, reduced body-weight gain and haematological and clinical chemistry changes. The most sensitive end-point, namely diarrhoea, was observed in all studies in dogs, but not in other species. In a 13-week study in dogs given capsules containing fenpyroximate, diarrhoea with reduced body-weight gain and food consumption was observed. A NOAEL was not identified in the 13-week study and the LOAEL was 2 mg/kg bw per day on the basis of diarrhoea occurring at all doses. In that study it was unclear whether the diarrhoea occurred after a single dose, since only the incidence per week was reported. In a follow-up study of acute toxicity, diarrhoea was again observed in some dogs at 5 mg/kg bw, but not at 2 mg/kg bw.

After considering previous evaluations of fenpyroximate and the new submitted study, the Meeting established an ARfD of 0.02 mg/kg bw based on the NOAEL of 2 mg/kg bw identified on the basis of induction of diarrhoea after a single dose in dogs and using a safety factor of 100. Since it remained unclear whether the diarrhoea observed in dogs was the result of a direct irritant or pharmacological effect of fenpyroximate, it was not possible to consider a modification in the safety factor.

A toxicological monograph was not prepared.

[35] Harvey, P.W. (2006) Fenpyroximate: tolerated dose and 5-day repeat dose study by bolus oral gavage dosing in the dog to assist in setting the acute reference dose. Unpublished report No. 0608-073 from Covance Laboratories Ltd, North Yorkshire, England. Submitted to WHO by Nihon Nohyaki Co. Ltd, Osaka, Japan. GLP: UK DHSS; OECD (1981).

***Levels relevant to risk assessment***

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Dog | Acute toxicity[a] | Diarrhoea | 2 mg/kg bw | 5 mg/kg bw |
| | Three-month studies of toxicity[b] | Clinical signs and reduced body-weight gain in females | — | 2 mg/kg bw per day |

[a] Gavage administration [b] Capsule administration.

*Estimate of acute reference dose*

0.02 mg/kg bw

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

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

## 5.14 FLUSILAZOLE (165)

### TOXICOLOGY

Flusilazole is the ISO approved name for 1-[[bis(4-fluorophenyl)methyl]silyl]methyl]-1*H*-1,2,4-triazole (CAS No. 85509-19-9). It is a broad-spectrum fungicide that belongs to the triazole subclass of ergosterol biosynthesis inhibitors. Flusilazole was previously evaluated by the Joint Meeting in 1989 (Annex 5, references *56*, *58*) and in 1995. An ADI of 0–0.001 mg/kg bw was allocated in 1989, based on a NOAEL of 0.14 mg/kg bw per day (5 ppm) for liver toxicity in a 1-year feeding study in dogs. This was confirmed in 1995. The compound was re-examined by the present Meeting as part of the Periodic Re-evaluation Programme of CCPR. Three new studies were provided, two studies of developmental toxicity in rats (one of oral and one of dermal administration) and a 28-day mechanistic study in dogs.

Owing to the age of the database, some studies predate GLP; however, all critical studies complied with GLP.

***Biochemical aspects***

In rats, orally administered [$^{14}$C] labelled flusilazole was readily absorbed from the gastrointestinal tract and rapidly excreted in urine (72% of triazole label) and faeces (up to 87% of phenyl label), with little or no radioactivity recovered in the expired air. The excretion half-life was approximately 34 h and > 90% of the administered dose was eliminated within 96 h. Tissue retention of radiolabelled material was low. Total tissue residues excluding the carcass (which accounted for approximately 2% of the administered dose) was < 1%, therefore demonstrating no evidence of bioaccumulation.

[$^{14}$C]Flusilazole was extensively metabolized in rats. Recovered parent compound accounted for only 2–11% of the given dose, found predominantly in the faeces (urinary concentration, < 1%). After absorption, flusilazole was cleaved at the triazole ring. With phenyl-labelled test material, the major faecal metabolites identified were [bis(4-fluorophenyl)methyl] silanol, [bis(4-fluoro - phenyl)methylsilyl] methanol and its fatty acid conjugates, and disiloxane. Except for the fatty acid conjugates, the same metabolites were found in the urine. With triazole-labelled material, the main metabolite identified was 1*H*-1,2,4-triazole, which was found predominantly in the urine (63.8% of the administered dose in males, 51.6% in females); faeces contained only a small amount of the metabolite.

***Toxicological data***

Flusilazole is moderately to slightly toxic in rats when given as a single oral dose; and minimally toxic to rats and rabbits when administered as a single dose dermally or by inhalation. The oral $LD_{50}$ in rats was 672–1216 mg/kg bw, the dermal $LD_{50}$ in rabbits was > 2000 mg/kg bw and the inhalation $LC_{50}$ in rats was 6.8–7.7 mg/L. Flusilazole was found to be minimally irritating to the eyes and the skin of New Zealand White rabbits. It was practically non-irritating to the skin and was not a dermal sensitizer in guinea-pigs in a Buehler test.

Short- and long-term studies of repeated oral doses of flusilazole in mice (90-day dietary study), rats (90-day studies of gavage and dietary administration) and dogs (90-day and 1-year dietary studies) resulted primarily in lesions of the liver (hepatocellular hypertrophy, fatty change, focal inflammation/necrosis (mouse only) and vacuolation) and urinary bladder (urothelial hyperplasia and vacuolation). In addition, the gastrointestinal tract was a target in dogs. Clinical chemistry was not assessed in the studies in mice, the only finding in the studies in rats was a decrease in cholesterol in both sexes in the 90-day study and increase in cholesterol in females only in the long-term studies. On the basis of the hepatic and/or urinary bladder histopathology, the NOAEL was 75 ppm (equal to 12 mg/kg bw per day) in mice, 125 ppm (equal to 9 mg/kg bw per day) in rats and 20 ppm (equal to 0.7 mg/kg bw per day) in dogs (1-year study). Lymphoid hyperplasia of the gastric mucosa was observed in all treated dogs in the 90-day study, but not in the controls. In the 1-year study, this finding was observed in all dogs, including controls, with severity increasing in a dose-related manner. Effects at the LOAEL in the 1-year study in dogs included hepatocellular hypertrophy, inflammatory infiltration and vacuolation (males only), decreased cholesterol, total protein and albumin, and increased alkaline phosphatase activity and leukocyte counts. A mechanistic study in male dogs at the doses used in the 1-year study indicated that after 28 days of exposure, the effects observed on the liver were adaptive and reversible (weight, increased aspartate aminotransferase activity and cytochrome P450). The dog appeared to be the most sensitive species in these studies, with a NOAEL of 0.7 mg/kg bw per day in the 1-year study, on the basis of histopathology changes in the liver and stomach and changes in clinical chemistry.

After repeated short-term (21-day) dermal application of flusilazole, there was no evidence of any treatment-related systemic toxicity in rabbits given doses of up to 200 mg/kg bw per day.

Flusilazole was tested for genotoxicity in an adequate range of assays in vitro and in vivo. It was not genotoxic in mammalian or microbial systems. The Meeting concluded that flusilazole was unlikely to be genotoxic.

Two 18-month dietary studies with flusilazole were conducted in mice. In the first study in which flusilazole was administered at concentrations of up to 200 ppm in the diet, the target organs identified were the liver (hepatocellular fatty changes), kidney (decreased weight), and urinary bladder (histopathological change). There was no evidence of carcinogenicity in this study. Concentrations from 100 to 2000 ppm were used in the second 18-month study. Systemic toxicity was observed at all doses. At doses of 500 and 1000 ppm in males (73.1 and 144 mg/kg bw per day, respectively) or 1000 and 2000 ppm in females (200 and 384 mg/kg bw per day, respectively), overt hepatic lesions (increased foci of hepatocellular alteration and hepatocellular hypertrophy with cytoplasmic vesiculation and/or vacuolation) and cellular hyperplasia in the urinary bladder were observed. Increased incidences of liver tumours (hepatocellular adenomas and carcinomas) were observed at concentrations of more than 1000 ppm. Liver tumours occurred at doses in excess of the maximum tolerated dose (MTD) and were preceded at lower concentrations by clear histopathological changes in the liver. The overall NOAEL for systemic toxicity was 25 ppm, equal to 3.4 mg/kg bw per day, on the basis of hepatotoxicity and urinary bladder hyperplasia at 100 ppm (14.3 mg/kg bw per day) in males and hepatocellular fatty changes at 200 ppm (27 mg/kg bw per day) in both sexes. The overall NOAEL for carcinogenicity was 200 ppm (equal to 36 mg/kg bw per day) in females and 1000 ppm (equal to 144 mg/kg bw per day) for males. The incidence of tumours at the NOAEL was within the range for historical controls.

The toxicity and carcinogenicity of flusilazole were investigated in two 2-year studies in rats. The target organs identified were the liver and bladder. The overall NOAEL for systemic toxicity was 50 ppm, equal to 2.0 mg/kg bw per day, on the basis of mild nephrotoxicity (pyelonephritis in females) and hepatotoxicity (hepatocellular hypertrophy in both sexes), acidophilic foci, and diffuse fatty change (females only). There was no treatment-related increase in the incidence of any tumour type AT up to 250 ppm (the highest dose tested in the first study). Concentrations of between 125 and 750 ppm, the latter exceeding the MTD, were used in the second study. Flusilazole was found to be tumorigenic at the highest dose of 750 ppm (30.8 mg/kg bw per day) causing bladder transitional cell neoplasia in both sexes and testicular Leydig cell tumours in males. There was no evidence of any treatment-related increase in tumour incidence at a dietary concentration of 375 ppm. The overall NOAEL for carcinogenicity was 375 ppm (14.8 mg/kg bw per day)

A special 2-week study to investigate the possible mechanism for the induction of testicular Leydig cell tumours was conducted in rats. The results demonstrated that flusilazole caused a dose-dependent lowering of estradiol concentrations at 20 mg/kg bw per day and above, and of serum and interstitial testosterone concentrations at 150 mg/kg bw per day in vivo after subcutaneous exposure ($n$=10) and a dose-related decrease in testosterone and androstenedione production in testicular Leydig cell cultures by inhibition of enzymes involved in steroid biosynthesis in vitro at less than 5 μmol/l. In the 90-day mechanistic study in rats given flusilazole at doses similar to those used in the second long-term study in rats (0, 10, 125, 375 or 750 ppm), there were no changes in serum concentrations of testosterone, estradiol or LH, which would be expected for this mode of action. However, there was appreciable inter-animal variability in the hormone measurements. Overall, the data suggested that flusilazole may induce Leydig cell tumours via an endocrine-related mechanism—inhibition of testosterone and estradiol biosynthesis could contribute to disruption of the hypothalamus–pituitary–testis axis, resulting in over stimulation of the testicular endocrine tissues. Exposure to flusilazole at doses not causing disruption of the hypothalamus–pituitary–testis axis would, therefore, be unlikely to induce an increase in Leydig cell tumours. Although this mode of action is relevant to humans, there was good evidence to suggest that humans are less sensitive to chemically-induced Leydig cell tumours than are rats, owing to differences in sensitivity to LH on the basis of number of Leydig-cell receptors and control of LH-receptor expression (e.g., by prolactin in rodents but not in humans).

The Meeting concluded that the weight of evidence indicated that the mode of action for bladder tumours was via cell injury and regenerative hyperplasia.

In view of the lack of genotoxicity and the finding of hepatocellular tumours in mice and testicular and bladder transitional cell tumours in rats only at doses at which marked toxicity was observed, the Meeting concluded that flusilazole is not likely to pose a carcinogenic risk to humans at dietary levels of exposure.

The effect of flusilazole on reproduction in rats was investigated in two two-generation studies. The first was a part of a 2-year feeding study. No parental toxicity was observed at doses of up to 250 ppm. The same doses were used in the second definitive two-generation study. The NOAEL for parental systemic toxicity was 50 ppm, equal to 4.04 mg/kg bw per day, on the basis of slightly lower body-weight gain in $F_1$ females. The main reproductive effects at 250 ppm included increased duration of gestation and increased maternal mortality during parturition. The NOAEL for reproductive toxicity was 50 ppm, equal to 3.46 mg/kg bw per day. Toxicity observed in offspring at 250 ppm included a reduced number of live pups per litter and decreased pup growth. The NOAEL for offspring toxicity was 50 ppm, equal to 4.04 mg/kg bw per day.

Nine studies of developmental toxicity were carried out with flusilazole administered orally, of which five were in rats (one dietary study and four with gavage administration) and four (one dietary study and three with gavage administration) in rabbits to characterize potential teratogenicity observed in some studies.

In most of the studies in rats, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reduced body-weight gain and decreased food consumption. In one study, the NOAEL for maternal toxicity was 2 mg/kg bw per day on the basis of increased incidence of red vaginal discharge

during the latter part of gestation and an increase in placental weights at 10 mg/kg bw per day, which was not assessed in the other studies. At maternally toxic doses, specific malformations noted were cleft palate, nares atresia and absent renal papillae. An increased incidence of anomalies (extra cervical ribs, patent ductus arteriosis) was also observed. The incidence of rudimentary cervical ribs was slightly, but not statistically significantly increased at 2 mg/kg bw per day (3 out of 3, 4 out of 4, 9 out of 6, 27 out of 15, and 141 out of 22 foetuses per litter in the groups at 0, 0.5, 2, 10, 50 mg/kg bw per day, respectively). The overall NOAEL for embryo/fetotoxicity was 2 mg/kg on the basis of a higher incidence of skeletal variations (extra cervical ribs) at 10 mg/kg bw per day. No malformations were found at doses of less than 50 mg/kg bw per day.

In four studies of developmental toxicity in rabbits, the NOAEL for maternal and embryo/foetal toxicity was 7 mg/kg bw per day on the basis of clinical signs of toxicity, increased incidence of abortion and total resorption at 15 mg/kg bw per day. There was no evidence for any teratogenic potential in rabbits given flusilazole at doses of up to 15 mg/kg bw per day, the maximum tolerated dose in this study.

A major metabolite identified was 1*H*-1,2,4-triazole, which was found predominantly in the urine (63.8% of the administered dose in males, 51.6% in females). Studies with this metabolite are summarized in the evaluation of difenoconazole in the present report.

No neurotoxic effects were seen during conventional repeat-dose studies with flusilazole.

There were no reports of adverse health effects in manufacturing plant personnel or in operators and workers exposed to flusilazole formulations during their use. Also, there was no evidence or data to support any findings in relation to poisoning with flusilazole.

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

## Toxicological evaluation

The Meeting established an ADI of 0–0.007 mg/kg bw based on the NOAEL of 0.7 mg/kg bw per day for lymphoid hyperplasia in the gastric mucosa, liver histopathology (hypertrophy, inflammatory infiltration in males and females, and vacuolation in males only), and clinical chemistry (decreased concentrations of cholesterol, total protein and albumin and increased alkaline phosphatase activity and leukocyte counts) in the 1-year dietary study in dogs and a safety factor of 100.

The Meeting established an ARfD of 0.02 mg/kg bw based on the NOAEL of 2 mg/kg bw per day for skeletal anomalies in the study of developmental toxicity in rats treated orally and a safety factor of 100.

A toxicological monograph was prepared.

***Levels relevant to risk assessment***

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | Two-year studies of toxicity and carcinogenicity [a] | Toxicity | 25 ppm, equal to 3.4 mg/kg bw per day | 200 ppm, equal to 27 mg/kg bw per day |
| | | Carcinogenicity[d] | 200 ppm equal to 36 mg/kg bw per day (females) | 1000 ppm equal to 384 mg/kg bw per day |
| Rat | Two-year studies of toxicity and carcinogenicity [a,c] | Toxicity | 50 ppm, equal to 2 mg/kg bw per day | 250 ppm, equal to 10 mg/kg bw per day |
| | | Carcinogenicity | 375 ppm, equal to 14.8 mg/kg bw per day | 750 ppm, equal to 30.8 mg/kg bw per day |

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| | Multigeneration reproductive toxicity[a,c] | Parental toxicity | 50 ppm, equal to 4.04 mg/kg bw per day | 250 ppm, equal to 19.6 mg/kg bw per day |
| | | Offspring toxicity | 50 ppm, equal to 4.04 mg/kg bw per day | 250 ppm, equal to 19.6 mg/kg bw per day |
| | | Reproduction | 50 ppm, equal to 4.04 mg/kg bw per day | 250 ppm, equal to 19.6 mg/kg bw per day |
| | Developmental toxicity [a,b,c] | Maternal toxicity | 2 mg/kg bw per day | 10 mg/kg bw per day |
| | | Embryo/fetotoxicity | 2 mg/kg bw per day | 10 mg/kg bw per day |
| Rabbit | Developmental toxicity[a,b,c] | Maternal toxicity | 7 mg/kg bw per day | 15 mg/kg bw per day |
| | | Embryo/fetotoxicity | 7 mg/kg bw per day | 15 mg/kg bw per day |
| Dog | One-year study of toxicity [a] | Toxicity | 20 ppm, equal to 0.7 mg/kg bw per day | 75 ppm, equal to 2.4 mg/kg bw per day |

[a] Dietary administration.
[b] Gavage administration.
[c] Two or more studies combined.
[d] Greater than the maximum tolerated dose (MTD).

*Estimate of acceptable daily intake for humans*

0–0.007 mg/kg bw

*Estimate of acute reference dose*

0.02 mg/kg bw

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

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

***Critical end-points for setting guidance values for exposure to flusilazole***

| | |
|---|---|
| *Absorption, distribution, excretion and metabolism in mammals* | |
| Rate and extent of oral absorption | Rapid and extensive (up to 80%) |
| Dermal absorption | Data not available |
| Distribution | Widely |
| Potential for accumulation | Low |
| Rate and extent of excretion | Rapidly excreted |
| Metabolism in animals | Extensively metabolized |
| Toxicologically significant compounds in animals, plants and the environment | Parent compound,1,2,4-triazole |
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | 674 mg/kg bw |
| Rat, $LD_{50}$, dermal | > 2000 mg/kg bw |
| Rat, $LC_{50}$, inhalation | 2.7–3.7 mg/L, 4 h |

| | |
|---|---|
| Guinea-pig, skin sensitization (test method used) | Non-sensitizing (Buehler) |
| *Short-term studies of toxicity* | |
| Target/critical effect | Liver and urinary bladder |
| Lowest relevant oral NOAEL | 0.7 mg/kg bw per day (1-year study in dogs) |
| Lowest relevant dermal NOAEL | 5 mg/kg bw per day (21-day study in rabbits) |
| Lowest relevant inhalation NOAEC | No data presented |
| *Genotoxicity* | |
| | Not genotoxic |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Liver and bladder |
| Lowest relevant NOAEL | 2.0 mg/kg bw per day (2-year study in rats) |
| Carcinogenicity | No carcinogenic concern at levels of dietary exposure |
| *Reproductive toxicity* | |
| Reproduction target/critical effect | Increased gestation length, reduced live born pups/litter and decreased pup growth |
| Lowest relevant reproductive NOAEL | 50 ppm (4.04 mg/kg bw per day) |
| Developmental target/critical effect | Skeletal anomalies, malformations at higher doses |
| Lowest relevant developmental NOAEL | 2 mg/kg bw per day (rats) |
| *Neurotoxicity/delayed neurotoxicity* | |
| | No indications of neurotoxicity in studies of acute toxicity or repeated doses |
| *Other toxicological studies* | Disruption of the hypothalamus–pituitary–testis axis |
| Mechanistic studies | Necrosis and hyperplasia in the rat bladder |
| *Medical data* | |
| | No occupational or accidental poisoning reported |

***Summary***

| | Value | Study | Safety factor |
|---|---|---|---|
| ADI | 0–0.007 mg/kg bw | Dog, 1-year study | 100 |
| ARfD | 0.02 mg/kg bw | Rat, study of developmental toxicity | 100 |

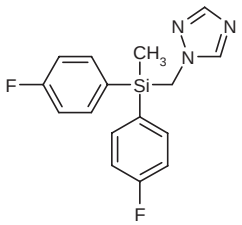
## RESIDUE AND ANALYTICAL ASPECTS

Flusilazole is a fungicide belonging to the ergosterol biosynthesis inhibitor class. It was evaluated by the JMPR for residues in 1989, 1990, 1991 and 1993. Toxicology was reviewed in 1989 and 1995, establishing an ADI of 0–0.001 mg/kg bw in 1989 (confirmed in 1995). Flusilazole was listed for the Periodic Re-Evaluation Programme at the 38th Session of the CCPR for periodic review by the 2007 JMPR for toxicology and residues.

***Chemical name:***

Flusilazole
Bis(4-fluorophenyl)(methyl)(1H-1,2,4-triazol-l-ylmethyl)silane (IUPAC)

1-[ [Bis(4-fluorophenyl)methyl)silyl]methyl]-1*H*-1,2,4-triazole (CA)




***Animal metabolism***

The Meeting received results of animal metabolism studies in rats, lactating goats, and laying hens.

Flusilazole is extensively metabolized in rats. Eight metabolites were identified. In addition to unchanged flusilazole, the major metabolites identified in urine and faecal samples were [bis(4-fluorophenyl)methyl]silanol (IN-F7321); [bis(4-fluorophenyl)methylsilyl]methanol (IN-H7169) and its glucuronide; 1H-1,2,4-triazole (IN-H9933); and 1,3-dimethyl-1,1,3,3-tetrakis(4-fluorophenyl)disiloxane (IN-G7072). Cleavage and rapid excretion of IN-H9933 (1H-1,2,4 triazole) was the primary step in the metabolism of flusilazole in rats. The silane molecule may then be excreted or further metabolized to fatty acid metabolites, β-D-gluco-pyranuronic acid conjugate and further degrade to more polar molecules.

Two lactating goats received daily doses of [$^{14}$C] labelled flusilazole orally by gelatine capsule at a level equivalent to 50 ppm in their diet. One lactating goat was dosed daily for 6 consecutive days (phenyl label) and one goat was dosed for 5 consecutive days (triazole label) with 50 mg of [$^{14}$C]-labelled flusilazole. For the goat dosed with phenyl-labelled flusilazole, muscle contained 0.05–0.07% of the total dose (0.41–0.70 mg/kg flusilazole equivalents); liver accounted for 5.3% (13.5 mg/kg); kidney had 1.2% of the dose (8.7 mg/kg); and fat contained 0.15–0.50% of the total administered dose (4.07–5.15 mg/kg). For the goat dosed with triazole-labelled flusilazole, muscle contained 0.10–0.15% of the total dose (0.52–0.53 mg/kg parent equivalents); liver accounted for 1.5% (3.5 mg/kg); kidney had 0.05% of the dose (0.75 mg/kg); and fat contained 0.01–0.07% of the total administered dose (0.15–0.94 mg/kg).

The transfer of radioactive residues to milk and tissues was low. Only 0.34 and 1.3% of the dose was present in milk for the phenyl and triazole labels, respectively. After 6 and 5 consecutive days of dosing, concentrations of total residues in milk were only 0.74 and 0.63 mg/kg (flusilazole equivalents) for the phenyl- and triazole-dosed goats, respectively. Residue levels in milk reached a plateau 2–5 days after the initial dose.

Percentages of extractable radioactivity varied from 89 to > 99% of the total radioactivity in the tissues for the goat dosed with phenyl-labelled flusilazole, and 90 to 94% for the goat dosed with triazole-labelled flusilazole. Flusilazole was extensively metabolized. Cleavage between the triazole and the silicon moieties was the predominant early metabolic transformation, followed by glucuronidation of one of the products. Except in the liver, unchanged flusilazole accounted for less than 10% of the tissue radioactivity. IN-F7321 (silanol) and IN-H9933 (1H-1,2,4-triazole) were the major metabolites found in tissues of goats dosed with phenyl- and triazole-labelled flusilazole, respectively.

In milk, unchanged flusilazole varied between 13–30% of TRR for the goat dosed with phenyl-labelled flusilazole, and < 1–13% for the goat dosed with triazole-labelled flusilazole. In the latter, metabolite IN-H9933 (1H-1,2,4-triazole) accounted for 87 to > 99% of the TRR in milk, which represented 0.16–0.30% of the administered dose. Metabolites IN-F7321 (silanol) and IN-G7072 (disiloxane) together accounted for 34 to 63% of the TRR in milk from the goat dosed with phenyl-labelled flusilazole. Polar material accounted for 7 to 28% of the radiolabel present in the milk of the goat dosed with phenyl-labelled flusilazole.

Laying hens were administered flusilazole ([$^{14}$C]-labelled at either the phenyl group or at the triazole group) at 0.36 or 18 mg/day, equivalent to 3 and 150 ppm in the diet. Hens from the low dose group were dosed for 14 days while those from the exaggerated dose group were dosed for 5 days (the higher dose served for metabolite isolation and identification only). Eggs and excreta were collected over the experimental period; edible tissues and blood were taken for analysis at sacrifice (approximately 6 h after the last dose).

Approximately 80% of the total radioactivity (both labels) was eliminated in the excreta. Elimination of radioactivity in the excreta became steady after 48 h. Residues in edible tissues were low, less than 1% of administered dose; thus bioaccumulation potential for flusilazole residues is low.

In hens receiving phenyl-labelled flusilazole at 0.36 mg/day dose level, highest residues were found in the liver (0.60 mg/kg flusilazole equivalents), followed by fat (0.52 mg/kg) and kidney (0.32 mg/kg). Residue levels in the muscle were the lowest. Residue levels in the hens dosed with triazole-labelled flusilazole were highest and essentially equal in whole blood (0.39 mg/kg), liver (0.38 mg/kg), kidney (0.38 mg/kg), and breast muscle (0.35 mg/kg) and much lower in fat (0.07 mg/kg). In eggs from hens dosed at 3 ppm for 14 days, radioactivity reached a steady state after about 8 days with a plateau residue level of approximately 0.2 mg flusilazole equivalents/kg (both labels).

[(4-Fluorophenyl)methyl]silanediol (IN-V5771) was the main metabolite in liver, kidney and muscle of hens dosed with phenyl-labelled flusilazole (33, 29 and 73–88% of the TRR, respectively). IN-F7321 (silanol) was the main residue in the fat (82% of the TRR) and a major one in the liver (17% of the TRR). Residues identified in the hens dosed with triazole-labelled flusilazole were IN-H9933 (1H-1,2,4-triazole), thymine and flusilazole, with IN-H9933 being the major metabolite in all tissues (76, 79 and 75–83% of the TRR in liver, kidney and muscle, respectively). 1H-1,2,4-triazole residues ranged from 0.057 mg triazole/kg in liver to non-detectable levels in fat. Flusilazole levels ranged from 0.018 mg/kg in kidney to 0.049 mg/kg in fat. No flusilazole was detected in muscle.

In eggs, the two major metabolites from the phenyl label dosed hens were IN-F7321 (silanol) and IN-V5771 (silanediol), at 32 and 38% of the TRR, respectively at 12 days. The major metabolite in eggs from the triazole label dosed hens was 1H-1,2,4-triazole (IN-H9933), with much smaller amounts of thymine and unchanged flusilazole. At 12 days, triazole, thymine and flusilazole residues were 0.197, 0.023 and 0.006 mg flusilazole equivalents/kg, respectively (77, 9 and 2% of the TRR, respectively). When calculated on a molar equivalent basis, the triazole and thymine residues were 0.043 and 0.009 mg/kg in the 12 day egg samples.

The residues found in goats and hens indicated a similar metabolic pathway to the rat. Generally, unchanged flusilazole was present at levels lower than the metabolites. In goat liver and chicken fat of animals dosed with triazole-labelled flusilazole, flusilazole levels were higher than levels of the metabolite 1,2,4-triazole, (IN-H9933) perhaps due to the polar nature of the triazole. Except in goat liver and chicken fat, 1,2,4-triazole was the major metabolite arising from triazole-labelled flusilazole. The silanol metabolite (IN-F7321) was also common to both goats and hens. The main difference between the goat study and the hen studies was the occurrence of the silanediol (IN-V5771) as a major metabolite in hens. Other phenyl-labelled metabolites, resulting from hydroxylation and conjugation reactions, were present at relatively low levels in chicken tissues and eggs.

Based on the results of the submitted studies, the Meeting concluded that, in rats, goats, and hens, flusilazole was rapidly and extensively converted to polar metabolites.

***Plant metabolism***

The Meeting received plant metabolism studies for flusilazole in wheat, sugar beet, apples, grapes, bananas and peanuts. The wheat, bananas and sugar beet were greenhouse grown. The grapes, apples and peanuts were grown in the field.

Wheat was treated with [phenyl(U)-$^{14}$C]flusilazole and [triazole-3-$^{14}$C]flusilazole at 200 g ai/ha. In forage, labelled residues (expressed as flusilazole) fell from initial values of 32 and

8.6 mg/kg for phenyl and triazole labels, respectively, to approximately 6 mg/kg by days 5 to 12. Flusilazole accounted for 56–59% of the residue in forage for days 5–12. Residues in straw were 8.6 and 7.9 mg/kg for phenyl and triazole labels, respectively. Unchanged flusilazole accounted for only about 14% of the residue in mature straw, and there was extensive metabolism to at least seven phenyl-labelled and six triazole-labelled metabolites. No single straw or forage metabolite accounted for more than 13.5% of the total radioactivity present. Unidentified minor metabolites were present in triazole and phenyl [$^{14}$C]flusilazole treated wheat straw; however, no unidentified metabolites exceeded 4% of the total radioactive residue.

There were negligible radioactive residues (0.01 mg/kg) in the grain from phenyl-labelled wheat. In the triazole-labelled wheat, grain residues of 4.4 mg/kg flusilazole equivalents (at 52 days after the treatment) were comprised of triazolyl alanine (IN-V9462) and triazole acetic acid (IN-D8722). No flusilazole was found in triazole-labelled grain samples harvested 69 days after the treatment. This data indicates that although metabolites containing the triazole ring can be translocated, intact flusilazole is not translocated to grain.

The metabolic pathway of flusilazole in wheat included hydroxylations, conjugations, and cleavage of the silicon-methylene bond. The major phenyl-labelled metabolites in straw and forage were glucose-6-phosphate of IN-37722 (2-fluoro-5-[(4-fluorophenyl) (methyl) (1H-1,2,4-triazol-1-ylmethyl)silyl]phenol); mono[6-deoxy-2-0-[2-fluoro-5-[(4-fluorophenyl) (methyl) (1H-1,2,4-triazol-1-ylmethyl) silyl] phenyl]-β-D-glucopyranos-6-yl] propanedioate (IN-37735); a conjugate of IN-37738 (2-fluoro-5-[(4-fluorophenyl) (hydroxy) (methyl) silyl] phenol) ; and [bis(4-fluorophenyl)methyl] silanol (IN-F7321). The major triazole-labelled metabolites were triazolyl alanine (IN-V9462); triazole acetic acid (IN-D8722); the glucose-6-phosphate of IN-37722; IN-37735; and IN-37722. Triazolyl alanine and triazole acetic acid accounted for 69 and 24% of the radioactivity in the grain, respectively.

The leaves and detached unpeeled green fruits of immature banana plants growing under greenhouse conditions were treated directly with phenyl- or triazole- labelled flusilazole, each formulated as an emulsifiable concentrate and diluted to a final concentration six times the label rate. The bananas were analysed at intervals of 0, 2, 4, 7, and 11 days and the leaves were analysed at intervals of 0, 7, 14, and 18 days. Autoradiographs showed that flusilazole applied to banana leaves did not translocate from the treated areas. In the case of banana fruit, flusilazole distribution from the peel to the pulp was negligible since 98–99% of the radioactivity applied to the peel remained in the washings and peel. Intact flusilazole accounted for more than 87% of the radioactivity in the peel rinses and peels.

Sugar beets were treated post-emergence with either phenyl- or triazole-labelled flusilazole as an over the top spray at application rates of 124–131 g ai/ha (three times at 14-day intervals). The sugar beets were harvested at 0, 14, 28, and 59 or 77 days (maturity). At each sampling interval, radioactive residues were consistently higher in the foliage than in the roots. Immediately after the third treatment, total radioactive residues in the foliage ranged between 1.5 and 7.2 mg/kg for triazole- and phenyl-labelled flusilazole, respectively. At each sampling interval, total radioactive residues in the roots were lower for the phenyl-treated plants (0.008 mg/kg maximum) than for the triazole-treated plants (0.15 mg/kg maximum). With time, the total radioactive residues in both the foliage and roots decreased.

Flusilazole was the major residue in the foliage, accounting for a maximum of 89% of the total radioactivity present in the foliage. Minor metabolites found included 1,3-dimethyl-1,1,3,3-tetrakis(4-fluorophenyl) disiloxane (IN-G7072) and 2-fluoro-5-[(4-fluorophenyl) (methyl) (1H-1,2,4-triazol-1-ylmethyl)silyl]phenol (IN-37722). No flusilazole was detected in root extracts. Other residues in the foliage and roots consisted of polar materials that were not resolved by HPLC.

Grape vines (separate branches of foliage and grapes) were treated with phenyl- or triazole-labelled flusilazole under field conditions. The berries were harvested 41 days after the application. Flusilazole was the predominant residue, extracted from grape berries, treated with either the phenyl-labelled or triazole-labelled compounds, comprising between 57 and 31% of the recovered radioactivity, respectively. The principal degradation product from phenyl-labelled flusilazole was

[bis(4-fluorophenyl)methylsilyl] methanol (IN-H7169), accounting for 11% of the residue. Four identified minor metabolites containing the phenyl label together accounted for < 10% of the recovered radioactivity. Those four minor metabolites included [bis(4-fluorophenyl)methyl] silanol (IN-F7321); [(4-fluorophenyl)methyl]silanediol (IN-V5571); bis(4-fluorophenyl) (1H-1,2,4-triazol-1-yl)silanol (IN-A7634); and bis(4-fluorophenyl)silanediol (IN-T7866). In addition to flusilazole, triazolyl alanine (IN-V9462) was a major degradation product in triazole-labelled grape berries, accounting 30% of the total radioactivity. Unextractable residues from fruit accounted for between 5 and 14% of the recovered radioactivity.

Apple trees were treated four times at 14-day interval with either phenyl- or triazole-labelled flusilazole at rates of approximately 8 mg/100 mL. Mature fruit were harvested 14 days after the final application. Flusilazole was the predominant residue extracted from apple fruit treated with either phenyl-labelled or triazole-labelled compounds, comprising between 71 and 48% of the recovered radioactivity, respectively. Three identified minor metabolites containing the phenyl label (IN-F7321, IN-V5571, and IN-H7169) together accounted for approximately 11% of the recovered radioactivity. Triazolyl alanine (IN-V9462) was a significant triazole-containing metabolite, accounting for 22% of TRR. Unextractable residues from the apple fruit accounted for between 8 and 14% of the recovered radioactivity.

Peanuts were treated with [phenyl (U)-$^{14}$C]flusilazole applied to the foliage at 140 g ai/ha, 52 days prior to harvest. Peanuts (nut and shells) were harvested at 52 days (maturity). Total radioactive residues in the foliage of peanut plants declined from 3.4 mg/kg at day 0 to 0.38 mg/kg at day 52. There was no significant translocation of phenyl-labelled metabolites to the peanut seed (total residue in the seed was 0.018 mg/kg) or peanut shell (0.03 mg/kg). Flusilazole was the major residue in the foliage at all sampling intervals, declining from 3.2 mg/kg at day 0 to 0.19 mg/kg at day 52. Flusilazole at 0.006 mg/kg and "water soluble metabolites," also at 0.006 mg/kg, were present in the seed with the remaining residue unextractable.

Based on the results of the submitted studies on wheat, apples, grapes and sugar beets, the Meeting concluded that qualitatively similar metabolism occurred among these crops. The metabolic pathway of flusilazole in plants involves hydroxylations, conjugations, and cleavage between the silicon and the triazole ring. As the interval between treatment and sampling increases, the residues of unchanged flusilazole decreased and the metabolism and conjugation increased.

Due to the extensive degradation of flusilazole by multiple mechanisms to many minor metabolites, there are no major flusilazole metabolites in plants, other than triazolyl alanine. With the exception of triazolyl alanine and triazole acetic acid, individual metabolites generally account for less than 14% of the total radioactivity in the plants.

***Environmental fate***

*Soil*

The Meeting received information on aerobic and anaerobic degradation of flusilazole in soil; photolysis on soil surface; mobility in soil; field dissipation studies; and flusilazole residues in rotational crops.

The aerobic degradation of [phenyl(U)-$^{14}$C] and [triazole-3-$^{14}$C] flusilazole was studied in two soils (sandy and silt loam soils) incubated in the dark at 25 °C for 1 year.

The primary route of degradation in non-sterile soils was cleavage of the methylene-silicon bond to form IN-F7321 (silanol) which was found < 5% of applied radioactivity after one year and IN-H9933 (triazole) which was not detected.

The anaerobic degradation of [phenyl(U)-$^{14}$C] and [triazole-3-$^{14}$C]-flusilazole was studied in two pond water/sediment systems (silt loam and a sand) under anaerobic conditions at 25 °C at a nominal concentration of 1.0 mg/kg sediment.

The major radiolabelled metabolite (found at 2% of the applied radioactivity) was identified as bis(4 fluoro-phenyl)methyl silanol (IN-F7321).

The photodegradation of flusilazole was studied using silt loam soils under artificial and natural sunlight. No significant degradation was observed in the studies. Under the artificial sunlight conditions, the observed half-life was greater than 30 days. Under the natural sunlight conditions, flusilazole degraded slowly with a $DT_{50}$ of about 97 days. Based on these results, the Meeting concluded that photolysis on soil is not an important mode of degradation for flusilazole.

Field dissipation studies on bare soil and cropped soils were performed in the United States, Canada and Europe.

The studies showed substantial metabolism of flusilazole with the majority of the applied radioactivity found near the top of the soil (5–15 cm). The major metabolite was the silanol (IN-F7321) which was present at no more than 14% of the applied radioactivity while the triazole metabolites reached a maximum of < 3%. In all studies, very limited mobility was observed. The $DT_{50}$ values ranged from 71–755 days. However, the residue in soil remained low after multiple applications, and the soil residues continued to decline after application of flusilazole was discontinued.

A field study designed to measure the potential for off-target movement of flusilazole into water-bodies adjacent to orchards showed low to undetectable levels of flusilazole detected in water and sediments adjacent to orchards. The study concluded that environmental exposure to non-target areas would be extremely low under normal use conditions.

A similar pattern was seen in the presence of a wide range of crops (e.g., cereals, oilseed rape and sugar beets). Soil samples of flusilazole remained low (< 0.09 mg/kg) even after a six year accumulation study (up to 3 kg flusilazole applied) and continued to decline after discontinuation of application. No accumulation was seen in soil or crops when used according to recommended use rates. Based on these results, the Meeting concluded that there is a little potential for flusilazole accumulation in soil or crops after multiple years of continuous use.

***Residues in rotational crops***

The Meeting received results of two confined [$^{14}$C]flusilazole rotational crop studies. The first study examined the potential for uptake of phenyl-containing residues into four crops (barley, beets, cabbage, and soya beans) from soil (sandy loam) treated with phenyl-labelled flusilazole at rates of 289 or 543 g ai/ha and aged for 30 or 120 days under greenhouse conditions. The second study examined the potential for uptake of phenyl- or triazole-containing residues into three crops (cabbage, wheat and beets) from soils (silt loam) treated with phenyl- or triazole-labelled flusilazole at 1129 g ai/ha and then aged for 120 or 360 days in the field.

During both confined rotational crop studies, radioactive residue levels in the soil remained relatively constant during the aging and plant growth periods. Soil residues ranged from 0.04 to 0.12 mg/kg (289 g ai/ha application rate), 0.12 to 0.20 mg/kg (543 g ai/ha application rate) and 0.21 to 0.44 mg/kg (1129 g ai/ha). Flusilazole levels and the percentage of extractable radioactivity decreased with time. Major soil residues included flusilazole and the silanol (IN-F7321).

There was no significant accumulation of residues from either label in cabbage, soya beans or beets in the confined rotation studies. Accumulation did occur in mature small grain fractions of wheat grown in soil treated with [triazole-3-$^{14}$C]flusilazole. Parts of matured wheat grown in 360-day aged soilcontained pheny and triazole labelled residues, respectively: chaff 0.60–9.5 mg/kg, straw 1.4–7.9 mg/kg and grain 0.081–17.5 mg/kg.The extent of accumulation was similar in comparable samples from all aging periods. A major wheat metabolite was triazolyl alanine with flusilazole comprising < 20% of the radioactivity in the wheat grain or straw. This suggests that a triazole-containing fragment, rather than intact flusilazole, translocates from soil into wheat.

The Meeting concluded that there is no significant uptake of flusilazole into rotational (succeeding) crops, except ceral grains.

### *Methods of Analysis*

The Meeting received description and validation data for analytical methods for flusilazole and its important metabolites, mainly [bis(4-fluorophenyl)methyl] silanol (IN-F7321), in samples of plant and animal origin.

The described methods are mostly based on extraction with an organic solvent (usually ethyl acetate or acetone); followed by a partition step, gel permeation chromatography (GPC) clean-up, and often also a silica solid-phase extraction (SPE) clean-up. The determination step employs mainly capillary GC with nitrogen-phosphorus detection (NPD), followed by a mass spectrometric (MS) confirmation, or a single-step GC-MS determination.

The typical LOQ is 0.01 mg/kg for most plant and animal matrices, with mean recoveries typically ranging between 70–120%.

Multiresidue methods, such as the DFG S19, are available for flusilazole.

The Meeting concluded that adequate multi- and single-residue methods exist for both gathering data in supervised trials and other studies and for monitoring and enforcing flusilazole MRLs in samples of plant and animal origin.

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

The Meeting received information on the stability of flusilazole and its silanol IN-F7321 metabolite in freezer-stored samples (at approximately -20 °C) of plant and animal origin, including apples, grapes, wheat grain, wheat straw, oilseed rape (seed and shoots) and bovine matrices (milk, muscle, kidney, liver and fat). Fortified samples were stored up to the following intervals: wheat grain: 40 months; wheat straw: 40 months; apples: 48 months (flusilazole) and 26 months (IN-F7321); grapes: 17 months (flusilazole) and 25 months (IN-F7321); oilseed rape: 14 months (flusilazole only); whole milk: 6 months (flusilazole) and 11 months (IN-F7321); bovine muscle: 6 months (flusilazole) and 15 months (IN-F7321); bovine kidney: 3.5 months (IN-F7321); bovine liver: 6 months (flusilazole) and 14.25 months (IN-F7321); and bovine fat: 6 months (flusilazole) and 16 months (IN-F7321).

No significant degradation of flusilazole and its silanol metabolite IN-F7321 was observed in the tested plant and bovine matrices and storage intervals, with the exception of IN-F7321 in liver (residues remained and corrected for recoveries were 35, 84, and 38% for 1, 3, and 14.25 months of storage, respectively). In the case of 3 month-storage of IN-F7321 in liver, samples were only partially thawed and rapidly refrozen after fortification, whereas the other samples (1 and 14.25 months of storage) were completely thawed and remained in contact with the fortification solution at ambient temperature for at least 30 minutes. The partially thawed and rapidly refrozen samples showed limited degradation, probably due to a much lower rate of enzyme activity at lower temperatures. While this does not directly reflect the stability of incurred residues of IN-F7321 in liver, it emphasises the need, when analysing residues in liver, to ensure that samples are processed expeditiously and are not allowed to remain at elevated temperatures prior to extraction and analysis.

### *Residue definition*

Flusilazole is extensively metabolized in animals and plants. The major metabolic reaction is cleavage of the Si-$CH_2$ bond to form silanol and triazole related metabolites.

In plants, there are no predominant metabolites with the exception of triazole alanine and triazole acetic acid. These plant metabolites are produced by all fungicides in the triazole class and are therefore excluded from the definition of the residue for flusilazole.

In ruminants (goats), the most abundant metabolites in tissues and milk were flusilazole, [bis(4-fluorophenyl)methyl] silanol(IN-F7321), and 1H-1,2,4-triazole(IN-H9933). In poultry, metabolites in tissues and eggs were flusilazole, [bis(4-fluorophenyl)methyl]silanol, 1H-1,2,4-triazole, and [(4-fluorophenyl)methyl]silanediol(IN-V771). As 1H-1,2,4-triazole is a common metabolite to all triazole fungicides, it is not deemed suitable as an indicator of flusilazole exposure to ruminants or

hens. The silanediol metabolite is only found in poultry tissues, and is not expected to be detectable at anticipated dietary exposure levels to laying hens.

Based on the above, the Meeting agreed in the following residue definitions:

*Definition of the residue in plant commodities for estimation of dietary intake and for compliance with MRLs:* flusilazole

*Definition of the residue in animal commodities for estimation of dietary intake and for compliance with MRLs:* flusilazole plus [bis(4-fluorophenyl)methyl]silanol (IN-F7321)

The log $K_{ow}$ is 3.87 (at 20 °C, pH 7), suggesting that flusilazole is fat-soluble. Both in the goat and hen metabolism studies the residues of flusilazole and its silanol, IN-F7321, in muscle was generally less than one-tenth that in the various fat depots. The Meeting concluded that the flusilazole residue is fat soluble.

***Results of supervised trials on crops***

The Meeting received supervised trials data for flusilazole on apple, pear, apricot, nectarine, peach, grapes, banana, cucumber, sweet corn, soya bean, sugar beet (root and leaves), barley (grain, forage, and straw), rye (grain, forage, and straw), wheat (grain, forage, and straw), maize, rice, rape seed, sunflower seed and oat (forage and fodder).

*Pome fruit*

*Apple*

The Meeting received results from supervised trials with flusilazole used on apples in southern Europe (Italy, Spain and southern France), Argentina, Canada, India, New Zealand and South Africa.

None of the trials in Argentina, India, or New Zealand were conducted according to the respective GAPs of Argentina (4 applications at 4 g ai/hL with a PHI of 21 days), India (4 g ai/hL with a PHI of 10 days), and New Zealand (3 g ai/hL, up to 6 applications, with a PHI of 35 days).

The critical GAP for the southern European trials conducted in Spain, Italy and southern France is the GAP of Spain that specifies a spray concentration of 4.8 g ai/hL in high-volume applications (more than 1500 L water/ha, i.e., a maximum of $\geq$ 72 g ai/ha), maximum of 4 applications per year, and a PHI of 14 days. Flusilazole residues from ten trials according to the GAP of Spain, in ranked order, were: 0.01, 0.01, 0.02, 0.04(2), 0.05(2), 0.06, 0.12 and 0.13 mg/kg.

Two trials in Canada were conducted according to the GAP of Canada: 40 g ai/ha, maximum of 4 applications, and a PHI of 77 days. Flusilazole residues (at 88 and 130% GAP) were < 0.01 mg/kg (below LOQ of the analytical method used).

The GAP of South Africa specifies a spray concentration of 2.4 g ai/hL in high-volume applications (1500–3500 L water/ha, i.e., 36–84 g ai/ha), 5 applications, and a PHI of 14 days. One trial was conducted according to this GAP. The residue of flusilazole from this trial was 0.06 mg/kg.

*Pear*

The Meeting received results from supervised trials with flusilazole used on pears in Italy, South Africa and China.

Trials in Italy were not conducted according to the critical GAP of the southern European region, i.e., that of Spain (the same treatment regime as for apples).

The GAP of South Africa specifies a spray concentration of 1.6 g ai/hL in high-volume applications (1500–3500 L water/ha, i.e., 24–56 g ai/ha), 5 applications, and a PHI of 14 days. Two trials were conducted at a higher application rate of 2 g ai/hL (125% GAP), 6 applications and 2-day longer PHI of 16 days. Flusilazole residues from these trials were 0.02 and 0.03 mg/kg.

Four trials in China were conducted according to the GAP of China (5 g ai/hL, 3 applications, with a PHI of 21 days), with the exception four applications were made instead of three. Flusilazole residues from these trials were: 0.01, 0.02, 0.03, and 0.13 mg/kg.

The Meeting agreed that the data on apples from southern Europe and South Africa and on pears from China appear to be from similar populations and could be used to support a "pome fruit" commodity group maximum residue level. Pome fruit is registered for use in New Zealand. Flusilazole residues in pome fruit, in ranked order, were: 0.01(3), 0.02(2), 0.03, 0.03, 0.04(2), 0.05(2), 0.06(2), 0.12 and 0.13(2) mg/kg. The Meeting estimated a maximum residue level for pome fruit of 0.3 mg/kg to replace the previous recommendation of 0.2 mg/kg, an STMR value of 0.04 mg/kg, and an HR value of 0.13 mg/kg.

*Apricot, nectarine and peach*

The Meeting received results from supervised trials with flusilazole used on apricots in France, on peaches in southern Europe (Greece, Italy, Spain, and southern France) and on peaches and nectarines in New Zealand.

The GAP of New Zealand for stone fruit (4 g ai/hL) does not specify a PHI. The label states that the product should not be applied after the start of shuck fall, which should be 86–113 days before harvest for most peach and nectarine cultivars. Nine trials were reported (three on peach and six on nectarine). The spray concentrations in these trials were 5, 10 and 20 g ai/hL, with very long PHIs of 91–113 days. All flusilazole residues from these trials were < 0.01 mg/kg (below LOQ of the analytical method used).

The critical GAP for the southern European trials conducted on peach in Spain, Greece, Italy and southern France is the GAP of Spain that specifies a spray concentration of 5 g ai/hL, maximum of 3 applications per year, and a PHI of 7 days. Flusilazole residues from twelve trials according to the GAP of Spain, in ranked order, were: 0.03, 0.04, 0.05(4), 0.06, 0.07, 0.08, 0.09 and 0.10 mg/kg.

The GAP of France for apricot (4 g ai/hL) does not specify a PHI. The critical GAP in the region is the GAP of Spain (5 g ai/hL, maximum of 2 applications per year, and a PHI of 7 days). Three apricot trials were conducted with a PHI of 7, one with 4 g ai/hL (8 applications) and two with 14 g ai/hL (4 and 6 applications). Flusilazole residues from these trials were 0.08, 0.05 and 0.06, respectively.

The critical GAP for the southern European trials (the GAP of Spain) is the same for peach and nectarine. The critical GAP for apricot (the GAP of Spain) specifies the same spray concentration and PHI as for peach and nectarine, with maximum of two applications instead of three. Flusilazole residues for apricot (a smaller fruit than peach) fell within the range of residues obtained for peach, even though exaggerated spray concentration (280% GAP) and/or significantly higher number of applications were used.

The Meeting decided to use the residue data from the eleven trials on peach in southern Europe to estimate a maximum residue level of 0.2 mg/kg for apricot, nectarine and peach to replace the previous recommendation of 0.5 mg/kg. The Meeting also estimated an STMR value of 0.05 mg/kg, and an HR value of 0.10 mg/kg for apricot, nectarine and peach.

*Grapes*

The Meeting received results from supervised trials with flusilazole on grapes in southern Europe (Greece, Italy, Portugal, Spain and southern France), Germany, Australia, China, India and South Africa.

None of the trials in India and South Africa were conducted according to the respective GAPs of India (4 g ai/hL with a PHI of 15 days) or South Africa (5 g ai/hL with a PHI of 21 days).

Flusilazole is not registered for use on grapes in Germany but it is registered in France, Switzerland and the Czech Republic. The GAPs of France and Switzerland do not specify a PHI. The

GAP of the Czech Republic for grapes specifies 30 g ai/ha (spray volume 1000 L water/ha, i.e., 3 g ai/hL), spraying interval 7–14 days (number of applications not specified), and a PHI of 42 days.

Five trials in Germany were conducted with a 42-day PHI and 32–36 g ai/ha (106–120% of GAP). Flusilazole residues in these trials were: 0.02, 0.03, 0.04, 0.10 and 0.11 mg/kg.

The GAP of Australia specifies maximum of 3 applications at 2 g ai/hL or 20 g ai/ha with a PHI of 14 days. In one trial in Australia, flusilazole was applied as a single application with 2 g ai/hL and a PHI of 14 days. Flusilazole residue from that trial was 0.11 mg/kg.

The critical GAP for the southern European trials conducted on grapes in Spain, Portugal, Greece, Italy and southern France is the GAP of Spain, specifying a spray concentration of 5 g ai/hL, a maximum of 5 applications and a PHI of 14 days. Flusilazole residues from eight trials according to the GAP of Spain (with 5–6 applications), in ranked order (median underlined), were: 0.01(2), 0.02(2), 0.03, 0.04, 0.10, and 0.11 mg/kg. One trial with a PHI of 15 days was also included as a higher residue of 0.11 mg/kg was recorded than from trials with a 14-day PHI.

The GAP of China specifies a spray concentration of 5 g ai/hL and 3 applications but does not specify a PHI or growth stage and could not be evaluated.

The Meeting decided to use the residue data from southern Europe and Germany to estimate a maximum residue level for grapes. Residues from these trials in ranked order were: 0.01(2), 0.02(3), 0.03(2), 0.04(2), 0.10(2) and 0.11(2) mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg to replace the previous recommendation of 0.5 mg/kg, an STMR value of 0.03 mg/kg, and an HR value of 0.11 mg/kg.

*Banana*

The Meeting received results from supervised trials with flusilazole used on bananas in the Caribbean Basin (Belize, Costa Rica, Guatemala, Honduras, Jamaica and West Indies, including Guadeloupe, Martinique and St. Lucia). The Meeting considered the GAP of Columbia (100 g ai/ha, 4–6 applications, and a PHI of 1 day) as the critical GAP for the evaluation of the submitted trials.

In the eleven submitted trials, bananas were treated with flusilazole at 100 g ai/ha (4–7 applications) using aerial application to bagged bunches with washing (normal practice) or without washing at the harvest. With a PHI of 1 day, flusilazole residues in the pulp were < 0.01 mg/kg for all the trials. With the same PHI, flusilazole residues in the peel of washed bananas (three trials) were: < 0.01 (2) and 0.01 mg/kg. Residues in the peel of unwashed bananas (eight trials) were: < 0.01 (3), 0.011, 0.012, 0.013, 0.017 and 0.02 mg/kg. Flusilazole was not analysed in the whole fruit.

Based on data in the published literature[36] an average pulp to peel ratio for bananas at harvest is 1.82. Assuming this ratio and combining the results from washed and unwashed bananas, flusilazole residues in whole fruit, in ranked order, were: < 0.01 (5) and 0.01 (6) mg/kg.

The Meeting estimated a maximum residue level for flusilazole in banana (whole fruit) of 0.03 mg/kg to replace the previous recommendation of 0.1 mg/kg. Based on the pulp data, the Meeting estimated an STMR value of 0.01 mg/kg and an HR value (for pulp) of 0.01 mg/kg for banana pulp.

*Cucumber*

Flusilazole is registered for foliar application on cucumber in China (5 g ai/hL, 3 applications, a PHI of 7 days) and Korea (2.5 g ai/hL, 3 applications, and a PHI of 3 days). The Meeting received results from supervised trials with flusilazole on cucumber in China. None of the trials were conducted according to the GAPs of China or Korea. Therefore, the Meeting could not estimate a maximum residue level for flusilazole in cucumber.

[36] Stover, R.H. and Simmonds, N.W., 1987, Bananas. Tropical Agriculture Series, Longman Scientific & Technical, 468 pp

*Sweet corn*

The Meeting received results from supervised trials with flusilazole on sweet corn in France and South Africa.

The GAP of France (200 g ai/ha, 2 applications) does not specify a PHI. The six reported trials on sweet corn in France were conducted as a single application at 200–420 g ai/ha (100–210% GAP) with PHIs of 10–31 days. Flusilazole residues in sweet corn kernels were < 0.01 mg/kg in all these trials.

The GAP of South Africa specifies a maximum of 2 applications at 125 g ai/ha with a PHI of 14 days. One trial conducted in South Africa at 250 g ai/ha (200% GAP) with 2 applications, resulted in flusilazole residues in cobs < 0.01 mg/kg for both tested PHIs of 0 and 14 days.

The Meeting estimated a maximum residue level for flusilazole in sweet corn (corn-on-the-cob) of 0.01* mg/kg an STMR value of 0.01 mg/kg and an HR value of 0.01 mg/kg.

*Soya beans (dry)*

The Meeting received results from supervised trials with flusilazole used on soya beans in Argentina, Canada, France, South Africa and the United States. The trials in France could not be evaluated because there is no GAP for soya beans in Europe.

None of the six trials reported from Argentina were conducted according to the GAP of Argentina (100 g ai/ha, 2 applications, and a PHI of 35 days). In three of these trials, a single application rate of 200 g ai/ha (200% GAP) resulted in flusilazole residues < 0.005 mg/kg (below LOQ of the used analytical method) 38–60 days after the application.

The critical GAP of South Africa specifies 125 g ai/ha for aerial application or 100 g ai/ha for ground application, maximum of 2 applications, and a PHI of 30 days. Four trials in South Africa were conducted with a PHI of 34 days and using either 75 or 150 g ai/ha in two applications (75 or 150% GAP assuming ground application). Flusilazole residues were < 0.005 mg/kg (below LOD of the used analytical method) in all these trials at 34 days.

The GAP of the United States specifies 116 g ai/ha, 2 applications, and a PHI of 30 days. Twenty-one trials in the United States and two trial in Canada were conducted at 103–109% of the GAP rate, resulting in flusilazole residues of < 0.01(3), 0.01(8), 0.02(9) and 0.03(3) mg/kg.

Based on the residues obtained in the trials in the United States and Canada, the Meeting estimated a maximum residue level for flusilazole in soya beans (dry) of 0.05 mg/kg, an STMR value of 0.02 mg/kg and an HR value of 0.03 mg/kg.

*Sugar beet (root)*

The Meeting received results from supervised trials with flusilazole used on sugar beet in southern Europe (Greece, Italy, and Spain) and in northern Europe (Belgium, Denmark, northern France, Germany, the Netherlands and the United Kingdom).

Five trials in southern Europe (two in Greece, two in Italy, and one in Spain) were conducted according to the GAP of Greece (80 g ai/ha, 3 applications, and a PHI of 15 days). The Meeting noted that there were four other trials conducted in southern Europe with a shorter PHI of 14 days (3 or 6 applications) or a higher application rate (132.5% GAP) that resulted in flusilazole residues of < 0.01 mg/kg. Thus, results of these trials were also included. Flusilazole residues in sugar beet root, in ranked order, were: < 0.01 (6), and 0.01 (3) mg/kg.

Sixteen trials in northern Europe (ten in Germany, two in the UK, and one in Belgium, Denmark, the Netherlands and northern France) were conducted according to the GAP of Germany (150 g ai/ha, 2 applications, a PHI of 42 days). Among these trials, one trial in northern France had only a 35-day PHI but the flusilazole residue was < 0.01 mg/kg. Flusilazole residues in sugar beet root, in ranked order, were: < 0.01 (11), 0.01(2), 0.02, < 0.03, and 0.03 mg/kg.

The Meeting noted that the residues obtained in southern and northern Europe were from similar populations and agreed to combine the results. Flusilazole residues in sugar beet root, in ranked order, were: ≤ 0.01 (17), 0.01 (5), 0.02, < 0.03, and 0.03 mg/kg.

The Meeting estimated a maximum residue level for flusilazole in sugar beet root of 0.05 mg/kg to replace the previous recommendation of 0.01* mg/kg, an STMR value of 0.01 mg/kg, and a highest residue value of 0.03 mg/kg.

*Cereal grains*

*Barley*

The Meeting received information on flusilazole residues in barley grains from supervised trials in Germany, the United Kingdom and South Africa.

The GAP of Germany specifies 200 g ai/ha, 2 applications, the second application up to the growth stage of BBCH 51 and a PHI of 42 days. Twelve trials in Germany on winter barley were conducted at 160-221 g ai/ha (80–111% GAP), 2 applications, with the growth stage at the last application of BBCH 51 (PHI of 57–86 days). Flusilazole residues, in ranked order, were: < 0.01 (3), 0.02, 0.03, 0.04 (2), 0.05, 0.06, 0.07 (2), and 0.08 mg/kg.

The critical GAPs of the United Kingdom specify 156–160 g ai/ha, 1 application, and the BBCH 71 or 73 (watery ripe stage or early milk stage, respectively) growth stage at the last application. Four trials in the United Kingdom on spring barley were conducted at 160 g ai/ha, 2 applications, and the BBCH 71 growth stage at the last application. Flusilazole residues, in ranked order, were: < 0.01 (2), 0.06, and 0.07 mg/kg.

The critical GAP of South Africa specifies 112.5 g ai/ha (aerial application) or 100 g ai/ha (ground application), 1–2 applications and a PHI of 56 days. One trial in South Africa was conducted as a single application at 125 g ai/ha with a PHI of 56 days (application method and spray volume were not specified). Flusilazole residue from this trial was < 0.02 mg/kg.

The Meeting noted that the residues obtained in Germany, the United Kingdom and South Africa were from similar populations and agreed to combine the results. Flusilazole residues in barley grain, in ranked order, were: < 0.01 (5), < 0.02, 0.02, 0.03, 0.04 (2), 0.05, 0.06 (2), 0.07 (3), and 0.08 mg/kg.

*Rye*

The Meeting received information on flusilazole residues in rye grains from supervised trials in winter rye Germany. The GAP of Germany specifies 200 g ai/ha, 2 applications, the second application up to the growth stage of BBCH 55. The Meeting noted that the growth stages (BBCH of 49, 65, 69, or 72) at the last application in the trials did not match the GAP specification. Two trials were conducted at 100–130% of the GAP rate, with 3 applications and a PHI of 42 days (BBCH 65). One additional trial resulted in a higher flusilazole residue at a PHI of 48 days *vs.* 35 days (BBCH 69). Flusilazole residues obtained in these trials were: 0.04 (2), and 0.05 mg/kg.

*Wheat*

The Meeting received information on flusilazole residues in wheat grains from supervised trials in Germany, Spain, the United Kingdom and South Africa.

None of the trials in South Africa were conducted according to the critical GAP of South Africa: 112.5 g ai/ha (aerial application) or 100 g ai/ha (ground application), 1–2 applications and a PHI of 56 days.

The GAP of Germany specifies 200 g ai/ha, 2 applications, the second application up to the growth stage of BBCH 55, and a PHI of 42 days. The Meeting agreed that the growth stage at the last application is a better indication of the GAP than the PHI. Three trials in Germany were conducted at 160–250 g ai/ha (80–125% GAP), with 2-3 applications, and the last application at the growth stage of BBCH 55 (PHI of 58–63 days). Flusilazole residues were < 0.01 mg/kg. The Meeting noted that

several other trials at approx. the GAP rate (2–3 applications) but with later growth stages at the last application also resulted in flusilazole residues < 0.01 mg/kg.

The GAP of Spain specifies 200 g ai/ha, 1 application, and the BBCH 61 (beginning of flowering) growth stage at the last application. The trials in Spain were conducted at approximately 200 g ai/ha, with 2 applications, but the growth stage at the last application was in the range of 73–85 (a PHI of 28 days). Flusilazole residues from two of these trials (at BBCH 75 and 83) were < 0.01 mg/kg.

The critical GAPs of the United Kingdom specify 156–160 g ai/ha, 1–2 applications, and the BBCH 71 or 73 (watery ripe stage or early milk stage, respectively) growth stage at the last application. Four trials in the United Kingdom on winter wheat were conducted at 160 g ai/ha, 3 applications, and the BBCH 71 growth stage at the last application. Flusilazole residues were: < 0.01(4) mg/kg. Three other trials that were conducted as a single at 200 or 400 g ai/ha and later growth stages at the last application (75, 84, or 90) resulted in flusilazole residues < 0.01 (3) mg/kg.

The Meeting noted that flusilazole residues in wheat grain obtained in the sixteen trials in Germany, Spain and the United Kingdom were all < 0.01(16) mg/kg.

*Maize*

The Meeting received information on flusilazole residues in maize grains from supervised trials in France.

The GAP of France (200 g ai/ha, 2 applications) does not specify a PHI (the other available GAP in Europe, the GAP of Romania for cereal grains, specifies 100 g ai/ha and a PHI of 42 days). Five trials on maize were conducted at approx. 200 g ai/ha (2 applications) with a PHI of 28 days. Flusilazole residues in maize grain were < 0.01 mg/kg in all these trials.

The Meeting agreed that the data on barley, rye, wheat and maize could be used to support a "cereal grains" commodity group maximum residue level. The Meeting decided to recommend a maximum residue level of 0.2 mg/kg for cereals except rice, an STMR value of 0.04 mg/kg based on the barley data and a highest residue of 0.08 mg/kg based on the barley data.

The Meeting also agreed to withdraw its previous recommendations of maximum residue levels of 0.1 mg/kg for barley, rye and wheat grains.

*Rice*

The Meeting received information on flusilazole residues in rice grains from supervised trials in Spain. The GAP of Spain specifies 125 g ai/ha, 2 applications and a PHI of 30 days. Four trials were conducted at 129 g ai/ha (2 applications) with PHIs of 30 or 33 days. Flusilazole residues in rice grain, in ranked order, were: 0.06, 0.09, 0.11, and 0.18 mg/kg.

The meeting considered four trials insufficient to estimate a maximum residue level for flusilazole in rice.

*Rape seed*

The Meeting received results from supervised trials with flusilazole used on oilseed rape in Belgium, Denmark, France, Germany, the Netherlands and the United Kingdom. The critical GAPs in France, Germany, and the United Kingdom specify 200 g ai/ha, 1–2 applications and a PHI of 56 days (Germany) or a PHI that is not specified. The submitted trials were conducted at about the GAP rate with a PHI longer than 56 days. Flusilazole residues in these trials were generally below the LOQ of the used analytical methods: < 0.01 (9) or < 0.02 (5) mg/kg (PHIs in the range of 58–92 days). Results above LOQ: 0.01, 0.01, 0.03, and 0.04 mg/kg; were obtained with a PHI of 72, 109, 61, and 77, respectively.

Flusilazole residues in ranked order were: < 0.01(9), 0.01(2), < 0.02(5), 0.03 and 0.04 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg for flusilazole in rape seed, an STMR value of 0.01 mg/kg and a highest residue of 0.04 mg/kg.

The meeting recommended withdrawal of the previous recommendation for rape seed of 0.05 mg/kg.

*Sunflower seed*

Flusilazole is registered for foliar application on sunflower in Czech Republic, Bulgaria, France, Hungary, Romania and Slovakia. The GAPs for sunflower in these countries specify 75–200 g ai/ha, 1–2 applications, and a PHI of 56 or 60 days (or a PHI is not specified, which is the case of the highest rate of 200 g ai/ha).

The Meeting received results from supervised trials with flusilazole used on sunflower in France. The critical GAP of France specifies 200 g ai/ha and 2 applications (1 application for late infections) but does not specify a PHI. Eight trials in France were conducted at approx. 200 g ai/ha, one application, and a PHI of 50 days (BBCH 63–71). Flusilazole residues, in ranked order, were: < 0.01 (4), 0.01, 0.03, and 0.04 (2) mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg for flusilazole in sunflower seed, an STMR value of 0.01 mg/kg and a highest residue value of 0.04 mg/kg.

*Barley, rye and wheat forage*

The Meeting received information on flusilazole residues in barley, rye and wheat forage from supervised trials in Germany. The GAP of Germany for barley, rye and wheat specifies 200 g ai/ha, 2 applications, the second application up to the growth stage of BBCH 51 (barley) or BBCH 55 (rye and wheat). In the case of livestock grazing, it is assumed that animals are unlikely to be foraging within 7 days of the application of the fungicide. Data was available for residues in forage at 0, 21, 34 and 42 days according to the above gap. For the purposes of animal exposure through grazing, a value at 7 days, interpolated from the 0 and 21 day values is a satisfactory measure of the average residue that livestock would be exposed to for a 14 day period.

The results were considered from all trials conducted at the GAP rate (± 30%) with 2 applications (independent of the growth stage at the last application). Five trials on barley matching the criteria resulted in flusilazole residues of 0.9 (2), 1.35, 2.2, and 3.0 mg/kg. One trial on rye matched the criteria with flusilazole residues being 2.0 mg/kg. Five trials on wheat matching the criteria resulted in flusilazole residues of 0.9, 1.2, 3.3, 4.2 and 4.5 mg/kg. Combined flusilazole residues, in ranked order, were: 0.9 (3), 1.2, 1.35, 2.0, 2.2, 3.0, 3.3, 4.2 and 4.5 mg/kg; resulting in an STMR value of 2.0 mg/kg and a highest residue value of 4.5 mg/kg for flusilazole in barley, rye and wheat forage.

*Barley, rye, and wheat straw and fodder, dry*

The Meeting received information on flusilazole residues in barley straw from supervised trials in Germany. The GAP of Germany specifies 200 g ai/ha, 2 applications, the second application up to the growth stage of BBCH 51 and a PHI of 42 days. Thirteen trials in Germany on winter barley were conducted at 160–221 g ai/ha (80–111% GAP), 2 applications, with the growth stage at the last application of BBCH 51 (PHI of 57–86 days). Flusilazole residues, in ranked order, were: 0.11, 0.48, 0.62, 1.2, 1.4, 1.5, 2.0 (2), 2.1 (2), 2.2, 2.3, and 2.5 mg/kg.

The Meeting received information on flusilazole residues in rye straw from supervised trials on winter rye in Germany. The GAP of Germany specifies 200 g ai/ha, 2 applications, the second application up to the growth stage of BBCH 55 and a PHI of 42 days. The Meeting noted that the growth stages (BBCH of 49, 65, 69, or 72) at the last application in the trials did not match the GAP specification.

The Meeting received information on flusilazole residues in wheat straw from supervised trials in Germany, Spain and the United Kingdom.

The GAP of Germany specifies 200 g ai/ha, 2 applications, the second application up to the growth stage of BBCH 55, and a PHI of 42 days. Three trials in Germany were conducted at 160–

250 g ai/ha (80–125% GAP), with 2–3 applications and the last application at the growth stage of BBCH 55 (PHI of 58–63 days). Flusilazole residues, in ranked order, were: 0.12, 0.23 and 1.6 mg/kg.

The GAP of Spain specifies 200 g ai/ha, 1 application and the BBCH 61 (beginning of flowering) growth stage at the last application. The trials in Spain were conducted at approx. 200 g ai/ha, with 2 applications, but the growth stage at the last application was in the range of 73–85.

The critical GAPs of the United Kingdom specify 156–160 g ai/ha, 1–2 applications, and the BBCH 71 or 73 (watery ripe stage or early milk stage, respectively) growth stage at the last application. None of the submitted trials on wheat (straw) in the United Kingdom matched were conducted according to the GAP (growth stage at the last application was in the range of 39–65).

The Meeting noted that flusilazole residues obtained in barley and wheat straw in Germany appeared to be from similar populations and agreed to combine the results. Flusilazole residues, in ranked order, were: 0.11, 0.12, 0.23, 0.48, 0.62, 1.2, 1.4, 1.5, 1.6, 2.0 (2), 2.1 (2), 2.2, 2.3 and 2.5 mg/kg. The Meeting also agreed to extrapolate the results for barley and wheat straw to rye straw and estimated a maximum residue level of 5 mg/kg for flusilazole in barley, rye and wheat straw and fodder, dry (to replace the previous recommendation of 2 mg/kg), an STMR value of 1.6 mg/kg and a highest residue value of 2.5 mg/kg.

*Oat forage and fodder*

The Meeting received information on flusilazole residues in oat forage and dry foliage (dry fodder) from two supervised trials in South Africa. The GAP of South Africa for oat fodder specifies 75 g ai/ha, one application, and a PHI of 30 days. One trial was conducted at the GAP rate with a PHI of 29 days. Flusilazole residue in dry foliage (fodder) was < 0.1 mg/kg.

The Meeting considered one trial insufficient to estimate a maximum residue level for oat fodder.

*Sugar beet leaves or tops*

The Meeting received information on flusilazole residues in sugar beet leaves from supervised trials on sugar beet in southern Europe (Greece, Italy, and Spain) and in northern Europe (Belgium, Denmark, northern France, Germany, the Netherlands and the United Kingdom).

Six trials in southern Europe (two in Greece, three in Italy and one in Spain) were conducted according to the GAP of Greece (80 g ai/ha, 3 applications, and a PHI of 15 days). Flusilazole residues in sugar beet leaves, in ranked order, were: 0.10, 0.31, 0.45, 0.66, 0.89 and 1.0 mg/kg.

Sixteen trials in northern Europe (ten in Germany, two in the UK, and one in Belgium, Denmark, the Netherlands, and northern France) were conducted according to the GAP of Germany (150 g ai/ha, 2 applications, a PHI of 42 days). Flusilazole residues in sugar beet leaves, in ranked order, were: 0.11(2), 0.17, 0.19, 0.21, 0.22, 0.25(2), 0.26, 0.27, 0.33, 0.34, 0.37, 0.58, 0.84 and 0.88 mg/kg.

The Meeting noted that the residues obtained in southern and northern Europe were from similar populations and agreed to combine the results. Flusilazole residues in sugar beet leaves, in ranked order (median underlined), were: 0.10, 0.11 (2), 0.17, 0.19, 0.21, 0.22, 0.25 (2), 0.26, 0.27, 0.31, 0.33, 0.34, 0.37, 0.45, 0.58, 0.66, 0.84, 0.88, 0.89 and 1.0 mg/kg.

The Meeting estimated an STMR value of 0.29 mg/kg and a highest residue value of 1.0 mg/kg for flusilazole in sugar beet leaves.

*Rice hulls*

The Meeting received information on flusilazole residues in rice hulls (husks) from supervised trials in Spain. The GAP of Spain specifies 125 g ai/ha, 2 applications and a PHI of 30 days. Four trials were conducted at 129 g ai/ha (2 applications) with PHIs of 30 or 33 days. Flusilazole residues in rice hulls, in ranked order, were: 0.34, 0.39, 0.44, and 0.68 mg/kg.

The Meeting made no recommendation for rice hulls as none could be made for the primary commodity rice.

***Fate of residues during processing***

The Meeting received information on the fate of flusilazole residues during processing of apples, grapes, soya beans, wheat and barley grain and on flusilazole fate under hydrolysis conditions simulating commercial food processing.

In a high-temperature hydrolysis study greater than 99% of flusilazole remained unchanged under conditions simulating industrial processing (temperatures ranging from 90–120°C; pH 5 and 7). Therefore, flusilazole can be considered stable to simulated pasteurization, baking, brewing, boiling and sterilization.

The STMR-P values calculated from the processing factors are summarized in the table below.

| Raw agricultural commodity | | Processed commodity | | |
|---|---|---|---|---|
| Commodity | STMR (mg/kg) | Commodity | Processing factor* | STMR-P (mg/kg) |
| Apple | 0.04 | Apple juice | 0.19(2) | 0.008 |
| | | Apple pomace, wet | 2.4(2) | 0.094 |
| | | Apple pomace, dry | 12(2) | 0.48 |
| Grapes | 0.03 | Grape juice | 0.42(4) | 0.012 |
| | | Wine | 0.09(5) | 0.003 |
| | | Dried Grapes (raisins) | 1.8(3) | 0.054 |
| | | Grape pomace, wet | 3.6(2) | 0.108 |
| | | Grape pomace, dry | 11(2) | 0.33 |
| Soya beans | 0.02 | Soya bean meal | 0.38 | 0.008 |
| | | Soya bean hulls | 1.1 | 0.022 |
| | | Soya bean oil, refined | 2.2 | 0.044 |
| Wheat | 0.04 | Wheat bran | 0.29 | 0.012 |
| | | Wheat flour, low-grade | < 0.91 | < 0.036 |
| | | Wheat milled by products | 0.59 | 0.024 |

*mean value of (no. trials) except for soya beans where only one trial was performed

The Meeting estimated a maximum residue level of 2 mg/kg for *apple pomace, dry*, based on the highest residue of 0.13 mg/kg in pome fruits and the processing factor of 12.

Based on the HR value of 0.11 mg/kg in grapes and the processing factor of 1.8, the Meeting estimated a maximum residue level of 0.3 mg/kg for *dried grapes (including currants, raisins, and sultanas)* to replace its previous recommendation of 1 mg/kg.

Based on the highest residue of 0.03 mg/kg in soya beans and the processing factors of 1.1 and 2.2, the Meeting estimated a maximum residue level of 0.05 mg/kg for *soya bean hulls* and 0.1 mg/kg for *soya bean oil, refined*.

***Livestock dietary burden***

The Meeting estimated the dietary burden of flusilazole in farm animals on the basis of the diets listed in Annex 6 of the 2006 JMPR Report (OECD Feedstuffs Derived from Field Crops). Calculation from the highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating maximum residue levels, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities.

The table below shows estimated maximum and mean dietary burdens for beef cattle, dairy cattle, broilers and laying poultry based on the animal diets from the United States/Canada, the European Union, and Australia. The calculations are provided in Annex 6.

| | Flusilazole, Animal dietary burden (mg/kg) | | | | | |
|---|---|---|---|---|---|---|
| | US-Canada | | EU | | Australia | |
| | Maximum | Mean | Maximum | Mean | Maximum | Mean |
| Beef cattle | 7.5 | 2.25 | 6.3 | 2.9 | 18[1] | 8.0[2] |
| Dairy cattle | 7.5 | 3.4 | 6.7 | 2.9 | 11.5[3] | 5.3[4] |
| Poultry - broiler | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.03 |
| Poultry - layer | 0.04 | 0.04 | 2.3[5] | 1.1[6] | 0.02 | 0.02 |

[1] Highest maximum beef cattle dietary burden suitable for MRL estimates for mammalian meat.
[2] Highest mean beef cattle dietary burden suitable for STMR estimates for mammalian meat.
[3] Highest maximum dairy cattle dietary burden suitable for MRL estimates for milk
[4] Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.
[5] Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs
[6] Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs.

### *Farm animal feeding studies*

The Meeting received information on lactating dairy cow and laying hen feeding studies.

Twelve lactating cows were randomly assigned among 4 dosing groups of 3 animals each: one control group and 3 groups dosed at one of 3 flusilazole feeding levels each (2, 10, and 50 mg/kg based on measured feed intake, corresponding. All groups were fed for 28 days. Residues in milk reached a plateau at about 7 days. During the withdrawal period, residues decreased significantly in all milk and tissue samples, indicating no bioaccumulation of flusilazole or its metabolites.

Total residues of flusilazole and [bis(4-fluorophenyl)methyl]silanol (IN-F7321) in whole milk (on days 7–28, i.e., at the plateau) and tissues obtained at the 2, 10, and 50 mg/kg dosing levels in the diet are summarized in the table below.

| Matrix | Dose (mg/kg) | Highest residue | Mean residue |
|---|---|---|---|
| Whole milk | 2 | < 0.01 | < 0.01 |
| | 10 | 0.05 | 0.02 |
| | 50 | 0.10 | 0.06 |
| Muscle | 2 | < 0.01 | < 0.01 |
| | 10 | 0.06 | 0.05 |
| | 50 | 0.19 | 0.19 |
| Kidney | 2 | 0.21 | 0.21 |
| | 10 | 0.85 | 0.77 |
| | 50 | 5.0 | 3.9 |
| Liver | 2 | 0.18 | 0.15 |
| | 10 | 0.65 | 0.55 |
| | 50 | 1.6 | 1.4 |
| Fat [a] | 2 | 0.06 | 0.06 |
| | 10 | 0.56 | 0.36 |
| | 50 | 1.4 | 1.35 |

[a]Residues for omental, renal, and subcutaneous fat for the 2, 10 and 50 mg/kg dose, respectively. These were the highest residues at the respective dose levels for the three kinds of analysed fat samples.

In a hen feeding study, eighty laying hens were divided into 4 groups and each group was divided into 4 subgroups of 5 hens each. Each subgroup of a group was dosed for 28 days at 0, 2, 10, or 50 mg/kg of flusilazole in the diet. Residues in eggs reached a plateau at about 7 days. During the withdrawal period, residues decreased significantly in all egg and tissue samples, indicating no bioaccumulation of flusilazole or its metabolites.

Total residues of flusilazole and [bis(4-fluorophenyl)methyl]silanol (IN-F7321) in eggs (on days 7–28, i.e., at the plateau) and tissues (on day 28) obtained at the 2, 10, and 50 mg/kg dosing levels in the diet are summarized in the table below.

| Matrix | Dose (mg/kg) | Highest residue, mg/kg | Mean residue, mg/kg |
|---|---|---|---|
| Whole egg | 2 | 0.05 | 0.03 |
| | 10 | 0.40 | 0.16 |
| | 50 | 1.8 | 0.85 |
| Muscle | 2 | < 0.02 | < 0.02 |
| | 10 | 0.10 | 0.05 |
| | 50 | 0.37 | 0.19 |
| Liver [a] | 2 | 0.08 | 0.04 |
| | 10 | 0.13 | 0.10 |
| | 50 | 0.58 | 0.41 |
| Fat | 2 | 0.10 | 0.09 |
| | 10 | 0.54 | 0.45 |
| | 50 | 3.7 | 3.2 |

[a] Flusilazole was not analysed in liver for the 2 and 10 mg/kg dosing levels, but the residues can be assumed to be < 0.01 mg/kg because < 0.01 mg/kg was obtained for the 50 mg/kg dosing level.

In both the cattle and poultry feeding studies, the flusilazole residues in muscle were significantly lower than in fat and confirms that the residue (sum of flusilazole and [bis(4-fluorophenyl)methyl]silanol) is fat-soluble and that fat is the target tissue.

***Animal commodity maximum residue levels***

The dietary burdens for the estimation of maximum residue levels for animal commodities are 18 mg/kg for beef cattle, 11.5 mg/kg for dairy cattle and 2.3 mg/kg for poultry. The dietary burdens for the estimation of STMR values for animal commodities are 8.0 mg/kg for beef cattle, 5.3 mg/kg for dairy cattle and 1.1 mg/kg for poultry. The sum of flusilazole and [bis(4-fluorophenyl)methyl]silanol (IN-F7321) residues was used for the estimation of "flusilazole residue" levels in animal commodities.

The maximum dietary burden of 18 mg/kg for beef cattle fell between the 10 and 50 mg/kg dosing levels in the cattle feeding study. The residues in muscle were significantly lower than in fat. The target tissue for flusilazole residues is fat. Using the highest residues of 0.56 and 1.4 mg/kg in fat for 10 and 50 mg/kg dosing levels, respectively, the interpolated highest residue in fat for the dietary burden of 18 mg/kg was 0.73 mg/kg. Similarly, for beef liver and kidney the highest residues were 0.84 and 1.68 mg/kg, respectively.

The mean dietary burden was 8.0 mg/kg for beef cattle. By interpolation, the mean residues obtained in fat, liver and kidney were 0.285, 0.45 and 0.65 mg/kg, respectively.

On the fat basis, the Meeting estimated a maximum residue level of 1.0 mg/kg for meat (fat) from mammals (other than marine mammals), an STMR value of 0.285 mg/kg and an HR value of 0.73 mg/kg. Based on the liver and kidney results, the Meeting estimated a maximum residue level of 2 mg/kg for mammalian edible offal and, based on the kidney data, an STMR value of 0.65 mg/kg and an HR value of 1.68 mg/kg.

The mean dietary burden of 5.3 mg/kg for dairy cattle fell between the 2 and 10 mg/kg dosing levels in the feeding study. The interpolated highest residue in whole milk, using the mean residues in the feeding study, was 0.03 mg/kg. Similarly, the mean residue based upon a dietary burden of 5.3 mg/kg, in whole milk was 0.01 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg for whole milk, an STMR value of 0.01 mg/kg and an HR value of 0.03 mg/kg.

Maximum and mean dietary burdens for poultry (2.3 and 1.1 mg/kg, respectively) were near the lowest dosing level of 2 mg/kg. By interpolation, the highest residues obtained in fat, liver and eggs between the 2 and 10 mg/kg feeding level were 0.13, 0.09 and 0.07 mg/kg, respectively. Extrapolating the mean residues gave 0.05 mg/kg for fat, 0.02 mg/kg for liver and 0.02 mg/kg for eggs.

On the fat basis, the Meeting estimated a maximum residue level of 0.2 mg/kg for poultry meat (fat), an STMR value of 0.05 mg/kg and an HR value of 0.13 mg/kg. Based on the liver results, the Meeting estimated a maximum residue level of 0.2 mg/kg for poultry edible offal, an STMR value of 0.02 mg/kg and an HR value of 0.09 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg for eggs, an STMR value of 0.02 and HR value of 0.07 mg/kg.

The Meeting agreed to withdraw its previous recommendations of maximum residue levels of 0.01* mg/kg for cattle fat, cattle meat, cattle milk, chicken meat, chicken eggs, and chicken edible offal; and 0.02* mg/kg for cattle edible offal.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The International Estimated Daily Intakes (IEDIs) of flusilazole based on STMR and STMR-P values estimated for 22 commodities for the thirteen GEMS/Food regional diets were 2–10% of the maximum ADI (0.007 mg/kg bw). The results are shown in Annex 3 of the Report. The Meeting concluded that the long-term dietary intake of flusilazole residues is unlikely to present a public health concern.

### *Short-term intake*

The International Estimated Short Term Intake (IESTI) of flusilazole calculated on the basis of the recommendations made by the JMPR represented for the general population 0–40% and for children 0–100% of the ARfD (0.02 mg/kg bw). The results are shown in Annex 4 of the Report. The Meeting concluded that the short-term intake of residues of flusilazole resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

## 5.15 FOLPET (041)

## TOXICOLOGY

### Evaluation for an acute reference dose

Folpet, the ISO approved name for *N*-(trichloromethylthio)phthalimide, is registered for the control of fungal diseases in crops (CAS No. 133-07-3). The toxicology of folpet was evaluated by the JMPR in 1969 and 1995 and addenda to the monograph were prepared in 1973, 1984, 1986, 1990 and 2004. In 1995, an ADI of 0–0.1 mg/kg bw was established based on 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. In 2004, the Meeting established an ARfD for folpet of 0.2 mg/kg bw for women of childbearing age only, based on a NOAEL of 20 mg/kg bw per day for increased incidences of hydrocephalus at 60 mg/kg bw per day in rabbits and using a safety factor of 100.

The Meeting concluded that the database was insufficient (particularly with regard to information about the possible developmental effects of the metabolite phthalimide) to establish the mode of action by which the increased incidence of hydrocephalus was induced.

The sponsor conducted a study of developmental toxicity with phthalimide, and studies to evaluate the potential effects of folpet and phthalimide on the intestinal flora of the rabbit. It is known that the rabbit is dependent on the presence of caecotrophs for adequate nutrition. The sponsor suggested that disruption of the intestinal flora might result in maternal malnutrition, with possible consequent adverse effects on foetal development.

At the request of the CCPR at its 39th Session,[37] the present Meeting reconsidered the ARfD for folpet on the basis of new data.

All pivotal studies with folpet and phthalimide were certified as being compliant with GLP.

***Toxicological data***

*Data evaluated by JMPR 2004*

With respect to the kinetics and metabolism of folpet, the following description is quoted from JMPR 2004:

> 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.

With respect to the developmental toxicity of folpet the following description is quoted from JMPR 2004:

> 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 two out of three studies, no foetal 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 foetal toxicity was 10 mg/kg bw per day on the basis of reduced foetal body weights. The maternal toxicity and the associated reduction in foetal 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 foetuses out of three litters. In these same foetuses, skull, gastric, and pulmonary abnormalities were also observed. As the observation of hydrocephaly and cleft palate in one foetus 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 foetal 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 foetuses 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 foetuses 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.

The results of studies considered by the Meeting in 2004 suggested that folpet was rapidly degraded to phthalimide. The other component of the parent molecule, thiophosgene, is rapidly

[37] Codex Alimentarius Commission. *Report of the 39th Session of the Codex Committee on Pesticide Residues, 7–12 May 2007, Beijing, China* (ALINORM07/30/24).

detoxified by reaction with cysteine or glutathione, for example, and is ultimately rapidly excreted. During the present Meeting, the sponsor provided a toxicokinetic study in rats, not previously evaluated by JMPR.

***Toxicokinetics***

In a toxicokinetic study in rats, concentrations of folpet and its metabolites were measured in the faeces and urine. The study was evaluated by the present Meeting, focusing on concentrations of folpet in order to establish the amount of folpet that reaches the distal parts of the gastrointestinal tract.

Rats were given [$^{14}$C] labelled folpet at a dose of 10 or 500 mg/kg bw by gavage. Extracts of urine were qualitatively analysed by high-performance liquid chromatography (HPLC) and GC/MS. Phthalamic acid was found only in the urine. Extracts of faeces were qualitatively analysed by TLC by comparison with reference compounds. Quantification of faecal metabolites was performed by linear plate scanner and autoradiography. Several compounds were identified in faeces, including phthalimide, phthalamic acid, phthalic anhydride and parent folpet. Toxicokinetic data are presented in Table 11.

Table 11. Toxicokinetic data for rats given [$^{14}$C] labelled folpet by gavage

| Dose | Radioactivity excreted, males/females (% of administered dose) | | Folpet in urine (% of radioactivity) | Folpet in faeces | |
|---|---|---|---|---|---|
| | Urine | Faeces | | % of radiolabel (males/females) | % of total dose |
| 10 mg/kg bw, single dose | 91.7/92.7 | 6.4/5.1 | ND | 15/27 | 0.5–1.5 |
| 10 mg/kg bw, repeated doses | 88.3/84.0 | 7.6/7.8 | ND | 18/17 | 1.3–1.4 |
| 500 mg/kg bw | 56.5/60.5 | 41.3/39.6 | ND | 93/92 | 36.8–38.4 |

ND, not detected.

After a single dose at 10 mg/kg bw, about 92% and 6% of the radiolabel administered was recovered from the urine and faeces, respectively. At this single dose, no folpet was detected in the urine. Of the radiolabel recovered from the faeces, 0.5–1.5% was associated with folpet. After 14 consecutive doses at 10 mg/kg bw per day, the proportions of folpet in faeces were similar to those found after a single dose at 10 mg/kg bw; folpet was not detected in the urine. At 500 mg/kg bw, 56–60% and 39–41% of the radiolabel administered was recovered from the urine and faeces, respectively. No folpet was detected in the urine. Of the radiolabel recovered from the faeces, 36.8–38.4% was identified as folpet.[38]

***Developmental toxicity***

In a study of developmental toxicity, groups of 25 time-mated female New Zealand White rabbits received daily administrations of phthalimide (purity, 100%) at a dose of 0, 5, 15 or 30 mg/kg bw per day by gavage from days 6 to 28 after mating. The vehicle was water containing 0.5% w/v Tween 80 and 0.7% w/v carboxymethylcellulose. In view of the relative molecular masses of folpet (296.6) and phthalimide (147.1), the dose of phthalimide of 30 mg/kg bw per day would be equimolar to a dose of folpet of about 60 mg/kg bw per day. All animals were examined twice per day for clinical signs. Body weight was recorded daily from the day of mating until day 29 of gestation, when they were

[38] Wood, S.G., Chasseaud, L.F., Cheng, K., Hall, M., Fitzpatrick, K., Iqbal, S., Barlett, A. (1991) Metabolic fate of $^{14}$C-folpet in Sprague-Dawley rats. Unpublished report No HRC/MBS 41/91499 from Huntingdon Life Sciences Limited, Woolley Road, Alconbury, Huntingdon, Cambridgeshire. Submitted to WHO by Makhteshim Chemical Works, Beer-Sheva, Israel.

killed. Food intake was recorded daily from the first day after mating until day 29 of gestation. On day 29, the animals were killed and examined macroscopically. In females in the control group and in the group receiving the highest dose, the duodenum and sphincter of Oddi (hepatopancreatic sphincter) were examined microscopically. The ovaries and uterus were removed and the foetuses were weighed and examined for visceral and skeletal abnormalities.

There were no mortalities. At necropsy, in the control group, and the groups at 5 and 15 mg/kg bw per day, three, five and two females, respectively, did not appear to be pregnant. One female in the control group aborted on day 21 and one female in the group at 15 mg/kg bw per day appeared to have total litter resorption. In the dams, no treatment-related clinical signs or effects on body weight and food consumption, and no macroscopic or microscopic abnormalities were observed. Increases in implantation losses were observed in the treated groups (19.3%, 24.0%, 26.8% and 36.0% in the control group and the groups receiving the lowest, intermediate and highest dose, respectively), reaching statistical significance for pre-implantation loss in the group receiving the highest dose. Since implantation in rabbits occurs at around days 7–8 after mating, the effects on pre-implantation loss may have been treatment-related. Increases in pre-implantation losses were observed in the treated groups (13.4%, 16.9%, 19.5% and 25.7% in the control group and in the groups receiving the lowest, intermediate and highest dose, respectively), reaching statistical significance in the group receiving the highest dose. In the group at the highest dose, reductions in the mean number of implantations and number of live foetuses were considered to be the result of increased implantation loss. The slightly lower mean litter weights and slightly increased foetal weights in the group at the highest dose were considered to reflect the decreased number of implantations in this group.
In the foetuses, no treatment-related effects on visceral and skeletal parameters were observed.

The NOAEL for maternal toxicity was 30 mg/kg bw per day i.e., the highest dose tested. The NOAEL for embryo/fetotoxicity was 15 mg/kg bw per day on the basis of increased pre-implantation loss at the highest dose.[39]

***Inhibition of microbial activity in vitro***

A study was performed to determine minimum inhibitory concentrations (MIC) of folpet (purity, 95.8%) against two bacterial species (*Bacteroides* sp. and *Enterococcus faecalis*) and one species of yeast (*Candida albicans*). These bacteria were considered to be representative of anaerobic bacteria in the rabbit gut. *Candida albicans* was considered to be representative of yeast that may occur in the rabbit gut. The MIC values for *Bacteroides* sp., *Enterococcus faecalis* and *Candida albicans* were 20–50, 50–200 and 5 µg/mL, respectively. The Meeting concluded that folpet demonstrates antimicrobial activity against organisms considered representative of rabbit gut flora.[40]

In a study to determine MIC of phthalimide (purity, 100%), the MIC values for *Bacteroides* sp., *Enterococcus faecalis and Candida albicans* were all > 1000 µg/mL, except for one strain of *C. albicans* strain for which the MIC value was 1000 µg/mL. The Meeting concluded that phthalimide demonstrates no significant antimicrobial activity against organisms considered representative of rabbit gut flora.[41]

The Meeting concluded that the existing database, i.e., the new studies conducted after 2004 and the previously evaluated studies, was adequate to characterize the potential hazards of folpet to foetuses, infants and children.

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[39] Blee, M.A.B. (2006) Tetrahydrophthalimide. Prenatal toxicity study in the rabbit by oral gavage administration. Unpublished report No R-18202, MAK 864/053232 from Huntingdon Life Sciences Limited, Woolley Road, Alconbury, Huntingdon, Cambridgeshire. Submitted to WHO by Makhteshim Chemical Works, Beer-Sheva, Israel.

[40] Akhurst, L.C (2005a) Captan: determination of minimum inhibitory concentration against selected micro-organisms representative of rabbit gut microflora. Unpublished report No. R-18666, MAK 0888/052848 from Huntingdon Life Sciences Ltd, Huntingdon, Cambridgeshire, England. Submitted to WHO by Makhteshim Chemical Works, Beer-Sheva, Israel.

[41] Akhurst, L.C (2005b) THPI: determination of minimum inhibitory concentration against selected micro-organisms representative of rabbit gut microflora. Unpublished report No. R-18735, MAK 0890/053252 from Huntingdon Life Sciences Limited, Huntingdon, Cambridgeshire, England. Submitted to WHO by Makhteshim Chemical Works, Beer-Sheva, Israel.

### Toxicological evaluation

In 2004 JMPR established an ARfD of 0.2 mg/kg bw for women of childbearing age only based on a NOAEL of 20 mg/kg bw per day identified on the basis of an increased incidence of hydrocephalus at 60 mg/kg bw per day in the study in rabbits and using a safety factor of 100.

On the basis of the study of developmental study with phthalimide in rabbits, the Meeting considered that it is unlikely that phthalimide (or its metabolites, including phthalamic acid) is a teratogenic agent.

In view of the results of studies of microflora inhibition, the hypothesis that the inhibition of caecal microflora in the rabbit by folpet causes malnutrition was plausible. However, although unchanged folpet was not detected in the urine of rats given single low or high doses, this does not necessarily imply a lack of systemic absorption of the parent compound, as folpet is rapidly metabolized. Certainly, toxicokinetic studies with structurally-related captan suggested that this compound is systemically available after oral administration. Thus it could not be excluded that the embryo/fetotoxic effects observed in a study of developmental toxicity with folpet in rabbits could be a result of a direct action of folpet or one of its metabolites. Furthermore, equivalent toxicokinetic and metabolism studies in rabbits, the species in which the critical developmental effects of concern were seen, did not appear to have been performed.

In view of these considerations, the Meeting concluded that there was no sound basis on which to change the ARfD established in 2004. The Meeting reconfirmed the ARfD of 0.2 mg/kg bw based on a NOAEL of 20 mg/kg bw per day identified on the basis of an increased incidence of hydrocephalus at 60 mg/kg bw per day in the study in rabbits and using a safety factor of 100. This ARfD applies to women of childbearing age. The Meeting concluded that it was unnecessary to establish an ARfD for the general population.

An addendum to the toxicological monograph was not prepared.

*Estimate of acute reference dose*

0.2 mg/kg bw, for women of childbearing age
Unnecessary for the rest of the general population

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

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

## 5.16 INDOXACARB (216)

### RESIDUE AND ANALYTICAL ASPECTS

Indoxacarb was evaluated for the first time by JMPR in 2005 and an ADI of 0-0.01 mg/kg bw was established. An ARfD of 0.1 mg/kg bw was also established. MRLs were recommended for a number of crop and animal commodities.

An MRL of 3 mg/kg was recommended for head cabbages.

CCPR at its 39th Session (2007) decided to return the MRL for head cabbages to Step 6 because of short-term intake concerns and noted that indoxacarb had been scheduled for evaluation by 2007 JMPR (alternative GAP) (ALINORM 07/30/24 – Rev 1, paragraph 127).

The 2005 JMPR evaluated the supervised residue trials for indoxacarb uses on cabbage. The recommended maximum residue level for cabbage was based on the combined residue data from USA (0.21, 0.34, 0.38 and 2.7 mg/kg) and South Africa (0.40, 0.47, 0.83 and 2.0 mg/kg). The IESTI was based on the estimated HR of 2.7 mg/kg.

Data on residues including and excluding wrapper leaves were provided in the US trials on head cabbage recorded in the JMPR Evaluations of 2005. The cabbages including wrapper leaves are intended to represent the commodity in trade, so data on cabbages including wrapper leaves are used to support the MRL. The Meeting was informed that, in the USA, cabbages excluding wrapper leaves are intended to represent the edible portion.

In the four US trials at the GAP PHI of 3 days, mean residues of indoxacarb + R enantiomer in cabbages including wrapper leaves were: 0.21, 0.34, 0.38 and 2.7 mg/kg; and without wrapper leaves were: 0.020, 0.034, 0.025 and 0.054 mg/kg respectively. The highest residue in edible portion from the US trials was 0.054 mg/kg.

In the four South African trials at PHI 3 days (GAP PHI of 3 days), mean residues of indoxacarb + R enantiomer in cabbages were: 0.40, 0.47, 0.83 and 2.0 mg/kg. The commodity analysed was described as "whole heads".

A letter from SABS Commercial[42], where the cabbage samples were analysed, explained that the laboratory policy is to remove obviously damaged, decomposed or withered leaves before shredding and mixing. The laboratory does not automatically remove the outer leaves of a fresh head of cabbage as the heads are picked in such a way that damaged and non-edible parts will remain on the fields.

This information suggests that the intention in the South African trials was to analyse edible portion. The highest residue in edible portion from the South African trials was 2.0 mg/kg.

The Meeting estimated an HR for head cabbage of 2.0 mg/kg.

### DIETARY RISK ASSESSMENT

***Short-term intake***

The IESTI of indoxacarb calculated on the basis of the recommendations for cabbage made by the JMPR represented 90% of the ARfD (0.1 mg/kg bw) for children and 40% for the general population.

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

## 5.17 PHOSMET (103) – ALTERNATIVE GAP

Phosmet has been evaluated several times for residues by the JMPR from 1976 to 1997. Additional residue information on citrus fruits, pears, nectarines and blueberries was evaluated by the JMPR in 2002. The 2002 JMPR estimated short-term intakes that exceeded the ARfD of 0.02 mg/kg bw for apple, blueberry, citrus fruits, nectarine and pear. The Meeting noted that the ARfD of 0.02 mg/kg bw was conservative and might be refined.

A new ARfD of 0.2 mg/kg bw was established in 2003. The Meeting estimated short-term intakes that exceeded the ARfD for apple (230% children) and pear (150% children). No acute intake concern was estimated for the other commodities (JMPR Report 2003, p. 20 and p. 173).

At the 38th Session of the CCPR in 2006, the Committee noted the acute intake concerns expressed by Australia, the European Union and the USA. The Committee decided to return the draft MRLs for apricot, blueberries, citrus fruit, nectarine and pome fruits to Step 6 and decided to request JMPR to consider using alternative GAP to recommend lower MRLs for these commodities.

New data for GAP and new supervised residue trials were submitted to the 2007 JMPR for pome fruits. New supervised residue trials data were also submitted for oranges and peaches.

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[42] Garbers HV. 8-Jan-2007. Indoxacarb residues in cabbage. Letter. Reference 17/36/8. SABS Commercial (Pty) Ltd, Pretoria, South Africa.

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

Data from new supervised trials on oranges, apples, pears and peaches/nectarines were evaluated. Furthermore, data on citrus fruits, apricots/peaches/nectarines and blueberries which were reviewed in the 1997 and 2002 monographs were interpreted by the current Meeting in the light of the acute intake concerns expressed at the 38th Session of CCPR.

*Citrus fruits*

In Brazil, phosmet may be used on citrus fruits at 1.5 kg ai/ha and 0.075 kg ai/hL with a PHI of 14 days.

Two Brazilian trials on oranges carried out in 2002 were submitted to the current Meeting. In one Brazilian trial where phosmet was used five times at 2 kg ai/ha and 0.1 kg ai/hL with a PHI of 10 days, the residue found was 1.3 mg/kg. In the second trial (5 × 4 kg ai/ha, 0.2 kg ai/hL with a PHI of 10 days), the residue was 2.2 mg/kg. The Meeting noted that the field trial application rates did not match the GAP rates; as a consequence the residue data could not be used.

Phosmet is registered in Spain for use on citrus fruits at 0.075–0.15 kg ai/hL with a PHI of 30 days.

The 2002 JMPR estimated a maximum residue level and an STMR for phosmet in citrus fruits of 3 mg/kg and 0.64 mg/kg (whole fruit) on the basis of 16 residue supervised trials data for mandarins, tangerines and oranges matching the Spanish GAP. Furthermore, STMR and HR values for phosmet in citrus edible portion of 0.21 and 0.52 mg/kg were estimated.

The current Meeting noted that the acute dietary risk assessment for phosmet, as presented in the 2003 JMPR Report (ARfD: 0.2 mg/kg bw), is unlikely to present a public health concern for citrus (≤ 10% for children and the general population). Therefore, it is not necessary to retrospectively consider an alternative GAP for citrus fruits.

The Meeting estimated a maximum residue level of 3 mg/kg, confirming the previous recommendation, and an STMR and HR of 0.21 and 0.52 mg/kg for citrus edible portion.

*Pome fruits*

Phosmet is registered in the USA for use on apples at 1.7–4.1 kg ai/ha and on pears at 1.7–5.6 kg ai/ha with a PHI of 7 days.

Based on US residue trials and the US GAP, the 2002 JMPR estimated a maximum residue level, an STMR and an HR value for phosmet in pome fruits of 10, 3.3 and 7.3 mg/kg, respectively. The 2003 Meeting estimated short-term intakes that exceeded the ARfD of 0.2 mg/kg bw for apple (230% for children) and pear (150% for children).

New GAP data on pome fruit from Brazil and Spain were submitted to the 2007 JMPR. The Meeting also received new supervised residue trial data on apples and pears from Brazil, Spain, France and Italy.

Phosmet is registered in Brazil for use on apples at two applications of 1 kg ai/ha at 0.1 kg ai/hL with a PHI of 14 days.

Ten apple trials were carried out in Brazil from 2002–2006 (5 × 1–2 kg ai/ha, at 0.1–0.2 kg ai/hL, PHI 7 days) however, none matched the Brazilian GAP.

Phosmet is registered in Spain for use on pome fruits at 0.075–0.125 kg ai/hL with a PHI of 30 days.

In one French and one Italian trial on apples in 2004 (2 × 0.125 kg ai/hL, PHI 28 or 29 days) matching Spanish GAP, the residues were 0.34 and 0.41 mg/kg.

In Spain, residue trials were carried out from 2001 to 2002 on apples and pears with three applications of 0.125 kg ai/hL and a PHI of 21 days. The residues in apples were 0.06, 0.26, 0.31, 0.32, 0.47, 0.83, 0.92, 1.3 and 1.8 mg/kg. The residues in pears were 0.07, 0.16 and 0.79 mg/kg. The

Meeting noted that the PHI of 21 days was shorter than the registered 30 days but considered the trials for evaluation as they were within ± 30% of the GAP.

The Meeting decided to combine the European apple and pear data for pome fruit. The combined pome fruit data (14 values), in ranked order were: 0.06, 0.07, 0.16, 0.26, 0.31, 0.32, 0.34, 0.41, 0.47, 0.79, 0.83, 0.92, 1.3 and 1.8 mg/kg.

Based on the alternative GAP from Spain and new residue supervised trials data from Spain, Italy and France, the Meeting estimated a maximum residue level of 3 mg/kg for phosmet in pome fruit to replace the previous recommendation of 10 mg/kg.

The Meeting estimated an STMR and an HR for phosmet in pome fruits of 0.38 and 1.8 mg/kg.

*Apricots and nectarines*

The previous MRL recommendation was based on the GAP of the USA and USA residue data. New GAP data on peaches from Brazil and on stone fruit from Spain were submitted to the 2007 JMPR. The Meeting also received new supervised residue trial data on peaches and nectarines from Brazil and Spain.

Phosmet is registered in Brazil for use on peaches at three applications of 0.6–0.8 kg ai/ha and 0.075–0.1 kg ai/hL with a PHI of 7 days.

Ten trials on peaches and nectarines were carried out in 2000 in Brazil but only three of them matched GAP. Residues of phosmet were 0.5, 1.0 and 2.7 mg/kg.

Phosmet is registered in Spain for use on stone fruits at 0.075–0.125 kg ai/hL with a PHI of 30 days.

In Spain, residue trials were carried out in 2001 and 2002 on peaches and nectarines with two applications of 0.125 kg ai/hL and a PHI of 21 days. The residues were 0.31, 0.34, 0.37, 0.42, 0.71 and 1.5 mg/kg. The Meeting noted that the PHI of 21 days was shorter than the registered 30 days but considered the trials for evaluation as they were within ± 30% of the GAP.

Phosmet is registered in the USA for use on apricots, peaches and nectarines at 1.7–3.3 kg ai/ha with a PHI of 14 days.

The 1997 JMPR estimated a maximum residue level, an STMR and an HR value for phosmet in apricots of 10, 1.6 and 6.8 mg/kg, respectively, based on US residue data for peaches and apricots matching the US GAP. No maximum residue level was estimated for nectarines.

The 2002 JMPR noted that the GAP reported for peaches and apricots in the evaluation by the 1997 JMPR was the same as for nectarines. The 2002 Meeting agreed that the residues trials reported for peaches and apricots could be used to support a recommendation for nectarines. The Meeting estimated a maximum residue level, an STMR and an HR value for phosmet in nectarines of 10, 1.6 and 6.8 mg/kg, respectively, based on US residue data for peaches and apricots matching the US GAP.

Based on the estimations of the 1997 and 2002 Meetings, the 2007 JMPR noted that the acute dietary risk assessment for phosmet, as presented in the 2003 JMPR Report, shows an acceptable consumer risk for apricots (ARfD: 0.2 mg/kg bw per day - general population 20%, children 90%) and nectarines (general population 40%, children 100%). Therefore, it was deemed unnecessary to retrospectively consider an alternative GAP for both commodities. The current Meeting confirmed the recommendation by the 2002 JMPR.

The Meeting estimated a maximum residue level of 10 mg/kg which confirms the previous recommendation, and an STMR and HR of 1.6 and 6.8 mg/kg for apricots and nectarines.

*Blueberries*

US GAP permits application of phosmet to blueberries at 1 kg ai/ha and harvest 3 days after the final application.

Based on nine US residue trials, matching the GAP of the USA, the 2002 JMPR estimated a maximum residue level, an STMR value and an HR value for phosmet in blueberries of 15, 4.0 and 9.9 mg/kg, respectively.

The current Meeting noted that the acute dietary risk assessment for phosmet, which is presented in the 2003 JMPR Report (ARfD: 0.2 mg/kg bw per day), shows an acceptable consumer risk for blueberries (general population 10%, children 40%). Therefore, it was deemed unnecessary to retrospectively consider an alternative GAP for blueberries.

The Meeting estimated a maximum residue level of 15 mg/kg which confirms the previous recommendation, and an STMR and HR of 4.0 and 9.9 mg/kg for blueberries.

### DIETARY RISK ASSESSMENT

***Long-term intake***

The estimates of long-term dietary intake for phosmet (ADI 0–0.01 mg/kg bw) calculated by the JMPR in 2002 for the five regional diets were 5–40% of the ADI. Because the STMR for pome fruit has changed, the dietary intakes were recalculated by the current Meeting for the 13 GEMS/Food Consumption Cluster Diets on the basis of the STMRs estimated by the JMPR in 2002 (cotton seed, grapes, peach, potato, tree nuts) and 2007 (apricot, blueberries, citrus fruits, nectarine, pome fruit). The results are shown in Annex 3.

The International Estimated Daily Intakes (IEDI) of phosmet, based on estimated STMRs were 2–90% of the maximum ADI (0.01 mg/kg bw). The Meeting concluded that the long-term intake of residues of phosmet from uses considered by the JMPR is unlikely to present a public health concern.

***Short-term intake***

The International Estimated Short Term Intake (IESTI) of phosmet was calculated for the commodities for which residue levels were estimated. The results are shown in Annex 4.

The IESTI of phosmet calculated on the basis of the recommendations made by the 2007 JMPR represented 0–100% of the ARfD (0.2 mg/kg bw) for children and 1–50% for the general population. The Meeting concluded that the short-term intake of residues of phosmet resulting from uses considered by the JMPR is unlikely to present a public health concern.

## 5.18 PROCYMIDONE (136)

### TOXICOLOGY

Procymidone is the ISO approved name for *N*-(3,5-dichlorophenyl)-1,2-dimethylcyclopropane-1,2-dicarboximide (IUPAC), CAS No. 32809-16-8. It is a dicarboximide fungicide that is used on a range of vegetables, fruits, soya bean, sunflowers, tobacco and oil seed rape, as well as on ornamental plants and flower bulbs. The mechanism of pesticidal action involves the inhibition of triglyceride synthesis in fungi.

Procymidone was previously evaluated by JMPR in 1981, 1982 and 1989 (Annex 5, references *37*, *39*, *58*). No ADIs were established when procymidone was evaluated by the JMPR in 1981 and 1982. In 1989, an ADI of 0–0.1 mg/kg bw was established based on the NOAEL of 12.5 mg/kg bw per day identified in studies of reproductive toxicity in rats. Procymidone was re-evaluated by the present Meeting as part of the Periodic Re-evaluation Programme of the CCPR. A range of new studies was submitted to the present Meeting; these studies addressed kinetics, developmental toxicity and hormonal effects across different species.

Many of the conventional studies of toxicity with procymidone were relatively old, were performed before the widespread use of GLP and some contained relatively limited information. Overall, the Meeting considered that the database was adequate for the risk assessment.

### *Biochemical aspects*

Studies with [$^{14}$C] labelled procymidone showed that radiolabel was rapidly absorbed ($C_{max}$, 2–8 h) and rapidly eliminated (> 80% in 24 h) in mice and rats. Absorption was extensive, as shown by the high level of urinary excretion (> 80% of the administered dose), with similar results obtained in mice and rats receiving doses of up to 100 mg/kg bw. At higher doses, the proportion of the administered dose excreted in the faeces increased: at 250 mg/kg bw, 24–33% was eliminated by that route after 168 h; the increase in faecal radioactivity was mainly attributable to an increase in unabsorbed procymidone (18–27% of the administered dose). Only low levels (< 0.3%) of radioactivity were retained 168 h after oral administration; the highest levels were found in fat. The major metabolic pathway for procymidone in mice and rats involved the oxidation of the methyl groups to hydroxymethyl or carboxylic acid derivatives, cleavage of the imide, and glucuronide formation of the resultant metabolites. In cynomolgus monkeys, rabbits and chimeric mice with humanized livers (i.e., liver repopulated with human hepatocytes), there was more extensive urinary excretion of glucuronide conjugates than in rats or normal mice. In rats, the glucuronides were formed, but were present in the bile and appear to be deconjugated and the aglycone was reabsorbed giving a prolonged elimination phase and relatively high AUC. Studies in vitro with liver preparations from humans, rabbits, cynomolgus monkeys and rats showed that the rate of metabolism of procymidone and hydroxy-procymidone was significantly lower in rats than in the other species studied.

In female cynomolgus monkeys, there was an increase in $C_{max}$ and AUC values after repeated doses. In other species, the routes and rates of tissue distribution, biotransformation and excretion of procymidone were similar in males and females and after single or repeated administration.

Procymidone has a high binding affinity in vitro (92–98% bound) for plasma proteins when incubated with plasma from female rats, cynomolgus monkeys, rabbits and humans. The alcohol metabolite PCM-$CH_2OH$ had a slightly lower binding affinity (77–91% in all species) than procymidone, with the highest affinity being for human plasma proteins.

Kinetic studies in rats, rabbits and cynomolgus monkeys (dams and foetuses of each species) have been performed as part of investigations of the effects on male rat reproductive tissues. After a single dose, cynomolgus monkeys had much lower $C_{max}$ values for total radioactivity than did rabbits and rats, but at doses of up to 125 mg/kg bw rabbits had relatively low AUC values owing to rapid elimination. In cynomolgus monkeys, the predominant compound in plasma was procymidone; in rabbits, acid metabolites and glucuronides of alcohol metabolites were the major components in plasma; in rats, free alcohol metabolites predominated. After 14 doses at 37.5–500 mg/kg bw per day, $C_{max}$ and AUC values for total radioactivity were similar for rats and cynomolgus monkeys. These findings show that the doses used in the studies of developmental toxicity in cynomolgus monkeys would have produced similar plasma concentrations of total radioactivity, but with different metabolite profiles, to those in rats at doses resulting in hypospadias. Investigations of the transfer of procymidone and metabolites to foetuses again showed species differences. After dosing at 125 mg/kg bw per day, the concentrations of procymidone and metabolites in the foetus were significantly greater (10-fold or greater) in rats than in rabbits or cynomolgus monkeys. In rats, the relative concentrations of PCM-$CH_2OH$ in the foetus versus the dam were much higher than in rabbits or cynomolgus monkeys.

### *Toxicological data*

Procymidone was of low acute toxicity by the oral ($LD_{50}$ > 5000 mg/kg bw) and dermal ($LD_{50}$ > 2500 mg/kg bw) routes, and after a 4-h exposure by inhalation ($LC_{50}$ > 1.5 mg/L). Procymidone is not an eye irritant, but is a slight, transient skin irritant. Procymidone did not produce delayed contact hypersensitivity in guinea-pigs in either the maximization or repeat-injection tests.

The primary target organs in rats and mice exposed to procymidone in repeat-dose studies were the liver and testes. The major effect of short-term dietary administration of procymidone in ICR mice was on the liver. Centrilobular hepatocyte hypertrophy was noted in male mice and hepatocyte granuloma in females that received procymidone at 500 ppm, equal to 71 mg/kg bw per day, for 13

weeks; the NOAEL was 150 ppm, equal to 22 mg/kg bw per day. In a subsequent study with B6C3F$_1$ mice, multifocal coagulative necrosis of hepatic parenchyma, centrilobular cytoplasmic swelling, nuclear enlargement, coarsely dispersed chromatin and multinucleate hepatocytes were noted in mice receiving procymidone at 10 000 ppm, equivalent to 1430 mg/kg bw per day. This was accompanied by increased liver weight and serum alanine aminotransferase activity in males and higher cholesterol concentrations in females. The histopathological effects were apparent to a lesser extent in animals treated with procymidone at 500 or 2500 ppm, equivalent to 71 and 355 mg/kg bw per day respectively. The NOAEL was 100 ppm, equal to 19.6 mg/kg bw per day. An increase in the incidence of testicular atrophy was noted in mice receiving procymidone at 500 ppm for 26 weeks, the NOAEL was 150 ppm, equal to 20 mg/kg bw per day. In an additional 6-month study, the NOAEL for effects on the testes was 300 ppm, equal to 37 mg/kg bw per day. The Meeting considered that the overall NOAEL in three short-term studies in mice was 300 ppm, equal to 37 mg/kg bw per day.

The only short-term study in rats included a 6-month exposure period with or without a 3-month recovery phase, and a 9-month exposure period. In Sprague-Dawley rats, there was a significant reduction in body-weight gain among females receiving procymidone at 1500 ppm, equivalent to 75 mg/kg bw per day, for 6 months (although this was not significant after an exposure of 9 months) and an increase in liver-to-body-weight ratio in both sexes. The liver-to-body-weight ratio was also increased in female rats at 500 ppm, equivalent to 25 mg/kg bw per day, and there was an increase in spleen-to-body-weight ratio at 500 and 1500 ppm. Absolute and relative weights of the testes were increased after 9 months at 1500 ppm. The only treatment-related histopathological effect was swelling of the liver cells in male rats at 1500 ppm. The findings showed clear evidence of reversal over the 3-month recovery phase. The NOAEL was 500 ppm, equivalent to 25 mg/kg bw per day.

In a 28-day study of dermal exposure, there were no treatment-related local or systemic changes when doses of up to 1000 mg/kg bw per day were applied to the shaved backs of rats.

Emesis and diarrhoea were the principal signs of toxicity in dogs given procymidone at 500 mg/kg bw per day for 26 weeks. At that dose, there was also an increase in serum alkaline phosphatase activity, blood urea nitrogen (BUN) and calcium concentrations. The NOAEL was 100 mg/kg bw per day. In a 52-week study in dogs, there was an increase in emesis and soft faeces and increases in serum globulin and alkaline phosphatase activity at 500 mg/kg bw per day. The NOAEL was 100 mg/kg bw per day.

Procymidone gave negative results in an adequate range of assays for genotoxicity in vitro and in vivo. The Meeting concluded that procymidone was unlikely to be genotoxic.

The toxicity and carcinogenicity of procymidone had been investigated in long-term studies in mice and rats. In the study in mice, treatment-related effects were limited to the liver. Higher liver weights and liver-to-body-weight ratios were apparent in males at 100 ppm, equal to 15 mg/kg bw per day, and in both sexes at 300 and 1000 ppm, equal to 46 and 153 mg/kg bw per day respectively, and there were histopathological changes in the liver, comprising increased incidences of centrilobular cytomegaly in males at 1000 and 300 ppm and in females at 1000 ppm. In addition, focal or multifocal hepatocellular hyperplasia, and eosinophilic foci were noted in females at 1000 ppm. There was an increased incidence of hepatocellular adenomas in females at the highest dose. There was also an increase in the incidence of hepatoblastomas in males receiving procymidone at 1000 ppm. The NOAEL for toxicity was 100 ppm, equal to 15 mg/kg bw per day, on the basis of a range of liver effects at 300 ppm. The NOAEL for carcinogenicity was 300 ppm, equal to 46 mg/kg bw per day, on the basis of increases in liver tumours in males and females at 1000 ppm.

In the long-term study in rats, the liver was a target organ and reproductive organs were also affected. There was a reduction in body-weight gain among rats given procymidone at 1000 and 2000 ppm , equal to 48 and 97 mg/kg bw per day respectively. Effects on organ weights were noted at both these doses and consisted of increased relative and absolute weight of the liver in both sexes and increased weights of the testes and ovaries at dietary concentrations of 1000 ppm and greater. Histopathology revealed an increased incidence of centrilobular cytomegaly in the liver of both sexes at dietary concentrations of 1000 ppm and greater. At 1000 and 2000 ppm, there were increases in the

incidence of interstitial cell tumours and interstitial cell hyperplasia in the testes; the incidence of ovarian stromal hyperplasia was statistically significantly increased at 2000 ppm. The NOAEL for general toxicity and for carcinogenicity was 300 ppm, equal to 14 mg/kg bw per day.

Procymidone induced liver tumours in mice and testicular tumours in rats. No specific mechanistic studies have been performed to investigate the liver tumours; however, hepatocellular hypertrophy was present in shorter-term studies, and mice are sensitive to the production of liver tumours in response to such effects produced by high levels of xenobiotics. Procymidone gave negative results in assays for genotoxicity in vitro and in vivo. A clear threshold for induction of liver tumours was identified in the study of carcinogenicity in mice. Investigative work on the endocrine effects of procymidone indicated that it binds to the androgen receptor with a similar potency to that of the prostate-cancer drug flutamide, and that in rats the mechanism of hormonal action appeared to be via binding to the androgen receptor, disrupting the feedback controls on LH and testosterone levels. Overall, the data suggest that procymidone may induce testicular interstitial cell tumours via an endocrine-mediated mechanism. Although this mode of action is relevant to humans, there is good evidence to suggest that humans are less sensitive to chemically-induced interstitial cell tumours of the testis than rats, owing to differences in sensitivity to LH based on Leydig-cell receptor number and control of LH receptor expression (e.g., via prolactin in rodents but not in humans).

The Meeting concluded that procymidone was unlikely to present a carcinogenic risk to humans at typical levels of dietary exposure.

The reproductive toxicity of procymidone had been investigated in two studies in rats. The developmental toxicity of procymidone had been studied in conventional studies in rats and rabbits and in special investigative studies in rats, rabbits and cynomolgus monkeys.

In the first generation of the two-generation study in rats, there was no effect on mating and reproduction, but at 750 ppm, equivalent to 50 mg/kg bw per day, there was an increase in the number of male pups with hypospadia and reduced anogenital distance. In the second generation, male fertility was reduced and the incidence of hypospadia was increased at 750 ppm. In parents and pups, there were increases in testes weights and decreases in body-weight gain, prostate and epididymis weights at 750 ppm, with the organ-weight changes also present in pups at 250 ppm. There were no adverse effects on female reproductive performance or on female offspring. The NOAELs for effects on parents and on reproduction were 250 ppm, equivalent to 17 mg/kg bw per day. The NOAEL for pup development was 50 ppm, equivalent to 3 mg/kg bw per day, on the basis of the alterations in weights of the testes, prostate and epididymis at 250 ppm. In a subsequent one-generation study, designed to investigate the effects on male pups in the previous study, there was a reduction in body-weight gain and reduced litter size at 37 mg/kg bw per day. Increases in the incidence of hypospadia and in testes weights, and decreases in weights of the prostate and seminal vesicles were seen in pups at 37 mg/kg bw per day. The NOAELs for parental toxicity, pup development and reproduction were 12.5 mg/kg bw per day.

Studies of developmental toxicity with procymidone have been performed in rats, rabbits and cynomolgus monkeys. In a conventional study of developmental toxicity in rats, there were significant (60%) reductions in maternal body-weight gain during the first 6 days of dosing at 300 mg/kg bw per day, but no adverse findings in pups. This study did not include specific investigations of anogenital distance or the external genitalia. The NOAEL for fetotoxicity and teratogenicity was 300 mg/kg bw per day, the highest dose tested. The NOAEL for maternal effects was 100 mg/kg bw per day. In a modified study of developmental toxicity, pregnant rats were dosed with procymidone on days 6–19 of gestation; on day 20, half the dams had caesarian sections and the other half were allowed to deliver normally. Examinations focused on the male reproductive tract. Maternal toxicity (body-weight loss and poor appearance) was evident at doses of 125 mg/kg bw per day and greater. A range of effects was seen on male foetuses and offspring from dams receiving doses of 125 mg/kg bw per day and greater: reduced anogenital distance, undescended testes, hypospadias, testicular atrophy, distended preputial grand, inflammatory changes in the accessory sex organs (seminal vesicles, prostate and coagulating glands), and lower organ weights of testes and prostate. At 500 mg/kg bw per day, there was a significant increase in the incidence of bifid thoracic vertebral centra in foetuses and prostate

lesions in male offspring. The NOAEL for maternal and developmental toxicity was 12.5 mg/kg bw per day. A further investigative study of developmental toxicity, in which dams were allowed to deliver normally, confirmed the production of hypospadia and undescended testes at 37 mg/kg bw per day, the lowest dose tested.

In rabbits, an initial study of developmental toxicity found no evidence of maternal toxicity or teratogenicity, but there was a reduction in sternebrae ossification at 1000 mg/kg bw per day, the highest dose tested. The NOAEL for developmental toxicity was 750 mg/kg bw per day. In a subsequent study that concentrated on the external genitalia of foetuses, maternal toxicity (anorexia and abortions) was seen at 125 mg/kg bw per day, the only dose used. There were equivocal effects on measurements of the external genitalia in female offspring. Only a single dose level, which produced overt maternal toxicity, was used in the study, and the findings are considered to be of uncertain toxicological relevance.

In an initial study focusing on effects on male foetuses, groups of four pregnant cynomolgus monkeys received doses of 62.5 or 125 mg/kg bw per day. There were no indications of maternal toxicity or fetotoxicity. In a more extensive investigation in groups of 16 pregnant cynomolgus monkeys, there was no maternal toxicity or effects on the external genitalia of offspring (six and eight male offspring in controls and in the test group, respectively) at 125 mg/kg bw per day, the only dose tested.

The characteristics of procymidone were similar in assays for binding to androgen receptors in rats and humans. The concentration required to inhibit activity by 50% ($IC_{50}$) values for procymidone (approximately 0.3 μmol/L) were similar to those of the anti-androgen prostate-cancer drug flutamide. The $IC_{50}$ values for the procymidone metabolites PCM-$CH_2OH$, PA-$CH_2OH$ and PCM-NH-COOH were approximately 5–10-fold that of procymidone; PCM-$CH_2OH$-glucuronide, PCM-COOH and PA-COOH showed no activity. However, these results might have been influenced by the non-enzymatic interconversion of procymidone metabolites. Under acid conditions ($pH < 6.4$), procymidone and PCM-$CH_2OH$ are stable, but under alkaline conditions ($pH \geq 7.8$) the imide bond was shown to be cleaved to give PCM-NH-COOH and PA-$CH_2OH$.

The mechanism of the effect of procymidone on the reproductive organs has been investigated by measuring hormone levels in mice, rats and cynomolgus monkeys. Procymidone had no adverse effects on testes, sperm and serum or tissue levels of LH in cynomolgus monkeys receiving up procymidone at doses of up to 1000 mg/kg bw per day for 7 days or up to 100 mg/kg bw per day for 91 days. There was evidence of a reduction in ejaculate mass in cynomolgus monkeys at a dose of 100 mg/kg bw per day or greater, but there was no statistically significant effect on ejaculate sperm counts. The small group size and extent of variation between animals and in values recorded before dosing makes it difficult to reach firm conclusions about the toxicological significance of these results. The NOAEL in this study was considered to be 30 mg/kg bw per day. Two studies in rats provided qualitatively similar results, but although the protocols were similar and the same strain was used, there were differences in the doses that produced effects. There were increases in human chorionic gonadotrophin hormone (hCG) stimulated production of testosterone and circulating testosterone levels in rats receiving diets containing procymidone at 700 ppm, equal to 47 mg/kg bw per day, for 13 weeks. LH concentrations were increased at 6000 ppm after 2 weeks. Epididymis weights were reduced after exposure to procymidone at a dietary concentration of 2000 ppm or greater for 2 weeks, but not after 3 months. Testes weights were increased at dietary concentrations of 700 ppm and greater. All effects showed signs of reversal during a recovery phase. Findings in mice were similar to those in rats, but the stimulation of testosterone production by hCG had returned to control levels after 3 months owing to a decrease in the binding affinity of hCG to the LH/hCG receptor.

The Meeting concluded that the existing database on procymidone was adequate to characterize the potential hazards to foetuses, infants and children

Procymidone has not been studied specifically for neurotoxicity, but there were no indications from the results of conventional studies that it has significant neurotoxic potential.

A number of studies have been performed with procymidone metabolites. 3,5-Dichloroaniline (DCA) was of moderate acute toxicity in *dd* mice, having an oral $LD_{50}$ of approximately 850 mg/kg

bw. Procymidone-NH-COOH was also of moderate acute toxicity in *dd* mice, with an oral $LD_{50}$ of approximately 1450 mg/kg bw. 1,2-Dimethylcyclopropane-dicarboxylic acid (DMCPA) was of low acute toxicity in *dd* mice, having an oral $LD_{50}$ of approximately 4400 mg/kg bw and a subcutaneous $LD_{50}$ of approximately 2400 mg/kg bw. DMCPA gave negative results in an Ames test and an assay for micronucleus formation in vivo. DMCPA was rapidly absorbed and excreted with minimal metabolism. Retention of radioactivity in tissues was low.

Hydroxy-procymidone (PCM-$CH_2OH$) was investigated in a modified study of developmental toxicity in which rats were allowed to deliver normally. No abnormal findings were seen in dams or female offspring. In the male offspring, a dose-related shortening of the anogenital distance was seen and there were increases in the incidence of male offspring and litter with abnormities of the external genitalia. The incidence of hypospadia was increased in pups from dams receiving procymidone at 62.5 mg/kg bw per day, the lowest dose tested. In addition, small testis and epididymis and undescended testis and epididymis were observed occasionally in groups treated with hydroxy-procymidone. These results are similar to those seen with procymidone at similar doses. The benchmark dose (BMD) 95% lower limit for a 10% response ($BMDL_{10}$) for hypospadias was 43.8 mg/kg bw per day for hydroxy-procymidone and 23.7 mg/kg bw per day for procymidone. The Meeting considered the data on the relative androgen receptor and plasma-protein binding affinities of hydroxy-procymidone and procymidone, and the marked species differences in formation and elimination of procymidone and its metabolites. The Meeting concluded that while hydroxy-procymidone might be a significant contributor to the effects seen in rats, due to the much higher systemic and foetal exposure, the contribution of procymidone could not be discounted in other species, particularly due to limitations in the studies in cynomolgus monkeys.

Surveys of the medical records of production-plant workers had not identified any symptoms or diseases related to the manufacture of procymidone. There were no documented cases of procymidone intoxication nor any significant effects associated with its use.

## Toxicological evaluation

The Meeting established an ADI of 0–0.1 mg/kg bw based on a NOAEL of 12.5 mg/kg bw per day in a two-generation study of reproductive toxicity and a study of developmental toxicity in rats, on the basis of hypospadias and alterations in testes, prostate and epididymis weights, and a safety factor of 100. The ADI was supported by NOAELs of 14 mg/kg bw per day in the 2-year study in rats and 15 mg/kg bw per day in the 2-year study in mice.

The Meeting established an ARfD of 0.1 mg/kg bw based on a NOAEL of 12.5 mg/kg bw on the basis of hypospadias, which might have been a consequence of a single exposure, in a study of developmental toxicity in rats, and using a safety factor of 100. The Meeting concluded that the effects on organ weights observed in the multigeneration study were largely a consequence of postnatal exposure over a period of time and therefore not appropriate for the establishment of the ARfD. The Meeting considered that, on the basis of the observed differences between species in terms of kinetics, metabolism and toxicological sensitivity to procymidone, this ARfD might be conservative. However, uncertainties regarding potential responses in species other than rats were such that it was not possible to modify the default safety factor.

### *Levels relevant to risk assessment*

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | Two-year studies of toxicity and carcinogenicity[a] | Toxicity | 100 ppm, equal to 15mg/kg bw per day | 300 ppm, equal to 46mg/kg bw per day |
| | | Carcinogenicity | 300 ppm, equal to 46mg/kg bw per day | 1000 ppm, equal to 153mg/kg bw per day |

| | | | | |
|---|---|---|---|---|
| Rat | Two-year studies of toxicity and carcinogenicity [a] | Toxicity | 300 ppm, equal to 14 mg/kg bw per day | 1000 ppm, equal to 48mg/kg bw per day |
| | | Carcinogenicity | 300 ppm, equal to 14mg/kg bw per day | 1000 ppm, equal to 48mg/kg bw per day |
| | Multigeneration study of reproductive toxicity[ae] | Parental toxicity | 250 ppm, equivalent to 17mg/kg bw per day | 750 ppm, equivalent to 50 mg/kg bw per day |
| | | Offspring toxicity | 12.5mg/kg bw per day | 250 ppm, equivalent to 17mg/kg bw per day |
| | Developmental toxicity[b,e] | Maternal toxicity | 100 mg/kg bw per day | 125 mg/kg bw per day |
| | | Embryo/fetotoxicity | 12.5 mg/kg bw per day | 37.5 mg/kg bw per day |
| Rabbit | Developmental toxicity[b,e] | Maternal toxicity | — | 125 mg/kg bw per day [f] |
| | | Embryo/fetotoxicity | 750 mg/kg bw per day | 1000 mg/kg bw per day |
| Monkey | Developmental toxicity[b,e] | Maternal toxicity | 125 mg/kg bw per day[c] | — |
| | | Embryo/fetotoxicity | 125 mg/kg bw per day[c] | — |
| Dog | Six-month and 1-year studies of toxicity[d] | Emesis, soft faeces, increased alkaline phosphatase activity | 100 mg/kg bw per day | 500 mg/kg bw per day |

[a] Dietary administration.
[b] Gavage administration.
[c] Highest dose tested.
[d] Capsule administration.
[e] More than one study combined.
[f] Lowest dose tested.

*Estimate of acceptable daily intake for humans*

0–0.1 mg/kg bw

*Estimate of acute reference dose*

0.1 mg/kg bw

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

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

***Critical end-points for setting guidance values for exposure to procymidone***

| *Absorption, distribution, excretion and metabolism in mammals* | |
|---|---|
| Rate and extent of oral absorption | Rapid, $C_{max}$ 2–8 h; extensive, > 80% excreted in the urine |
| Dermal absorption | 4% concentrate, 13% for dilution in rats in vivo |
| Distribution | Extensive, highest concentrations in fat |
| Potential for accumulation | Low |
| Rate and extent of excretion | Rapid, > 80% in 24 h; enterohepatic recirculation in rats |
| Metabolism in animals | Hydroxylation, oxidation and conjugation. Some species differences. |

| | |
|---|---|
| Toxicologically significant compounds in animals, plants and the environment | Procymidone, hydroxy-procymidone |
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | > 5000 mg/kg bw |
| Rat, $LD_{50}$, dermal | > 2500 mg/kg bw |
| Rat, $LC_{50}$, inhalation | > 1.5 mg/L |
| Rabbit, skin irritation | Slight transient irritant |
| Rabbit, eye irritation | Not irritating |
| Guinea-pig, skin sensitization (test method used) | Negative (Magnusson & Kligman maximization test) |
| *Short-term studies of toxicity* | |
| Target/critical effect | Decreased body-weight gain, liver effects, testes |
| Lowest relevant oral NOAEL | 25 mg/kg bw per day |
| Lowest relevant dermal NOAEL | 1000 mg/kg bw per day |
| Lowest relevant inhalation NOAEC | No data |
| *Genotoxicity* | |
| | Not genotoxic |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Body weight, liver effects |
| Lowest relevant NOAEL | 14 mg/kg bw per day (rat) |
| Carcinogenicity | Liver tumours in mice; testes tumours in rats. |
| *Reproductive toxicity* | |
| Reproduction target/critical effect | Hypospadias; altered testes and epididymis weight |
| Lowest relevant reproductive NOAEL | 12.5 mg/kg bw per day |
| Developmental target/critical effect | Hypospadias (rat) |
| Lowest relevant developmental NOAEL | 12.5 mg/kg bw per day |
| *Neurotoxicity/delayed neurotoxicity* | |
| | No evidence in conventional studies |
| *Special studies* | |
| | Kinetic and metabolism studies in rats, monkeys, rabbits, mice and with human tissues showed differences between species. Rats having a relatively high area-under-the curve and a low capability to metabolize procymidone and hydroxy-procymidone. |
| | Receptor-binding assays showed that procymidone and hydroxy-procymidone could bind to rat and human androgen receptors. Both procymidone and hydroxy-procymidone were extensively bound (≥ 77%) to plasma proteins. |
| | Procymidone produced increases in luteinizing hormone and human chorionic gonadotrophin-stimulated production of testosterone in rats at 6000 ppm and ≥ 700 ppm respectively. |
| | Ejaculate mass was reduced in monkeys exposed to procymidone for 13 weeks at ≥ 100 mg/kg bw per day. NOAEL was 30 mg/kg bw per day |

| | |
|---|---|
| | Hydroxy-procymidone induced hypospadias in rats at ≥ 62.5 mg/kg bw per day; $BMDL_{10}$ was 43.8 mg/kg bw per day. |
| *Medical data* | |
| | No adverse findings reported |

***Summary***

| | Value | Study | Safety factor |
|---|---|---|---|
| ADI | 0–0.1 mg/kg bw | Rat, studies of developmental and reproductive toxicity | 100 |
| ARfD | 0.1 mg/kg bw | Rat, study of developmental toxicity | 100 |

## 5.19 PROFENOFOS (171)

### TOXICOLOGY

Profenofos is the ISO approved name for (*RS*)-*O*-4-bromo-2-chlorophenyl *O*-ethyl *S*-propyl phosphorothioate (IUPAC), CAS No. 41198-08-7. It is a broad-spectrum organophosphorus insecticide that is used to control insect pests in cotton, maize, sugar beet, soya bean, potato, vegetables and other crops. Its mode of action is by inhibition of acetylcholinesterase activity.

Profenofos was previously evaluated by JMPR in 1990 (Annex 5, reference *171*) and an ADI of 0–0.01 mg/kg bw per day was established. The ADI was based on the NOAEL of 20 ppm, equal to 1.0 mg/kg bw per day, the highest dose tested, in a three-generation study of reproduction in rats.

Profenofos was re-evaluated by the present meeting within the Periodic Re-evaluation Programme of the CCPR. All pivotal studies with profenofos were certified as complying with GLP.

***Biochemical aspects***

[Phenyl-$^{14}$C]profenofos was rapidly absorbed and eliminated after oral administration to rats. Total radioactivity eliminated via the urine and faeces exceeded 99% of the administered dose for a single dose of 1 or 100 mg/kg bw by gavage and repeated doses of 1 mg/kg bw by gavage. Elimination was rapid, with about of 95% of the total radiolabel being excreted in the urine within the first 24 h in all treated groups. For all doses, less than 4% of the radiolabel was excreted in the faeces. The concentration of radiolabel in tissues and organs reached a maximum after 2 h and remained at similar levels until 8 h after dosing. By 72 h, the tissue concentration of radiolabel was minimal. The absorption, distribution and excretion of $^{14}$C-labelled profenofos was not sex- or dose-dependent in the range of 1 to 100 mg/kg bw and was unaffected by pre-treatment with unlabelled profenofos for 14 days. Unchanged profenofos was detected in the faeces, but the amount was very small (approximately 1–2% of the administered dose), and this was probably the proportion of the dose that was not absorbed. Four major metabolites were present in urine and no unchanged profenofos was detected. The major metabolites were the sulfate and glucuronide conjugates of 4-bromo-2-chloro-phenol that were formed by hydrolysis of the aryloxy–phosphorus bond followed by conjugation with sulfate or glucuronic acid. The other two metabolites were formed by cleavage of the phosphorus–sulfur bond either by loss of the propyl group or hydrolysis. The 4-bromo-2-chloro-phenol was detected in some urine samples, but probably arose as a result of hydrolysis of the conjugates after excretion.

***Toxicological data:***

The acute oral $LD_{50}$ for profenofos ranged from 358 to 1178 mg/kg bw in rats. The acute oral $LD_{50}$ for profenofos was 298 mg/kg bw in mice and 700 mg/kg bw in rabbits. The clinical signs detected in all

the studies of acute toxicity were typical of cholinergic poisoning, which appeared at doses greater than 100 mg/kg bw. Profenofos was of low toxicity when administered by the dermal route to rats ($LD_{50}$s, > 2000 and 3300 mg/kg bw). More varied results were obtained after dermal application to rabbits with $LD_{50}$s ranging from 131 to 2560 mg/kg bw depending on method of application (semi-occlusive, abraded skin or massaging). Profenofos was of low toxicity on exposure by inhalation, the $LC_{50}$ being > 3.36 mg/L. Profenofos was moderately irritating to skin and mildly irritating to the eye and was shown to be a sensitizer under the conditions of the Magnusson & Kligman test and in the local lymph-node assay.

The primary effect of profenofos in studies of acute toxicity, short- and long-term studies of toxicity was inhibition of acetylcholinesterase activity and this was associated with signs of neurotoxicity at high levels of inhibition. Profenofos is a racemic mixture of the two optical isomers at the chiral phosphorus atom. The *S* (-) isomer is a markedly more potent inhibitor of acetyl cholinesterase in vitro than the *R* (+) isomer. The inhibited acetyl cholinesterase ages rapidly, an effect that prevents spontaneous reactivation. Rapid ageing would lead to a cumulative inhibitory effect after repeated exposures to profenofos, and would also render reactivation therapy with oximes ineffective (see item 2.4 under General considerations).

In a short-term repeat-dose study, no clinical signs of toxicity were observed in rats given diet containing profenofos at a concentration of 1000 ppm, equal to 85 mg/kg bw per day, for 8 weeks. Reduced food intake and body-weight gain were apparent at this dose and also at a dose of 100 ppm, equal to 8.4 mg/kg bw per day, which was given for 13 weeks. Inhibition of cholinesterase activity was the only other effect noted. Erythrocyte cholinesterase activity was inhibited by more than 20% at doses of 30 ppm, equal to 2.4 mg/kg bw per day, and greater. Brain acetylcholinesterase activity was inhibited at 1000 ppm, equal to 85 mg/kg bw per day. The NOAEL for inhibition of brain acetylcholinesterase activity was 300 ppm, equal to 22.0 mg/kg bw per day.

Inhibition of brain acetylcholinesterase activity and clinical signs consistent with neurotoxicity were observed in rats exposed to profenofos at a concentration of 0.07 mg/L per day by inhalation for 21 days.

In three studies of dermal toxicity in rabbits, the overall NOAEL for inhibition of brain acetylcholinesterase was 2.5 mg/kg bw per day on the basis of significantly reduced activity at 5 mg/kg bw per day.

Three studies were carried out in dogs given profenofos orally for 90 days, 6 months, or 1 year. Profenofos was given in the diet in the 90-day and 6-month studies, and daily in gelatin capsules in the 1-year study. No clinical signs of toxicity were recorded in these studies, the 6-month and 1-year studies including neurological examinations (NOAEL for clinical signs, 12.5 mg/kg bw per day). Brain acetylcholinesterase activity was significantly inhibited in males at 5 mg/kg bw per day in the 90-day study, but not in either sex at 2.9 or 14.4 mg/kg bw per day in the 6-month study, or at 1 or 12.5 mg/kg bw per day (the highest dose tested) in the 1-year study. Hence, for brain acetylcholinesterase inhibition, the overall NOAEL in these three studies in dogs was 2.9 mg/kg bw per day. Haematology parameters (erythrocyte count, haemoglobin concentration and erythrocyte volume fraction) were reduced; however, they were not considered to be toxicologically significant since there was no clear dose–response relationship, and the small changes observed were within the range for historical controls. Treatment of dogs with profenofos at 12.5 mg/kg bw per day for 1 year was also associated with an increase in binucleated perilobular hepatocytes, bile-duct hyperplasia and an increase in bile pigments in kidney tubules. These pathological findings were minimal in severity, were not observed in the 90-day or 6-month studies of toxicity.

Profenofos was not mutagenic in an adequate battery of studies of genotoxicity.

The Meeting concluded that profenofos is unlikely to be genotoxic.

In long-term studies, treatment of mice and rats with profenofos did not adversely affect survival; there were no clinical signs of toxicity, no increase in the incidence of tumour formation and no treatment-related changes in either gross pathology or histopathology. Plasma and erythrocyte cholinesterase activity were significantly reduced in mice given diet containing profenofos at 30 ppm,

equal to 4.5 mg/kg bw per day, and in rats at 100 ppm, equal to 5.7 mg/kg bw per day. In female mice, there was a statistically significant inhibition of brain acetylcholinesterase activity (25%) at termination of the group at 100 ppm, equal to 14.2 mg/kg bw per day, resulting in a NOAEL of 30 ppm, equal to 4.5 mg/kg bw per day. The NOAEL in the 2-year study of carcinogenicity in rats was 100 ppm, equal to 5.7 mg/kg bw per day, the highest dose tested. Profenofos was not carcinogenic in mice and rats up to the highest dose tested. Although overt toxicity was not observed in the study in rats, the Meeting considered that the available database was sufficient to evaluate the carcinogenic potential of profenofos.

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

Multigeneration studies have shown that profenofos has no effect on reproduction at doses of up to 400 ppm, equivalent to 35 mg/kg bw per day. The NOAEL for parental and pup toxicity was 100 ppm, equivalent to 7.0 mg/kg bw per day, on the basis of reduced body-weight gains and food consumption at 400 ppm, equivalent to 35 mg/kg bw per day, and the NOAEL for reproductive toxicity was 400 ppm, the highest dose tested.

Profenofos did not cause developmental effects in rats or rabbits. Clinical signs typical of cholinesterase inhibition were noted in rabbits given profenofos at 175 mg/kg bw per day and approximately 50% of the animals died. There were no treatment-related effects on the mean number of implantations, litter size, foetal body weight or embryolethality and there were no significant increases in variations or malformations in the foetuses. The NOAEL for maternal toxicity was 30 mg/kg bw per day and the NOAEL for developmental toxicity was 175 mg /kg bw per day, the highest dose tested. Studies of developmental toxicity in rats, maternal toxicity, which included clinical signs typical of cholinesterase inhibition, and deaths were observed at the highest dose of 120 mg/kg bw per day. There was no evidence for prenatal toxicity at either of these doses and the type and incidence of foetal malformations and variations was unaffected by treatment. The NOAEL for maternal toxicity was 90 mg/kg bw per day and the NOAEL for developmental toxicity was 120 mg/kg bw per day, the highest dose tested.

The Meeting concluded that profenofos is not teratogenic.

The potential for profenofos to cause developmental neurotoxicity had also been investigated in rats. In a preliminary range-finding study, rats were given diets containing profenofos at a concentration of 0, 4, 200, 400 or 600 ppm, equal to 0, 0.7, 33.9, 66.0 or 97.6 mg/kg bw per day. In this study, dose-dependent inhibition of the brain acetylcholinesterase activity was observed in dams at ≥ 200 ppm on postnatal day 22. The NOAEL for inhibition of brain acetylcholinesterase activity in dams was 4 ppm, equal to 0.7 mg/kg bw per day. A statistically significant inhibition of brain acetylcholinesterase activity of > 20% and 16% was found in female pups at ≥400 ppm and male pups at 600 ppm, respectively. In the main study of developmental neurotoxicity, rats were given diets containing profenofos at a concentration of 0, 3, 60 or 600 ppm (equal to 0, 0.3, 5.1 or 50.6 mg/kg bw per day). At 600 ppm in dams, brain acetylcholinesterase activity was decreased by 44% on day 22 of gestation, and by 26% (not statistically significant) on day 22 of lactation, and body weights and food consumption were reduced. A statistically significant inhibition of brain acetylcholinesterase activity was observed in female pups at 600 ppm compared with controls on day 5 (11% lower) but not at later times. At 600 ppm, there was a statistically significant reduction in pup body weights (11–12%). No effects on functional parameters or neurohistopathology were observed. The NOAEL for maternal toxicity was 60 ppm, equal to 5.1 mg/kg bw per day, on the basis of inhibition of brain acetylcholinesterase activity on day 22 of gestation and day 22 of lactation, reductions in body weight and food consumption at 600 ppm, equal to 50.6 mg/kg bw per day. The overall NOAEL for inhibition of brain acetylcholinesterase in pups was 60 ppm, equal to 5.1 mg/kg bw per day. The NOAEL for developmental neurotoxicity was 600 ppm, equal to 50.6 mg/kg bw per day, highest dose tested.

In two studies of acute neurotoxicity in rats, there were reversible signs typical of poisoning with acetylcholinesterase inhibitors (diarrhoea, meiosis, lacrimation, tremor), peaking 4 h after

administration of profenofos at 380 mg/kg bw by gavage. Lesser effects were seen at 200 mg/kg bw (hypoactivity, soft faeces), and there were no effects in the FOB at 190 mg/kg bw (the NOAEL for clinical signs). There was significant inhibition of brain acetylcholinesterase activity (by 37% in males and 43% in females) at 4 h after dosing at 400 mg/kg bw, with a NOAEL of 100 mg/ kg bw. Inhibition was absent after a recovery period of 14 days.

There were also no clinical signs of toxicity, and no adverse findings in a FOB or effects on motor activity in a 90-day study of neurotoxicity in rats. Pathological investigation revealed no evidence of treatment-related toxicity. At the highest dose of 600 ppm, equal to 36 mg/kg bw per day, there was a reduction of approximately 10% in body-weight gain. At 600 ppm, there was a statistically significant inhibition of brain acetylcholinesterase activity of 12% in males and 20% in females at week 13. The NOAEL for brain acetylcholinesterase inhibition was 135 ppm, equal to 7.7 mg/kg bw per day.

Profenofos did not induce delayed neuropathy in hens given two doses at 45.7 mg/kg bw (maximum tolerated dose) and then at 17.1 mg/kg bw, separated by an interval of 21 days (atropine protection being given as soon as clinical signs appeared).

No cases of adverse effects have been reported among workers involved in the manufacture of profenofos. In a biological monitoring study, whole-blood cholinesterase activity was inhibited by less than 30% in six workers who were monitored daily for 4 days during spraying of profenofos.

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

## Toxicological evaluation

Erythrocyte acetylcholinesterase activity was found to be significantly more sensitive to profenofos than was brain acetylcholinesterase activity in rats, mice, rabbits, and dogs. However, in no species were any signs of toxicity seen at doses that did not also produce significant inhibition of brain acetylcholinesterase. The Meeting thus concluded that inhibition of brain acetylcholinesterase activity was the more appropriate end-point for risk assessment of profenofos.

The Meeting established an ADI of 0–0.03 mg/kg bw per day based on an overall NOAEL of 2.9 mg/kg bw per day identified on the basis of inhibition of brain acetylcholinesterase activity in three short-term studies in dogs and using a safety factor of 100. This ADI was supported by the NOAEL of 5.1 mg/kg bw per day identified on inhibition of maternal and pup brain acetylcholinesterase activity in a study of developmental neurotoxicity in rats and a NOAEL of 4.5 mg/kg bw per day identified on the basis of inhibition of brain acetylcholinesterase activity in a 2-year study in mice.

The Meeting established an ARfD of 1 mg/kg bw based on a NOAEL of 100 mg/kg bw in studies of acute neurotoxicity in rats, identified on the basis of clinical signs of neurotoxicity seen $\geq$ 200 mg/kg bw and inhibition of brain acetylcholinesterase activity at 400 mg/kg bw and using a safety factor of 100. The appropriate study for establishing the ARfD was the study of acute neurotoxicity since there was no evidence of developmental effects. This ARfD was considered to be protective against any clinical signs of acetylcholinesterase inhibition seen in studies of acute oral toxicity.

A toxicological monograph was prepared.

***Levels relevant to risk assessment***

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | Two-year studies of toxicity and carcinogenicity[a] | Toxicity | 4.5 mg/kg bw per day | 14.2 mg/kg bw per day |
| | | Carcinogenicity | 14.2 mg/kg bw per day[c] | — |

| | | | | |
|---|---|---|---|---|
| Rat | Two-year studies of toxicity and carcinogenicity[a] | Toxicity | 5.7 mg/kg bw per day[c] | — |
| | | Carcinogenicity | 5.7 mg/kg bw per day[c] | — |
| | Multigeneration study of reproductive toxicity[a] | Parental | 7.0 mg/kg bw per day | 35.0 mg/kg bw per day |
| | | Reproductive toxicity | 35.0 mg/kg bw per day[c] | — |
| | | Offspring toxicity | 7.0 mg/kg bw per day | 35.0 mg/kg bw per day |
| | Developmental toxicity[b] | Maternal toxicity | 90.0 mg/kg bw per day | 120.0 mg/kg bw per day |
| | | Embryo/fetotoxicity | 120.0 mg/kg bw per day[c] | — |
| | Developmental neurotoxicity[a] | Parental toxicity | 5.1 mg/kg bw per day | 50.6 mg/kg bw per day |
| | | Offspring toxicity | 5.1 mg/kg bw per day | 50.6 mg/kg bw per day |
| | Acute neurotoxicity[b,d] | Toxicity | 100.0 mg/kg bw | 400.0 mg/kg bw per day |
| Rabbit | Developmental toxicity[b] | Maternal toxicity | 30.0 mg/kg bw per day | 60.0 mg/kg bw per day |
| | | Embryo/fetotoxicity | 175.0 mg/kg bw per day[C] | — |
| Dog | Studies of toxicity[d] | Toxicity | 2.9 mg/kg bw per day | 12.5 mg/kg bw per day |

[a] Dietary administration.
[b] Gavage administration.
[c] Highest dose tested.
[d] The results of two or more studies were combined.

*Estimate of acceptable daily intake for humans*

0–0.03 mg/kg bw

*Estimate of acute reference dose*

1 mg/kg bw

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

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

***Critical end-points for setting guidance values for exposure to profenofos***

| *Absorption, distribution, excretion and metabolism in mammals* | |
|---|---|
| Rate and extent of oral absorption | About 94% within 24 h |
| Dermal absorption | Approximately 90% |
| Distribution | Widely distributed |
| Potential for accumulation | Low, no evidence of accumulation |
| Rate and extent of excretion | 94% in urine within 24 h |
| Metabolism in animals | > 95% by conversion of the phosphorothiolate group to a variety of hydrolysis products |

| Toxicologically significant compounds in animals, plants and the environment | Parent |
|---|---|
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | 358–1178 mg/kg bw |
| Rat, $LD_{50}$, dermal | 3300 mg/kg bw |
| Rat, $LC_{50}$, inhalation | 3.36 mg/L |
| Skin irritation | Moderately irritating |
| Eye irritation | Mildly irritating |
| Guinea-pig, skin sensitization (test method used) | Sensitizer (Magnusson & Kligman and local lymph-node assay) |
| *Short-term studies of toxicity* | |
| Target/critical effect | Inhibition of brain acetylcholinesterase activity |
| Lowest relevant oral NOAEL | 2.9 mg/kg bw per day (dogs) |
| Lowest relevant dermal NOAEL | 2.5 mg/kg bw per day |
| Lowest relevant inhalation NOAEC | < 0.07 mg/L |
| *Genotoxicity* | |
| | No genotoxic potential |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Inhibition of brain acetylcholinesterase activity |
| Lowest relevant NOAEL | 4.5 mg/kg bw per day (2-year study in mice) |
| Carcinogenicity | Not carcinogenic |
| *Reproductive toxicity* | |
| Reproduction target/critical effect | No reproductive effects |
| Lowest relevant reproductive NOAEL | 400 ppm (35 mg/kg bw per day) (rats) |
| Developmental target/critical effect | No developmental effects |
| Lowest relevant developmental NOAEL | 120 mg/kg bw per day (rats) |
| *Neurotoxicity/delayed neurotoxicity* | |
| Acute neurotoxicity | Inhibition of brain acetylcholinesterase activity, NOAEL was 100 mg/kg bw per day (rats) |
| Developmental neurotoxicity | Inhibition of brain acetylcholinesterase activity, NOAEL was 5.1 mg/kg bw per day (rats) |
| Delayed neuropathy | No delayed neurotoxicity, NOAEL was 45.7 mg/kg bw (chickens) |
| *Medical data* | |
| | No detrimental effects on agricultural workers |

***Summary***

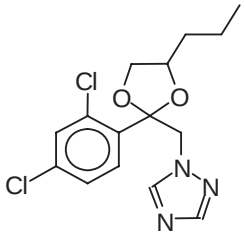
| | **Value** | **Study** | **Safety factor** |
|---|---|---|---|
| ADI | 0–0.03 mg/kg bw | Dog, studies of oral toxicity | 100 |
| ARfD | 1 mg/kg bw | Rat, study of acute neurotoxicity | 100 |

## 5.20 PROPICONAZOLE (160)

### RESIDUE AND ANALYTICAL ASPECTS

Propiconazole, one of the triazole fungicides, was first evaluated by the JMPR in 1987 and has been reviewed for residues in 1991 and 1994. It was listed by the 2004 CCPR (36th session, ALINORM 01/24, Appendix XI) for periodic re-evaluation for residues by the 2007 JMPR. The toxicology of propiconazole was re-evaluated by the 2004 JMPR which estimated an ADI of 0-0.07 mg/kg bw and an ARfD of 0.3 mg/kg bw.

Propiconazole is a racemic mixture of four stereoisomers, which are separated into *cis*- and *trans*-diastereomers. All four stereoisomers of propiconazole provide biological activity. The intrinsic activity of each isomer is different from pathogen to pathogen. The broad spectrum and high level of activity of propiconazole is the result of the combined activity of all isomers.




The Meeting received a full data package including animal and plant metabolism studies (goats, hens, grape vines, carrots, celery, wheat, rice, peanuts, sugarcane), rotational crop studies, hydrolysis and photolysis studies in water and degradation in water/sediment systems, information on analytical methods, GAP information, supervised residue trial data from use as a foliar spray on a range of fruit, cereal and oil seed crops, sugar beets and sugarcane, nuts, coffee and tea, processing studies and livestock feeding studies. GAP information was also submitted by Australia and The Netherlands.

Metabolites mentioned in this appraisal are given in the table below.

| Name used in this evaluation | Systematic chemical names, CAS numbers, and other abbreviations used in study reports |
|---|---|
| *propiconazole (CGA-64250)* | *1-{[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl}-1H-1,2,4-triazole;* |
| *β-hydroxy alcohol (CGA-118244)* | *1-{[2-(2,4-dichlorophenyl)-4-(2-hydroxypropyl)-1,3-dioxolan-2-yl]methyl}- 1H-1,2,4-triazole;* |
| | *2-(2,4-dichlorophenyl)-α-methyl-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolane-4-ethanol;* |
| *γ-hydroxy alcohol (CGA-118245)* | *3-[2-(2,4-dichlorophenyl)-2-[1,2,4]triazol-1-yl-methyl-[1,3]dioxolan-4-yl]-propan-1-ol;* |
| | *2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolane-4-propanol;* |
| *ketone (CGA-91304)* | *CGA-58533;* |
| | *1-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl) ethanone;* |
| | *1-(2,4-dichlorophenyl)-2-[1,2,4]-triazol-1-yl-ethanone;* |
| | *ω-(1,2,4-triazole-1-yl)-2,4-dichloroacetophenone;* |
| *alkanol (CGA-91305)* | *CGA-77502;* |
| | *1-(2,4-dichlorophenyl)-2-[1,2,4]triazol-1-yl-ethanol;* |
| | *1-{[2-(2,4-dichlorophenyl)-2-hydroxy]ethyl}-1H-1,2,4-triazole;* |
| | *α-(2,4-dichlorophenyl)-1H-1,2,4-triazole-1-ethanol;* |
| *triazole (CGA-71019)* | *1H-[1,2,4]-triazole* |

| Name used in this evaluation | Systematic chemical names, CAS numbers, and other abbreviations used in study reports |
|---|---|
| *triazolyl alanine (CGA-131013)* | *1,2,4-triazole-1-alanine; 2-amino-3-[1,2,4]triazol-1-yl-propionic acid; α-amino-1,2,4-triazole-1-propionic acid* |
| *triazolyl acetic acid (CGA-142856)* | *[1,2,4]triazol-1-yl-acetic acid* |
| *triazolyl lactic acid (CGA-205369)* | - |
| *N-acetylated-1,2,4-triazole-1-alanine* | - |
| *2,4-DCBA (CGA-177291)* | *2,4-dichloro-benzoic acid;* |

### *Animal metabolism*

The Meeting received information on the fate of orally dosed propiconazole in lactating goats and in laying hens. Experiments were carried out using uniformly $^{14}$C- phenyl and uniformly $^{14}$C-triazole labelled propiconazole. Metabolism in laboratory animals (mice, rats) was summarized and evaluated by the WHO panel of the JMPR in 2004.

Propiconazole is extensively metabolized in rats and mice and < 5% of the dose remains as the 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.

Three studies were performed on lactating goats. One lactating goat, orally treated once daily for 10 consecutive days with triazole-$^{14}$C-propiconazole at a calculated dose rate of 4.4 ppm in the feed, was sacrificed approximately 24 hrs after the last dose. The largest amount of radioactivity was found in the urine and faeces, which contained around 69% and 21% of the total dose, respectively. Tissues contained only 0.04%, while milk contained 0.18%. The radioactivity in the tissues did not exceed 0.02 mg/kg eq except for kidney (0.029 mg/kg eq) and liver (0.096 mg/kg eq). Radioactivity in milk reached a plateau on the sixth day of dosing at an average level of 0.015 mg/kg eq (range 0.015–0.016 mg/kg eq). The majority of the radioactivity in milk (> 74%) was associated with the whey fraction.

Radioactivity was characterized in goat milk and liver. Of the total radioactivity in milk, 3.0–5.6% could be identified as olefin, 13%–16% as ketone (CGA-91304) and 39% as triazole (CGA-71019). Sixteen to twenty percent remained unidentified. After a modified Kjeldahl digestion, 89% and 38% of the radiolabel in milk and liver, respectively, co-chromatographed with triazole.

In the second goat study, two lactating goats, orally treated once daily for four consecutive days with phenyl-$^{14}$C-propiconazole at calculated dose rates of 67 and 92 ppm in the feed, were sacrificed approximately 6 hrs after the last dose. Most of the administered [$^{14}$C] dose (86–96%) was eliminated in the urine (48–56%) and faeces including rumen contents at sacrifice (38–39%). Tissues and milk exhibited low levels of $^{14}$C-residues. Highest levels were found in liver (average 3.8 mg/kg eq) and kidney (average 2.5 mg/kg eq), whereas muscle and fat were found to contain the lowest levels (average 0.08 mg/kg eq). Radioactivity in milk increased during the four day dosing period for both animals reaching an averaged maximum of 0.22 mg/kg eq on day 4.

In liver, kidney, tenderloin muscle and omental fat three major components of the residue were identified:

- parent propiconazole (liver 12%, kidney 4%, muscle 2%, fat 20% of the total radiolabel)

- a β-hydroxy alcohol (CGA-118244; liver 19%, kidney 9%, muscle 16%, fat 33%),
- and an alkanol (CGA-91305; liver 14%, kidney 17%, muscle 36%, fat 31%).

In liver, kidney and tenderloin muscle several other components were present at relatively low levels. They were not further characterized. Similar to tissue extracts, milk contained the relatively non-polar metabolites β-hydroxy alcohol (CGA-118244; 24%) and alkanol (CGA-91305; 24%). In addition, milk extracts were found to contain several other more polar residues at low levels. Unchanged parent propiconazole was not found in milk. Treatment with aryl sulfatase suggested the presence of sulfate conjugates of ring-hydroxylated species.

In the third goat study, two lactating Alpine goats, orally treated once daily for seven consecutive days with triazole-$^{14}$C-propiconazole at calculated dose rates of 44 and 40 ppm in the feed, were sacrificed approximately 20 hrs after the last dose. Approximately 92% of the administered dose was recovered. The majority of the radiolabelled material was found in the urine (66%) and faeces (21%). Tissues and milk exhibited low levels of $^{14}$C-residues. Highest residue levels were found in liver (average 0.64 mg/kg eq) and kidney (average 0.28 mg/kg eq), whereas fat and muscle were found to contain the lowest levels (average 0.088 and 0.022 mg/kg eq, respectively). After 4 days radioactive residues in milk reached an average plateau concentration of 0.15 mg/kg eq (range 0.14–0.16 mg/kg eq) and 0.12 mg/kg eq (range 0.12–0.13 mg/kg eq) goats 1 and 2, respectively.

The most abundant residues were parent propiconazole in fat, alkanol (CGA-91305) in liver and kidney and triazole (CGA-71019) in kidney, muscle, fat and milk. Following enzyme hydrolysis of milk, triazole accounted for 40% of the total radiolabel and none of the unidentified components exceeded 6.1% (0.009 mg/kg). Parent was found at low levels in milk, but not in muscle.

Based on the above, it is proposed that the degradation of propiconazole in lactating goats proceeds primarily via the following pathways:

- Oxidation of the aliphatic side-chain of propiconazole to the alcohols CGA-118244 and CGA-118245.
- Further oxidation of the aliphatic side-chain to the carboxylic acid CGA-121676 observed in the urine and the hydroxy carboxylic acid metabolite SYN-542636 observed in the urine and kidney.
- Cleavage of the dioxolane ring to the ketone CGA-91304 followed by reduction of to the alkanol CGA-91305
- Cleavage of the alkyl bridge to release triazole CGA-71019, observed in muscle, milk and kidney.

Phase 1 metabolism products are then subject to phase 2 metabolism, i.e., glucuronide/sulphate conjugation. The metabolites triazolyl alanine (CGA-131013) and triazolyl acetic acid (CGA-142856), often observed in crop metabolism studies of triazole fungicides, were not present at detectable levels in lactating goats.

Two laying hens (Leghorn), orally treated once daily with $^{14}$C-propiconazole for 16 consecutive days at calculated dose rates of 54 and 47 ppm in the feed, were sacrificed approximately 24 hrs after the last dose. One hen (HA) was dosed with $^{14}$C-phenyl labelled and one hen (HB) with [$^{14}$C]triazole labelled propiconazole. Total recovered radioactivity was 94%–104%; most of the radioactivity (> 94%) was eliminated in the excreta.

Residue levels in egg yolk and white increased to a maximum level at days 11–15 and thereafter decreased; no real plateau was found. A maximum residue level was reached at day 11 at 1.2 and 0.98 mg/kg eq, respectively, for the triazole label and at days 13–15 at 0.87 and 0.90 mg/kg eq, respectively for the phenyl label. Levels of radioactive residues were different for the two labels in most of the tissues. The levels were generally higher for the triazole label, which was most pronounced for muscle (factor 7) and skin (1.5 fold). No significant label difference was found in the fat. These level differences indicate a cleavage between the phenyl and triazole ring and formation of label specific metabolites which are absorbed differently by different tissues.

In a second hen study, four laying hens (white Leghorn), orally treated once daily for 8 consecutive days with phenyl-$^{14}$C-propiconazole at a calculated dose rate of about 70 ppm in the feed, were sacrificed approximately 6 hrs after the last dose. Of the total dose, 73% to 87% was found to be eliminated in the excreta. Highest levels of radioactive residue were found in kidney (average 4.2 mg/kg eq) and liver (average 3.9 mg/kg eq). Levels of [$^{14}$C] residues in yolks for individual hens increased during the dosing period (average maximum 1.7 mg/kg eq), no plateau was reached. Average $^{14}$C-residues for the four hens were found to be higher in yolks (reaching a maximum of 1.7 mg/kg at day 7) than in whites (reaching a maximum of 0.70 mg/kg at day 5). In tissues and eggs, three major components of the recovered radioactivity were parent propiconazole (1.5% in liver, 2% in kidney, 7% in muscle, 40% in skin/fat, 12% in egg yolk and 28% in egg white), β-hydroxy alcohol CGA-118244 (3% in liver, 2% in kidney, 2% in muscle, 4% in skin/fat, 9% in egg yolk and 52% in egg white) and alkanol CGA-91305 (59% in liver, 44% in kidney, 85% in muscle, 43% in skin/fat, 51% in egg yolk and 18% in egg white).

Based on the structures identified, it is proposed that the degradation of propiconazole in laying hens treated with phenyl-$^{14}$C-propiconazole proceeds primarily via the following pathways:

- hydroxylation of the propyl side-chain to form CGA-118244
- hydrolysis of the dioxolane ring to form the ketone CGA-91304, which is then reduced to the corresponding alcohol CGA-91305

In conclusion, although the metabolism of propiconazole in farm animals was qualitatively similar to that in laboratory animals, the level of the different metabolites could quantitatively be very different.

***Plant metabolism***

The Meeting received information on the fate of propiconazole after foliar spray treatment of fruits (grape vines), root crops (carrots), stem crops (celery), cereals (wheat, rice) and oilseeds (peanuts). In addition, the Meeting received information on the fate of propiconazole after dip treatment of sugarcane pieces. Further, the Meeting received information on the fate of 1,2,4-triazole after topical treatment of tomato fruits.

Four grapevine plants (variety Riesling and Sylvaner) were grown outdoors in Sisseln (Switzerland). One plant was treated with a phenyl-$^{14}$C-labelled and three plants were treated with a triazole-$^{14}$C-labelled EC-formulation of propiconazole. All plants were sprayed four times until run-off at a rate of 0.0025 kg ai/hl water at 14-18 day intervals. A first aliquot of grapes was harvested 30 days after the last application ('Aliquot' sample), and mature grapes were harvested 63 days after the final application ('Harvest' sample). For both labels, the content of radioactivity in grapes was low, i.e. < 0.05 mg/kg propiconazole equivalents. Unchanged propiconazole accounted only for 15% of [$^{14}$C] residues (0.006 mg/kg) in whole grapes; a number of metabolites were identified but at lower concentrations.

Eight green tomatoes were treated topically by surface streaking and injection with propiconazole metabolite [$^{14}$C]1,2,4-triazole at 20–30 mg ai/kg tomato and placed for two weeks in a greenhouse under a 12 hr dark/light cycle. Total radioactive residues amounted to 19 mg/kg eq. The major metabolite in tomatoes was identified as a 1,2,4-triazole-1-alanine conjugate (80% TRR). No free triazole was found.

Carrots, var. Danvers Half-Long, were grown in pots in the greenhouse. Phenyl-U-$^{14}$C-propiconazole formulated as a 3.6 EC was spray applied as foliar spray. Four equal applications were made at approximately one week intervals, with the final application 14 days before harvest. Carrots were harvested at maturity, and separated in tops (leaves) and roots. Residue levels in root were considerably lower than in leaves. Parent propiconazole was the major residue in roots, accounting for up to 75% TRR (0.62 mg/kg) in the roots. A number of metabolites were present in very low levels (< 3%).

Celery, var. Tall Utah 52/70, was grown in sandy loam soil in the greenhouse. Phenyl-U-$^{14}$C-propiconazole formulated as a 3.6 EC was applied as a foliar spray.

Unchanged parent propiconazole was the main component in mature celery (approximately 90% of the TRR).

The metabolism of propiconazole was investigated in field and greenhouse grown wheat (variety Svenno) after foliar application using phenyl-[$^{14}$C] and triazole-[$^{14}$C] radiolabelled test material.

Samples of upper plant parts harvested after 5 h, 11 and 25 days and of mature straw, husk and grain of triazole-$^{14}$C-propiconazole treated plants were extracted and partitioned.

The relative amount of parent propiconazole in the upper plant parts decreased from initially 93% at 5 h PHI to 28% and 9.8% at 11 and 25 days PHI, respectively. With degradation of parent propiconazole an increase in polar metabolites could be observed. At maturity, no parent propiconazole could be detected in the grains (< 0.01 mg/kg) whereas the straw still contained 0.18 mg/kg. Most of the radioactivity in grains was water-soluble (85%). A number of other metabolites at generally < 10% were identified in straw, husks and grains of triazole-[$^{14}$C] treated plants at maturity.

A very similar distribution of radioactivity as described above for triazole-$^{14}$C treated plants was found for the phenyl-$^{14}$C treated plants. However, [$^{14}$C] residues consisting of acidic compounds (not found in any other plant parts) were higher in grains of the triazole-[$^{14}$C]-experiment. This major (54% of radioactivity in grain) triazole-specific metabolite in the $H_2O$-phases of wheat grains was identified as 1,2,4-triazole-1-alanine.

Spring wheat, var. Butte 86, was grown in sandy loam soil in the greenhouse. Phenyl-U-$^{14}$C-propiconazole as a 3.6 EC formulation was spray applied to pots at a rate equivalent to the maximum recommended use rate (1 ×) and at a rate equivalent to five times the maximum recommended use rate (5 ×).

Parent propiconazole represented 0.4%–17% of the radiolabel in wheat samples, with the highest amounts in 50% mature wheat and very small amounts in mature grains (0.4–0.8%) of both 1 × and 5 × treated plants. The low amount of parent compound and phase 1 metabolites indicated extensive metabolism of propiconazole in greenhouse grown wheat. In the 50% mature wheat from the 5 × treatment four metabolites were identified as the glucose- and malonyl glucose conjugates of β-hydroxy alcohol CGA-118244 and γ-hydroxy alcohol CGA-118245. The 5 × mature wheat forage contained a metabolite that consisted of various isomers of the malonyl glucose conjugate of CGA-118244. A total of 83% of the non-extractable radioactivity from mature wheat forage was characterized and demonstrated to be similar to the extractable metabolites.

Rice, variety Labelle (Texas) was seeded in buckets on moist soil (silt loam) in the greenhouse at a density corresponding to 100 kg seeds/ha. A 2–3 cm paddy water layer was maintained in the buckets during the main growing period until 2 weeks before harvest. The plants were treated twice, under the practical conditions in the USA, first in the booting stage and again at full heading, 67 and 83 days after seeding, respectively. Applications were performed by over-top spraying with triazole-[$^{14}$C] labelled propiconazole formulated as EC 430, each at a rate of 580 mL formulated product/ha or 250 g ai/ha (in 500 L water/ha).

Overall losses from the first application up to harvest time amounted to about 63% of the effectively applied radioactivity. Autoradiography showed that almost no radioactivity was taken up by the young shoots. Total [$^{14}$C] residues at harvest were 5.2 mg/kg eq in stalks, 2.8 mg/kg eq in husks, 0.29 mg/kg eq in grains, 0.06 mg/kg eq in roots and 0.05 mg/kg eq in the upper 0–5 cm soil layer. Parent propiconazole was degraded in the shoots with a half life of about 15 days. Residual parent concentration at harvest time was highest in soil (78%) and roots (73%), husks (47%) and lowest in the stalks and grains (28% each).

The remaining organosoluble radioactivity in stalks, husks and grains was identified as mono-hydroxy-metabolites including CGA-118244 (all four $\beta$-isomers identified in stalks and grains) and CGA-91305. O-glycosides of CGA-118244 (all four $\beta$-isomers identified in stalks) and CGA-91305 amounted to 11% and 14% of the radioactivity in husks and stalks, whereas only 0.2% of the

radioactivity in grains was attributable to sugar conjugates. The two major fractions attributing to 35% and 6.7% of the radioactivity in grain extracts were identified as triazolyl acetic acid and triazolyl alanine, conjugates of triazole.

Two sets, one for each label (triazole-[$^{14}$C] and phenyl-[$^{14}$C] propiconazole), of a variety of Virginia peanut plants were grown in the greenhouse. Plant material was harvested at the equivalent of a 14 day PHI.

At maturity the triazole- and phenyl-label treated plants respectively, contained 2.9 and 4.4 mg/kg eq in the stalks, 0.33 and 0.05 mg/kg in the kernels, and 0.09 mg/kg in the shells for both labels. Despite the initially lower radioactivity in triazole-$^{14}$C-propiconazole treated plants, relatively higher amounts were translocated to the kernels.

In mature stalks unchanged parent propiconazole represented 18% of the total [$^{14}$C] residues for both labels. The nonpolar metabolites of the mature stalks from the two labels were the alkanol CGA-91305 and β-hydroxy alcohol CGA-118244. The [$^{14}$C] distribution in the mature kernels was significantly different for the two labels, reaching amounts of 0.33 mg/kg eq [$^{14}$C] residues for the triazole label and 0.05 mg/kg eq for the phenyl label. Most of the radioactivity (74%) in the triazole-labelled kernels was co-chromatographing with triazole.

In another study, peanut plants were sprayed eight times at two week intervals, with the first time 5 weeks after planting, each time at a rate of 28.3 g ai/ha. The soil in the plot was treated at a rate of 69 g ai/ha triazole-$^{14}$C labelled propiconazole at early pegging and again at the same rate 21 days later. The mature harvest was taken two weeks after the last application, approximately a 14 day PHI. Radioactivity was translocated from the leaves to the nuts.

At maturity two weeks after the last application, the plants contained 12, 2.4 and 14 mg/kg eq [$^{14}$C] residues in the stalks, shells and kernels respectively. These levels in the field study are much higher than those observed in the greenhouse, i.e., about a factor 40 for mature kernels, although the greenhouse plants received comparable amounts of the test substance as foliar treatment. It is therefore likely that the differences in the radioactive levels resulted from the additional soil applications in the field. Therefore, radioactivity was very likely translocated to the kernels not only from leaves but also from the roots.

The distribution of radioactivity was comparable in field and greenhouse grown plants, however the data indicate that metabolism of propiconazole in field grown peanuts is more extensive than in greenhouse grown peanuts.

Unchanged parent propiconazole, metabolites alkanol CG-91305, β-hydroxy alcohol CGA-118244 isomers, and their acidic sugar conjugates together constituted 44% of the total [$^{14}$C] residue in the mature peanut stalk. Of the total radioactivity in kernels 94% was co-chromatographing with the triazole standard. In a further (greenhouse) study based on TLC, HPLC, GC-MS and IR data, the major metabolite in mature peanut kernels was found to be the 1,2,4-triazole-1-alanine conjugate. This major metabolite also gives rise to other metabolites, most likely alterations of the alanine moiety.

The metabolism of propiconazole in seed piece dipped sugarcane was investigated in two field studies either using triazole-[$^{14}$C] or phenyl-[$^{14}$C] labelled propiconazole. The treated seed pieces were planted in the field. Plant samples were taken at 4, 8, 12, and 16 weeks after germination.

After 4 weeks, [$^{14}$C] residues were detected, indicating that translocation from the seed pieces to the plants occurred. At the recommended use rate $^{14}$C-residue levels had decreased to 0.01 mg/kg by 8 weeks and to non-detectable levels (< 0.01 mg/kg) by 12 weeks. In conclusion, following dip treatment of sugarcane seed pieces, radioactive residues of all mature samples were below 0.01 mg/kg. This was confirmed by a second study.

Comparisons of the metabolic pathways in the different crops indicate that the biotransformation of propiconazole is qualitatively similar in all crops. Degradation takes place via hydroxylation of the propyl side-chain to form β-hydroxy alcohol CGA-118244 and γ-hydroxy alcohol CGA-118245; hydrolysis of the dioxolane ring and subsequent reduction leads to the alkanol CGA-91305. The various hydroxylated metabolites are effectively conjugated with sugars. The

phenyl-triazole bridge is cleaved primarily via conjugation of free 1.2.4-triazole with endogenous serine to give triazolyl alanine. This can then be converted to triazolyl acetic acid and triazolyl lactic acid. Radiolabelled propiconazole residues were able to translocate to other parts of the crops.

***Environmental fate in soil***

The Meeting received information on confined and field rotational crop studies. The uptake and distribution of triazole-$^{14}$C-propiconazole was investigated in field-grown rotational crops (lettuce, carrots, corn) following applications to peanuts. The uptake and distribution of [$^{14}$C] propiconazole was investigated in a greenhouse-grown rotational crop (peanut, winter wheat, field corn) following application to soil. Root uptake of **[**$^{14}$C] propiconazole and [$^{14}$C] triazole from soil was studied for spring wheat seedlings. Uptake of non-extractable aged soil residues of triazole-$^{14}$C-propiconazole was studied for spring wheat. Two sets of rotational crop studies were conducted with soya beans and rice as target crops.

As first rotational crop in the soya bean plots, winter wheat was planted in autumn following soya bean harvest. In the following spring, further rotational crops were planted into the soya bean plots including corn, sweet potatoes, sugar beets, lettuce and cabbage. A second rotation crop of winter wheat was planted one year after the soya bean harvest and was grown into the second year after soya bean harvest. Second crops of corn, sugar beets and lettuce were planted in the second spring after soya bean harvest. As first rotational crop in the rice plots, winter wheat was planted in autumn following rice harvest. Other rotational crops including sorghum, cabbage and sweet potatoes were planted in the following spring. A field rotational crop study was conducted with rape and sugar beet after application of propiconazole to bare soil.

From these studies it can be concluded that the metabolic pathway of propiconazole in rotational crops is similar to that in the target crop, differences being quantitative rather than qualitative. Metabolism was more extensive in rotational crops than in target crops. The major non-polar metabolites (β-hydroxy alcohol CGA-118244, γ-hydroxy alcohol CGA-118245, alkanol CGA-91305) and their conjugates found in the target crops were present only in very small quantities in the rotational crops. The major metabolites in rotational crops were polar and identified as conjugates of 1.2.4-triazole, i.e., triazolyl alanine and triazolyl acetic acid. As an example for spring wheat (uptake aged soil residues) 42% triazolyl alanine and 32% triazolyl acetic acid was found in grain and 40% triazolyl lactic acid and 22% triazolyl acetic acid in straw. It is concluded that more cleavage of the triazole-phenyl bridge occurred in rotational crops than in target crops, and that uptake of polar soil degradation products occurred in rotational crops.

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

The Meeting received information on the hydrolysis and photolysis of propiconazole in sterile water, and degradation in water/sediment systems.

Propiconazole is hydrolytically stable under relevant environmental conditions. Although stable to photolysis in pure buffer solutions, propiconazole is rapidly degraded in natural waters, presumably via photosensitisation. Any degradation in the water phase by biotic processes is expected to be minimal. Propiconazole will however rapidly adsorb to sediments and 14 days after application 15–20% parent remained in the water; at the end of the study (175 days) only 0.9–2% was left. In the sediment it undergoes slow degradation. At the end of the study at 175 days, 77–82% of the residue in the sediment was still parent, with a small amount of carbon dioxide, alkanol CGA-91305, triazole and bound residues identified as end products.

***Methods of analysis***

The Meeting received information on methods of residue analysis for enforcement/monitoring and residue methods used in the various study reports. In the EU, the residue definition in commodities of plant and animal origin is parent propiconazole only. In the USA and Canada, residues are determined as total residues having the 2.4-dichlorobenzoic acid (DCBA) moiety. Therefore methods are divided into two groups: methods where only the parent compound propiconazole is determined and methods

where all residues containing the 2,4-DCBA (CGA-177291) moiety are determined ('total residue method').

Multi-method DFG S19 was shown to be sufficiently validated for post-registration monitoring and enforcement of parent propiconazole for commodities of plant and animal origin

In the parent-only methods for plant commodities, macerated samples are typically extracted with methanol and the extract is cleaned up by solvent partition and solid phase column chromatography. The final residue can then be determined by GLC with ECD or NPD or alternatively by LC-MS-MS. LOQs are typically in the 0.01–0.05 mg/kg range. The analytical methods for animal commodities are similar, but with extraction methods tailored for milk, eggs and animal tissues. The LOQ for milk, eggs and tissues is 0.01 mg/kg.

In the total residue methods, homogenized samples were extracted with methanol or acetonitrile and washed with hexane. Homogenized crops or aqueous extracts of oilseeds and nuts were typically refluxed for 16 h with 12 M $HNO_3$ to convert DCBA-containing residues to 2,4-DCBA. The refluxed solution was diluted with water and partitioned with dichloromethane. The dichloromethane layer was evaporated to dryness and derivatised with diazomethane. The derivative was cleaned-up using silica column chromatography. The 2,4-DCBA methyl ester derivative was determined by GC-MS (CI, at m/z 206) or GC-ECD. Calibration standards were prepared by in-situ derivatisation of 2,4-DCBA standards. Results were expressed as mg/kg eq, by using a factor 1.79. LOQs are typically in the 0.05–0.1 mg/kg range.

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

The Meeting received information on storage stability of residues in extracts and frozen samples.

Parent propiconazole was stable in the following crop commodities for the intervals tested: soya bean fodder and soya bean grain 6 months at -15 °C, cereal straw and cereal grain 21 months at -20 °C. The Meeting considered these studies sufficient to cover the crops addressed by this Meeting. However, in future more storage stability studies would be desirable if further commodities are to be submitted in which the residue was measured as parent.

Total residues containing the 2,4-DCBA moiety were stable in the following crop commodities for the intervals tested:

- corn silage 8 months at 4 °C,
- soya beans 3.5 months at 4 °C,
- soya bean fodder and grain 6 months, peanut fodder, peanut shell, peanut nutmeat 25 months at -15 °C,
- rye and tall fescue grass (straw and seeds) 38 months at -20 °C, peaches, bananas, corn meal, wheat grain, peanut hay, peanut hulls, peanut nutmeat, celery, corn oil and carrots 3 years at -20 °C.

The stability of propiconazole in products of animal origin was investigated in addendum studies to metabolism studies in hens and goats. Propiconazole residues were found to be stable for up to 223 days in animal tissue when stored frozen.

***Definition of the residue***

Propiconazole is efficiently degraded in farm animals and is only found in significant amounts in goat liver and fat and hen skin/fat and eggs. Lower amounts are also present in other edible tissues and milk. The major metabolites are the alkanol (CGA-91305) in goat liver and kidney and triazole (CGA-71019) in goat kidney, muscle, fat and milk. In hen edible tissues and eggs, the major metabolites were the alkanol CGA-91305 and the β-hydroxy alcohol CGA-118244. Triazole, the major residue in milk, is not specific for propiconazole since it can be derived from conazole pesticides and is therefore not a good indicator for propiconazole use. Therefore parent is considered to be a suitable residue for enforcement in animal products.

The metabolites containing the dichlorophenyl-moiety were also found in laboratory animals and are therefore included in the toxicological evaluation of JMPR 2004. The Meeting concluded that these metabolites will not be of greater toxicity than the parent and could well be of lower toxicity. However, because of the lack of more specific data, the Meeting decided that all metabolites containing the dichlorophenyl-moiety (=metabolites convertible to 2,4-DCBA) should be taken into consideration for the dietary risk assessment.

The metabolism of propiconazole is qualitatively similar in all plant species tested and resembles that of other fungicides of the triazole family.

Parent propiconazole, although effectively degraded, is still a major component of the total recovered residue in the edible portion of most crops over a longer period following application. The Meeting decided that parent propiconazole is a suitable analyte for enforcement purposes in plant commodities.

In grapes, 33% of the radiolabel was composed of the ketone (CGA-91304) moiety and 5% the alkanol (CGA-91305) moiety, while triazolyl alanine accounted for 10%. In carrots β-hydroxy alcohol CGA-118244, alkanol CGA-91305 and α-hydroxy alcohol CGA-136735 were the most significant metabolites.

Three plant-specific metabolites - triazolyl alanine, triazolyl acetic acid and triazolyl lactic acid - were mainly found in wheat grain, rice grain and rotational crops. They are derived from triazole, which is also found in animal metabolism. These triazole metabolites are of toxicological concern, but are not specific for propiconazole since they are formed from all conazole pesticides. Therefore they should not be part of the propiconazole residue definition for dietary risk assessment. Although national authorities may wish to conduct a separate cumulative risk assessment for these metabolites; in the case of propiconazole, the levels of the triazole metabolites are low under practical conditions.

The Meeting recommended the following as residue definitions for propiconazole.

*For plants*:

*Definition of the residue for compliance with the MRL*: propiconazole

*Definition of the residue for estimation of dietary intake:* propiconazole plus all metabolites convertible to 2.4-dichlorobenzoic acid, expressed as propiconazole

*For animals:*

*Definition of the residue for compliance with the MRL:* propiconazole

*Definition of the residue for estimation of dietary intake:* propiconazole plus all metabolites convertible to 2.4-dichlorobenzoic acid, expressed as propiconazole

*The residue is fat soluble.*

***Results of supervised trials on crops***

The propiconazole residues in cranberries were evaluated by the 2006 JMPR. That Meeting estimated a maximum residue of 0.3 mg/kg, an HR of 0.13 mg/kg and STMR of 0.058 mg/kg for cranberries, based upon the residue definition for enforcement, i.e. propiconazole. The present Meeting endorsed those recommendations. As a result of the residue definition for dietary risk assessment, in order to convert from propiconazole to total residue, the STMR and HR values were then multiplied by a factor of 3 to yield 0.39 and 0.174 mg/kg, respectively.

Supervised trials were reported to the present Meeting on apricots, cherries, nectarines, peaches, plums, blackberry, blueberries, raspberry, bananas, pineapples, sugar beets, barley, rye, sorghum, wheat, corn, popcorn, rice, sugarcane, almond, pecan, peanuts, rapeseed, canola seed, soya bean, coffee and tea.

The residues were analysed either as the parent compound or as total residues measured as 2,4-dichlorobenzoic acid (2,4-DCBA) and calculated back to parent compound. The total residues

listed hereunder are the parent compound equivalent of residues measured as 2,4-DCBA. The performance of the analytical methods was within the parameters expected, based on the validation data. The untreated samples contained detectable 2,4-DCBA in several cases. The results reported were not corrected for analytical recoveries or blank values.

The definition of residues specifies the parent propiconazole as the residue for enforcement purposes. Therefore the maximum residue estimates should be based on the parent residues. Residue data on parent compound was available for bananas, sugar beet, barley, rye, wheat, rape and canola seed, soya bean, coffee and tea. For dietary intake calculation purposes, the Meeting estimated in each case what the STMR and HR would be taking into account all residues convertible to 2,4-DCBA.

The Meeting decided (based on the metabolism studies available) to apply a conservative default factor of 3 to food commodities. This would convert parent-only residues to total residues convertible to 2,4-DCBA, except when additional data were available to make a more realistic assessment. For cereal straw a conversion factor of 10 is applied based on metabolism studies.

The Meeting could recommend maximum and median residue levels based on the LOQs of the parent compounds because the maize, corn, pineapple, sugar cane, and pecan residues were measured as total residues based on the determination of 2,4-DCBA. This also took into account that the total residues were below or at the LOQ in all samples.

As the proportion of parent residues and the total residues based on the determination of 2,4-DCBA varied significantly among various crops, the Meeting could not use the residue data for estimation of maximum residue levels for stone fruits, prunes, berries, rice, sorghum, almonds and peanuts. The Meeting withdraws its previous recommendations of maximum residue levels for almonds, peanuts and stone fruits.

No residue data were provided for grapes, mango, oats, and whole peanut, and consequently the Meeting withdraws its previous recommendations for maximum residue levels for these crops.

***Residue trials based on the determination of the parent compound***

*Banana*

Field trials were performed on bagged bananas in Honduras applying propiconazole at both the maximum and double rate. Samples were taken between 0 and 9 days after last application (GAP in Honduras for both bagged and non-bagged bananas): 8–10-cycle programme at every 18–21 days. PHI=0). The parent propiconazole was measured in peel and pulp separately. The peel/pulp weight ratio was not reported. The pulp contained non-detectable residues in all bagged samples ($10 \times < 0.02$ mg/kg) regardless of the PHI, and number of applications. Two peel samples out of 10 contained detectable residues (0.024, 0.03 mg/kg).

The compound was also applied 7 or 13 times on non-bagged banana. The banana pulp contained detectable residues in two samples (0.025 and 0.029 mg/kg), while the other pulp samples contained non-detectable residues < 0.02 (12). Following the treatments at the recommended rate (0.1 kg ai/ha) the peel contained residues of < 0.02 (3) 0.021, 0.026, 0.032, 0.044, 0.045, 0.046, 0.07, < 0.072, 0.075, 0.1 mg/kg.

The Meeting took into account that the peel amounts to about 30% of the weight of the whole banana; consequently the calculated maximum residue level in whole banana would be ($0.3 \times 0.1+0.7 \times 0.029=0.052$): 0.02, 0.021, 0.021, 0.022, 0.027, 0.028, 0.044, 0.052 mg/kg.

The Meeting confirmed its previous recommendation of 0.1 mg/kg for whole banana and using the default conversion factor of 3 estimated a median residue of 0.06 mg/kg and an HR of 0.087 ($3 \times 0.029$) mg/kg in banana pulp.

*Sugar beet*

Twelve trials were performed in France, Germany and UK applying EC formulation of propiconazole at a rate of 3 times 0.1–0.125 kg ai/ha. The GAP in Denmark (0.125 kg ai/ha PHI 30 days) and

Germany (0.1125 kg ai/ha, PHI 28 days) are very similar. Even after three applications the parent propiconazole residues were below the LOQ (< 0.01 to < 0.05 mg/kg) of the methods in all root samples. The LOQ of the method was 0.01 or 0.02 mg/kg in the more recent trials.

Based on the Danish and German GAP, the Meeting estimated a maximum residue level of 0.02 mg/kg for sugar beet roots. The Meeting withdrew its previous recommendation of 0.05 mg/kg for the maximum residue level. Using the default conversion factor of 3 the Meeting estimated a median residue of 0.06 mg/kg.

*Cereals*

*Barley*

Field trials were performed in France, Germany and Switzerland applying propiconazole in accordance with the GAP in France (2 × 0.12 kg ai/ha with 42 days PHI). The parent propiconazole residues in barley grains were: < 0.02 (7), 0.02 (4), 0.025, 0.03, 0.03, 0.03, 0.03, 0.03, 0.04, 0.04, 0.05, 0.1, and 0.11 mg/kg.

Based on the GAP in France, the Meeting estimated a maximum residue level of 0.2 mg/kg, and an STMR of 0.0675 (3 × 0.0225) mg/kg for barley. The Meeting withdrew its previous recommendation of 0.05 mg/kg for barley.

*Rye*

Two trials were performed with 2 × 0.125 kg ai/ha application rate. Grain samples taken 48–50 days after the second application did not contain detectable parent residues (< 0.01, < 0.02 mg/kg).

*Wheat*

Field trials were performed in France Germany and UK applying propiconazole in accordance with the GAP in France (2 × 0.12 kg ai/ha with 42 days PHI). The parent propiconazole residues in wheat grains were below the LOQ (< 0.01, < 0.02 mg/kg) in all samples (12).

As the GAP for wheat rye and triticale are the same, and in both commodities the residues were below the LOQ, the Meeting decided to combine residues in wheat and rye.

The Meeting estimated a maximum residue level of 0.02 mg/kg and an STMR of 0.06 (3 × 0.02) mg/kg for wheat and rye and triticale.

The Meeting withdrew its previous recommendation of 0.05 mg/kg for wheat and rye.

*Rape and Canola seed*

Five trials were conducted in Canada during 2 years applying double rate. The GAP is maximum 3 applications at 0.125 kg ai/ha with a PHI of 60 days. None of the samples (one rape and four canola) contained detectable parent propiconazole residues (0.02 mg/kg). Triazolylalanine (which is not part of the residue definition) was determined separately ranging from 0.38 mg/kg to 2.2 mg/kg.

The Meeting estimated a maximum residue level of 0.02 mg/kg and an STMR residue of 0.06 (3 × 0.02) mg/kg for canola and rape seed.

The Meeting withdrew its previous recommendation of 0.05 mg/kg for rape seed.

*Soya bean*

Field trials on soya bean were performed in 16 states in the USA. The GAP of the USA allows 2 applications at 0.12–0.18 kg ai/ha at a 21 day interval up to growth stage R6 (first flowers opened). Propiconazole was applied twice by post foliar broadcast spray at 0.19 kg ai/ha. Dried soya bean samples were collected 30 days after the last application. The parent propiconazole residues in dried seed were: < 0.01 (12), 0.01 (3)0.02 (3), 0.04 and 0.05 mg/kg.

The Meeting estimated a maximum residue level of 0.07 mg/kg and an STMR of 0.03 (3 × 0.01) mg/kg.

*Coffee*

Four trials were performed in Brazil and Mexico at the recommended and double rates. The parent propiconazole residues were below the LOQ of 0.02 and 0.04 mg/kg in the three samples taken 30–40 days after last application.

Based on the Brazilian GAP (apply at 30–60 days interval with 0.15–0.175 kg ai/ha) and Costa Rican GAP (apply at a rate of 0.19–0.25 kg ai/ha maximum 5 times PHI 30 days) the Meeting estimated a maximum residue level of 0.02 mg/kg and an STMR of 0.06 (3 × 0.02) mg/kg for coffee beans.

The Meeting withdrew its previous recommendation of 0.1 mg/kg for coffee.

*Tea*

Six trials were conducted in Bangladesh and Indonesia following approximately the Indonesian GAP (0.15 kg ai/ha at 10–14 days) in three trials. The green tea leaves 14 days after last application contained the parent propiconazole at the following concentrations: 0.05, 0.08 and 0.11 mg/kg.

As the sampled and analysed commodities did not correspond to the Codex Commodity description, the Meeting could not recommend maximum residue limits.

***Recommendations based on total residue***

*Maize, Sweet corn and popcorn*

Numerous field trials were performed in the USA with EC and WP formulation at the recommended maximum and exaggerated rates (1.5 × maximum seasonal rate). The total residue was measured as 2,4-DCBA.

In 19 field corn grain samples the residues were below the LOQ (< 0.05 mg/kg) except in two trials (0.05 and 0.06 mg/kg) regardless of the PHI and the application rate.

Two of eleven popcorn samples contained 0.06, 0.065 (1.2 × rate) mg/kg residue.

Ear samples from four sweet corn trials did not contain any detectable residues (< 0.05 mg/kg).

The Meeting took into account that the parent compound is not the major part of the residues, and estimated a maximum residue level and an STMR value of 0.05 mg/kg for field, sweet and popcorn.

*Pineapple*

Propiconazole is authorised for seed pieces treatment. No measurable residues of propiconazole, determined as 2,4-dichlorobenzoic acid, were detected (< 0.05 mg/kg) in pineapple fodder, shells, bran or cores from any of the three locations at the exaggerated treatment rates (1.5–3 × label rates).

The Meeting concluded that the registered use of propiconazole does not lead to detectable residues, and estimated a maximum residue level of 0.02* mg/kg and an HR and STMR of 0.02 mg/kg for pineapple.

*Sugarcane*

Propiconazole is registered for use on sugarcane as a cold and hot dip treatment. A radio-label study indicated that following treatment of seed pieces at 5 × and 10 × rate, there were no measurable residues in cane six months after planting. Furthermore, no TRR (< 0.01 mg/kg) was detected in any plant parts (chopped cane, bagasse, raw sugar, molasses) grown from the seed treated at 5 ×, 10 × and 20 × rates.

The Meeting concluded that the registered use of propiconazole does not lead to detectable residues, and estimated a maximum residue level of 0.02* mg/kg and an STMR of 0 mg/kg in sugar.

The Meeting withdrew its previous recommendation of 0.05 mg/kg for sugar cane.

*Pecan*

Eight trials were carried out at about 1.5–3 × the registered rate at different locations in the USA during 1980–1984. Samples were collected 7–21 days after last application which is much shorter than the permitted minimum 45 days. The total residues were determined as 2,4-dichlorobenzoic acid (2,4-DCBA). None of the 38 pecan nut samples contained residues above the LOQ of 0.05–0.1 mg/kg.

The Meeting concluded that the registered use of propiconazole does not lead to detectable residues, and estimated a maximum residue level of 0.02* mg/kg and an HR and STMR of 0.02 mg/kg for pecan nuts.

The Meeting withdrew its previous recommendation of 0.05 mg/kg for pecan.

***Trials providing data on total residues***

As the residues measured do not match the residue definition, the Meeting was unable to estimate residue levels for the following commodities.

*Stone fruits*

Trials carried out in typical growing areas of the USA were reported to the meeting. The total residues were measured as 2,4-dichlorobenzoic acid (2,4-DCBA).

*Apricots*

Three trials performed at the maximum recommended rate (0.12 kg ai/ha) resulted in total residues at day 0: 0.08, 0.23 and 0.29 mg/kg.

*Nectarines*

Sixteen trials were performed in seven States of the USA applying 3–5 times 0.123 kg ai/ha. Samples taken at day 0 (GAP) contained total propiconazole residues of: 0.05, 0.06, 0.12, 0.12, 0.12, 0.12, 0.15, 0.24, 0.26, 0.29, 0.33, 0.4, 0.42, 0.45, 0.65, and 1 mg/kg.

*Peaches*

Sixteen samples taken at day 0 from trials performed in seven states of the USA where propiconazole was applied 1–5 times at 0.123 kg ai/ha (GAP) contained total propiconazole residues of: 0.05, 0.07, 0.08, 0.14, 0.14, 0.18, 0.24, 0.25, 0.27, 0.27, 0.29, 0.3, 0.32, 0.42, 0.57, and 0.72 mg/kg.

*Cherries*

Fourteen trials on cherry, tart cherry and sweet cherry were conducted with EC, gel and WP formulations applying propiconazole 5 times at 0.123 kg ai/ha. Samples taken at day 0 contained total residues of: 0.15, 0.18, 0.18, 0.28, 0.36, 0.4, 0.41, 0.46, 0.5, 0.5, 0.66, 0.74, 0.82, and 0.99 mg/kg.

*Plums*

Eight samples taken at day 0, from trials performed in three states of the USA applying propiconazole 5 times at 0.123 kg ai/ha, contained total propiconazole residues of: < 0.05(4), 0.09, 0.09, 0.12, and 0.17 mg/kg.

*Prunes*

Four samples taken at day 120, from trials performed in three States of USA applying propiconazole 3 times at 0.123 kg ai/ha, contained total propiconazole residues of: < 0.05(3) mg/kg. Residues in dry prunes were: < 0.05(3) and 0.07 mg/kg.

*Berries*

Seven field trials were performed in the USA on blueberries and raspberry at the maximum recommended rate. Samples taken 30 days after last application (GAP) contained residues of: 0.16, 0.23, 0.29, 0.31, 0.4, 0.44, and 0.62 mg/kg.

*Rice*

Twenty two trials were conducted in various states of the USA in 1998 according to US GAP (0.19–0.32 kg ai/ha, 2 application before head emergence). The total residues in rice grain were: 0.09, 0.14, 0.14, 0.41, 0.48, 0.74, 0.86, 0.94, 0.99, 1, 1.15, 1.6, 1.68, 1.75, 1.95, 2, 2.4, 3.6, 3.7, 3.9, 5, and 6.3 mg/kg.

*Sorghum*

Trials were performed according to the US GAP (0.09–0.12 kg ai/ha with maximum 0.5 kg ai/ha/season) in several states of the USA. The total residues, measured as 2,4-DCBA, found in samples taken at around 21 days were: 0.71, 0.93, 1, 1, 1.3, 1.45, 1.65, 2.05, 2.15, and 2.25 mg/kg.

*Almonds*

Trials were conducted with concentrate and dilute spray applications of EC and WP formulations in the USA. Following 4 applications at the maximum recommended rate and PHI (0.25 kg ai/ha with 60 day PHI), the total propiconazole residues in almonds were: < 0.05 (8), 0.05, 0.05, 0.06, 0.06, 0.06, 0.06, 0.07, 0.09, 0.09, and 0.1 mg/kg.

*Peanut*

Six trials were performed at the recommended maximum rate and another 13 trials at about double that rate. The label specifies 14 days PHI for the lower rate and 21 days PHI for the high rate.

The total propiconazole residues at about 21 days after the last application were: < 0.05, 0.05, 0.07, 0.07, 0.08 and 0.08 mg/kg.

Residues at 14 days were: < 0.05, < 0.05, 0.05, 0.06, 0.06, and 0.1 mg/kg.

There was no significant difference between the residues in peanut at 14 and 21 days.

***Residues in animal feed***

The residues in animal feed resulting from the trials described above are summarized below.

***Trials providing data on residues of parent compound***

*Sugar beet leaves*

Following treatments according to the GAP in Denmark and Germany (0.1125–0.125 kg ai/ha and PHI of 28–30 days) propiconazole residues in sugar beet leaves were: 0.01, 0.01, 0.02, 0.04, < 0.1, < 0.1, 0.1, 0.1, 0.2, 0.22, 0.25, 0.25, 0.25, and 0.32 mg/kg.

The Meeting estimated a highest residue level of 0.96 (3 × 0.32) mg/kg and a median residue level of 0.3 (3 × 0.1) mg/kg for sugar beet leaves.

*Barley straw*

Following applications according to French GAP (2 × 0.125 kg ai/ha with a PHI of 42 days) the residues in barley straw were: 0.03, < 0.04 (4), 0.05, 0.05, 0.07, 0.07, 0.12, 0.14, 0.15, 0.15, 0.22, 0.3, 0.32, 0.36, 0.41, 0.42, 0.68, 0.83, and 0.97 mg/kg.

*Wheat straw*

Following applications according to French GAP (2 × 0.125 kg ai/ha with PHI of 42 days) the residues in wheat straw in ranked order, median underlined, were: < 0.04, < 0.04, < 0.04, 0.06, 0.1, 0.13, 0.15, 0.19, 0.3, 0.3, 0.32, 0.41, 0.43, 0.49, 0.54, 0.58, 0.65, 0.77, 0.8, 0.81, 0.82, and 0.89 mg/kg.

The Meeting considered that the residue distribution in barley and wheat straw is the same and combined the two data sets. Residue found, in ranked order were: 0.03, < 0.04 (7), 0.05, 0.05, 0.06, 0.07, 0.07, 0.1, 0.12, 0.13 0.14, 0.15, 0.15, 0.15, 0.19, 0.22, 0.3 (3), 0.32, 0.032, 0.36, 0.41, 0.41, 0.42, 0.43, 0.49, 0.54, 0.58, 0.65, 0.68, 0.77, 0.8, 0.81, 0.82, 0.83, 0.89 and 0.97 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg for barley, rye, triticale and wheat straw. For cereal straw a conversion factor of 10 is applied to convert to total residue based on metabolism studies. The Meeting estimated a highest residue of 9.7 (10 × 0.97) and an STMR of 2.6 (10 × 0.26) mg/kg for barley, rye, triticale and wheat straw.

*Soya bean*

*Soya bean forage*

Following the US GAP (2 × 0.12–0.18 kg ai/ha at 21 days intervals up to growth stage R6) the residues 14 days after second application were: 0.1, 0.13, 0.165, 0.2, 0.45, 0.46, 0.5, 0.5, 0.75, 0.77, 0.78, 0.8, 0.8, 0.8, 0.84, and 1.15 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg, and using the default conversion factor of 3 a highest residue of 3.45 (3 × 1.15) mg/kg, and an STMR of 1.875 (3 × 0.625) mg/kg.

*Soya bean fodder*

Following the US GAP (2 × 0.12–0.18 kg ai/ha at 21 days intervals up to growth stage R6) the residues 14 days after second application were: 0.12, 0.15, 0.17, 0.335, 0.4, 0.48, 0.65, 0.65, 0.7, 0.77, 1.1, 1.15, 1.2, 1.4, 1.5, and 3.2 mg/kg.

The Meeting estimated a maximum residue level of 5 mg/kg, and using the default conversion factor of 3 a highest residue of 9.6 (3 × 3.2) mg/kg, and an STMR of 2.025 (3 × 0.675) mg/kg.

***Trials providing data on total residues based on 2,4-DCBA measurement***

Following the corresponding GAPs the residues measured are listed below.

*Sorghum forage* (total residue): 2.45, 3.1, 3.6, 4.3, 4.55, 4.65, 5, 6.6, 6.9, 7.95, and 8.1 mg/kg.

*Sorghum stover* (total residue): 4.35, 5.05, 6.25, 6.6, 6.85, 7.3, 7.7, 8, 9.5, and 13.5 mg/kg.

*Rice straw* (total residue): 0.98, 1.1, 1.15, 1.4, 1.6, 1.65, 1.75, 2, 2.35, 2.35, 2.8, 3.3, 3.45, 3.7, 4, 7.75, 10, 11.5, 13.5, and 16.5 mg/kg.

*Corn forage (*total residue): < 0.05, 0.08, 0.1, 0.35, 0.4, 0.58, 0.69, 1, 1.55, 2.05, 2.1, 2.76, 2.9, and 5.0 mg/kg.

*Corn stover and fodder* (total residue): < 0.02, 0.02, 0.075, 0.09, 0.46, 0.68, 1.3, 1.5, 1.9, 2.2, 2.4, 2.42, 2.6, 2.65, 3.4, 3.7, 3.72, 3.8, 3.9, 4.1, 4.2, 5, 6.9, 7.7, 8.2, 10, 12.5, 16, and 17 mg/kg.

*Almond hull* contained total propiconazole residues of: 0.74, 0.75, 0.86, 1.5, 1.75, 1.9, 2.2, 2.6, 2.75, 2.8, 2.9, 3.1, 4.0, 4.7, 6.75, 6.8, 7.2, and 7.4 mg/kg.

*Peanut hay* contained total propiconazole residues of: 1.7, 2.49, 6.5, 8.7, 13.4 and 14 mg/kg.

As the residues measured do not match the residue definition, the Meeting was not able to estimate residue levels for sorghum forage and stover; rice straw; corn forage, stover and fodder; almond hull and peanut hay.

***Fate of residues during processing***

The Meeting received information on the fate of radiolabelled propiconazole in grapes processed to grape juice and sugarcane processed to chopped cane, bagasse, raw sugar and molasses. Furthermore the fate of incurred residues of propiconazole during the processing of sugar beet, corn grain, rice, sorghum, wheat, sugarcane, peanut and tea was reported. The processing factors (PF) shown below were calculated from the residues for the commodities for which maximum residue levels, STMRs and HRs were estimated.

In all trials, except for those on grape, sugarcane and tea, residues were measured as 2,4-DCBA and expressed as propiconazole equivalents. Since the Meeting decided that the residue definition is propiconazole, these trials cannot be used for the estimation of MRL, STMR, HR or in calculations of animal dietary burden.

| RAC | Processed product | No. | PF | Median PF (or best estimate) |
|---|---|---|---|---|
| Grape[1] | Grape juice<br>Grape presscake | 1 | 0.05<br>0.95 | 0.05<br>0.95 |
| Tea[2] | Brewed green tea | 9 | 0.03, 0.02, 0.02, 0.03, 0.02, 0.03, 0.02, 0.02, 0.02 | 0.02 |

[1] radioactive parent propiconazole; [2] residue measured as parent propiconazole

Grape juice (from grapes in the metabolism study) contained < 0.001 mg/kg unchanged parent propiconazole. The major metabolite in grape juice is 1,2,4-triazole-l-alanine.

Freshly cut sugarcane seed pieces were treated by dipping for one minute in triazole-labelled propiconazole. The seed pieces were then planted and mature sugarcane was collected at 58 weeks after treatment. Sugarcane was processed into chopped cane, bagasse (fibre), raw sugar and molasses. No radioactive residues (< 0.01 mg/kg eq) were found in the raw agricultural commodity or any of the processed commodities. Based on the STMR value of 0 mg/kg for sugar cane, the Meeting decided to estimate an STMR-P of 0 mg/kg for sugar.

Homogenised green tea leaves were extracted with 200 mL boiling water for 2 minutes. The processing factor for brewed green tea was 0.02. Since no MRL and STMR recommendation could be made, the Meeting was unable to recommend an STMR-P for brewed green tea.

***Residues in animal commodities***

*Farm animal feeding*

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

*Lactating dairy cows*

Groups of three lactating Holstein dairy cows were dosed once daily either in the feed (low dose) or via gelatin capsule or intra-rumen injection with propiconazole at 15 ppm (1 ×), 75 ppm (5 ×) and 150 ppm (10 ×) in the dry-weight diet for 14–28 consecutive days. Milk samples for analysis were taken at 0, 1, 4, 7, 12, 14, 21 and 28 days and samples of muscle, liver, kidney and fat were collected on 14, 21 and 28 days. Both total residues containing the 2,4-DCBA moiety and parent propiconazole *per se* were determined.

No parent propiconazole (< 0.01 mg/kg) was found in any of the milk samples at all feeding levels. In muscle and kidney, no parent propiconazole (< 0.05 mg/kg) was detectable at all feeding levels. The maximum level in liver was 0.14 mg/kg at the 15 ppm feeding level (average 0.08 mg/kg), 0.34 mg/kg in the 75 ppm feeding level (average 0.22 mg/kg) and 0.66 mg/kg at the 150 ppm feeding level (average 0.42 mg/kg); in fat it was < 0.05 mg/kg at the 15 ppm and 75 ppm feeding levels and 0.08 mg/kg at the 150 ppm feeding level (average 0.06 mg/kg).

No 'total DCBA-residue' (< 0.01 mg/kg) was found in any of the milk samples at the 15 ppm feeding level. At the 75 ppm feeding level, the average total residue in milk was 0.044 mg/kg eq, while the maximum total residue found was 0.08 mg/kg eq. At the 150 ppm feeding level, the average total residue in milk was 0.10 mg/kg eq, while the maximum total residue found was 0.11 mg/kg eq.

In muscle, no 'total DCBA-residue' (< 0.05 mg/kg) was detectable at the 15 ppm feeding level. The maximum level in muscle was 0.11 mg/kg at the 75 ppm feeding level (average 0.08 mg/kg) and 0.18 mg/kg at the 150 ppm feeding level (average 0.14 mg/kg). The maximum level in liver was 0.81 mg/kg at the 15 ppm feeding level (average 0.63 mg/kg), 4.3 mg/kg in the 75 ppm feeding level (average 3.7 mg/kg) and 5.6 mg/kg at the 150 ppm feeding level (average 5.2 mg/kg); in kidney it was 0.63 mg/kg at the 15 ppm feeding level (average 0.60 mg/kg), 4.7 mg/kg in the 75 ppm feeding level (average 3.8 mg/kg) and 6.5 mg/kg at the 150 ppm feeding level (average 5.7 mg/kg); in fat it was < 0.05 mg/kg at the 15 ppm feeding level, 0.23 mg/kg at the 75 ppm feeding level (average 0.15 mg/kg) and 0.26 mg/kg at the 150 ppm feeding level (average 0.21 mg/kg).

*Laying hens*

Groups of 15 mature white Leghorn hens were fed propiconazole at 7.5 (1 × rate), 37.5 (5 × rate) and 75 (10 × rate) ppm in the feed. Eggs were sampled on 0, 1, 3, 7, 10, 14, 17, 21 and 28 days and pooled by treatment and sampling day. Three birds per treatment group were sacrificed on days 7, 14, 21, and 28. Both total residues containing the 2,4-DCBA moiety and parent propiconazole *per se* were determined. No propiconazole residues (< 0.05 mg/kg) were found in the eggs or the tissue sample analysed regardless of feeding level.

In eggs, no 'total DCBA-residue' (< 0.05 mg/kg) was detectable at the 7.5 ppm feeding level. At the 37.5 ppm feeding level a maximum total residue of 0.18 mg/kg was found (average 0.11 mg/kg). At the 75 ppm feeding level a maximum total residue of 0.37 mg/kg was found (average 0.27 mg/kg).

In muscle, no 'total DCBA-residue' (< 0.05 mg/kg) was detectable at the 7.5 and 37.5 ppm feeding level. The highest average level in muscle was 0.07 mg/kg at the 75 ppm feeding level. In liver, no 'total DCBA-residue' (< 0.1 mg/kg) was detectable at the 7.5 ppm feeding level. The highest average level in liver was 0.16 mg/kg at the 37.5 ppm feeding level and 0.47 mg/kg at the 75 ppm feeding level. In fat, no 'total DCBA-residue' (< 0.05 mg/kg) was detectable at the 7.5 ppm feeding level. The highest average level in fat was 0.05 mg/kg at the 37.5 ppm feeding level and 0.07 mg/kg at the 75 ppm feeding level.

***Livestock dietary burden***

The Meeting estimated the dietary burden of propiconazole in farm animals on the basis of the diets listed in Annex 6 of the 2006 JMPR Report (OECD Feedstuffs Derived from Field Crops). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

*Estimated maximum and mean livestock dietary burdens*

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the animal diets from US-Canada, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report).

| | Animal dietary burden, propiconazole, ppm of dry matter diet | | | | | |
|---|---|---|---|---|---|---|
| | US-Canada | | EU | | Australia | |
| | max | mean | max | mean | max | mean |
| Beef cattle | 3.0 | 1.35 | 4.14 | 1.18 | 10.0 [1] | 3.35 [2] |
| Dairy cattle | 3.0 | 1.34 | 4.55 | 1.02 | 4.70 [3] | 1.96 [4] |
| Poultry - broiler | 0.07 | 0.07 | 0.06 | 0.06 | 0.06 | 0.06 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Poultry - layer | 0.07 | 0.07 | 1.98 [5] | 0.75 [6] | 0.05 | 0.05 |

1 Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat.

2 Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.

3 Highest maximum dairy cattle dietary burden suitable for MRL estimates for milk

4 Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

5 Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.

6 Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs.

### *Animal commodities, MRL estimation*

In a feeding study where lactating cows were dosed at 15 ppm dry feed, no parent propiconazole residues were detected in tissues and milk. Therefore no residues are to be expected at the maximum calculated dietary burden of 10 ppm feed for beef cattle and 4.7 ppm for dairy cattle.

In the feeding study where laying hens were dosed at 7.5 ppm feed, no parent propiconazole residues were detected in tissues and eggs. Therefore no residues are to be expected at the maximum calculated dietary burden of 1.98 ppm feed for poultry.

The Meeting estimated a maximum residue level of 0.01* mg/kg in mammalian meat, offal and milk. The Meeting estimated a maximum residue level of 0.01* mg/kg in poultry meat and eggs.

STMRs and HRs are derived from the measurements of total DCBA-containing residues. The mean calculated dietary burden for dairy cattle is 1.96 ppm. No 'total DCBA-residue' (< 0.01 mg/kg) was found in any of the milk samples at the 15 ppm feeding level. Therefore the Meeting estimated an STMR of 0.01 mg/kg in milk.

The highest calculated dietary burden for cattle is 10 ppm. In muscle and fat, no 'total DCBA-residue' (< 0.05 mg/kg) was detectable at the 15 ppm feeding level. The Meeting estimated STMRs and HRs of 0.05 mg/kg in muscle and fat.

In liver and kidney, at the 15 ppm feeding level the maximum total residues were 0.81 and 0.63 mg/kg respectively while the mean values were 0.63 and 0.60 mg/kg, respectively. Because of all the uncertainties involved in the calculation of the dietary burden based on total residue, the Meeting did not extrapolate down but decided to use an STMR of 0.6 mg/kg and an HR of 0.8 mg/kg for edible offal.

The highest calculated dietary burden for poultry is 2 ppm. In eggs, muscle and fat no 'total DCBA-residue' (< 0.05 mg/kg) was detectable at the 7.5 ppm feeding level. The Meeting estimated STMRs and HRs of 0.05 mg/kg in eggs, muscle and fat.

## DIETARY RISK ASSESSMENT

*Refer to general item on common triazole metabolites*.

### *Long term intake*

The evaluation of propiconazole has resulted in recommendations for MRLs and STMRs for raw and processed[1] commodities. Consumption data were available for 21 food commodities and were used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 0–2% of the maximum ADI of 0.07 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of propiconazole from uses that have been considered by the JMPR is unlikely to present a public health concern.

[1] Banana pulp

***Short-term intake***

The international estimated short-term intake (IESTI) for propiconazole was calculated for the food commodities (and their processing fractions) for which maximum residue levels, STMRs and HRs were estimated and for which consumption data were available. The results are shown in Annex 4.

The IESTI varied from 0–1 % of the ARfD (0.3 mg/kg bw) for the general population. The IESTI varied from 0–3% of the ARfD for children 6 years and below. The Meeting concluded that the short-term intake of residues of propiconazole from uses considered by the Meeting was unlikely to present a public health concern.

## 5.21 PYRIMETHANIL (226)

### TOXICOLOGY

Pyrimethanil is the approved ISO name for *N*-(4,6-dimethylpyrimidin-2-yl)aniline (IUPAC), also known as 4,6-dimethyl-*N*-phenyl-2-pyrimidinamine (CAS; CAS No. 53112-28-0). Pyrimethanil is an anilinopyrimidine fungicide that inhibits the secretion of fungal enzymes. It is a fungicide that is intended for the control of *Botrytis cinerea* on grapes and strawberries.

Pyrimethanil has not been evaluated previously by JMPR and was evaluated by the present Meeting at the request of the 39th Session of the CCPR.[43] All pivotal studies with pyrimethanil were certified as complying with GLP.

***Biochemical aspects***

In rats given radiolabelled pyrimethanil orally, about 80% of the administered dose was absorbed (for the lower dose, 11.8 mg/kg bw, and for the higher dose, 800 mg/kg bw) on the basis of urinary excretion (cage-wash included) in 96 h. About 72% of the dose was absorbed after pre-treatment with pyrimethanil at a dose of 10 mg/kg bw per day for 14-days, on the basis of urinary excretion (cage-wash included). Pyrimethanil was rapidly excreted at both doses, with more than 95% of the lower dose and 63–67% of the higher dose being excreted within the first 24 h. At the lower dose, plasma concentrations of radioactivity peaked at 1 h after dosing. At the higher dose, plasma concentrations of radioactivity initially peaked at 1 h after dosing. After an initial decline, a second peak of plasma radioactivity was observed at 5 h after dosing. The elimination half-life was about 4.8 h and 11.8 h at the lower and higher dose, respectively. Most of a radiolabelled dose was eliminated in the urine (79–81%) with the remainder in faeces (15–23%) at the lower and higher doses. No bioaccumulation of pyrimethanil was observed. A similar excretion pattern was observed in mice and dogs.

Systemically absorbed pyrimethanil was extensively metabolized. The major metabolites of pyrimethanil in the urine and faeces resulted from aromatic oxidation to form phenols in either or both rings and conjugation with glucuronic acid and sulfate. A minor pathway included oxidation of the methyl group on the pyrimidine ring to produce alcohol. The same six metabolites were identified in the urine and faeces. Unchanged pyrimethanil was isolated only in the faeces of males and females (0.3% and 2.1% of the faecal radioactivity at 10 and 1000 mg/kg bw, respectively). Distribution, metabolite profiles and excretion were essentially independent of pre-treatment with unlabelled compound and of sex.

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[43] Codex Alimentarius Commission. *Report of the 39th Session of the Codex Committee on Pesticide Residues, 7–12 May 2007, Beijing, China* (ALINORM07/30/24).

***Toxicological data***

Pyrimethanil has low acute toxicity when administered by oral, dermal or inhalation routes. The $LD_{50}$ in rats treated orally was 4149 mg/kg bw in males and 5971 mg/kg bw in females. The $LD_{50}$ in rats treated dermally was > 5000 mg/kg bw. The $LC_{50}$ in rats treated by inhalation (nose only) was > 1.98 mg/L (dust). Pyrimethanil was minimally irritating to the eyes of rabbits and not irritating to the skin of rabbits. Pyrimethanil was not a skin sensitizer as determined by Buehler and Magnusson & Kligman (maximization) tests in guinea-pigs. Clinical signs after oral administration consisted of reduced activity, reduced muscle tone, urogenital soiling, coolness to touch, which generally resolved within 1 day. There were no pathological findings.

In short-term and long-term studies in mice, rats and dogs, the major toxicological findings included decreased body weight and body-weight gains, often accompanied by decreased food consumption. The major target organs in mice and rats were liver and thyroid organs as evidenced by organ-weight changes, histopathological alterations, and clinical chemistry parameters (including increased cholesterol, and gamma-glutamyl transferase levels).

In a 90-day dietary study of toxicity in mice, decreased body-weight gains, slightly increased cholesterol and total bilirubin concentrations, an increase in liver weights and histopathological findings in thyroid, kidney and kidney stones were seen at 10000 ppm, equal to1864 mg/kg bw per day. Increases in thyroid weights were associated with exfoliative necrosis and pigmentation of follicular cells. The NOAEL was 900 ppm, equal to 139 mg/kg bw per day).

In a 90-day dietary study of toxicity in rats, decreased body weights, body-weight gains (28–33%) and decreased food consumptions, brown urine and increased urinary proteins, decreased organ weights (heart, adrenal, spleen, thymus), increased liver, kidney, gonad weights, and hypertrophy in liver and thyroid were seen at 8000 ppm, equal to 529.1 mg/kg bw per day, in both sexes. Thyroid effects in rats were manifested as increased incidence and severity of follicular epithelial hypertrophy and follicular brown pigment. The NOAEL was 800 ppm, equal to 54.5 mg/kg bw per day.

Gavage administration of pyrimethanil at > 600 mg/kg bw per day, the highest dose tested, induced vomiting in dogs within 4 h after dosing, suggesting local gastrointestinal tract irritation. This was not considered to be a toxicologically relevant effect for establishing an ARfD. In a 90-day study of toxicity in dogs, diarrhoea, salivation hypoactivity (within 3 h after dosing) and slightly decreased water consumption was observed at 800 mg/kg bw per day. The NOAEL was 80 mg/kg bw per day. In a 52-week study of toxicity in dogs, decreases in body-weight gains (6% and 17% in males and females, respectively), food consumption and feed-conversion efficiency, water consumption, reduced clotting time and increased count of neutrophils were observed at 250 mg/kg bw per day. The NOAEL was 30 mg/kg bw per day. The overall NOAEL was 80 mg/kg bw per day when results of 90-day and 1-year studies of toxicity in dogs were combined.

Pyrimethanil was not mutagenic in an adequate battery of studies of genotoxicity in vitro and in vivo.

The Meeting concluded that pyrimethanil is unlikely to be genotoxic.

The carcinogenicity potential of pyrimethanil was studied in mice and rats. In a study of carcinogenicity in mice, an increased incidence of urinary tract lesions including bladder distension and thickening were observed in male mice during the first weeks at 1600 ppm, equal to 210.9 mg/kg bw per day. The NOAEL was 160 ppm, equal to 20.0 mg/kg bw per day. There were no treatment-related neoplastic findings in the bioassay in mice.

In the study of carcinogenicity in rats, decreased body-weight gains, increased serum cholesterol and GGT levels, necropsy (dark thyroids), and histopathological findings (increases in centrilobular hepatocyte hypertrophy, and increased incidence of colloid depletion and hypertrophy of the follicular epithelium in thyroids) were observed at 5000 ppm, equal to 221 mg/kg bw per day). The NOAEL was 400 ppm, equal to 17 mg/kg bw per day. In rats given pyrimethanil, the thyroid was the only tissue to show a higher incidence of tumours than the controls. The number of benign follicular

cell adenomas in both sexes at the highest dose was higher than in concurrent controls and historical controls.

Special studies were conducted to evaluate the toxicity seen in the liver and thyroid. Mechanistic data suggest that thyroid hormone imbalance caused by increased thyroid hormone clearance by the induction of liver enzymes resulted in increased thyroid-stimulating hormone (TSH) activity and persistent stimulation of the thyroid. Such effects may lead to changes in thyroid homeostasis and alterations in morphology. Rodent thyroid tumours induced by this mode of action are not relevant to humans because rats are much more sensitive to thyroid hormone imbalance and elevations in TSH levels. Thus, the results of bioassays in rats do not raise a cancer concern for humans.

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

In a two-generation study of reproduction in rats, reproductive parameters were not affected at the highest dose tested (5000 ppm, equal to 293.4 mg/kg bw per day). The NOAEL for parental systemic toxicity was 400 ppm (equal to 23.1 mg/kg bw per day) on the basis of decreases in body-weight (11–13%) and body-weight gains (11–17%). Offspring toxicity was manifested as a decrease in pup body weights (17%) on postnatal day 21 at 5000 ppm, equal to 293.3 mg/kg bw per day. The NOAEL for offspring toxicity was 400 ppm, equal to 23.1 mg/kg bw per day. Pyrimethanil was not embryotoxic, fetotoxic or teratogenic at doses of up to 1000 mg/kg bw per day in rats. Pyrimethanil was not teratogenic in rabbits. Decreases in foetal body weights were observed at 300 mg/kg bw per day. These decreases in foetal weights (described as “runts” in the study report) were observed in the presence of severe maternal toxicity manifested as a significant decrease in body-weight gain and food consumption, reduced production and size of faecal pellets and death of three rabbits (moribund condition) at 300 mg/kg bw per day. The NOAEL for maternal toxicity in rabbits was 45 mg/kg bw per day and the NOAEL for developmental toxicity was 300 mg/kg bw per day, the highest dose tested.

The Meeting concluded that pyrimethanil is not teratogenic.

In a study of acute neurotoxicity in rats, transient functional observational battery (FOB) effects (gait, ataxia, decreased hind limb-grip strength in males, decreased body temperature) were observed at 1000 mg/kg bw on day 1. Total motor activity was also decreased by $\geq 52\%$ at 1000 mg/kg on day 1 in both sexes compared with controls. All animals appeared normal on days 8 and 15. As these transient and non-specific effects occurred at a high dose administered by gavage, the Meeting concluded that they were not an appropriate basis for establishing an ARfD. The NOAEL was 100 mg/kg bw. In a short-term study of neurotoxicity in rats, no treatment-related changes in mortality, clinical signs, FOB, motor activity, brain measurements (weight, length, and width), gross necropsy, or neurohistopathology were observed at doses of up to 6000 ppm, equal to 391.9 mg/kg bw per day. In females, an overall decrease in body-weight gain of 21% was observed at 6000 ppm, equal to 429.9 mg/kg bw per day. The NOAEL in females was 600 ppm, equal to 38.7 mg/kg bw per day, and 6000 ppm, equal to 319.9 mg/kg bw per day, in males.

The Meeting considered that pyrimethanil is not neurotoxic on the basis of the available data.

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

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

## Toxicological evaluation

The Meeting established an ADI of 0–0.2 mg/kg bw based on a NOAEL of 400 ppm (equal to 17.0 mg/kg bw per day) on the basis of increased cholesterol and GGT levels, and histopathological changes in the liver and thyroid at 5000 ppm (equal to 221 mg/kg bw per day) in a 2-year study in rats, and using a safety factor of 100. This ADI is supported a by two-generation study of reproduction in rats in which the NOAEL for parental systemic toxicity was 400 ppm, equal to 23.1 mg/kg bw per

day, on the basis of decreased body weights and body-weight gains at 5000 ppm, equal to 293.3 mg/kg bw per day. This ADI is also supported by the NOAEL of 160 ppm, equal to 20.0 mg/kg bw per day, in males in a 2-year study of toxicity in mice; this NOAEL was identified on the basis of increased incidences of urinary tract lesions including bladder distension and thickening seen at 1600 ppm, equal to 210.9 mg/kg bw per day.

The Meeting concluded that it was not necessary to establish an ARfD for pyrimethanil because no toxicity could be attributable to a single exposure in the available database, including a study of developmental toxicity in rats and rabbits. Observations in the study of acute toxicity in rats and clinical signs of toxicity in the pyrimethanil database appeared at doses of 640 mg/kg bw per day and greater were not considered to be relevant for establishing an ARfD since they were transient, non-specific and occurred at high doses. The Meeting also considered clinical signs (vomiting) in several studies of toxicity in dogs; these were considered to be local effects and therefore not relevant in establishing an ARfD.

A toxicological monograph was prepared.

***Levels relevant to risk assessment***

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | Eighty-week study of toxicity and carcinogenicity[a] | Toxicity | 160 ppm, equal to 20.0 mg/kg bw per day | 1600 ppm, equal to 210.9 mg/kg bw per day |
| | | Carcinogenicity | 1600 ppm, equal to 210.9 mg/kg bw per day[c] | — |
| Rat | Two-year study of toxicity and carcinogenicity[a] | Toxicity | 400 ppm, equal to 17 mg/kg bw per day | 5000 ppm, equal to 221 mg/kg bw per day |
| | | Carcinogenicity | 5000 ppm, equal to 221 mg/kg bw per day[c] | — |
| | Multigeneration study of reproductive toxicity[a] | Parental toxicity | 400 ppm, equal to 23.1 mg/kg bw per day | 5000 ppm, equal to 293.3 mg/kg bw per day |
| | | Offspring toxicity | 400 ppm equal to 23.1 mg/kg bw per day | 5000 ppm, equal to 293.3 mg/kg bw per day |
| | Developmental toxicity[b] | Maternal toxicity | 85 mg/kg bw per day | 1000 mg/kg bw per day |
| | | Embryo/fetotoxicity | 1000 mg/kg bw per day[c] | ____ |
| Rabbit | Developmental toxicity[b] | Maternal toxicity | 45 mg/kg bw per day | 300 mg/kg bw per day |
| | | Embryo/fetotoxicity | 45 mg/kg bw per day | 300 mg/kg bw per day |
| Dog | Ninety-day and 1-year study of toxicity[b] | Toxicity | 80 mg/kg bw per day | 400/250 mg/kg bw per day |

[a] Dietary administration.
[b] Gavage administration.
[c] Highest dose tested.

*Estimate of acceptable daily intake for humans*

0–0.2 mg/kg bw per day

*Estimate of acute reference dose*

Unnecessary

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

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

***Critical end-points for setting guidance values for exposure to pyrimethanil***

| | |
|---|---|
| *Absorption, distribution, excretion, and metabolism in mammals* | |
| Rate and extent of oral absorption | Rapid and nearly complete absorption; maximum plasma concentration reached by 1 h |
| Distribution | Widely distributed in tissues |
| Potential for accumulation | Low, no evidence of accumulation |
| Rate and extent of excretion | Approximately 97% (77% in urine and 20% in faeces) within 24 h at 11.8 mg/kg bw per day |
| Metabolism in animals | Extensive; metabolic pathways include aromatic oxidation to form phenols and conjugation with glucuronic acid and sulfate, minor pathway included oxidation of methyl group to produce alcohol |
| Toxicologically significant compounds in animals, plants and the environment | Pyrimethanil |
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | 4149 mg/kg bw for males |
| Rat, $LD_{50}$, dermal | > 5000 mg/kg bw |
| Rat, $LC_{50}$, inhalation | > 1.98 mg/L dust (4-h exposure, nose only) |
| Rabbit, skin irritation | Not an irritant |
| Rabbit, eye irritation | Minimal irritation |
| Guinea-pig, skin sensitization | Not a sensitizer (Magnussen & Kligman and Buehler test) |
| *Short-term studies of toxicity* | |
| Target/critical effect | Liver and thyroid hypertrophy |
| Lowest relevant oral NOAEL | 54.5 mg/kg bw per day (90-day-rat) |
| Lowest relevant dermal NOAEL | No data |
| Lowest relevant inhalation NOAEC | No data |
| *Genotoxicity* | |
| | No genotoxic potential |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | Liver and thyroid |
| Lowest relevant NOAEL | 17 mg/kg bw per day (2-year study of carcinogenicity in rats) |
| Carcinogenicity | No relevant carcinogenicity in mice and rats |
| *Reproductive toxicity* | |
| Reproduction target/critical effect | No toxicologically relevant effects |
| Lowest relevant reproductive NOAEL | 239.9 mg/kg bw per day (rats; highest dose tested) |

| | |
|---|---|
| Developmental target/critical effect | No developmental toxicity in rats and rabbits |
| Lowest relevant developmental NOAEL | 300 mg/kg bw per day (highest dose tested; rabbits) |
| *Neurotoxicity/delayed neurotoxicity* | |
| Acute neurotoxicity | No sign of specific neurotoxicity |
| *Mechanistic data* | |
| | Studies on hepatic clearance and thyroid hormone perturbations |
| *Medical data* | |
| | No significant adverse health effects reported |

***Summary***

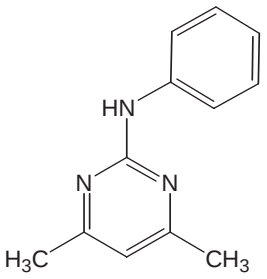
| | Value | Study | Safety factor |
|---|---|---|---|
| ADI | 0–0.2 mg/kg bw per day | Rats, 2-year study of toxicity | 100 |
| ARfD | Unnecessary | — | — |

## RESIDUE AND ANALYTICAL ASPECTS

Pyrimethanil is an anilinopyrimidine fungicide that inhibits the secretion of hydrolytic enzymes by the fungi that are needed during the infection process. Pyrimethanil blocks the ability of fungi to degrade and digest the plant tissues, thus stopping penetration and development of the disease.

At the 37th session of the CCPR (ALINORM 04/27/24), pyrimethanil was listed as a candidate for evaluation of a new compound by the 2007 JMPR.

***Chemical name:*** N-(4,6-dimethylpyrimidin-2-yl) aniline




### *Animal metabolism*

The Meeting received results of an animal metabolism study in lactating dairy cows. A lactating dairy cow was orally dosed for seven consecutive days with [$^{14}$C]pyrimethanil at a daily dose rate of 10 ppm in the diet, which corresponds to 0.4 mg/kg bw per day for a 600 kg cow. Residues in muscle and fat were too low to isolate and identify (0.02–0.04mg/kg total radioactive residue, TRR). The TRR in milk reached a plateau on about day 5 (0.07 mg/kg). No pyrimethanil was found in the milk from any day of the treatment. The major metabolite present in milk (64% TRR) was identified 2-anilino-4,6-dimethylpyrimidin-5-ol. Also present in milk were metabolites (27% TRR) characterized as highly polar.

Parent pyrimethanil was not found in kidney or liver. The TRR in kidney was identified as 46% 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine, 5% 2-anilino-4,6-dimethylpyrimidin-5-ol, and 7% 2-(4-hydroxyanilino)-4-hydroxymethyl-6-methylpyrimidine. Again, 42% TRR was characterized as

highly polar. No metabolite was identified in liver, but the TRR was characterized as 48% protein, 9% lipid, 7% ribonucleic acid and 6% sulfurated glycoamino-glycans.

Metabolism in the rat was quite similar to that of the cow. In the rat, only small amounts of the administered pyrimethanil were found in faeces and none was found in urine. The major metabolite in urine and faeces was 2-(4-hydroxyanalino)-4,6-dimethylpyrimidine and its sulfate, 13–52%. Other metabolites, generally < 10% of total extracted radioactivity in the excreta, were 2-anilino-4,6-dimethylpyrimidin-5-ol, 2-(4-hydroxyanilino)-4-hydroxymethyl-6-methylpyrimidine, 2-(4-hydroxyanilino)-6-dimethyl-pyrimidin-5-ol and 2-anilino-6-methylpyrimidine-4-methanol.

The Meeting concluded that pyrimethanil is very extensively metabolised in cattle, forming monohydroxy and dihydroxy derivatives in milk and kidney, and being incorporated into biological substrates in liver. No accumulation occurs in muscle or fat.

***Plant metabolism***

The Meeting received plant metabolism studies for the foliar application of [$^{14}$C]pyrimethanil, radiolabelled either on the aniline ring or at C-2 of the pyrimidine ring, for apples, grapes, carrots, tomato, leaf lettuce and strawberry. Generally the majority of the radioactivity was removed in a dichloromethane surface wash (56% grapes, 90% tomato). In all instances, the major component of the TRR was pyrimethanil (apple fruit, 70–77%; carrot root, 70–89%; tomato fruit, 95–96%; leaf lettuce 44%; strawberry fruits, no identifications made). Minor metabolites identified included hyrdoxylated and conjugated derivatives of pyrimethanil 2% TRR, and the ß-O-glucoside of 2-anilino-4-hydroxymethyl-6-hydroxymethylpyrimidine 3% TRR in apples; malonyl-β-O-glucoside of 2-anilino-hydroxymethyl-6-methylpyrimidine 6% TRR, and the β-glucoside of 2-anilino-4-hydroxymethyl-6-methylpyrimidine 6% TRR on carrot foliage (< 1% TRR each on carrot root); hydroxylated and conjugated compounds of pyrimethanil 6–28% TRR on tomato leaves; conjugate of 2-(4-hydroxyanilino)-4,6-dimethylpyridine 5% TRR and conjugate of 2-anilino-4,6-dimethylpyrimidin-5-ol, 8% TRR on leaf lettuce. Where both radiolabels were tested on the same crop, no significant differences were found in the compositions of the TRRs.

The Meeting concluded that the metabolism of pyrimethanil had been adequately defined via studies on three distinct crop types: fruit, root and leafy. Very little metabolism occurs, and the major portion of the residue is the parent pyrimethanil. The similarity in metabolic profiles between studies conducted with the radiolabel in either the aniline ring or the pyrimidine ring indicates no cleavage at the ring junction (aniline amino group). Minor metabolites identified are hydroxylated and conjugated derivatives of pyrimethanil, and are generally less than 10% TRR.

***Environmental fate***

The Meeting received studies on aqueous hydrolysis, aerobic and anaerobic degradation in soil, photolysis in water and residues in succeeding crops. Pyrimethanil is stable to hydrolysis in water at pH 5, 7 and 9 at 20 °C.

Under aerobic conditions, pyrimethanil slowly degraded in soil with about 80% remaining after 130 days. This was followed by a rapid decline in both extractable radioactivity and pyrimethanil levels. At higher soil treatment rates (500 mg/kg) differences were seen in the apparent degradation of the pyrimidine and aniline labels. With the pyrimidinyl label, about 60% of the extractable radioactivity was identified as 2-amino-4,6-dimethylpyrimidine. Cleavage of the aniline linkage is indicated.

Pyrimethanil does undergo photolytic degradation in water (sterile buffer) at pH 4 and pH 7 with estimated half-lives of 1 and 80 days, respectively. In a separate experiment using in sterile water containing humic acids, the half-life was reduced to less than 2 days at pH 7.

The Meeting concluded that pyrimethanil is stable under aqueous hydrolysis at pH 2–9 and is relatively stable on soil under aerobic conditions. It was also concluded that pyrimethanil is not stable in water under photolysis.

The uptake of 2-[$^{14}$C]pyrimidinyl-labelled pyrimethanil in *rotational crops* under confined conditions was reported to the Meeting. The pyrimethanil was applied to soil at a rate of 2.4 kg ai/ha. Substantial residues were found in crops planted 30 days after the treatment, 0.23 to 8.2 mg/kg TRR as pyrimethanil. Pyrimethanil comprised 1% (radish top) to 45% (wheat forage) of the TRR. The major identified metabolite (> 10% TRR) was 2-anilino-4-hydroxymethyl-6-methylprimidine in wheat forage and lettuce. Pyrimethanil was < 0.05 mg/kg in all rotational crops at the 30 day plantback interval, *except* for wheat grain (73 day, 0.41 mg/kg TRR, < 0.001 mg/kg pyrimethanil), forage (35 day immature, 1 mg/kg TRR, 1.1 mg/kg pyrimethanil), and straw (73 day, 8.2 mg/kg TRR, 0.22 mg/kg pyrimethanil). At a 130 day plantback interval, total residues in the crops declined to 0.01 to 0.03 mg/kg, with parent comprising 1–26% of the TRR. No extractable metabolite exceeded 10% TRR.

Three field rotational crop studies with a single crop, wheat, were conducted. Using a 30 day plantback interval following harvest of treated potatoes (3 applications at 0.8 kg ai/ha), residues of pyrimethanil and 2-anilino-4-hydroxymethyl-6-methylprimidine were below the limits of detection (< 0.012 mg/kg for pyrimethanil and < 0.015 mg/kg for 2-anilino-4-hydroxymethyl-6-methylprimidine), except for one wheat forage sample (< 0.05 mg/kg LOQ). The intervals from plantback to harvest were 128–232 days for forage and 190–316 days for straw.

The Meeting concluded that residues of pyrimethanil, in rotational crops planted 30 days or more after the final application of pyrimethanil to the primary crop, will most likely be below the LOQ (< 0.05 mg/kg), with the possible exception of forages and straws.

***Methods of Analysis***

The Meeting received information for analytical methods on the quantitative determination of pyrimethanil in a variety of crops and for the determination of pyrimethanil and metabolites 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine and 2-anilino-4,6-dimethylpyrimidine in bovine commodities.

The plant commodity methods consist of organic solvent extraction (acetone or methanol), clean-up, and analysis by either gas chromatography, with a mass spectrometer detector (GC/MS, m/z 198), or by high performance liquid chromatography with an ultraviolet detector (HPLC). The HPLC method was validated for apples, tomatoes, grapes, green beans, wine, grape juice, and grape pomace. The validated limits of quantitation (LOQs) are 0.05, 0.05, 0.02, 0.05, 0.02 and 0.02 mg/kg, respectively. The GC/MS method was validated for potatoes, carrots, tomatoes, green beans, lettuce, sweet peppers, strawberries, raspberries, apples, peaches, plums and oranges. A LOQ of 0.05 mg/kg was demonstrated for all of these commodities.

A radiovalidation study was conducted for the GC/MS procedure. Lettuce from the metabolism study was subjected to the extraction and analysis procedures of the method. Extraction efficiency was 97%.

A GC/MS method was described for the determination of pyrimethanil and metabolites 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine and 2-anilino-4,6-dimethylpyrimidin-5-ol in milk, fat, muscle, liver and kidney. The metabolites are converted to methylated derivatives prior to analysis. The demonstrated LOQs are 0.01 mg/kg for each of the analytes in milk and 0.05 mg/kg in each of the analytes in the various tissues. The independent laboratory validation encountered considerable problems and did not achieve acceptable validation for precision for pyrimethanil in meat at 0.05 mg/kg and overall at levels of 0.05 and 0.5 mg/kg. No radiovalidation of the method was reported.

Multiresidue methods (US FDA and DFG S 19) were reported for pyrimethanil in various plant commodities.

The Meeting concluded that adequate analytical methods exist for both data collection and enforcement purposes for pyrimethanil residues in plant commodities and for pyrimethanil, 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine (SN 614276), and 2-anilino-4,6-dimethylpyrimidin-5-ol (SN 614277) in milk and bovine tissues.

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

The Meeting received information on the stability of pyrimethanil in a variety of crop matrices, but no information on stability in livestock commodities. Pyrimethanil is stable (< 30% loss) in apples, grapes, tomatoes, lettuce, carrots, peas (dried), peaches and plums for at least 365 days when the commodities are stored frozen at about -20 °C.

The Meeting concluded that pyrimethanil is stable on frozen plant commodities for at least one year. No conclusions are possible on the stability of pyrimethanil or its metabolites in livestock commodities.

***Residue definition***

The major component of the residue on numerous plant commodities, from the foliar application of pyrimethanil, is pyrimethanil. Minor amounts of hydroxylated pyrimethanil derivatives are found, generally < 10% each of the total residue. The two analytical methods determine only pyrimethanil.

In livestock (cow) commodities, pyrimethanil is not found following oral administration of the compound. The major metabolites are 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine and 2-anilino-4,6-dimethylpyrimidin-5-ol, in kidney and milk, respectively. The analytical method provided determines the parent and the two named metabolites.

The log of the octanol/water partition coefficient is 2.8. In the cow feeding study, no pyrimethanil (< 0.05 mg/kg) was found in either fat or muscle at a 50 ppm feeding level. In the same study, the milk fat contained 0.031 mg/kg of 2-anilino-4,6-dimethylpyrimidin-5-ol, and the skim milk contained 0.064 mg/kg of 2-anilino-4,6-dimethylpyrimidin-5-ol and 0.015 mg/kg 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine. Thus, the total residue concentrated slightly in the non-fat portion of milk.

The Meeting concluded that the residue definition for both enforcement and dietary exposure considerations for plant commodities is pyrimethanil. The Meeting further concluded that the residue definition for both enforcement and dietary exposure considerations for milk is the sum of pyrimethanil and 2-anilino-4,6-dimethylpyrimidin-5-ol, expressed as pyrimethanil and for livestock tissues (excluding poultry) is the sum of pyrimethanil and 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine, expressed as pyrimethanil.

The Meeting also decided that pyrimethanil is not fat-soluble.

***Results of supervised trials on crops***

The Meeting received supervised trials data for the foliar application of pyrimethanil as a suspension concentrate formulation (SC) to a variety of fruit, vegetable, and nut crops. Additionally, supervised trial data reports were received for the post-harvest treatment of citrus, pome fruit and cherries.

*Citrus*

Various post-harvest treatments of lemon, orange, tangelo, tangerine, and grapefruit were reported for 45 trials from the USA. The USA GAP is: 204 g/L pyrimethanil + 263 g/L imazalil SC, dip or wash at 0.08 kg ai/hL or drench at 0.08 kg ai/hL or aqueous line spray at 0.1 kg ai/hL or wax line spray/storage and pack wax at 0.2 kg ai/hL, with a maximum of two treatments (of all types); 400 g/L pyrimethanil SC, dip or wash at 0.1 kg ai/hL or drench at 0.05 kg ai/hL or aqueous line spray at 0.2 kg ai/hL or wax line spray/storage and pack wax at 0.2 kg ai/hL, with a maximum of 2 or 3 treatments. Additionally, eight trials for the post-harvest treatment of oranges and mandarins in Spain were reported. No GAP was supplied, and the GAP of the USA was utilized. Thirty-three USA trials (9 × lemon, 10 × orange, 5 × grapefruit, 4 × tangelo and 4 × tangerines) were at maximum GAP. No Spanish trials matched the USA GAP.

Residues in the 32 trials in ranked order (median underlined) were: 1.2 (3), 1.4, 1.5 (2), 1.7 (2), 1.9, 2.1, 2.2, 2.3, 2.6, 2.7 (3), 2.8 (3), 2.9, 3.1, 3.3, 3.4 (2), 3.6, 4.1 (2), 4.2, 4.3, 4.6, 5.5,

5.8 mg/kg. No data were provided on the analysis of the edible portion (pulp). The Meeting estimated a maximum residue level of 7 mg/kg (Po) and an STMR of 2.8 mg/kg.

*Pome fruit*

Pre-harvest apple trials were reported from Europe and the USA. Pear trials were reported from the USA.

Two apple trials were conducted in Germany, two in northern France, and one in the UK. None of the trials matched the GAP of Belgium, 400 g/L SC, 0.45 kg ai/ha, 0.22 kg ai/hL, 5 applications, 28 day PHI. Two apple trials were conducted in southern France, two in Italy and one in Spain. One trial matched the GAP of Italy, 400 g/L SC, 0.04 kg ai/hL, 5 applications, 14 day PHI. The residue (Italy) was 0.56 mg/kg.

Twelve apple trials were conducted in the USA at the GAP, 400 g/L SC, 0.45 kg ai/ha, 1.8 kg ai/ha per season, 72 day PHI. The residues in ranked order are: < 0.05 (7), 0.06, 0.10, 0.12, 0.15, 0.16 mg/kg.

Six pear trials were conducted in the USA under the same USA GAP as apples. The residues found were: < 0.05 (6) mg/kg.

Post-harvest treatment of apples was reported from Spain and France and the USA. The GAP of Belgium is 200 g/L pyrimethanil + 200 g/L imazalil SC, spray or dip at 0.04 kg ai/hL, one treatment. Two of nine European trials were at the maximum GAP, and residues are 0.57 and 1.7 mg/kg. An additional trial matched the GAP of Chile, 3.78 mg/kg.

The GAP of the USA is dipping, drenching or aqueous line spray at 0.1 kg ai/hL or wax line spray at 0.2 kg ai/hL. Up to 2 treatments (of any combination) may be used. The GAP of Chile is identical, but only one treatment is permitted. Using the GAP of the USA, no trials are at GAP. Using the GAP of Chile, 10 of 32 trials were at maximum GAP. The residues in ranked order on apples were: 0.27, 0.28, 0.33, 0.39, 0.64, 0.70, 1.1 (2), 1.2, 1.5 mg/kg. Studies on the post-harvest treatment of pears in the USA were also reported. The GAPs of Chile and the USA are the same as for apples. Using the GAP of the USA, the residues of two trials are at GAP 1.01 and 1.18 mg/kg. Using the GAP of Chile, an additional eight of 35 trials were at the maximum GAP. Residues of pyrimethanil in ranked order were: 0.13, 0.18, 0.32, 0.45, 0.56, 0.86, 1.1 (2) mg/kg. Six post-harvest treatment trials on pears were reported from France, Spain and Belgium. No trials matched the GAPs of Chile or the USA. Two trials (BE, FR) matched the GAP of Belgium (200 g/L pyrimethanil + 200 g/L imazalil SC, spray or dip at 0.04 kg ai/hL, one treatment), and the residue values are 0.32 and 0.55 mg/kg.

Studies on the thermofogging post-harvest treatment of apples and pears in Europe was reported. However, the only GAP supplied (Chile) has yet to be approved by the national government. The Meeting noted that the maximum residue under the proposed GAP was 3.5 mg/kg on pears in Italy.

The residue values for post-harvest treatment of apples and pears in the USA and Europe at the GAPs of Chile or the USA are from the same population and may be combined. Residues in the 21 trials in ranked order (median underlined) were: 0.13, 0.18, 0.27, 0.28, 0.32, 0.33, 0.39, 0.45, 0.56, 0.64, 0.70, 0.86, 1.0, 1.1 (4), 1.2 (2), 1.5, 3.8 mg/kg. Based on the post-harvest treatments, the Meeting estimated an STMR of 0.70 mg/kg and a maximum residue level of 7 mg/kg for pome fruit (Po).

*Stone fruit*

Apricot, peach and plum trials were reported from the USA. The GAP is identical for all: 600 g/L SC, 0.8 kg ai/ha, 2.4 kg ai/ha/season, 2 day PHI. Five apricot trials were at maximum GAP: 0.61, 0.64, 1.2, 1.3, 1.7 mg/kg. Twelve peach trials were at maximum GAP: 0.38, 0.54, 0.94, 1.1, 1.2, 1.3 (3), 1.5, 1.6, 2.6 mg/kg. Eight plum trials were at maximum GAP: 0.05, 0.44, 0.58, 0.59 (2), 0.61, 0.62, 1.2 mg/kg.

The Meeting considered the apricot, peach and plum trials not to be from the same population. The Meeting estimated an STMR of 1.2 mg/kg and a maximum residue level of 3 mg/kg for apricots.

The meeting estimated an STMR of 1.3 mg/kg and a maximum residue level of 4 mg/kg for peaches and for nectarines. The Meeting estimated an STMR of 0.59 mg/kg and a maximum residue level of 2 mg/kg for plums.

Reports on the post-harvest treatment of peaches and plums in the USA were reported, but no GAP was provided.

Reports on the post-harvest treatment of cherries in Germany were reported. A GAP was supplied for Chile (400 g/L SC, dipping, 0.04 kg ai/hL, 1 application. Eight trials were at maximum GAP, and the values in ranked order were: 0.82, 1.0, 1.1, 1.2, 1.4(3), 2.5 mg/kg. The Meeting estimated an STMR of 1.3 mg/kg and a maximum residue level of 4 mg/kg (Po) for cherries.

*Berries and other small fruits*

Supervised trials for the foliar application of pyrimethanil to grapes were reported from the EU and the USA. Five trials in northern Europe (two from Germany and three from France) were evaluated against the GAP of France (400 g/L SC, 1 kg ai/ha, 1 application, 21 days PHI: 0.37, 0.44, 0.59, 0.97, 1.1 mg/kg); and 10 trials in southern Europe (2 Spain, 6 France, 2 Italy: 0.28, 0.48, 1.0, 1.5 mg/kg) were evaluated against the GAP of Spain (400 g/L SC, 0.08 kg ai/hL, one application, 21 day PHI). Nine trials were at maximum GAP, and the residues in ranked order were: 0.28, 0.37, 0.44, 0.48, 0.59, 0.92, 1.0, 1.1, 1.5 mg/kg.

Twelve trials were reported from the USA (USA GAP: 600 g/L SC, 0.8 ka ai/ha, 1.6 kg ai/ha/season, 7 day PHI). All trials were at maximum GAP, and the residues found were: 0.12, 0.44, 0.49, 0.64, 0.66, 0.71, 0.89, 1.2, 1.5, 1.6, 2.0, 2.5 mg/kg.

The Meeting considered the EU and USA trials to be from the same population and combined the results. Residues in the 21 trials in ranked order (median underlined) were: 0.12, 0.28, 0.37, 0.44(2), 0.48, 0.49, 0.59, 0.64, 0.66, 0.71, 0.89, 0.92, 1.0, 1.1, 1.2, 1.5 (2), 1.6, 2.0, 2.5 mg/kg. The Meeting estimated an STMR of 0.71 mg/kg and a maximum residue level of 4 mg/kg for grapes.

Eight trial were conducted on the foliar application of pyrimethanil to strawberries in the USA, where the GAP is 600 g/L SC, 0.8 kg ai/ha, 2.4 kg ai/ha/season, 1 day PHI. All trials were at maximum GAP, and the residues in ranked order (median underlined) were: 0.79, 0.93, 0.99, 1.1, 1.2, 1.3(2), and 2.3 mg/kg. The Meeting estimated an STMR of 1.2 mg/kg and a maximum residue level of 3 mg/kg for strawberries.

*Bananas*

Eleven trials each on the foliar treatment of bagged and unbagged bananas with pyrimethanil were reported from Costa Rica (3), Ecuador (3), Colombia (3) and Guatemala (2). The GAP is identical in all these countries: 600 g/L SC, 0.3 kg ai/ha, 6 applications, 0 day PHI (constant harvesting). All residues were below the LOQ except one bagged banana sample in Ecuador. The residues in ranked order were: < 0.05 (21), 0.09 mg/kg. All pulp samples were < 0.05 mg/kg. The Meeting estimated an STMR of 0.05 mg/kg and a maximum residue level of 0.1 mg/kg for bananas.

*Bulb Vegetables*

Nine trials were conducted on the foliar application of pyrimethanil to dry bulb onions and spring onions in the USA, where the GAP is: 600 g/L SC, 0.8 kg ai/ha, 2.4 kg ai/ha/season, 7 days PHI. All trials were conducted at maximum GAP, and the residues in ranked order on bulb onions were: < 0.05 (3), 0.075, 0.087, 0.095 mg/kg. Residues on green onions in ranked order are: 0.26, 0.38, 1.6 mg/kg. The Meeting estimated an STMR of 0.062 mg/kg and a maximum residue level of 0.2 mg/kg for bulb onions (dry). The Meeting estimated an STMR of 0.38 mg/kg and a maximum residue level of 3 mg/kg for spring onions.

*Fruiting Vegetables, Other than Cucurbits*

Sixteen trials were conducted on the foliar application of pyrimethanil to tomatoes in the USA, where the GAP is: 600 g/L SC, 0.3 kg ai/ha, 1.6kg ai/ha/season, 1 day PHI. All trials were at maximum

GAP, and the residues in ranked order were: 0.06, 0.07 (3), 0.10, 0.13, 0.14 (2), 0.15, 0.16, 0.17, 0.20, 0.22, 0.23, 0.35, 0.37 mg/kg.

Eight glasshouse trials were conducted in Europe, 2 in France and 6 in the Netherlands. The GAP of France is 400 g/L SC, 0.8 kg ai/ha, 2 applications, 3 day PHI. All trials were at maximum GAP, and the residues in ranked order (median underlined) were: 0.26 (2), 0.31 (2), 0.33 (2), 0.36 (2) mg/kg.

The USA and EU trials were not considered to be from the same population, and the Meeting used the EU trials to estimate an STMR of 0.32 mg/kg and a maximum residue level of 0.7 mg/kg for tomatoes.

*Leafy Vegetables*

Trials were conducted on both head lettuce and leaf lettuce in Europe. The GAP of France (400 g/L SC, 0.8 kg ai/ha, 2 applications, 21 day PHI) was applied to field trials in the UK (4), the Netherlands (1), France (North, 2), and Germany (2): < 0.05 (5), 0.11, 0.13, 0.28, 0.43 mg/kg. The GAP of Italy (400 g/L SC, 0.8 kg ai/ha, 2 applications, 14 day PHI) were applied to trials in Italy (2), Greece (1), France (South, 1), and Spain (1): 0.05, 0.14, 0.31, 0.77, 1.2 mg/kg. The residues in ranked order for head lettuce were: < 0.05 (5), 0.05, 0.11, 0.13, 0.14, 0.28, 0.31, 0.43, 0.77, 1.2 mg/kg.

Glasshouse trials were also reported from Europe (UK, Netherlands and Germany) for head lettuce. The GAP of Italy is 400 g/L SC, 0.8 kg ai/ha low volume, 0.08 kg ai/hL high volume, 2 applications, 14 day PHI. All trials were at maximum GAP, using high volume, and the residues in ranked order were: 0.37, 0.41, 0.49, 0.61, 0.85, 0.97 (2), 1.4, 1.6 mg/kg.

The Meeting considered the field and glasshouse trials in Europe not to be from the same population and used the glasshouse trials to estimate an STMR of 0.85 mg/kg and a maximum residue level of 3 mg/kg for head lettuce.

Field trials were also conducted in France, Greece, Italy and Portugal for leaf lettuce. Using the GAP of Italy (400 g/L SC, 0.8 kg ai/ha, 2 applications, with a 14 day PHI), three of the four trials were at maximum GAP. The residues in ranked order are 0.62, 0.68, 7.5 mg/kg. The Meeting considered three trials an insufficient number for the estimation of an STMR and a maximum residue level for leaf lettuce.

*Legume Vegetables*

Trials for the application of pyrimethanil to common beans (green beans) were reported from France (4) and Germany (3). The GAP in France is 400 g/L SC, 0.6 kg ai/ha, 1 application, 14 day PHI. Residues in ranked order were: < 0.05 (3), 0.05, 0.07, 0.08, 0.09.

Trials were also reported for the treatment of green beans in glasshouses in France (2), Italy (1), Spain (3), and Greece (2). The GAP of France is 400 g/L SC, 0.6 kg ai/ha, 14 day PHI. The residues in ranked order (median underlined) were: < 0.05, 0.12, 0.13, 0.20, 0.25, 0.28, 0.91, 1.9 mg/kg.

The Meeting considered the field and glasshouse trials on green beans not to be from the same population and used the glasshouse trials to estimate an STMR of 0.22 mg/kg and a maximum residue level of 3 mg/kg for common beans.

*Root and tuber vegetables*

Trials were reported on the foliar application of pyrimethanil to carrots in Brazil and Europe. Two trials in Brazil did not match the GAP of Brazil (300 g/L SC, 0.6 kg ai/ha, with a 14 day PHI). Nine trials, conducted in Northern Europe were received from the UK, France, Germany and the Netherlands. Eight trials were at the maximum GAP of France, i.e., 400 g/L SC, 0.8 kg ai/ha × 2 applications, with a 21 day PHI. Residues in rank order were: < 0.05 (2), 0.07 (2), 0.24, 0.28, 0.35, 0.36 mg/kg. Nine trials were conducted in Southern Europe in Spain, France, Greece, Italy and Portugal, and all were conducted at the maximum GAP of Italy (400 g/L SC, 0.8 kg ai/ha × 2

applications, with a 7 day PHI), residues in rank order were: < 0.05, 0.05, 0.08, 0.09, 0.14, 0.21, 0.33, 0.44, 0.54 mg/kg. Residues in the two areas were comparable, and the combined residue values in ranked order (median underlined) were: < 0.05 (3), 0.07 (3), 0.08, 0.09, 0.13, 0.14, 0.21, 0.24, 0.28, 0.33, 0.35, 0.36, 0.44, 0.54 mg/kg. The Meeting estimated an STMR of 0.14 mg/kg and a maximum residue level of 1 mg/kg for carrots.

Supervised trials for the foliar application of pyrimethanil to potatoes were reported from the USA where the GAP is 0.3 kg ai/ha (600 g/L SC), with a maximum of 1.6 kg ai/ha/season, with a 7 day PHI. The ranked order of residue values for 16 trials at maximum GAP was: < 0.05(16). The Meeting estimated an STMR of 0.05 mg/kg and a maximum residue level of 0.05* mg/kg for potatoes.

*Tree Nuts*

The Meeting received a report on supervised field trials on almonds in the USA, where the GAP is 0.8 kg ai/ha (600 g/L SC), with a maximum of 2.4 kg ai/ha/season, and a 30 day PHI. Six trials were at the maximum GAP and the ranked order of residue values on almond hulls were: 1.9, 2.4, 2.6, 2.7, 3.6, 9.2 mg/kg. The ranked order of values on almond nutmeat was: < 0.05(4), 0.06, 0.10 mg/kg. The Meeting estimated an STMR of 2.6 mg/kg and a maximum residue level of 12 mg/kg for almond hulls. The Meeting also estimated an STMR of 0.05 and a maximum residue level of 0.2 mg/kg for almond nutmeats.

*Legume Animal Feeds*

Thirteen supervised trials were carried out in Europe (France, Germany and the UK) for the foliar application of pyrimethanil to fodder peas (field peas, combining peas, protein peas). The GAP in France is 400 g/L SC, 0.6 kg ai/ha, with a 28 day PHI. Eleven trials were conducted at this maximum GAP, and the values in ranked order for dry seeds were: < 0.05 (4), 0.08, 0.09, 0.11, 0.12, 0.22, 0.25, 0.30 mg/kg. The highest residue was 0.30 mg/kg. The values in ranked order for straw were: < 0.05 (3), 0.15(2), 0.24, 0.28, 0.64, 0.66, 1.0 mg/kg. The highest residue was 1.0 mg/kg. The Meeting estimated an STMR of 0.09 mg/kg and a maximum residue level of 0.5 mg/kg for fodder pea seed (dry) and an STMR of 0.20 mg/kg and a maximum residue level of 3 mg/kg for fodder pea straw.

***Fate of residues during processing***

The Meeting received processing studies for oranges, apples, grapes, tomatoes, green beans and carrots. No information was supplied on the fate of radiolabelled pyrimethanil under general processing conditions.

Oranges with incurred residues of pyrimethanil from post-harvest treatment (2.9 mg/kg; 7.5 mg/kg) were processed by a commercial process into juice, dried pulp and citrus oil. The average processing factors were 0.01 for juice, 0.45 for pulp (dried), and 20 for citrus oil. Applying these factors to the STMR for citrus (2.8 mg/kg), the Meeting estimated the following STMR-Ps for citrus juice, citrus pulp (dried) and citrus oil, respectively: 0.028 mg/kg; 1.3 mg/kg; 56 mg/kg.

Apple processing studies were conducted in Germany (four trials) and the USA (one trial). The median processing factor for juice was 0.45 (n=5), the average factor for puree (n=2) was 0.37, and the factor for wet pomace (n=1) was 4.1. Applying these factors to the STMR, the Meeting estimated: STMR-P of 0.32 mg/kg for juice; a STMR-P of 2.9 mg/kg for wet apple pomace, and a STMR-P of 0.26 mg/kg for apple puree. The STMR-P and maximum residue limit estimates for dry apple pomace are 7.2 mg/kg (0.7 mg/kg × 4.1/0.40) and 40 mg/kg (3.8 mg/kg × 4.1/0.4), respectively, assuming that wet apple pomace contains 40% dry matter (*Table of OECD Feedstuffs Derived from Field Crop).*

A plum to prune processing study was conducted in the USA. The processing factor of 0.81 applied to the STMR of fresh plums (0.59 mg/kg) yields an STMR-P of 0.48 mg/kg for (dried) prunes.

Processing studies for the conversion of grapes to white wine was reported from Italy. The median processing factor (n=11, one value > 1 with all others < 1) was 0.48. Applying this factor to the STMR for grapes of 0.71 mg/kg yields a STMR-P of 0.34 mg/kg for wine.

A processing study for the conversion of grapes to juice and raisin (USA) was reported to the Meeting. The processing factors for juice, wet pomace and raisins are 0.7, 2.4 and 1.6, respectively (n=1). Applying these factors to the appropriate STMRs or HR levels the Meeting estimated the following: STMR-P for juice 0.50 mg/kg; STMR-P for wet grape pomace 1.7 mg/kg; STMR-P for grape raisins 1.1. The Meeting also estimated a maximum residue level of 5 mg/kg for grape raisins.

A tomato processing study was conducted in the USA in which tomatoes with incurred residues were processed by a commercial-type method into puree and paste, with processing factors (n=1) of 0.31 and 1.1, respectively. Applying these factors to the STMR for tomatoes (0.32 mg/kg) yields STMR-Ps of 0.10 mg/kg and 0.35 mg/kg for tomato puree and tomato paste, respectively.

Samples of green beans with incurred pyrimethanil residues (Europe) were processed utilizing commercial canning and freezing techniques (n=4). The median processing factor was 0.40 for canning and the median factor for freezing was 0.50. Using the freezing factor, the STMR-P for processed green (common) beans was estimated as 0.11 mg/kg (0.50 × 0.22).

Samples of carrot from four locations in Southern Europe with incurred residues of pyrimethanil were processed by commercial-type procedures into canned carrots, frozen carrots, carrot juice and carrot puree. The median processing factors (n=4) for canned carrots and frozen carrots were 0.59 and 0.45, respectively. The median processing factors (n=4) for juice and puree were 0.20 and 0.45, respectively. Using these factors, STMRs were derived for canned carrots, 0.083 mg/kg, and frozen carrots, 0.063 mg/kg; the average STMR for canned/frozen carrots, 0.073 mg/kg; carrot juice 0.028 mg/kg; and carrot puree 0.063 mg/kg. The HR for canned/frozen carrots is 0.28 mg/kg (the average of 0.59 × 0.54 mg/kg and 0.45 × 0.54 mg/kg).

*Livestock dietary burden*

Based on the *Table of OECD Feedstuffs Derived from Field Crops*, Annex 4, ENV/JM/MONO (2006) 32, also published as Annex 6 of the 2006 JMPR *Report*, the following feed items are potentially available: pea hay (straw), carrot culls, potato culls, pea seed, almond hulls, apple pomace (wet), citrus (dried pulp), potato (processed waste), grape pomace (wet). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

***Estimated maximum and mean livestock dietary burdens***

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

Poultry metabolism, poultry analytical methods and poultry feeding studies were not provided. The manufacturers noted a lack of poultry feed items. However, the *Table of OECD Feedstuffs Derived from Field Crop* indicates several poultry feeding items that potentially contain pyrimethanil residues: carrot culls (10% Australia); pea seed (20% US, EU), pea hay (straw) (10% Europe) and potato culls (10% Europe).

| | Animal dietary burden, pyrimethanil, ppm of dry matter diet | | | | | |
|---|---|---|---|---|---|---|
| | US-Canada | | EU | | Australia | |
| | max | mean | max | mean | max | mean |
| Beef cattle | 2.42 | 1.90 | 2.49 | 1.70 | 3.52[1] | 2.76 |
| Dairy cattle | 1.69 | 1.18 | 1.76 | 0.93 | 3.52[1] | 2.86[2] |

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

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

***Animal commodity maximum residue levels***

The Meeting received a report on the feeding of Holstein lactating cattle for 28 days with pyrimethanil. Dosing was made on a daily basis at the nominal dose rates of 1, 3, 10 and 50 ppm in the diet. The total residue (pyrimethanil + 2-(4-hydroxyanilino-4,6-dimethylpyrimidine + 2-anilino-4,6-dimethylpyrimidin-5-ol) reached a plateau in milk between day 15 and day 22 at the 50 ppm dosing level.

Residues in milk (final day 27) were below the LOQ (0.01 mg/kg per compound) at the 50 ppm dosing level for each of pyrimethanil and 2-(4-hydroxyanilino-4,6-dimethylpyrimidine. The metabolite 2-anilino-4,6-dimethylpyrimidin-5-ol had a maximum concentration of 0.088 mg/kg and an average concentration of 0.069 mg/kg in final milk from the 50 ppm dosing regimen. The same metabolite was found at a maximum concentration of 0.017 mg/kg in milk at the 10 ppm feeding level and was absent (< 0.01 mg/kg) at the 3 ppm dosing level.

A milk sample from day 27 was separated into skim milk and milk fat. The residue in skim milk consisted of 0.015 mg/kg 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine and 0.064 mg/kg 2-anilino-4,6-dimethylpyrimidin-5-ol. Milk fat contained 0.031 mg/kg 2-anilino-4,6-dimethylpyrimidin-5-ol. Thus, the residue is not fat soluble.

At the 50 ppm level, each of the parent and metabolite 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine was absent at the LOQ (0.05 mg/kg) in all tissues except kidney. Pyrimethanil was absent in kidney (at the 50 ppm feeding level). The average concentration of 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine in kidney was 0.63 mg/kg and the maximum residue was 0.88 mg/kg. At the 3 ppm feeding level, the average concentration of 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine in kidney was 0.066 mg/kg and the maximum was 0.08 mg/kg. At the 10 ppm feeding level, the average concentration of 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine in kidney was 0.12 mg/kg and the maximum was 0.13 mg/kg.

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

Pyrimethanil total residues[1], mg/kg

| Dietary burden (ppm)<br>Feeding level [ppm] | Milk | Muscle | Liver | Kidney | Fat |
|---|---|---|---|---|---|
| MRL | | | | | |
| | Mean | Highest | Highest | Highest | Highest |
| MRL, beef cattle<br>(3.52)<br>[3.0] | | (< 0.1)<br>[< 0.1] | (< 0.1)<br>[< 0.1] | (0.09[2] + < 0.05[3])<br>[0.08[2] + < 0.05[3]] | (< 0.1)<br>[< 0.1] |
| MRL, dairy cattle<br>(3.52)<br>[3.0] | (< 0.03)<br>[< 0.03[4]] | (< 0.1)<br>[< 0.1] | (< 0.1)<br>[< 0.1] | (0.09[2] + < 0.05[3])<br>[0.08[2] + < 0.05} | (< 0.1)<br>[< 0.1] |
| STMR | | | | | |
| | Mean | Mean | Mean | Mean | Mean |
| STMR beet cattle<br>(2.76)<br>[3.0] | | (< 0.1)<br>[< 0.1] | (< 0.1)<br>[< 0.1] | (0.058 [2]+ < 0.05[3])<br>[0.066[2] + < 0.05[3]] | (< 0.1)<br>[< 0.1] |
| STMR dairy cattle<br>(2.86)<br>[3.0] | (< 0.02)<br>[< 0.02] | (< 0.1)<br>[< 0.1] | (< 0.1)<br>[< 0.1] | (0.060 + < 0.05[3])<br>[0.066 [2]+ < 0.05[3]] | (< 0.1)<br>[< 0.1] |

[1]The LOQ is 0.05 for each of pyrimethanil and 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine, in animal tissues. The LOQ is 0.01 mg/kg for each of pyrimethanil, 2-anilino-4,6-dimethylpyrimidin-5-ol, 2-anilino-4,6-dimethylpyrimidin-5-ol in milk.
[2] 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine.
[3] Pyrimethanil. At a 50 ppm pyrimethanil feeding level, pyrimethanil was < 0.05 mg/kg. By extrapolation, at the 3 ppm feeding level, the pyrimethanil concentration would be < 0.005 mg/kg.
[4] pyrimethanil + 2-(4-hydroxyanilino-4,6-dimethylpyrimidine + 2-anilino-4,6-dimethylpyrimidin-5-ol. At a 50 ppm feeding level only 2-anilino-4,6-dimethylpyrimidin-5-ol had quantifiable residues.

The Meeting estimated an STMR of 0.01 mg/kg for milk and estimated a maximum residue level of 0.01 mg/kg for milk. The Meeting estimated STMRs of 0.0 mg/kg for each of meat and fat and maximum residue levels of 0.05 (*) mg/kg for meat. The Meeting estimated an STMR of 0.065 mg/kg for edible offal based on the STMR value for dairy cow kidney. The Meeting estimated a maximum residue level of 0.1 mg/kg for edible offal (mammalian) based on the value of kidney.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The International Estimated Daily Intakes (IEDI) of pyrimethanil based on the STMRs estimated for 32 commodities for the thirteen GEMS/Food cluster diets were in the range of 0% to 5% of the maximum ADI (0.2 mg/kg bw). The Meeting concluded that the long-term intake of residues of pyrimethanil resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

### *Short-term intake*

The 2007 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of pyrimethanil residues is unlikely to present a public health concern.

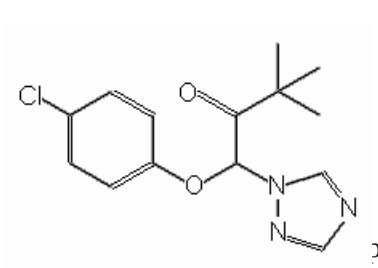
## 5.22 TRIADIMEFON (133)/ TRIADIMENOL (168)

## RESIDUE AND ANALYTICAL ASPECTS

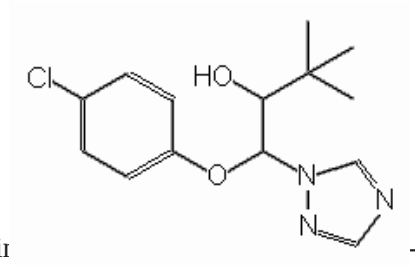
Triadimenol and triadimefon are related substances and follow the same metabolic pathways in all matrices investigated. Both compounds were evaluated by JMPR several times since 1978 and the last time in 2004, when an ADI of 0–0.03 mg/kg bw and an ARfD of 0.08 mg/kg bw were established for triadimefon and triadimenol each. The residue evaluation of the compounds was completed by the current Meeting within the periodic re-evaluation program.

Data submitted by the manufacturer and evaluated at this Meeting include metabolism in animal and plants, degradation in soil, residues in succeeding crops, analytical methods, supervised residue trials and processing studies.

The following appraisal includes the evaluation of the residue behaviour for both triadimefon and triadimenol.




ophenoxy)-3,3-dir




-butanone

Triadimenol β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol

Triadimefon and triadimenol are structurally related systemic fungicides with registered uses in many countries. Their main mode of action is inhibitors of ergosterol biosyntheses in fungi.

The following abbreviations are used for the metabolites discussed below:

| | |
|---|---|
| M02 | γ-(4-chlorophenoxy)-β-hydroxy-α,α-dimethyl-1H-1,2,4-triazole-1-butanoic acid |

| | |
|---|---|
| M09 | 1-(4-chlorophenoxy)-4-hydroxy-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone |
| M10 | β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol |

***Animal metabolism***

The Meeting received results of animal metabolism studies in rats, lactating goats and laying hens.

*Rats*

The metabolism of triadimefon and triadimenol in rats was evaluated within the toxicological assessment by the JMPR in 2004. In the following paragraphs the summaries of the metabolism for both active substances in rats from the 2004 Report are presented.

*Triadimefon*

In a study on the absorption, distribution, metabolism and excretion of triadimefon in rats, the dose given and pre-treatment with non-labelled triadimefon did not significantly affect excretion and metabolism patterns. In males about one-third and in females about two-thirds of the administered dose was excreted in the urine and vice versa in the faeces. After 96 h, 2% of the radioactivity remained in females and 9% in males, with the highest residue levels found in liver and kidneys.

The metabolism of triadimefon starts either by direct oxidation of a t-butyl methyl group to the hydroxy or the carboxy compound with subsequent glucuronidation, or these steps are preceded by reduction of the keto group of triadimefon to the putative intermediate, triadimenol. As a consequence, many of the metabolites found in triadimenol metabolism studies are also found with triadimefon. Nevertheless, the metabolism of triadimefon in rats provides a pathway for demethylation of the t-butyl group, which is not seen with triadimenol. This might be a result of the very low biotransformation of triadimenol via triadimefon as an intermediate.

*Triadimenol*

In rats, radiolabelled triadimenol is rapidly absorbed from the gastrointestinal tract, with radioactivity reaching peak concentrations in most tissues between 1 and 4 h after dosing. Up to 90% of the administered dose was excreted, with an elimination half-life for the radiolabel of between 6 and 15 h. Excretion was essentially complete within 96 h. After 5–6 days, radioactivity in most organs was below the limits of quantification.

Renal excretion accounted for up to 21% of the orally administered dose in males and up to 48% in females. The remainder was found in the faeces. In bile-duct cannulated males, 93% of the administered dose was recovered in the bile and only 6% in the urine, indicating that a substantial amount of the administered dose undergoes enterohepatic recycling. Radioactivity in expired air was negligible.

Triadimenol was extensively metabolized, predominantly by oxidation of one of the t-butyl methyl groups to give hydroxy or carboxy derivatives. The putative intermediate triadimefon has not been isolated. Cleavage of the chloro-phenyl and the triazole group was of minor significance. In the urine and faeces most of the metabolites were not conjugated, but in bile the metabolites were found to be extensively glucuronidated.

*Goats*

One lactating goat was dosed with [phenyl-UL-$^{14}$C]triadimefon at a rate of 2.6 mg ai/kg body weight for three consecutive days. Approximately 83% of the total radioactivity administered was excreted until sacrifice. At sacrifice the total radioactive residues (TRR) in the edible tissues were 3.5 mg/kg in kidney, 1.6 mg/kg in liver, 0.29 mg/kg in fat and 0.07 mg/kg in muscle. For milk TRR values of 0.027 to 0.029 mg/kg were detected.

Triadimefon was rapidly metabolised in the lactating goat. It was not identified in urine (0–24 h), kidney, liver and muscle and was present at low amounts in milk (1% of the TRR, < 0.001 mg/kg) and in fat (4% of the TRR, 0.013 mg/kg). Triadimenol as a metabolite of triadimefon was only identified in relevant amounts in the liver (20% of the TRR). In the fat, muscle and milk only minor amounts, 1–3% of the TRR, were detected. No triadimenol could be found in the kidney. The majority of the radioactive residues (57–82% of the TRR) in the tissues, milk and urine were identified as glucuronic acid or sulfate conjugates of the metabolites M02, M09 and M10. Unconjugated M02 accounted for 0.039–0.3 mg/kg or 4–17% of the TRR in kidney, liver, muscle, fat and urine. Unconjugated M09, unconjugated M10, and p-chlorophenol sulfate and triadimenol glucuronide were minor metabolites.

It was concluded that the metabolism of triadimefon in the goat is comparable to the metabolism in the rats.

*Hens*

A group of ten laying hens was fed with [phenyl-UL-$^{14}$C]triadimefon for three consecutive days at a dose rate of 2.5 mg/kg bw each. Data for the rate of absorption in hens was not presented in the study. At sacrifice the TRR in the edible tissues were 0.73 mg/kg in liver, 0.17 mg/kg in fat, 0.12 mg/kg in muscle and up to 0.09 mg/kg in whole eggs.

Triadimefon was rapidly metabolised in laying hens. It was not identified from liver and muscle and was detected in fat (0.038 mg/kg or 22% of the TRR) and in eggs (0.004–0.007 mg/kg or 4–9% of the TRR). For triadimenol in fat and eggs amounts of about 20% of the TRR were detected. In liver about 5% of the TRR was identified as triadimenol, while in muscle no detectable triadimenol residues could be found. As with the metabolism in lactating goats, a wide spectrum of metabolites could be identified, mostly in quantities below 10% of the TRR. The major metabolites detected were M10 in eggs (18% of the TRR; 0.016 mg/kg) and desmethyl-hydroxyl triadimenol (M31) in liver (13% TRR), muscle (24% TRR) and eggs (23% TRR).

The metabolism of triadimefon in hens is comparable to the metabolism in the rats.

***Plant metabolism***

The Meeting received plant metabolism studies for triadimefon following foliar application on grapes, barley and wheat. The metabolism of triadimenol was investigated after foliar application on grapes, wheat and sugar beets as well as after seed dressing application on barley and wheat. For tomatoes and cucumbers additional studies comparing foliar and soil treatment with triadimenol were conducted.

In each crop tested, triadimefon and triadimenol were found to be the main residue remaining (grapes: 55–61% TRR, barley: 30–36% TRR, wheat: 52–62% TRR, sugar beets: 26–73% TRR, cucumber: 61–98% TRR and tomato: 76–92% TRR). After foliar application, triadimefon was metabolised to triadimenol. After 14 to 28 days a higher level of triadimenol compared to triadimefon could be observed (except for tomatoes). The investigation of the metabolic pattern showed that the biochemical transformation processes involved consist mainly of conjugation reactions of the parent compound and to a lesser degree in the partial oxidation of the tertiary butyl group of the parent. The product M10 from this oxidation is also subsequently conjugated. A complete cleavage of the triadimenol and triadimefon chemical structure leading to formation of 4-chlorophenol and 1,2,4-triazole is observed in soil only. The 1,2,4-triazole is taken up by the plant via the roots and is conjugated through an enzymatic reaction with serine to form triazole alanine. Subsequent transformation into triazole hydroxy propanoic acid and triazole acetic acid also occurred. The other part of the active substance molecule, 4-chlorophenol, is conjugated in the plants into 4-chlorophenyl-glucoside.

***Environmental fate in soil***

The Meeting received information on the environmental fate of triadimefon and triadimenol in soil, including aerobic soil metabolism, field dissipation and crop rotational studies. In addition soil photolysis studies with both triadimefon and triadimenol were submitted.

The soil photolysis studies conducted with [phenyl-UL-$^{14}$C]triadimefon and [phenyl-UL-$^{14}$C]triadimenol showed that no accelerated degradation occurs under irradiation. Metabolites were identified only in small amounts mainly consisting of 1,2,4-triazole and p-chlorophenol.

In a confined rotational crop study, soil was treated with [phenyl-UL-$^{14}$C] triadimenol or [triazole-3,5-$^{14}$C] triadimenol. Over three subsequent years wheat was treated with a seed dressing application (corresponding to 0.038 kg ai/100 kg seeds) followed by an additional foliar treatment with identically labelled triadimefon at a rate of 0.25 kg ai/ha. In this part of the study most of the radioactivity identified in grain consisted of triazole alanine (approximately 50% of the TRR, 0.46-1.06 mg/kg) and triazole -lactic-acid (approximately 30% of the TRR, 0.24–0.72 mg/kg). Triazole acetic acid was only identified in traces at the level of the LOQ (< 0.01 mg/kg). No parent triadimefon or triadimenol could be identified in the harvested wheat grain.

In the fourth year wheat and sugar beets were planted as rotational crops without additional treatment. In grain, low amounts of TRR (0.03 mg/kg) could be identified for the phenyl-labelled substance. For the triazole-label, higher residues of 1.18 mg/kg were detected in grain. In grain most of the residues identified consisted of triazole-alanine (0.33 mg/kg) and triazole -lactic-acid (0.12 mg/kg). The rest of the plant showed comparable amounts of radioactivity between both labels ranging from 0.33 mg/kg (roots) up to 0.78 mg/kg (straw). The identification of the total radioactivity showed no triadimefon/triadimenol-residues above 0.01 mg/kg in grain. In straw and glumes triadimefon and triadimenol residues were detected at levels up to 0.14 mg/kg.

In four field rotational crop studies barley was treated with a dose rate of unlabelled triadimenol corresponding to 0.125–0.25 kg ai/ha. Fourteen days after harvesting the barley, turnips and oilseed rape were planted and grown to maturity. In barley no residues above the LOQ of 0.1 mg/kg were detected in all matrices. Further identification of the residues was not performed. The sampling of the rotational crops was conducted 103 (turnips) to 167 days (oilseed rape) after planting. In all plant matrices and in analysed soil layers of 0–10 cm and 10–20 cm no triadimenol residues above the LOQ of 0.1 mg/kg were detected.

The Meeting concluded that residues from the use of triadimefon and triadimenol under field conditions are unlikely to occur in concentrations above 0.01 mg/kg in succeeding crops.

***Methods of analysis***

The Meeting received description and validation data for analytical methods of triadimefon and triadimenol in plant and animal matrices. All enforcement methods are based on variations of the DFG S19 multi-residue method. The samples are extracted using acetone/water (2:1 v/v) and a subsequent clean-up by GPC or solid phase extraction. The residue of triadimefon and triadimenol is analysed on a gas chromatograph using an alkali-flame ionisation detector (GC-FID(N)). A mass selective detector (MS) is used for confirmatory purposes. MS detection was done at a mass charge ratio of m/z=208 for triadimefon and m/z=168 for triadimenol. For plant matrices an LOQ of 0.05 mg/kg for all commodities was achieved.

In animal matrices the enforcement methods follow the same scheme as in plant matrices and are validated with an LOQ of 0.01 mg/kg for all commodities. The recovery rates were within the range of 70% to 110%.

In addition the Meeting received information on various specialised methods. Most methods include only minor variations in the extraction technique according to the matrix analysed. In these specialised methods LOQs for triadimefon and triadimenol in plant matrices of 0.01 mg/kg up to 0.05 mg/kg were achieved with recovery rates above 70%. For animal matrices specialised methods to measure the total residues of all compounds containing 4-chlorophenyl were reported. Treatment with hypochloric acid resulted in complete transformation of the residues into 4-chlorophenyl. After

derivatisation with 2,4-dinitrofluorobenzene the total amount of residue is detected using GC-MS techniques.

The Meeting concluded that adequate analytical methods exist for the determination of triadimefon and triadimenol in crops and livestock commodities both for data collection and MRL enforcement purposes.

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

The Meeting received information on the stability of triadimefon and triadimenol in wheat, grapes, tomatoes, apples, cucumbers, pineapples, sugar beets, asparagus and coffee beans. All samples were stored at -20 °C for up to 24 months. Animal matrices eggs, fat, liver, muscle and milk were fortified with triadimenol and stored from 432 days (milk) up to 873 days (liver). In all matrices the remaining triadimenol and triadimefon levels were above 70% of the initial fortification concentrations.

The Meeting concluded that triadimefon and triadimenol are stable in plant and animal matrices under frozen storage conditions.

***Residue definition***

The plant metabolism studies with triadimefon used in foliar applications and triadimenol in seed dressing and foliar treatments show that a large part of the remaining residues consist of triadimefon and/or triadimenol. Further metabolites were identified in all matrices, but the amounts were much lower than for the active substances.

In rotational crop studies on barley and in a 3 year study on wheat with radiolabelled triadimefon and triadimenol, the triazole-metabolites triazole-alanine, triazole-lactate and triazole-acetic-acid were found in the grain. Triazole acetic acid was detected in traces at the limit of detection only. Triazole-alanine (0.33 mg/kg) and triazole-lactic-acid (0.12 mg/kg) formed the major part of the total radioactivity found in grain.

The available analytical enforcement methods for plant matrices determine triadimefon and triadimenol. Additional methods for M09 and M10 are available.

The Meeting concluded that the residue definition for plant matrices is the sum of triadimefon and triadimenol for both enforcement and risk assessment purposes.

The animal metabolism studies conducted with triadimefon show a substantial degradation for triadimefon as well as for triadimenol. Although the metabolic pathways for goats and hens are similar, significant residues of triadimefon and triadimenol were only detected in goat liver and poultry fat and eggs. Goat muscle, fat and milk as well as poultry liver contained both active substances of between 1 and 5% of the TRR. In goat kidney and poultry muscle no triadimefon or triadimenol was detected. The main part of the radioactivity found consisted of glucuronide- and sulphate-conjugates of M09 and M10. No 1,2,4-triazole metabolites were identified in the animal matrices.

The available analytical enforcement methods determine triadimefon and triadimenol. Specialised methods for the measurement of all structures containing 4-chlorophenyl were submitted.

4-chlorophenyl is a common moiety in various pesticides and has a broad spectrum of other uses. The Meeting decided that the total residue based on 4-chlorophenyl would not be a specific marker for triadimefon and triadimenol and concluded the residue definition for enforcement of animal matrices to be the sum of triadimefon and triadimenol. As triadimefon and triadimenol were identified as the only compounds of toxicological concern, the Meeting concluded that the sum of triadimefon and triadimenol is also an appropriate residue definition for risk assessment purposes for animal matrices.

The log of the octanol/water partition coefficients for triadimefon and triadimenol are 3.1 and 3.3 respectively. In ruminant as well as in poultry metabolism studies, fat tissues contained much higher triadimefon and triadimenol residues than the corresponding muscle matrices (muscle: non-detect up to 0.001 mg/kg, fat: 0.009 mg/kg up to 0.043 mg/kg).

Based on the above, the Meeting agreed:

*Definition of the residue in plant and animal commodities (for the estimation of dietary intake and for compliance with MRLs):* sum of triadimefon and triadimenol

The Meeting also decided that triadimefon and triadimenol are fat-soluble.

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

The Meeting received supervised trials data for the application of triadimefon and triadimenol to a variety of crops, including apples, grapes, strawberries, currants, bananas, pineapples, sugar beets, cucumbers, courgettes, melons, watermelons, tomatoes, peppers, artichoke, barley, oats, wheat, oats and coffee.

*Apples*

Field trials involving triadimenol foliar applications to apples are available from France, Germany, Israel, Italy, New Zealand, Spain, South Africa and United Kingdom.

In Cyprus, triadimenol may be applied at a rate of 0.0025 kg ai/hL with a PHI of 14 days. The residues from trials in Germany and the United Kingdom, matching this GAP, were: < 0.05, 0.06(3) and 0.08(3) mg/kg (sum of triadimefon and triadimenol) in apples.

The GAP of Algeria consists of an application rate of 0.005 kg ai/hL and a PHI of 7 days. From one supervised residue trial on apples matching this GAP from Israel the corresponding residue in was 0.4 mg/kg (sum of triadimefon and triadimenol).

From Italy a GAP using 0.004 kg ai/hL and a PHI of 14 days was reported. The corresponding residues from trials in France, Germany, Italy, Spain and United Kingdom matching this GAP were < 0.05(3), 0.05, 0.06, 0.06, 0.07, 0.09, 0.1, 0.11, 0.14 and 0.18 mg/kg (sum of triadimefon and triadimenol) in apples.

The GAP of Spain for apples is 0.013 kg ai/hL with a PHI of 15 days. The residues from trials in Germany matching this GAP were: < 0.05(3), 0.07, 0.09 and 0.1 mg/kg (sum of triadimefon and triadimenol) in apples.

The Meeting decided to pool the data from all GAPs with the exception of the supervised trial data from Israel, as the PHI of 7 days results in a different residue population and insufficient data for an evaluation of that GAP was submitted. The combined residue trial results (n=25) for apples from the other GAPs in ranked order (median underlined) were: < 0.05(7), 0.05, 0.06(5), 0.07, 0.07, 0.08(3), 0.09, 0.09, 0.1, 0.1, 0.11, 0.14 and 0.18 mg/kg (sum of triadimefon and triadimenol).

The Meeting estimated an STMR value of 0.06 mg/kg, an HR value of 0.18 mg/kg and a maximum residue level of 0.3 mg/kg for the sum of triadimefon and triadimenol in apples.

The Meeting withdraws both of its previous recommendations for triadimefon and for triadimenol in pome fruits of 0.5 mg/kg.

*Grapes*

Field trials involving the foliar applications of triadimefon and triadimenol to grapes were made available from Australia, Chile, France, Germany, Greece, Italy, South Africa, Spain, Turkey and the United States. In several supervised residue trials the analysed commodities referred to grape bunches rather than grape berries. The Meeting decided that both results may be used for the evaluation as the differences are likely to have a negligible influence on the residue levels.

*Triadimefon*

The GAP of Croatia and Macedonia consists of an application rate of 0.0025 kg ai/hL with a PHI of 35 days. Residues from trials in Germany matching this GAP were: < 0.04, < 0.04, 0.09, 0.25 and 3.2 mg/kg (sum of triadimefon and triadimenol).

The GAP of Russia is 0.005 kg ai/hL with a PHI of 30 days. The residues from trials in Germany matching this GAP were: 0.21, 0.33, 0.43 and 0.69 mg/kg (sum of triadimefon and triadimenol).

The GAP of Belarus and Kazakhstan is 0.0075 kg ai/hL with a PHI of 30 days. The residues from trials in Germany matching this GAP were: < 0.05, < 0.05, 0.07, 0.07, 0.09, 0.15, 0.15, 0.28 and 1.7 mg/kg (sum of triadimefon and triadimenol).

The maximum GAP in South Africa is 0.095 kg ai/ha (0.0063 kg ai/hL) with a PHI of 7 days. The residues from trials in South Africa matching this GAP were: 0.11, 0.27, 0.36 and 0.37 mg/kg (sum of triadimefon and triadimenol).

The GAP of the United States is 0.21 kg ai/ha with a PHI of 14 days. The residues from trials in the US matching this GAP were: 0.03, 0.08, 0.15, 0.27, 0.59, 0.78 and 0.78 mg/kg (sum of triadimefon and triadimenol).

*Triadimenol*

The GAP of Australia and New Zealand is 0.0025 kg ai/hL with a PHI of 7 days. The residues from trials in Australia and New Zealand matching this GAP were: < 0.05, 0.05, 0.16, 0.18 and 0.6 mg/kg (sum of triadimefon and triadimenol).

The GAP of Bulgaria is 0.0025 kg ai/hL with a PHI of 30 days. The residues from trials in Germany matching this GAP were: < 0.05(3), 0.06, 0.07, 0.09, 0.1 and 0.15 mg/kg (sum of triadimefon and triadimenol).

The GAP of Cyprus and Italy is 0.005 kg ai/hL with a PHI of 14 days. The residues from trials in Germany, Italy, Israel and Turkey matching this GAP were: 0.04, 0.05, 0.06, 0.07, 0.08 and 0.6 mg/kg (sum of triadimefon and triadimenol).

The GAP of France is 0.075 kg ai/ha with a PHI of 15 days. The residues from trials in France, Greece and Spain matching this GAP were: < 0.02, < 0.02, 0.04, 0.04, 0.1 and 0.11 mg/kg (sum of triadimefon and triadimenol).

The GAP of Georgia, Moldova and the Ukraine is 0.013 kg ai/ha with a PHI of 30 days. The residue from one trial in France matching this GAP was < 0.02 mg/kg (sum of triadimefon and triadimenol).

The GAP of South Africa is 0.12 kg ai/ha (0.0075 kg ai/hL) with a PHI of 14 days. The residues from trials in South Africa matching this GAP were: 0.17, 0.3, 0.32, 0.46, 0.54, 0.58, 0.8, 1.4 and 1.9 mg/kg (sum of triadimefon and triadimenol).

The Meeting decided to pool the data from all GAPs for triadimefon and triadimenol in grapes. The combined results (n=63) in grapes in ranked order (median underlined) were: < 0.02(3), 0.03, < 0.04, < 0.04, 0.04(3), < 0.05(5), 0.05, 0.05, 0.06, 0.06, 0.07(4), 0.08, 0.08, 0.09(3), 0.1, 0.1, 0.11, 0.11, <u>0.15</u>(4), 0.16, 0.17, 0.18, 0.21, 0.25, 0.27, 0.27, 0.28, 0.3, 0.32, 0.33, 0.36, 0.37, 0.43, 0.46, 0.54, 0.58, 0.59, 0.6, 0.6, 0.69, 0.78, 0.78, 0.8, 1.4, 1.7, 1.9 and 3.2 mg/kg (sum of triadimefon and triadimenol).

Based on the uses of both triadimefon and triadimenol the Meeting estimated an STMR value of 0.15 mg/kg, an HR value of 3.2 mg/kg and estimated a maximum residue level of 5 mg/kg for the sum of triadimefon and triadimenol in grapes. The IESTI calculation indicates that the consumption of grapes at the HR level of 6.1 mg/kg will lead to an exceedance of the ARfD, but no residue data was available from an alternative GAP to estimate a lower HR value.

The Meeting withdraws both of its previous recommendations for triadimefon in grapes of 0.5 mg/kg and for triadimenol in grapes of 2 mg/kg.

*Strawberries*

Field trials involving foliar application of triadimenol to glasshouse <u>strawberries</u> are available from Belgium, Italy, Netherlands and Spain.

A GAP for protected strawberries is only available from Spain, with a spray concentration of 0.013 kg ai/hL and a PHI of 3 days. The residues from trials matching this GAP in ranked order (median underlined) were: 0.08, 0.09, 0.13, 0.24, 0.26, 0.27, 0.29, 0.3, 0.31 and 0.41 mg/kg (sum of triadimefon and triadimenol).

Based on the use of triadimenol in strawberries the Meeting estimated an STMR value of 0.265 mg/kg, a HR value of 0.41 mg/kg and a maximum residue level of 0.7 mg/kg for the sum of triadimefon and triadimenol in strawberries.

The Meeting withdraws both of its previous recommendations for triadimefon and triadimenol in strawberries of 0.1 mg/kg each.

*Currants*

Field trials involving foliar application of triadimenol to currants were reported from Germany, Netherlands and the United Kingdom.

The GAP from the Netherlands consists of a spray concentration of 0.0075 kg ai/hL with a PHI of 14 days. The residues from trials matching the GAP of the Netherlands in ranked order (median underlined) were: 0.06, 0.07, 0.19, 0.19, 0.23, 0.23, 0.25, 0.39 and 0.49 mg/kg (sum of triadimefon and triadimenol).

Based on the use of triadimenol in currants the Meeting estimated an STMR value of 0.23 mg/kg, a HR value of 0.49 mg/kg and a maximum residue level of 0.7 mg/kg for the sum of triadimefon and triadimenol in currants.

The Meeting withdraws both of its previous recommendations for triadimefon in currants (black, red) of 0.2 mg/kg and for triadimenol in currants (red, black) of 0.5 mg/kg.

*Raspberries*

GAP information for the use of triadimefon and triadimenol on raspberries was reported from Belarus and the United States. Field trials involving either active substance were not made available.

The Meeting withdraws both of its previous recommendations for triadimefon in raspberries (red, black) of 1 mg/kg and for triadimenol in raspberries (red, black) of 0.5 mg/kg.

*Bananas*

Field trials involving triadimenol in foliar application to bananas are available from Cameroon, Costa Rica, Honduras, Ivory Coast, Martinique, Puerto Rico, South Africa and the USA.

The GAP of Cuba is 0.14 kg ai/ha with a PHI of 7 days. The residues from trials matching this GAP were: < 0.01, < 0.04, < 0.04, 0.1, 0.11, 0.18 and 0.8 mg/kg (sum of triadimefon and triadimenol) in whole bananas (unbagged). In banana pulp (unbagged) the corresponding residues were: < 0.01, < 0.04, < 0.04, 0.09, 0.14, 0.18 and 0.3 mg/kg (sum of triadimefon and triadimenol).

The GAP of Brazil is 0.1 kg ai/ha with a PHI of 14 days. The residues from trials matching this GAP were: < 0.01, < 0.02, < 0.05, < 0.05, 0.08 and 0.14 mg/kg (sum of triadimefon and triadimenol) in whole bananas (unbagged). In banana pulp (unbagged) the corresponding residues were: < 0.01, < 0.02, < 0.05, < 0.05, 0.07 and 0.14 mg/kg (sum of triadimefon and triadimenol).

Field trials involving triadimenol a broadcast application of granules in bananas are available from Cameroon, Costa Rica, Ecuador and Ivory Coast.

Maximum GAPs in Guatemala and Nicaragua reported for the spreading of triadimenol in bananas is 1 kg ai/ha with a PHI of 21 days. The residues from trials matching the GAP were: < 0.01, 0.01, < 0.04, < 0.04, 0.04 and < 0.05 mg/kg (sum of triadimefon and triadimenol) in whole bananas. In banana pulp the corresponding residues were: < 0.01(4), 0.02, < 0.04, < 0.04, 0.04 and < 0.05 mg/kg (sum of triadimefon and triadimenol).

The Meeting decided to pool the data from all GAPs for foliar and spreading applications of triadimenol in bananas. The combined results (n=19) in whole banana fruits were: < 0.01(3), 0.01, < 0.02, < 0.04(4), 0.04, < 0.05(3), 0.08, 0.1, 0.11, 0.14, 0.18 and 0.8 mg/kg (sum of triadimefon and triadimenol). In banana pulp the combined result (n=22) were: < 0.01(6), < 0.02, 0.02, < 0.04(4), 0.04, < 0.05(3), 0.07, 0.09, 0.14, 0.14, 0.18 and 0.3 mg/kg (sum of triadimefon and triadimenol).

Based on the residue data on banana pulp the Meeting estimated an STMR value of 0.04 mg/kg and an HR of 0.3 mg/kg (sum of triadimefon and triadimenol) for bananas.

Based on the use of triadimenol in bananas the Meeting estimated a maximum residue level of 1 mg/kg for the sum of triadimefon and triadimenol in bananas.

The Meeting withdraws its previous recommendation for triadimenol in bananas of 0.2 mg/kg.

*Mango*

GAP information for the use of triadimefon and triadimenol on mangoes was reported from a number of countries. Field trials involving either active substance were not made available.

The Meeting withdraws both of its previous recommendations for triadimefon and triadimenol in mangoes of 0.05* mg/kg.

*Pineapples*

Field trials involving triadimefon in post-harvest dipping of pineapples are available from Ivory Coast and the United States.

The GAP of the Ivory Coast consists of a dipping solution of 0.01 kg ai/hL with a 0 days PHI. The residues from trials matching this GAP were: 0.1, 0.46 and 0.56 mg/kg (sum of triadimefon and triadimenol) in whole fruits. In pineapple pulp the corresponding residues were: < 0.06, < 0.06 and 0.1 mg/kg (sum of triadimefon and triadimenol).

The GAP of Costa Rica, Dominican Republic, Guatemala and Honduras involves a dipping solution of 0.05 kg ai/hL with a 0 days PHI. The residues from trials matching the GAP were: 0.82, 0.85, 0.97, 1.1, 1.1, 1.4, 1.5, 1.6, 1.6, 1.8, 2.0, 2.2 and 2.5 mg/kg (sum of triadimefon and triadimenol) in whole fruits. In pineapple pulp the corresponding residues in ranked order (median underlined) were: 0.07, 0.07, 0.09, 0.1, 0.1, 0.11, 0.11, 0.13, 0.13, 0.14, 0.14, 0.15 and 0.16 mg/kg (sum of triadimefon and triadimenol).

Based on the residue data on pineapple pulp complying with the GAPs of Costa Rica, the Dominican Republic, Guatemala and Honduras the Meeting estimated an STMR value of 0.11 mg/kg and a HR of 0.16 mg/kg (sum of triadimefon and triadimenol) for pineapples.

Based on the use of triadimenol in pineapples according to the GAPs from Costa Rica, the Dominican Republic, Guatemala and Honduras the Meeting estimated a maximum residue level of 5 mg/kg (Po) for the sum of triadimefon and triadimenol in pineapples.

The Meeting withdraws both of its previous recommendations for triadimefon in pineapples of 2 mg/kg and for triadimenol in pineapples of 1 mg/kg.

*Sugar beets*

Field trials involving triadimenol in sugar beets are available from Germany and the United Kingdom. The GAP of the United Kingdom for sugar beets consists of an application rate of 0.13 kg ai/ha with a PHI of 14 days. The residues from trials matching the GAP were: < 0.05(9) mg/kg (sum of triadimefon and triadimenol) in sugar beet roots.

Based on the use of triadimenol in sugar beets the Meeting estimated an STMR value of 0.05 mg/kg, an HR value of 0.05 mg/kg and a maximum residue level of 0.05* mg/kg for the sum of triadimefon and triadimenol in sugar beets.

The Meeting withdraws both of its previous recommendations for triadimefon and triadimenol in sugar beets of 0.1* mg/kg.

*Onion, spring and welsh*

GAP information for the use of triadimefon and triadimenol on onions was reported from Columbia, Japan and Korea. Field trials involving either active substance were not made available.

The Meeting withdraws all of its previous recommendations for triadimefon and triadimenol in onion, spring and onion, welsh of 0.05* mg/kg.

*Fruiting vegetables, cucurbits*

*Triadimefon*

Field trials involving triadimefon in cucumbers are available from Australia, Japan and the United States. The GAP of New Zealand for the field application on cucumbers is 0.005 kg ai/hL with a PHI of 1 day. The residue from one trial matching the GAP was < 0.2 mg/kg (sum of triadimefon and triadimenol) in fruits.

Maximum GAP in Mexico, for the field application of triadimefon to cucumbers consists of an application rate of up to 0.13 kg ai/ha with a PHI of 0 days. The residues from United States trials matching this GAP were < 0.02, 0.02, 0.02, 0.03(3), 0.04, 0.04, 0.05, 0.08(3) and 0.11 mg/kg (sum of triadimefon and triadimenol) in fruits.

The GAP of the Ukraine for the application of triadimefon in glasshouse cucumbers is 0.0025 kg ai/hL with a PHI of 5 days. The residues from Japanese trials matching this GAP were: < 0.02, < 0.02 mg/kg (sum of triadimefon and triadimenol) in fruits.

Field trials involving triadimefon in melons are available from Mexico and the United States. Maximum GAP in Mexico for triadimefon in field application to melons is 0.15 kg ai/ha with a PHI of 0 days. The residues from trials in Mexico and the United States, matching this GAP, were: < 0.02, < 0.02, 0.03, 0.04, 0.05(4), 0.11, 0.11, 0.13 and 0.13 mg/kg (sum of triadimefon and triadimenol) in whole fruits. In melon pulp the corresponding residues were: 0.03, 0.03, 0.04 and 0.04 mg/kg (sum of triadimefon and triadimenol).

*Triadimenol*

Field trials involving triadimenol in cucumbers were made available from Australia and the United States. GAP in Australia involves the field application to cucumbers at a rate of 0.1 kg ai/ha with a PHI of 1 day. The residue from one trial matching this GAP was 0.1 mg/kg (sum of triadimefon and triadimenol) in fruits.

The GAP of Greece and Italy for triadimenol applications to glasshouse cucumbers is 0.005 kg ai/hL with a PHI of 14 to15 days. The residues from trials matching this GAP were: < 0.05(4) mg/kg (sum of triadimefon and triadimenol) in fruits.

In Spain the GAP for the application of triadimenol to glasshouse cucumbers is 0.013 kg ai/hL with a PHI of 3 days. The residues from trials matching this GAP were: < 0.05(5), 0.06, 0.06, 0.07, 0.08, 0.1, 0.1 and 0.12 mg/kg (sum of triadimefon and triadimenol) in the fruits.

Field trials involving triadimenol in melons are available from France, Greece, Italy and Spain. GAP from Morocco for triadimenol in field application to melons is 0.075 kg ai/hL with a PHI of 3 days. The residues from trials matching the GAP were: < 0.05(6), 0.05 and 0.06 mg/kg (sum of triadimefon and triadimenol) in whole fruits. In melon pulp the corresponding residues were < 0.05 and < 0.05 mg/kg (sum of triadimefon and triadimenol). GAP in Spain for triadimenol applications to glasshouse melons is 0.013 kg ai/hL with a PHI of 3 days. The residues from trials in Italy matching this GAP were: < 0.05(3), and 0.13 mg/kg (sum of triadimefon and triadimenol) in whole fruits. In melon pulp the corresponding residues were < 0.05(4) mg/kg (sum of triadimefon and triadimenol).

Field trials involving triadimenol in watermelons were made available from Italy and Spain. The GAP of Greece for the field application of triadimenol to watermelons is 0.005 kg ai/hL with a

PHI of 15 days. The residue from one trial in Italy matching this GAP was < 0.05 mg/kg (sum of triadimefon and triadimenol) in whole fruits. In melon pulp the corresponding residue was < 0.05 mg/kg (sum of triadimefon and triadimenol).

The GAP for triadimenol in glasshouse application to watermelons (as a GAP for cucurbits) was reported from Chile at 0.13 kg ai/ha with a PHI of 3 days. The residues from glasshouse trials in Italy matching this GAP were < 0.05(3), 0.05 mg/kg (sum of triadimefon and triadimenol) in whole fruits. In melon pulp the corresponding residues were < 0.05(4) mg/kg (sum of triadimefon and triadimenol).

The Meeting decided to pool the data for triadimefon and triadimenol from all GAPs for field and glasshouse application in cucurbits. The combined results (n=61) in whole fruits were: < 0.02(5), 0.02, 0.02, 0.03(4), 0.04(3), < 0.05(22), 0.05(7), 0.06(3), 0.07, 0.08(4), 0.1(3), 0.11(3), 0.12, 0.13(3) and < 0.2 mg/kg (sum of triadimefon and triadimenol). In the edible part (whole fruit or pulp) the combined results (n=48) in ranked order (median underlined) were: < 0.02(3), 0.02, 0.02, 0.03(5), 0.04(4), < 0.<u>05</u>(20), 0.05, 0.06, 0.06, 0.07, 0.08(4), 0.1(3), 0.11, 0.12 and < 0.2 mg/kg (sum of triadimefon and triadimenol).

The Meeting estimated an STMR value of 0.05 mg/kg and a HR of 0.2 mg/kg (sum of triadimefon and triadimenol) for cucurbits, including melons and watermelons.

Based on the uses of both triadimefon and triadimenol the Meeting estimated a maximum residue level of 0.2 mg/kg for the sum of triadimefon and triadimenol in fruiting vegetables, cucurbits.

The Meeting withdraws both of its previous recommendations for triadimefon in fruiting vegetables, cucurbits of 0.1 mg/kg and for triadimenol in fruiting vegetables, cucurbits of 2 mg/kg.

*Fruiting vegetables other than cucurbits, except fungi and except sweet corn*

*Triadimefon*

Field trials involving triadimefon in <u>peppers</u> were made available from Australia. The GAP of Japan for the field application of triadimefon to peppers is 0.005 kg ai/hL with a PHI of 1 day. The residues from trials matching the GAP were < 0.05 and < 0.05 mg/kg (sum of triadimefon and triadimenol).

Field trials involving triadimefon in <u>tomatoes</u> were made available from Australia and Japan. GAP in Belarus for triadimefon in glasshouse application to tomatoes is 0.5 kg ai/ha with a PHI of 10 days. The residues from Japanese trials matching the GAP were: 0.14, 0.15, 0.43 and 0.68 mg/kg (sum of triadimefon and triadimenol).

*Triadimenol*

Field trials involving triadimenol in <u>peppers</u> were made available from Germany and Spain. The GAP of Spain for triadimenol in glasshouse peppers is 0.013 kg ai/hL with a PHI of 3 day. The residues from trials matching the GAP were 0.11, 0.16, 0.21, 0.21, 0.23, 0.33, 0.33 and 0.38 mg/kg (sum of triadimefon and triadimenol).

Field trials involving triadimenol in <u>tomatoes</u> are available from Belgium, France, Germany, Greece, Italy and Spain.

The GAP of Italy for the field application of triadimenol to tomatoes is 0.005 kg ai/hL with a PHI of 14 days. The residues from trials matching this GAP were < 0.05(4) mg/kg (sum of triadimefon and triadimenol).

The GAP of Morocco and Spain for the field application of triadimenol to tomatoes is 0.013 kg ai/hL with a PHI of 3 days. The residues from trials matching this GAP were < 0.05 and 0.21 mg/kg (sum of triadimefon and triadimenol).

The GAP of Italy for the glasshouse application of triadimenol to tomatoes is 0.005 kg ai/hL with a PHI of 14 days. The residues from trials matching this GAP were < 0.05(3) and 0.08 mg/kg (sum of triadimefon and triadimenol).

The GAP of Morocco and Spain for triadimenol in glasshouse application to tomatoes is 0.013 kg ai/hL with a PHI of 3 days. The residues from trials matching this GAP were 0.05, 0.05, 0.11, 0.12, 0.13, 0.15, 0.25, 0.27 and 0.29 mg/kg (sum of triadimefon and triadimenol).

The Meeting decided to pool the data for triadimefon and triadimenol from all GAPs for application in glasshouse for tomatoes and peppers. The combined results (n=25) in whole fruits in ranked order (median underlined) were: < 0.05(3), 0.05, 0.05, 0.08, 0.11, 0.11, 0.12, 0.13, 0.14, 0.15, 0.15, 0.16, 0.21, 0.21, 0.23, 0.25, 0.27, 0.29, 0.33, 0.33, 0.38, 0.43 and 0.68 mg/kg (sum of triadimefon and triadimenol).

The Meeting estimated an STMR value of 0.15 mg/kg and an HR of 0.68 mg/kg (sum of triadimefon and triadimenol) for fruiting vegetables other than cucurbits, except fungi and except sweet corn.

Based on the uses of both triadimefon and triadimenol the Meeting estimated a maximum residue level of 1 mg/kg for the sum of triadimefon and triadimenol in fruiting vegetables other than cucurbits, except fungi and except sweet corn.

The Meeting withdraws its previous recommendations for the triadimefon in peppers, sweet of 0.1 mg/kg and for tomatoes of 0.2 mg/kg. The Meeting also withdraws its previous recommendations for triadimenol in peppers, sweet of 0.1 mg/kg and in tomatoes of 0.5 mg/kg.

*Peas and chick-peas*

GAP information for the use of triadimefon and triadimenol on peas and chick-peas were reported from various countries. Field trials involving either active substance were not made available.

The Meeting withdraws its previous recommendations for triadimefon in chick-peas and in peas of 0.05(*) mg/kg. The Meeting also withdraws its previous recommendations for triadimenol in chick-peas of 0.05(*) mg/kg and in peas of 0.1 mg/kg.

*Artichoke, globe*

Field trials involving triadimenol in globe artichoke were made available from Italy and Spain. The GAP of Cyprus for triadimenol in globe artichoke consists of an application rate of 0.01 kg ai/hL with a PHI of 5 days. The residues from trials matching this GAP in ranked order (median underlined) were: < 0.05, 0.08, 0.08, 0.13, 0.14, 0.15, 0.16, 0.24 and 0.55 mg/kg (sum of triadimefon and triadimenol).

The Meeting estimated an STMR value of 0.14 mg/kg and an HR of 0.55 mg/kg (sum of triadimefon and triadimenol) for globe artichokes.

Based on the use of triadimenol the Meeting estimated a maximum residue level of 0.7 mg/kg for the sum of triadimefon and triadimenol in globe artichokes.

The Meeting withdraws its previous recommendation for triadimenol in artichoke, globe of 1 mg/kg.

*Cereals, except maize and rice*

*Triadimefon*

Field trials involving triadimefon in barley are available from Germany. The GAP of the Ukraine for the foliar application of triadimefon to barley is 0.13 kg ai/ha with a PHI of 30 days. The residues from trials matching this GAP were < 0.1(9) mg/kg (sum of triadimefon and triadimenol) for barley grain.

Field trials involving triadimefon in oats are available from Germany. The GAP of Belarus, Kazakhstan and Russia for the foliar application of triadimefon to oats is 0.18 kg ai/ha with a PHI of 30 days. The residues from trials matching this GAP were < 0.1(3) mg/kg (sum of triadimefon and triadimenol) for oats grain.

Field trials involving triadimefon in rye are available from Germany. The GAP of Macedonia for the foliar application of triadimefon to rye is 0.25 kg ai/ha with a PHI of 35 days. The residues from trials matching this GAP were < 0.08 and < 0.08 mg/kg (sum of triadimefon and triadimenol) for rye grain.

The GAP of Croatia for the foliar application of triadimefon to rye is 0.1 kg ai/ha with a PHI of 42 days. The residues from trials matching this GAP were: < 0.1(3), 0.15 mg/kg (sum of triadimefon and triadimenol) for rye grain.

Field trials involving triadimefon in wheat are available from Germany. GAP in Croatia for the foliar application of triadimefon to wheat is 0.1 kg ai/ha with a PHI of 42 days. The residues from trials matching this GAP were < 0.1(8) mg/kg (sum of triadimefon and triadimenol) for wheat grain.

*Triadimenol*

Field trials involving triadimenol in barley are available from Australia, Canada, France, Germany, Italy, Spain, United Kingdom and the United States.

The GAP of Cyprus and Poland for the foliar application of triadimenol to barley is 0.13 kg ai/ha with a PHI of 35 days. The residues from trials matching this GAP were: < 0.05(14), 0.05, 0.06, 0.06, 0.08, 0.09, 0.09 and < 0.1(11) mg/kg (sum of triadimefon and triadimenol) for barley grain.

The GAP for the use of triadimenol as a seed dressing in barley were reported from Australia and New Zealand with application rates of 0.022 kg/100 kg seed. The residue from one trial matching this GAP was < 0.04 mg/kg (sum of triadimefon and triadimenol) for barley grain.

The GAP for the use of triadimenol as seed dressing in barley from Austria, Brazil, Germany, Ireland, Mexico and the United Kingdom is 0.04 kg ai/100 kg/seeds with no specified PHI. The residues from trials matching this GAP in ranked order (median underlined) were: < 0.01(15), 0.02, < 0.05(10) and < 0.1(19) mg/kg (sum of triadimefon and triadimenol) for barley grain.

Field trials involving triadimenol in oats were available from Brazil, Canada, Germany and the United States. The GAP of the United Kingdom for the foliar application of triadimenol to oats is 0.13 kg ai/ha with growth dependent PHI. The residues from trials matching this GAP were: 0.1, 0.11 and 0.12 mg/kg (sum of triadimefon and triadimenol) for oat grain.

The GAP for the use of triadimenol as a seed dressing in oats in Australia is 0.015 kg ai/100 kg seeds with no specified PHI. The residues from trials matching this GAP were < 0.1(4) mg/kg (sum of triadimefon and triadimenol) for oat grain.

GAP in oats for the use of triadimenol as a seed dressing was reported from Brazil, Ireland and the United Kingdom with application rates of 0.04 kg ai/100 kg seed. The residues from trials matching this GAP were: < 0.01(14) and < 0.1(3) mg/kg (sum of triadimefon and triadimenol) for oats grain.

The GAP of Finland for the use of triadimenol as a seed dressing in barley is 0.045 kg ai/100 kg seeds with no specified PHI. The residues from trials matching the GAP were: < 0.01 and < 0.01 mg/kg (sum of triadimefon and triadimenol) for oat grain.

Field trials involving triadimenol in rye were available from Canada, Germany and the United States. The GAP of Poland and the United Kingdom for the foliar application of triadimenol to rye is 0.13 kg ai/ha with a PHI of 35 days. The residues from trials matching this GAP were: < 0.05 and < 0.1(4) mg/kg (sum of triadimefon and triadimenol) for rye grain.

The GAP for Ireland and the United Kingdom, for the use of triadimenol as a seed dressing in rye is 0.038 kg ai/100 kg seed. The residues from trials matching this GAP were: < 0.01(6), 0.02 and < 0.1(4) mg/kg (sum of triadimefon and triadimenol) for rye grain.

Field trials involving triadimenol in wheat are available from Australia, Brazil, Canada, France, Germany, Hungary, Italy, New Zealand, Spain and the United States. The GAP of Australia, Bulgaria, Cyprus, Italy and Poland for the foliar application of triadimenol to wheat is 0.13 kg ai/ha

with PHI of 28 to 35 days. The residues from trials matching this GAP were: < 0.01, < 0.02, 0.03, < 0.05(39), 0.05 and 0.06 mg/kg (sum of triadimefon and triadimenol) for wheat grain.

In France GAP for the foliar application of triadimenol to wheat is 0.075 kg ai/ha with a PHI of 28 days. The residue from one trial matching this GAP was < 0.05 mg/kg (sum of triadimefon and triadimenol) for wheat grain.

The GAP for the use of triadimenol as a seed dressing in wheat were reported from Brazil, Ireland and the United Kingdom with application rates of 0.038 kg ai/100 kg seed. The residues from trials matching this GAP were: < 0.01(20), 0.03 and < 0.05(11) mg/kg (sum of triadimefon and triadimenol) for wheat grain.

The Meeting decided to pool the residue data for triadimefon and triadimenol from all foliar and seed dressing GAPs for cereals. The combined results (n=220) in grain in ranked order (median underlined) were: < 0.01(58), < 0.02, 0.02, 0.02, 0.03, < 0.05(76), 0.05, 0.05, 0.06(3), < 0.08, < 0.08, 0.08, 0.09, 0.09, < 0.1(68), 0.1, 0.11, 0.12 and 0.15 mg/kg (sum of triadimefon and triadimenol).

The Meeting estimated an STMR value of 0.05 mg/kg and a highest residue of 0.15 mg/kg (sum of triadimefon and triadimenol) for cereal grain, except maize and rice.

Based in the uses of both triadimefon and triadimenol the Meeting estimated a maximum residue level of 0.2 mg/kg for the sum of triadimefon and triadimenol in cereals, except maize and rice.

The Meeting withdraws its previous recommendations for the triadimefon in barley of 0.5 mg/kg and in oats, rye and wheat of 0.1 mg/kg. The Meeting also withdraws its previous recommendations for triadimenol in barley of 0.5 mg/kg and in oats, rye and wheat of 0.2 mg/kg.

*Coffee beans*

Field trials involving triadimenol in coffee were available from Brazil, El Salvador, Guatemala, Mexico and South Africa. The GAP of Brazil and Costa Rica for the foliar application of triadimenol to coffee is 0.25 kg ai/ha with a PHI of 30 days. The residues from trials matching this GAP were: 0.04, 0.04, < 0.05(3), 0.06, 0.07, < 0.1 and 0.4 mg/kg (sum of triadimefon and triadimenol) for coffee beans.

The GAP of Brazil for the broadcast application with incorporation of a granular formulation of triadimenol to coffee is 1.1 kg ai/ha with a PHI of 90 days. The residues from trials matching the GAP were: < 0.01, 0.01, < 0.05(3), 0.06, 0.07, 0.07 and 0.09 mg/kg (sum of triadimefon and triadimenol) for coffee beans.

A further GAP of Brazil, for the broadcast application of a granular formulation of triadimenol to coffee is 1.95 kg ai/ha with a PHI of 90 days. The residues from trials matching this GAP were: < 0.05 and 0.05 mg/kg (sum of triadimefon and triadimenol) for coffee beans.

The Meeting decided to pool the data for coffee beans from trials with foliar and spreading applications. The combined results (n=20) in ranked order (median underlined) were: < 0.01, 0.01, 0.04, 0.04, < 0.05(7), 0.05, 0.06, 0.06, 0.07(3), 0.09, < 0.1 and 0.4 mg/kg (sum of triadimefon and triadimenol) for coffee beans.

The Meeting estimated an STMR value of 0.05 mg/kg (sum of triadimefon and triadimenol) for coffee beans.

Based on the use of triadimenol the Meeting estimated a maximum residue level of 0.5 mg/kg for the sum of triadimefon and triadimenol in coffee beans.

The Meeting withdraws both of its previous recommendations for triadimefon in coffee beans of 0.05(*) mg/kg and for triadimenol in coffee beans of 0.1* mg/kg.

*Hops, dry*

GAP information for the use of triadimefon and triadimenol on hops was reported from Croatia and Spain. Field trials involving either active substance were not made available to the Meeting.

The Meeting withdraws both of its previous recommendations for triadimefon in hops, dry of 10 mg/kg and for triadimenol in hops, dry of 5 mg/kg.

*Sugar beet leaves or tops*

Field trials involving the application of triadimenol to sugar beets were available from Germany and the United Kingdom. The GAP of the United Kingdom for sugar beets is 0.13 kg ai/ha with a PHI of 14 days. The residues from trials matching this GAP in ranked order (median underlined) were: 0.08, 0.1, 0.1, 0.14, 0.14, 0.18, 0.19, 0.19 and 0.42 mg/kg (sum of triadimefon and triadimenol) in sugar beet leaves.

The Meeting estimated an STMR value of 0.14 mg/kg and a highest residue of 0.42 mg/kg for the sum of triadimefon and triadimenol in sugar beet leaves (fresh weight).

*Fodder beets*

GAP information for the use of triadimefon or triadimenol in fodder beets was not submitted.

The Meeting withdraws both of its previous recommendations for triadimefon and triadimenol in fodder beets of 0.05(*) mg/kg.

*Cereal forage, except maize forage*

*Triadimefon*

Field trials involving triadimefon in barley were available from Germany. The GAP of the Ukraine for the foliar application of triadimefon to barley is 0.13 kg ai/ha. The residues from trials matching this GAP were: 1.4, 1.7(4), 1.9, 1.9, 2.0 and 2.2 mg/kg (sum of triadimefon and triadimenol) for barley forage.

Field trials involving triadimefon in oats were available from Germany. The GAP of Belarus, Kazakhstan and Russia for the foliar application of triadimefon to oats is 0.18 kg ai/ha. The residues from trials matching this GAP were 0.76, 1.9 and 2.3 mg/kg (sum of triadimefon and triadimenol) for oats forage.

Field trials involving triadimefon in rye were available from Germany. The GAP of Macedonia for the foliar application of triadimefon to rye is 0.25 kg ai/ha. The residues from trials matching this GAP were 5.9 and 10 mg/kg (sum of triadimefon and triadimenol) for rye forage.

The GAP of Croatia for the foliar application of triadimefon to rye is 0.1 kg ai/ha. The residues from trials matching this GAP were: 2.3, 2.5, 5.0 and 5.9 mg/kg (sum of triadimefon and triadimenol) for rye forage.

Field trials involving triadimefon in wheat were available from Germany. The GAP of Croatia for the foliar application of triadimefon to wheat is 0.1 kg ai/ha. The residues from trials matching this GAP were: 1.6, 1.8, 1.8, 2.2, 2.7 and 2.8 mg/kg (sum of triadimefon and triadimenol) for wheat forage.

*Triadimenol*

Field trials involving triadimenol in barley were available from Australia, Canada, France, Germany, Italy, Spain, United Kingdom and the United States.

The GAP of Cyprus and Poland for the foliar application of triadimenol to barley is 0.13 kg ai/ha. The residues from trials matching the GAP were: 0. 0.28, 1.1, 1.2, 1.6, 1.7, 1.7, 1.8, 1.9(3), 2.0, 2.0, 2.3, 2.3, 2.5, 2.6, 2.8, 2.9, 3.3, 3.4, 3.6, 3.6, 4.4, 4.4, 4.7, 4.8 and 5.0 mg/kg (sum of triadimefon and triadimenol) for barley forage.

The GAP for the use of triadimenol as a seed dressing in barley of Austria, Brazil, Germany, Ireland, Mexico and United Kingdom is 0.04 kg ai/100 kg/seeds with no specified PHI. The residues from trials matching this GAP were: < 0.01(4), 0.02, 0.02, 0.03(3), 0.05, 0.05, 0.06, 0.07, 0.08, < 0.1(13), 0.1, 0.16, 0.2, 0.27 and 1.7 mg/kg (sum of triadimefon and triadimenol) for barley forage.

Field trials involving triadimenol in oats were available from Brazil, Canada, Germany and the United States. The GAP of the United Kingdom for the foliar application of triadimenol to oats is 0.13 kg ai/ha with growth dependent PHI. The residues from trials matching this GAP were 2.4 and 2.5 mg/kg (sum of triadimefon and triadimenol) for oats forage.

The GAP for the use of triadimenol as a seed dressing in oats from Australia is 0.015 kg ai/100 kg seeds with no specified PHI. The residues from trials matching this GAP were < 0.1(4) mg/kg (sum of triadimefon and triadimenol) for oat forage.

GAPs in oats for the use of triadimenol as a seed dressing was reported from Brazil, Ireland and United Kingdom with application rates of 0.04 kg ai/100 kg seed. The residues from trials matching this GAP were: < 0.01, < 0.01, 0.02, 0.03, 0.03, 0.05, 0.08, 0.09, < 0.1(2), 0.1, 0.12, 0.12, 0.15, 0.16, 0.2, 0.27 mg/kg (sum of triadimefon and triadimenol) for oat forage.

The GAP of Finland for the use of triadimenol as a seed dressing in barley is 0.045 kg ai/100 kg seeds with no specified PHI. The residues from trials matching the GAP were 0.2 and 0.23 mg/kg (sum of triadimefon and triadimenol) for oat forage.

Field trials involving triadimenol in rye were available from Canada, Germany and the United States. The GAP of Poland and the United Kingdom for the foliar application of triadimenol to rye is 0.13 kg ai/ha with a PHI of 35 days. The residues from trials matching this GAP were: 1.7, 2.2, 2.7, 4.6 and 6.1 mg/kg (sum of triadimefon and triadimenol) for rye forage.

The GAP of Ireland and the United Kingdom for the use of triadimenol as a seed dressing in rye is 0.038 kg ai/100 kg seed. The residues from trials matching this GAP were: 0.03, 0.05, < 0.1(4), 0.26, 0.28, 0.77, 1.1 and 1.1 mg/kg (sum of triadimefon and triadimenol) for rye forage.

Field trials involving triadimenol in wheat were available from Australia, Brazil, Canada, France, Germany, Hungary, Italy, New Zealand, Spain and the United States.

The GAP of Australia, Bulgaria, Cyprus, Italy and Poland for the foliar application of triadimenol to wheat is 0.13 kg ai/ha with PHI of 28 to 35 days. The residues from trials matching this GAP were: 0.5, 0.61, 0.64, 1.1, 1.4(3), 1.5, 1.7, 1.9(3), 2.0, 2.1, 2.2(3), 2.3, 2.4, 2.5(3), 2.6, 2.6, 2.7, 2.9, 2.9, 3.0, 3.7, 3.9, 4.7 and 5.7 mg/kg (sum of triadimefon and triadimenol) for wheat forage.

In France the GAP for the foliar application of triadimenol to wheat is 0.075 kg ai/ha with a PHI of 28 days. The residue from one trial matching the GAP was 1.0 mg/kg (sum of triadimefon and triadimenol) for wheat forage.

The GAP for the use of triadimenol as a seed dressing in wheat was reported from Brazil, Ireland, and the United Kingdom with an application rate of 0.038 kg ai/100 kg seed (PHI unnecessary). The residues from trials matching this GAP were: < 0.01, < 0.01, 0.04(4), < 0.05(6), 0.09, < 0.1, 0.13, 0.13, 0.15, 0.31, 0.37, 0.38, 0.5, 0.52, 1.1, 1.2 and 1.8 mg/kg (sum of triadimefon and triadimenol) for wheat forage.

The Meeting decided to combine the data for triadimefon and triadimenol from all foliar GAPs for barley, oats, rye and wheat forage. The combined results (n=90) in ranked order (median underlined) were: 0.28, 0.5, 0.61, 0.64, 0.76, 1.1, 1.1, 1.2, 1.4(4), 1.5, 1.6, 1.6, 1.7(8), 1.8(3), 1.9(9), 2.0(4), 2.1, 2.2(6), 2.3(5), 2.4, 2.4, 2.5(6), 2.6(3), 2.7(3), 2.8, 2.8, 2.9(3), 3.0, 3.3, 3.4, 3.6, 3.6, 3.7, 3.9, 4.4, 4.4, 4.6, 4.7, 4.7, 4.8, 5.0, 5.0, 5.7, 5.9, 5.9, 6.1 and 10 mg/kg (sum of triadimefon and triadimenol) for combined barley, oats, rye and wheat forage (fresh based).

The Meeting estimated an STMR value of 2.2 mg/kg and a highest residue of 10 mg/kg for the sum of triadimefon and triadimenol in cereal forage.

*Cereal hay*

*Triadimenol*

Field trials involving triadimenol in barley hay were available from the United States. The GAP for the use of triadimenol as a seed dressing in barley for Austria, Brazil, Germany, Ireland, Mexico and the United Kingdom is 0.04 kg ai/100 kg/seeds with no specified PHI. The residues from trials matching this GAP were: 0.02, 0.02, 0.03, 0.04, 0.05 and 0.12 mg/kg (sum of triadimefon and triadimenol) for barley hay.

Field trials involving triadimenol in oats hay were available from the United States. The GAP in oats for the use of triadimenol as seed dressing was reported from Brazil, Ireland and United Kingdom with application rates of 0.04 kg ai/100 kg seed (PHI unnecessary). The residues from trials matching the GAP were: < 0.01, 0.03, 0.05, 0.21, 0.33 and 0.98 mg/kg (sum of triadimefon and triadimenol) for oats hay.

Field trials involving triadimenol in wheat hay were available from the United States. The GAP for the use of triadimenol as a seed dressing in wheat were reported from Brazil, Ireland, and United Kingdom with an application rate of 0.038 kg ai/100 kg seed (PHI unnecessary). The residues from trials matching this GAP were: 0.05, 0.07, 0.07, 0.08, 0.15 and 0.19 mg/kg (sum of triadimefon and triadimenol) for wheat hay.

The Meeting decided to pool the data from barley, oats and wheat hay after seed dressing application of triadimenol. The combined results (n=18) in ranked order (median underlined) were: < 0.01, 0.02, 0.02, 0.03, 0.03, 0.04, 0.05(3), 0.07, 0.07, 0.08, 0.12, 0.15, 0.19, 0.21, 0.33 and 0.98 mg/kg (sum of triadimefon and triadimenol) for cereal hay.

The Meeting estimated an STMR value of 0.06 mg/kg and a highest residue of 0.98 mg/kg for the sum of triadimefon and triadimenol in cereal hay.

*Cereal straw, straw and fodder (dry) of cereal grains*

*Triadimefon*

Field trials involving triadimefon in barley were available from Germany. The GAP of the Ukraine for the foliar application of triadimefon to barley is 0.13 kg ai/ha with a PHI of 30 days. The residues from trials matching this GAP were: < 0.1(4), 0.35, 0.42, 0.48, 0.63, 0.7 mg/kg (sum of triadimefon and triadimenol) for barley straw.

Field trials involving triadimefon in oats were available from Germany. The GAP of Belarus, Kazakhstan and Russia for the foliar application of triadimefon to oats is 0.18 kg ai/ha with a PHI of 30 days. The residues from trials matching this GAP were: < 0.1, 0.22 and 0.63 mg/kg (sum of triadimefon and triadimenol) for oats straw.

Field trials involving triadimefon in rye were available from Germany. The GAP of Macedonia for the foliar application of triadimefon to rye is 0.25 kg ai/ha with a PHI of 35 days. The residues from trials matching this GAP were 0.91 and 1.9 mg/kg (sum of triadimefon and triadimenol) for rye straw.

The GAP of Croatia for the foliar application of triadimefon to rye is 0.1 kg ai/ha with a PHI of 42 days. The residues from trials matching this GAP were: 0.23, 1.5, 1.7 and 2.7 mg/kg (sum of triadimefon and triadimenol) for rye straw.

Field trials involving triadimefon in wheat are available from Germany. The GAP of Croatia for the foliar application of triadimefon to wheat is 0.1 kg ai/ha with a PHI 42 days. The residues from trials matching this GAP were: 0.45, 0.53, 0.53, 0.7, 0.83, 0.9, 1.1 and 2.7 mg/kg (sum of triadimefon and triadimenol) for wheat straw.

*Triadimenol*

Field trials involving triadimenol in barley were available from Australia, Canada, France, Germany, Italy, Spain, the United Kingdom and the United States. The GAP of Cyprus and Poland for the foliar

application of triadimenol to barley is 0.13 kg ai/ha with a PHI of 35 days. The residues from trials matching this GAP were: 0.07, < 0.1, 0.1, 0.13, 0.17, 0.21, 0.24, 0.25, 0.29, 0.31, 0.41, 0.45, 0.48, 0.5, 0.55, 0.61, 0.62, 0.64, 0.67, 0.69, 0.81, 0.84, 0.85, 0.86, 0.92, 0.98, 1.2, 1.3, 1.4 and 4.1 mg/kg (sum of triadimefon and triadimenol) for barley straw.

The GAP for the use of triadimenol as a seed dressing in barley were reported with application rates of 0.022 kg ai/100 kg seed (PHI unnecessary) from Australia and New Zealand. The residue from one trial matching this GAP was < 0.04 mg/kg (sum of triadimefon and triadimenol) for barley straw.

The GAP for the use of triadimenol as a seed dressing in barley for Austria, Brazil, Germany, Ireland, Mexico and the United Kingdom is 0.04 kg ai/100 kg/seeds with no specified PHI. The residues from trials matching this GAP were: < 0.01(14), 0.01, < 0.05(6), 0.05 and < 0.1(20) mg/kg (sum of triadimefon and triadimenol) for barley straw.

Field trials involving triadimenol in oats were available from Brazil, Canada, Germany and the United States. The GAP of the United Kingdom for the foliar application of triadimenol to oats is 0.13 kg ai/ha with growth dependent PHI. The residues from trials matching the GAP were: 1.6 and 2.1 mg/kg (sum of triadimefon and triadimenol) for oat straw.

The GAP in oats for the use of triadimenol as a seed dressing in Australia is 0.015 kg ai/100 kg seeds with no specified PHI. The residues from trials matching this GAP were < 0.1(4) mg/kg (sum of triadimefon and triadimenol) for oat straw.

The GAP in oats for the use of triadimenol as a seed dressing was reported from Brazil, Ireland and United Kingdom with application rates of 0.04 kg ai/100 kg seed (PHI unnecessary). The residues from trials matching this GAP were: < 0.01(9), 0.03(4), 0.05, < 0.1(3) mg/kg (sum of triadimefon and triadimenol) for oat straw.

The GAP of Finland for the use of triadimenol as a seed dressing in barley is 0.045 kg ai/100 kg seeds with no specified PHI. The residues from trials matching this GAP were: < 0.01 and 0.02 mg/kg (sum of triadimefon and triadimenol) for oat grain. Field trials involving triadimenol in rye are available from Canada, Germany and the United States.

The GAP of Poland and the United Kingdom for the foliar application of triadimenol to rye is 0.13 kg ai/ha with a PHI of 35 days. The residues from trials matching this GAP were: 0.36, 1.2, 1.4, 1.9 and 1.9 mg/kg (sum of triadimefon and triadimenol) for rye straw.

The GAP from Ireland and the United Kingdom for the use of triadimenol as a seed dressing in rye were reported with an application rate of 0.038 kg ai/100 kg seed. The residues from trials matching this GAP were: < 0.01(7) and < 0.1(4) mg/kg (sum of triadimefon and triadimenol) for rye straw.

Field trials involving triadimenol in wheat were available from Australia, Brazil, Canada, France, Germany, Hungary, Italy, New Zealand, Spain and the United States. The GAP of Australia, Bulgaria, Cyprus, Italy and Poland for the foliar application of triadimenol to wheat is 0.13 kg ai/ha with a PHI of 28 to 35 days. The residues from trials matching this GAP were: 0.12, 0.12, 0.15, 0.16, 0.27, 0.27, 0.29, 0.31, 0.32, 0.39, 0.46, 0.47, 0.53, 0.56, 0.59, 0.66, 0.68, 0.7, 0.72, 0.75, 0.79, 0.82, 0.82, 0.83, 0.89, 0.91, 0.93, 1.0(3), 1.2, 1.3(3), 1.4, 2.1 and 2.5 mg/kg (sum of triadimefon and triadimenol) for wheat straw.

In France the GAP for the foliar application of triadimenol to wheat is 0.075 kg ai/ha with a PHI of 28 days. The residue from one trial matching the GAP was 0.62 mg/kg (sum of triadimefon and triadimenol) for wheat straw.

The GAP for the use of triadimenol as a seed dressing in wheat were reported from Brazil, Ireland, and the United Kingdom with an application rate of 0.038 kg ai/100 kg seed (PHI unnecessary). The residues from trials matching this GAP were: < 0.01(17), 0.02, 0.03, 0.03, 0.04, < 0.05(8), < 0.1, < 0.1, 0.15 and 0.2 mg/kg (sum of triadimefon and triadimenol) for wheat straw.

The Meeting decided to pool the data for triadimefon and triadimenol from all foliar GAPs for cereal straw. The combined results (fresh, n=101) in ranked order (median underlined) were: 0.07,

< 0.1(6), 0.1, 0.12, 0.12, 0.13, 0.15, 0.16, 0.17, 0.21, 0.22, 0.23, 0.24, 0.25, 0.27, 0.27, 0.29, 0.29, 0.31, 0.31, 0.32, 0.35, 0.36, 0.39, 0.41, 0.42, 0.45, 0.45, 0.46, 0.47, 0.48, 0.48, 0.5, 0.53(3), 0.55, 0.56, 0.59, 0.61, 0.62, 0.62, 0.63, 0.63, 0.64, 0.66, 0.67, 0.68, 0.69, 0.7(3), 0.72, 0.75, 0.79, 0.81, 0.82, 0.82, 0.83, 0.83, 0.84, 0.85, 0.86, 0.89, 0.9, 0.91, 0.91, 0.92, 0.93, 0.98, 1.0(3), 1.1, 1.2(3), 1.3(4), 1.4(3), 1.5, 1.6, 1.7, 1.9(3), 2.1, 2.1, 2.5, 2.7, 2.7 and 4.1 mg/kg (sum of triadimefon and triadimenol).

The Meeting estimated an STMR value of 0.64 mg/kg and a highest residue of 4.1 mg/kg for the sum of triadimefon and triadimenol in cereal straw.

On a dry weight basis (88% DM) the values were: 0.08, < 0.11(6), 0.11, 0.14, 0.14, 0.15, 0.17, 0.18, 0.19, 0.24, 0.25, 0.26, 0.27, 0.28, 0.31, 0.31, 0.33, 0.33, 0.35, 0.35, 0.36, 0.4, 0.41, 0.44, 0.47, 0.48, 0.51, 0.51, 0.52, 0.53, 0.55, 0.55, 0.57, 0.6(3), 0.63, 0.64, 0.67, 0.69, 0.7, 0.7, 0.72, 0.72, 0.73, 0.75, 0.76, 0.77, 0.78, 0.8(3), 0.82, 0.85, 0.9, 0.92, 0.93, 0.93, 0.94, 0.94, 0.95, 0.97, 0.98, 1(4), 1.1(6), 1.3, 1.4(3), 1.5(4), 1.6(3), 1.7, 1.8, 1.9, 2.2(3), 2.4, 2.4, 2.8, 3.1, 3.1 and 4.7 mg/kg (sum of triadimefon and triadimenol).

Based on the uses of both triadimefon and triadimenol in barley, oats, rye and wheat after foliar treatment the Meeting estimated an MRL of 5 mg/kg (sum of triadimefon and triadimenol) for straw and fodder (dry) of cereal grains.

The Meeting withdraws its previous recommendations for the triadimefon in barley, oats, rye and wheat straw and fodder, dry of 2 mg/kg and for triadimenol in barley, oats, rye and wheat straw and fodder, dry of 5 mg/kg.

*Fate of residues during processing*

Triadimefon and triadimenol are in general stable to hydrolysis during pasteurization, baking and boiling conditions.

Information on the fate of triadimefon and triadimenol during food processing was available for apples, grapes, pineapples, tomatoes and coffee beans.

Calculated processing factors and the mean or best estimate are summarized in the following table (based on the total triadimefon and triadimenol residues).

| Raw agricultural commodity (RAC) | Processed commodity | Calculated processing factors | Estimate of the processing factor |
|---|---|---|---|
| Apples | washed | 0.83, 1.0 | 0.92 |
| | juice | 0.5, < 0.56, < 0.63, < 0.63, < 0.7, < 0.8, < 0.83 | 0.63 |
| | sauce | < 0.5, < 0.56, < 0.63, < 0.63, < 0.7, < 0.8, < 0.83 | 0.63 |
| Grapes | must | 0.13, 0.18, < 0.24, < 0.25, 0.29, < 0.35, < 0.41, < 0.42, < 0.47, 0.5, < 0.56, < 0.63, < 0.71(3), < 0.83 | 0.45 |
| | wine | 0.09, 0.1, < 0.25, 0.29, < 0.33, < 0.33, < 0.35, < 0.41, < 0.42, < 0.5, < 0.56, < 0.63, < 0.71(3), < 0.83 | 0.42 |
| | juice | < 0.25, 0.33, < 0.56, 1.1 | 0.45 |
| | raisins | 0.67, 1.6, 2.3, 3.1, 4.5, 5.7, 5.8 | 3.1 |
| | wet pomace | 1.3, 2.4, 3.5, 16 | 3 |
| | dry pomace | 3.5, 3.9, 7.4, 33 | 5.7 |
| Pineapples | bran | 1.3 | 1.3 |
| | peel washed | 0.4 | 0.4 |
| Tomatoes | washed | 0.94, 1 | 0.97 |
| | peeled | 0.29, 0.37 | 0.33 |
| | juice | 0.56, 0.59, 0.74 | 0.59 |
| | puree | 0.78 | 0.78 |
| | paste | 1.9, 5.2, 5.9 | 5.2 |
| | preserve | 0.58, 0.59 | 0.585 |

| Raw agricultural commodity (RAC) | Processed commodity | Calculated processing factors | Estimate of the processing factor |
|---|---|---|---|
| | catsup | 2.4 | 2.4 |
| | wet pulp | 3.6 | 3.6 |
| | dry pulp | 14 | 14 |
| Coffee | roasted beans | 1.1 | 1.1 |
| | instant coffee | 1.3 | 1.3 |

For apples the estimated processing factors are applied to the STMR value of 0.06 mg/kg for pome fruits from the supervised trials. The Meeting estimated STMR-P values for apple juice and apple sauce of 0.04 mg/kg. For apples no processing data for wet pomace is available.

For grapes the estimated processing factors are applied to the STMR value of 0.15 mg/kg from the supervised trials. The Meeting estimated STMR-P values for grape must of 0.07 mg/kg, wine of 0.06 mg/kg, grape juice of 0.07 mg/kg, raisins of 0.47 mg/kg, wet grape pomace of 0.45 mg/kg and dry grape pomace of 0.86 mg/kg. The processing factor for raisins (3.1) was applied to the HR for grapes (3.2 mg/kg) to produce an HR-P value for raisins (9.9 mg/kg).

The Meeting estimated a maximum residue level for the sum of triadimefon and triadimenol, calculated as triadimefon in dried grapes of 10 mg/kg.

For pineapples the estimated processing factors are applied to the STMR value of 1.5 mg/kg for whole pineapple fruits from the supervised trials. The Meeting estimated STMR-P values for pineapple bran of 1.95 mg/kg. For pineapple pulp, juice and syrup the submitted data is not sufficient for a proposal of processing factors.

For tomatoes the estimated processing factors are applied to the STMR value of 0.15 mg/kg from the supervised trials. The Meeting estimated STMR-P values for peeled tomatoes of 0.05 mg/kg, tomato paste of 0.78 mg/kg, tomato puree of 0.12 mg/kg, tomato juice of 0.09 mg/kg, tomato preserve of 0.09 mg/kg, tomato catsup of 0.36 mg/kg, wet tomato pulp of 0.54 mg/kg and dry tomato pulp of 2.1 mg/kg.

Based on the residue data for sweet peppers (< 0.05, < 0.05, 0.11, 0.16, 0.21, 0.21, 0.23, 0.33, 0.33 and 0.38 mg/kg) and the default processing factor for sweet peppers to dried chilli peppers of 10 the Meeting estimated a maximum residue level of 5 mg/kg and an STMR value of 2.1 mg/kg for dried chilli peppers.

For coffee the estimated processing factors are applied to the STMR value of 0.05 mg/kg from the supervised trials. The Meeting estimated STMR-P values for roasted coffee beans of 0.06 mg/kg and instant coffee of 0.07 mg/kg.

***Livestock dietary burden***

The Meeting estimated the dietary burden of triadimefon and triadimenol in farm animals on the basis of the diets listed in Annex 6 of the 2006 JMPR Report (OECD Feedstuffs Derived from Field Crops). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities.

***Estimated maximum and mean livestock dietary burdens***

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the animal diets from US-Canada, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report).

| | Livestock dietary burden, sum of triadimefon and triadimenol, ppm of dry matter diet | | |
|---|---|---|---|
| | US-Canada | EU | Australia |

| | max | mean | max | mean | max | mean |
|---|---|---|---|---|---|---|
| Beef cattle | 12 | 3.1 | 9.6 | 2.1 | 40 [1] | 8.8 [2] |
| Dairy cattle | 18 | 4.4 | 9.7 | 2.1 | 27 [3] | 7.7 [4] |
| Poultry - broiler | 0.1 | 0.04 | 0.1 | 0.04 | 0.1 | 0.04 |
| Poultry - layer | 0.1 | 0.04 | 4.7 [5] | 1.0 [6] | 0.09 | 0.03 |

[1] Highest maximum beef cattle dietary burden suitable for MRL estimates for mammalian meat.

[2] Highest mean beef cattle dietary burden suitable for STMR estimates for mammalian meat.

[3] Highest maximum dairy dietary burden suitable for MRL estimates for milk.

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

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

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

### *Livestock feeding studies*

The Meeting received animal feeding studies on dairy cattle and laying hens. In these studies residues were analysed with two different methods. Only the results from the specific determination of triadimefon and triadimenol are used in this appraisal according to the residue definition for animal matrices. Total triadimefon and triadimenol residues in animal matrices are reported in the evaluation.

Three groups of cows were dosed at levels equivalent to 25 ppm (0.75 mg/kg bw) (1 ×), 75 ppm (2.3 mg/kg bw) (3 ×) and 250 ppm (3.7 mg/kg bw) (10 ×) triadimefon and triadimenol (1:1 mixture) in the diet together with a control group (0 ×). In all matrices except fat (3 × and 10 ×) and milk (10 ×) no residues above the LOQs (0.001 mg/kg for milk, 0.01 mg/kg for other matrices) were detected. In cattle fat from the 3 × group the mean value of triadimefon and triadimenol residues was 0.017 mg/kg (highest value 0.02 mg/kg). In the 10 × group the mean fat residues were 0.02 mg/kg (highest value 0.025 mg/kg). For milk in the 10 × group residues at the LOQ of 0.001 mg/kg were detected.

In the study with laying hens four hens per dose group received levels of 10 ppm (0.71 mg/kg bw), 25 ppm (1.8 mg/kg bw), 75 ppm (5.2 mg/kg bw) and 250 ppm (16.6 mg/kg bw) triadimefon and triadimenol (1:1 mixture) in the diet together with a control group. In liver and muscle no residues above the LOQ of 0.01 mg/kg were detected in all dose groups. Poultry fat contained measurable residues of 0.015 mg/kg in the mean only in the highest dose group (highest value of 0.02 mg/kg). Poultry skin showed one detectable residue of 0.03 mg/kg in the 75 ppm group. In the higher dose group no residues above the LOQ were found in poultry fat. In eggs residues were found in all dose groups: 10 ppm=0.002 mg/kg (highest value 0.003 mg/kg), 25 ppm=0.004 mg/kg (highest value 0.006 mg/kg), 75 ppm=0.008 mg/kg (highest value 0.01 mg/kg) and 250 ppm=0.03 mg/kg (highest value 0.04 mg/kg).

A linear relation between the dose levels and the residue concentrations was observed.

### *Animal commodity maximum residue levels*

The dietary burden for beef and dairy cattle was estimated at a maximum level of 40 and 27 ppm respectively. For poultry the maximum burden was estimated at a level of 4.7 ppm. The mean dietary burdens were estimated at 8.8 and 7.7 ppm for beef and dairy cattle and 1.0 ppm for poultry.

| Dietary burden (ppm)<br>Feeding level [ppm] | | Milk | Muscle | Liver | Kidney | Fat |
|---|---|---|---|---|---|---|
| | | Mean | Highest | Highest | Highest | Highest |
| MRL, beef cattle | (40) | | (< 0.01) | (< 0.01) | (< 0.01) | (0.01) |
| | [25] | | | | | [< 0.01] |
| | [75] | | [< 0.01] | [< 0.01] | [< 0.01] | [0.02] |
| MRL, dairy cattle | (27) | (< 0.01) | | | | |
| | [25] | | | | | |
| | [75] | [< 0.001] | | | | |
| STMR beef cattle | (8.8) | | (< 0.01) | (< 0.01) | (< 0.01) | (< 0.01) |
| | [25] | | | | | [< 0.01] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | [75] | | [< 0.01] | [< 0.01] | [< 0.01] | [0.02] |
| STMR | (7.7) | (< 0.01) | | | | |
| dairy | [25] | | | | | |
| cattle | [75] | [< 0.001] | | | | |

| Dietary burden (ppm) Feeding level [ppm] | | Eggs | | Muscle | Liver | Fat |
|---|---|---|---|---|---|---|
| | | Highest | Mean | Highest | Highest | Highest |
| MRL, | (4.7) | (< 0.01) | | (< 0.01) | (< 0.01) | (< 0.01) |
| poultry- | [10] | | | | | |
| layer | [25] | 0.003 | | | | |
| | [75] | 0.006 | | [< 0.01] | [< 0.01] | [< 0.01] |
| STMR | (1.0) | | [< 0.01] | (< 0.01) | (< 0.01) | (< 0.01) |
| poultry- | [10] | | | | | |
| broiler | [25] | | 0.002 | | | |
| | [75] | | 0.004 | [< 0.01] | [< 0.01] | [< 0.01] |

No residues are expected above the LOQ of 0.01 mg/kg for all cattle animal matrices (except meat in the fat). For eggs detectable residues were found in the livestock feeding studies, but the levels for the sum of triadimefon and triadimenol are about an order of magnitude below the LOQ for the enforcement method.

The Meeting estimated maximum residue levels for the sum of triadimefon and triadimenol of 0.01* mg/kg in edible offal (mammalian), milk, poultry meat, poultry offal and eggs. The Meeting also estimated a maximum residue levels for the sum of triadimefon and triadimenol of 0.02 mg/kg in meat (from mammals except marine mammals) [in the fat].

The HR and STMR values for the sum of triadimefon and triadimenol for meat (from mammals except marine mammals) as muscle was estimated at 0 mg/kg. For meat (from mammals except marine mammals) as fat and eggs HR and STMR values were estimated at 0.01 mg/kg for both. The HR and STMR values for the sum of triadimefon and triadimenol for edible offal (mammalian), milk, poultry meat and poultry offal were estimated at 0 mg/kg.

The Meeting withdraws its previous recommendations for triadimefon in milk, meat (from mammals except marine mammals), poultry meat and eggs of 0.05* mg/kg. The Meeting also withdraws the previous recommendations for triadimenol in milk of 0.01* mg/kg and in meat (from mammals except marine mammals), poultry meat and eggs of 0.05* mg/kg.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The International Estimated Daily Intakes (IEDI) of triadimefon and triadimenol, based on the estimated STMRs were 1–4% of the maximum ADI (0.03 mg/kg bw). The Meeting concluded that the long-term intake of residues of triadimefon and triadimenol from the uses that have been considered by the JMPR is unlikely to present a public health concern.

### *Short-term intake*

The International Estimated Short Term Intake (IESTI) of triadimefon and triadimenol calculated on the basis of the estimations made by JMPR represented for children 0–60% and for the general population 0–20% of the $AR_fD$ (0.08 mg/kg bw). The IESTI for grapes (excluding wine) for children was 220% of the ARfD.

The Meeting concluded that the short-term intake of residues of triadimefon and triadimenol resulting from the uses that have been considered by the JMPR, except the use on grapes, is unlikely to present a public health concern. The information provided to the JMPR precludes an estimate that the dietary intake would be below the ARfD for consumption of grapes by children. The Meeting noted that no alternative GAP for triadimefon or triadimenol in grapes could be used to identify a lower HR value.

## 5.23 TRIAZOPHOS (143)

### RESIDUE AND ANALYTICAL ASPECTS

Triazophos is an organophosphorus insecticide used to control insect pests on a wide range of crops. It was originally evaluated for residues by the 1983 JMPR and re-evaluated four times in 1986, 1990, 1992 and 1993, with subsequent revisions in 1984 and 1991. It was scheduled for periodic re-evaluation by the 2007 JMPR.

The manufacturer submitted data on physical and chemical properties, metabolism and environmental fate, methods of residue analysis, use patterns, residues resulting from supervised trials on cotton and stability of residues during storage and processing. The government of Thailand provided GAP information and supervised trial data for soya bean (immature seeds).

#### *Animal metabolism*

The Meeting received information on the metabolism of triazophos in rats and dogs, but no information on the distribution, excretion or fate of triazophos in livestock and poultry. As both the rat and dog studies were described in detail in the toxicological evaluation of the 2002 JMPR, the studies were not reported here.

#### *Plant metabolism*

The Meeting received plant metabolism studies for triazophos on cotton and rice. Both studies included foliar application as well as uptake via water and/or soil.

When [$^{14}$C]triazophos was applied to leaves of cotton plants, the radioactivity was at first present on the leaf surface but quickly penetrated into the leaf itself, with little translocation into other parts of the plant. The predominant component of the radioactivity was parent triazophos. After field application of $^{14}$C-triazophos prior to boll opening, only very low residues of triazophos and its metabolites were present in cotton fibre and seeds. In both trials, the residues consisted of unchanged triazophos, 1-phenyl-3-hydroxy-l, 2, 4-triazole and an unidentified compound. Only traces of the P=O analogue of triazophos (O, O-diethyl-O-l-phenyl-lH-l,2,4-triazol-3-yl phosphate) were detectable on the leaves and stem. In general, triazophos penetrated quickly into deeper layers of the treated leaves but was not translocated in significant amounts into other parts of the plant or roots.

In uptake studies via both soil and a hydroponic medium, parent triazophos was the predominant component of the applied radioactivity, with most of the radioactive residues being present in the plant root, compared to the whole plant, or remaining in the soil or hydroponic medium. Again, most of the extracted radioactivity was composed of parent triazophos, although both the P=O analogue and 1-phenyl-3-hydroxy-l, 2, 4-triazole were also found. The results of field applications showed that only low levels of triazophos and its metabolites are likely to be present in cotton fibre and seeds if the last application takes place prior to boll opening.

Greenhouse grown rice plants were treated with [$^{14}$C]triazole at the growth stages of either stem elongation or heading. Initially the majority of the applied radioactivity was present on the surface of the rice plants, however by 8 weeks after the application, radioactivity was found in the rice panicles. Little radioactivity was found in rice grain. The major component of the extracted radioactivity was parent triazophos in rice panicles, husks, grain and whole plant. The 1-phenyl-3-hydroxy-l, 2, 4-triazole was also present in whole plant (< 10% of applied radioactivity) and very low levels were in rice grain (0.02% of applied radioactivity). The P=O analogue was also present, but in amounts lower than triazophos or the triazole (< 1% of applied radioactivity).

In addition, uptake studies were conducted in rice, with application of $^{14}$C-triazophos to water or soil and water. As with the cotton study a large proportion of the applied radioactivity remained in the soil or soil and water medium, with little radioactivity present in either the whole plant or the

panicle. Again parent triazophos was the major component of the radioactivity, although the 1-phenyl-3-hydroxy-l, 2, 4-triazole and the P=O analogue were also detected.

In conclusion, the results from the field study show that very little of the applied radioactivity is present in rice grain following multiple applications under field conditions.

***Uptake from soil by leek plants***

The Meeting received information on the uptake of triazophos from soil by leek plants.

Plots of loamy soil and sandy soil were treated with [$^{14}$C]triazophos at application rates equivalent to 0.48 and 0.96 kg ai/ha. Leek plants were present in the treated plots. At 90 days after application, samples of soil, taken at various depths, and leek plants were collected for determination of radioactivity. No detectable radioactivity was found in the leek plants. In the soil samples up to 2.2% of the applied radioactivity was found (0–10 cm depth), with lower concentrations (< 0.2% of applied radioactivity) present at 10–20 cm and 20–30 cm depths. The radioactivity was predominantly composed of parent triazophos and 1-phenyl-3-hydroxy-l, 2, 4-triazole.

***Methods of analysis***

The Meeting received information on methods capable of determining residues of triazophos in plant materials and animal commodities, using GC with N or P selective detectors. The limits of quantitation were typically 0.02 mg/kg for plant commodities and 0.01 for animal commodities. Reported recoveries were within acceptable limits of 70–110%.

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

Studies were provided to the Meeting demonstrating the stability of residues in stored samples of cotton fibre, cotton seed, oranges, carrots and soil. No significant decrease of triazophos was observed in analytical samples of cotton fibre, cotton seed, oranges and carrots stored at ≤ -18 °C for up to 24 months.

***Residue definition in Plants***

The results of the plant metabolism studies on cotton and rice, including foliar application and uptake from soil and water, indicate that parent triazophos is the major component of the recovered radioactivity, with the P=O analogue (O, O-diethyl-O-l-phenyl-lH-l, 2, 4-triazol-3-yl phosphate) and 1-phenyl-3-hydroxy-l, 2, 4-triazole also being present.

Analytical methods for plant matrices determine triazophos only.

On the basis of the metabolism in plants and the analytical methodology submitted, the Meeting confirmed the previous residue definition for the purposes of compliance monitoring and for estimation of dietary intake.

Definition of residue (for compliance with the MRL and for estimation of dietary intake): triazophos.

***Results of supervised trials on crops***

*Cotton*

Data were received from ten field trials for triazophos on cotton; nine trials were conducted in nine regions of India and a single trial was conducted in Brazil. In 2005 in India, 5 sprays were applied at 0.87 kg ai/ha (or 0.435 kg ai/hL) and in Brazil in 2001, 3 sprays were applied at 0.80 kg ai/ha (i.e., 0.27 kg ai/hL) or 1.60 kg ai/ha (i.e., 0.53 kg ai/hL). The GAP in India is 0.63 to 0.84 kg ai/ha with a 21 day PHI and 1–5 applications. In Brazil, the GAP is 0.3 to 0.8 kg ai/ha with a 28 day PHI and 1–3 applications.

The Meeting was informed that in India, as cotton plants do not mature simultaneously, harvest usually occurs over three separate picks, with the majority of cotton collected from first two

with an average interval of 10 days between these picks. The raw cotton from, the different picks, is generally pooled prior to sale. Following sale the raw cotton is ginned where the separation of lint and seed occurs. As a consequence the Meeting considered the supervised trials reported from India as representing local practice for the use of triazophos in cotton. In trials from India the cotton samples from two picks (at 21–23 days and 31–33 days after the last application) were pooled and processed by ginning to separate the lint and seeds. Cotton seed oil was then extracted from cotton seeds using n-hexane in soxhlet extractor, the solvent was removed by rotary evaporation with the resultant oil used for analysis.

Residues of triazophos measured in nine trials conducted according to the GAP in India were 0.020, 0.021 (2), 0.023, 0.028, 0.042, 0.054, 0.059 and 0.060 mg/kg in cotton seed and 0.042, 0.044, 0.085, 0.088, 0.13, 0.17, 0.26, 0.31 and 0.78 mg/kg in cotton seed oil.

From one trial matching GAP in Brazil the residue of triazophos in cotton seed was 0.03 mg/kg; residues in cotton seed oil were not determined. Residues from the trial conducted at double rate reached a maximum of 0.2 mg/kg in cotton seed.

Based on the 10 trials with GAP in India and Brazil, residues were 0.020, 0.021 (2), 0.023, 0.028, 0.03, 0.042, 0.054, 0.059 and 0.060 mg/kg in cotton seed and 0.042, 0.044, 0.085, 0.088, 0.13, 0.17, 0.26, 0.31 and 0.78 mg/kg in cotton seed oil.

The Meeting estimated an STMR of 0.029 mg/kg for triazophos in cotton seed and 0.13 mg/kg in cotton seed oil, and an HR of 0.060 mg/kg for triazophos in cotton seed and 0.78 mg/kg in cotton seed oil. The Meeting recommended a maximum residue level of 0.2 mg/kg in cotton seed and 1 mg/kg in cotton seed oil (crude) for triazophos.

The Meeting also recommended the withdrawal of the current MRL of 0.1 mg/kg for triazophos in cotton seed.

*Soya bean*

In six field trials conducted in Thailand during 1992 to 2006, 2 to 4 sprays of triazophos were applied at 0.1 kg ai/hL. The GAP in Thailand is 0.1 kg ai/hL with a 14 day PHI. Residues of triazophos in whole pod including immature seeds at 14–17 days after the last application were 0.05, 0.17, 0.31, 0.43, 0.52, and 0.60 mg/kg.

The Meeting recommended a maximum residue level of 1 mg/kg for triazophos in soya beans (immature seeds with the pod). The Meeting also estimated an STMR of 0.37 mg/kg and an HR of 0.60 mg/kg.

The Meeting recommended withdrawal of the previous recommendation of 0.05 mg/kg for triazophos in soya bean (dry).

*Other commodities*

No data on GAP and residues for triazophos was provided on broad bean (shelled), Brussels sprouts, cabbage (head), carrot, cauliflower, cereal grains, coffee beans, common bean, onion (bulb), pea, pome fruit, potato, strawberry and sugar beet. The Meeting recommended withdrawal of the previous recommendations made for these commodities.

***Fate of residues during processing***

Information regarding the magnitude of triazophos residues in different processed commodities of cotton was provided to the Meeting.

In three field trials conducted in the USA in cotton, residues were found in the processed non oily matrices and in the processed oil. No processing factors could be determined as residue concentrations in unprocessed cotton seed were not reported.

***Residues in animal commodities***

The Meeting received a feeding study on lactating Holstein cows. The dosing regime involved a 2-day pre-conditioning phase, one week prior to the dosing period, at a dose level of 100 mg triazophos per cow. During the following period of 7 days, one cow was dosed with 50 mg triazophos (2.38 ppm in the feed) and the second cow with 100 mg (4.76 ppm in the feed), the third cow received untreated feed. Neither the pre-conditioning at 100 mg per cow and day nor the dosing of 50 and 100 mg per cow and day resulted in any residues above the LOQ of 0.05 mg/kg for milk and 0.01 mg/kg for muscle, fat, kidney and liver. The Meeting noted that because of the lack of an appropriate livestock metabolism study, a residue definition for animal products could not be determined and therefore the Meeting could not make use of the results of the feeding study.

The Meeting agreed to withdraw the previous recommendations for triazophos of 0.01 mg/kg in cattle meat and cattle milk.

**DIETARY RISK ASSESSMENT**

***Long-term intake***

The evaluation of triazophos has resulted in recommendations for MRLs and STMR values for raw and processed commodities. Consumption data were available for 2 food commodities and were used in the dietary intake calculations. The results are shown in Annex 3.

The IEDIs for the 13 GEMS/Food regional diets, based on estimated STMRs were in the range 0–20% of the maximum ADI of 0.001 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of triazophos from uses that have been considered by the JMPR is unlikely to present a public health concern.

***Short-term intake***

The IESTI for triazophos was calculated for the food commodities for which maximum residue levels and HRs were estimated and for which consumption data were available. The results are shown in Annex 4.

The IESTI calculated for cotton seed oil for the general population and children were 2% and 5% of the ARfD (0.001 mg/kg bw), respectively. The IESTI calculated for soya bean (immature seeds with the pod) for the general population and children were 140% and 230% of the ARfD, respectively (Annex 4). The Meeting concluded that the short-term intake of residues of triazophos from the consumption of cotton seed oil is unlikely to present a public health concern. The information provided to the JMPR precludes an estimate that the dietary intake would be below the ARfD for consumption for soya bean (immature seeds with pod) by the general population and children.

The Meeting noted that the pod is not normally consumed and that no residue data relating to residues in the edible portion of soya bean pods or alternative GAP were submitted for soya bean (immature seeds with pod).

## 5.24 ZOXAMIDE (227)

**TOXICOLOGY**

Zoxamide is the ISO approved name for (*RS*)-3,5-dichloro-*N*-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide (CAS; CAS No. 156052-68-5). Zoxamide is a chlorinated benzamide fungicide acting against late blight (*Phytophthora infestans)* and powdery mildew (*Plasmopara viticola)*. The mechanism of fungicidal action involves disruption of microtubule formation by binding to β-tubulin.

Zoxamide has not been evaluated previously by the JMPR and was reviewed at the present Meeting at the request of the CCPR.

All the pivotal studies met the basic requirements of the relevant OECD or national test guideline and contained certificates of compliance with GLP.

***Biochemical aspects***

In rats given zoxamide, approximately 60% of a dose of 10 mg/kg bw was absorbed, with peak plasma concentrations of radioactivity occurring at 8 h after dosing. Zoxamide was extensively distributed among organs and tissues with highest concentrations reported in the liver. Excretion was primarily in the faeces, via the bile. The overall elimination half-life was 13–14 h. At 1000 mg/kg bw, there was some evidence of saturation of absorption, with $C_{max}$ and AUC values being approximately 40–50 times those at 10 mg/kg bw, but with a similar elimination half-life. Females excreted approximately twice as much radiolabel in the urine as males. Very little radioactivity remained in tissues (< 0.2% of the administered dose) or carcass (< 2% of the administered dose) at 5 days after dosing. Pre-treatment of animals with diets containing zoxamide for 2 weeks or with five daily gavage doses of radiolabelled zoxamide did not significantly alter the absorption or distribution of radiolabel compared with that in untreated animals.

The metabolism of zoxamide was extensive, involving a variety of pathways including hydrolysis, glutathione-mediated reactions, and reductive dehalogenation, secondary oxidation on both the aromatic methyl and the aliphatic side-chain, limited deamidation; and terminal glucuronic acid and amino-acid conjugation. Thirty-two separate metabolites were identified; no single metabolite accounted for more than 10% of the administered dose. After repeated doses, there was an indication of an increase in glutathione-mediated metabolism.

***Toxicological data***

Zoxamide was of low acute toxicity when administered orally ($LD_{50}$ > 5000 mg/kg bw), dermally ($LD_{50}$ > 2000 mg/kg bw) or after a 4-h inhalation exposure ($LC_{50}$ > 5.3 mg/L). Zoxamide is not a skin irritant, but is a slight, transient eye irritant. Zoxamide produced delayed contact hypersensitivity in guinea-pigs in the maximization and Buehler tests.

In repeat-dose studies, the main effects of zoxamide were reduced body-weight gain and liver hypertrophy. The reductions in body-weight gain were not consistent across studies. Investigative work performed as part of the study of reproductive toxicity indicated there might be palatability problems with diet containing zoxamide. However, food consumption was not reduced consistently in studies in which reduced body-weight gain was reported. Liver hypertrophy was not associated with any histopathological or clinical chemistry changes that indicated damage to liver cells. Therefore, in line with the guidance developed by the 2006 JMPR, increased liver weight and hepatocyte hypertrophy were considered to be adaptive rather than adverse effects of exposure to zoxamide.

In a 90-day study of toxicity in mice, the NOAEL was 2500 ppm (equal to 574 mg/kg bw per day) on the basis of reduced body-weight gains in females at 7000 ppm (equal to 1606 mg/kg bw per day). Increases in relative liver weights (by approximately 10%) were not associated with any pathological or clinical chemistry changes and are not considered to be adverse. In a 90-day study of toxicity and neurotoxicity in rats, the NOAEL was 20 000 ppm (equal to 1509 mg/kg bw per day), the highest dose tested.

In a 28-day study of toxicity in dogs, the NOAEL was 30 000 ppm, equal to 1045 mg/kg bw per day, the highest dose tested. Soft stools were present at an increased incidence at doses of 5000 ppm, equal to 175 mg/kg bw per day, and above, but as this finding was not seen consistently in other studies in dogs given similar doses and the same formulated diet, this finding is not considered to be an adverse effect of treatment. In the 90-day study of toxicity in dogs, the NOAEL was 7500 ppm, equal to 281 mg/kg bw per day, on the basis of reductions in body-weight gain, serum albumin concentrations and erythrocyte counts in both sexes at 30 000 ppm, equal to 1055 mg/kg bw per day. Increases in liver weights (by approximately 25%) in females at 7500 ppm were not associated with any histopathological or clinical chemistry changes and were not considered to be adverse. In the 1-year study of toxicity in dogs, reduced body-weight gain (45%) was present from the beginning of the

study in females at 7500 ppm, equal to 255 mg/kg bw per day, and a deficit in body-weight gain (20%) was still present at the end of the study. Males receiving zoxamide at 7500 ppm also had reduced body-weight gain during the early stages of the study, but these animals had terminal body weights that were higher than those of the controls. Although food consumption was reduced transiently, there was no clear link between body weights of individual animals and food consumption. At the highest dose of 30 000 ppm, there were marked effects on body weight and food consumption, with females taking up to 7 weeks to regain their pre-test body weight. Reduced concentrations of serum albumin, and increases in liver and thyroid weights and serum alkaline phosphatase activities were also seen in both sexes at 30 000 ppm. The NOAEL in the 1-year study was 1500 ppm, equal to 48 mg/kg bw per day.

In the 90-day and 1-year studies in dogs, cases of canine juvenile polyarteritis syndrome (CJPS) were seen in the groups receiving zoxamide, but not in the controls. CJPS is reported to be specific to beagle dogs, occurring spontaneously but with unknown aetiology. A genetic link has been postulated, which might explain the occurrence in the 90-day and 1-year studies, which were started at the same time and used animals from the same supplier. Therefore, CJPS was not considered to be related to exposure to zoxamide.

In a 28-day study of dermal toxicity in rats, zoxamide produced significant local effects at doses of ≥ 107 mg/kg bw per day. Findings of systemic toxicity were most likely to be secondary to the local effects and the NOAEL for systemic effects was 714 mg/kg bw per day.

Negative results were obtained in assays for gene mutation in vitro and in assays for micronucleus formation in bone marrow of rats and mice in vivo. Zoxamide was found to induce polyploidy in an assay for chromosomal aberration in Chinese hamster ovary cells in vitro. These findings are consistent with the mechanism of fungicidal action of zoxamide, involving binding to the β-subunit of tubulin. Zoxamide also inhibits microtubule assembly in mouse lymphoma cells ($IC_{50}$, 23.5 μmol/L). The induction of polyploidy after inhibition of tubulin polymerization and disruption of microtubule formation has been investigated for other compounds and is considered to be a threshold-mediated effect. The assay for micronucleus formation in rats included kinetochore staining and produced negative results for micronuclei and chromosomal damage. A supplementary kinetic study in mice demonstrated that there was exposure of the bone marrow after administration of zoxamide.

The Meeting concluded that zoxamide was unlikely to pose a genotoxic risk to humans at levels typical of dietary exposures.

In long-term studies of toxicity in mice and rats, zoxamide exhibited no general toxicity and was not carcinogenic in either species. Increased liver weights (approximately 20%) in female rats killed after a 1-year exposure to zoxamide at a dietary concentration of ≥ 5000 ppm were not considered to be adverse as there were no associated histopathological or clinical chemistry findings at any time during the study. An apparent increase in thyroid C-cell lesions in male rats at the highest dose was not statistically significant, did not exhibit a dose–response relationship, was not reproduced in females and was within the range for historical controls. The NOAEL in mice was 7000 ppm, equal to 1021 mg/kg bw per day, and the NOAEL in rats was 20 000 ppm, equal to 1058 mg/kg bw per day, both values being based on the absence of treatment-related toxicity at the highest doses tested.

In view of the absence of carcinogenic potential in rodents and the lack of genotoxicity in vivo, the Meeting concluded that zoxamide was unlikely to pose a carcinogenic risk to humans.

The reproductive toxicity of zoxamide has been investigated in a two-generation study in rats and studies of developmental toxicity in rats and rabbits. In the study of reproductive toxicity in rats, the NOAEL for effects on fertility, parental toxicity and pup development was 20 000 ppm, equal to 1474 mg/kg bw per day. Reductions in pup body-weight gain and spleen weights and reduced extramedullary haematopoiesis in the spleen were seen in $F_{1a}$ $F_{1b}$ and $F_{2a}$ offspring, but these effects appeared to be related to palatability as they were not evident in the $F_{2b}$ generation, when pups and dams received equivalent exposures of zoxamide by gavage, rather than from the diet, from postnatal days 14 to 21. Increased relative liver weight was noted at doses of ≥ 5000 ppm in males and females, and in absolute liver weight only in males at 20 000 ppm. The changes in liver weight were not

associated with any histopathological or clinical chemistry change and were not considered to be adverse.

There was no evidence of toxicity in the studies of prenatal developmental toxicity in rats or rabbits. The NOAEL in both studies was 1000 mg/kg bw per day on the basis of absence of toxicity to dams or foetuses at the highest dose tested. Zoxamide was not teratogenic in rats or rabbits.

Zoxamide was not neurotoxic in a study of acute neurotoxicity at doses of up to 2000 mg/kg bw. No adverse effects were seen during neurological and behavioural examinations performed during routine repeat-dose studies with zoxamide.

Studies on two plant metabolites of zoxamide, [RH-141,452 (3,5-dichloro-4-hydroxymethyl benzoic acid) RH-141,455 (3,5-dichloro-1,4-benzene-dicarboxylic acid)] formed to a limited extent in rats, showed them to be rapidly absorbed and rapidly excreted, essentially unchanged; to have low acute oral toxicities to mice ($LD_{50}$s, > 5000 mg/kg bw), and to be negative in assays for gene mutation with strains of *Salmonella typhimurium.*

There are two reports of mild adverse effects following exposure to a diluted formulation containing zoxamide and mancozeb. In one case there was a report of skin irritation, in the other "flu-like" symptoms were reported. It is considered to be unlikely that these effects are related directly to exposure to zoxamide.

## Toxicological evaluation

An ADI of 0–0.5 mg/kg bw was established for zoxamide based on the NOAEL of 48 mg/kg bw per day in the 1-year study in dogs, on the basis of reduced body-weight gain in females at 255 mg/kg bw per day.

An ARfD was considered to be unnecessary for zoxamide as it is of low acute toxicity did not produce developmental effects and did not produce any other significant effects following acute exposures.

A toxicological monograph was produced.

***Levels relevant to risk assessment***

| Species | Study | Effect | NOAEL | LOAEL |
|---|---|---|---|---|
| Mouse | Two-year studies of toxicity and carcinogenicity[a] | Toxicity | 7000 ppm, equal to 1021 mg/kg bw per day[c] | — |
| | | Carcinogenicity | 7000 ppm, equal to 1021 mg/kg bw per day[c] | — |
| Rat | Two-year studies of toxicity and carcinogenicity [a] | Toxicity | 20 000 ppm, equal to 1058 mg/kg bw per day[c] | — |
| | | Carcinogenicity | 20 000 ppm, equal to 1058 mg/kg bw per day[c] | — |
| | Multigeneration study of reproductive toxicity[a] | Reproductive toxicity | 30 000 ppm, equal to 1474 mg/kg bw per day[c] | — |
| | | Parental toxicity | 30 000 ppm, equal to 1474 mg/kg bw per day[c] | — |

| | | | | |
|---|---|---|---|---|
| | | Offspring toxicity | 30 000 ppm, equal to 1474 mg/kg bw per day[c] | — |
| | Developmental toxicity[b] | Maternal toxicity | 1000 mg/kg bw per day[c] | — |
| | | Embryo/fetotoxicity | 1000 mg/kg bw per day[c] | — |
| | Acute neurotoxicity[b] | | 2000 mg/kg bw per day[c] | — |
| Rabbit | Developmental toxicity[a] | Maternal toxicity | 1000 mg/kg bw per day[c] | — |
| | | Embryo/fetotoxicity | 1000 mg/kg bw per day[c] | — |
| Dog | One-year study of toxicity[a] | Reduced body-weight gain | 1500 ppm, equal to 48 mg/kg bw per day | 7500 ppm, equal to 255 mg/kg bw per day |

[a] Dietary administration.
[b] Gavage administration.
[c] Highest dose tested.

*Estimate of acceptable daily intake for humans*

0–0.5 mg/kg bw

*Estimate of acute reference dose*

Unnecessary

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

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

***Critical end-points for setting guidance values for exposure to zoxamide***

| | |
|---|---|
| *Absorption, distribution, excretion and metabolism in mammals* | |
| Rate and extent of oral absorption | Moderate ($C_{max}$, 8h); approximately 60% absorbed at 10 mg/kg bw |
| Dermal absorption | Approximately 1% from concentrate; 6% from dilution |
| Distribution | Extensive. Highest levels in liver. |
| Potential for accumulation | Low |
| Rate and extent of excretion | > 85% in 48 h. Urine (approximately 10–20%); bile (approximately 45%); faeces (approximately 50–80%). |
| Metabolism in animals | Extensive. Primarily via hydrolysis, dehalogenation, oxidation and conjugation. |
| Toxicologically significant compounds in animals, plants and the environment | Zoxamide. |
| *Acute toxicity* | |
| Rat, $LD_{50}$, oral | > 5000 mg/kg bw |
| Rat, $LD_{50}$, dermal | > 2000 mg/kg bw |
| Rat, $LC_{50}$, inhalation | > 5.3 mg/L |
| Rabbit, skin irritation | Not irritating |
| Rabbit, eye irritation | Slight transient irritant |

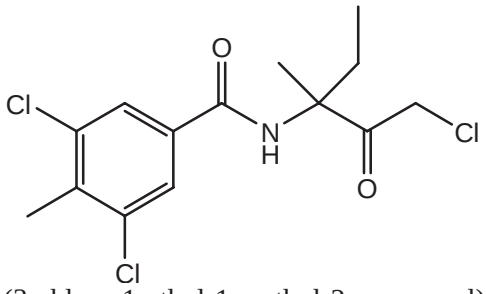
| | |
|---|---|
| Guinea-pig, skin sensitization (test method used) | A skin sensitizer (Buehler; Magnusson & Kligman) |
| *Short-term studies of toxicity* | |
| Target/critical effect | Body-weight gain |
| Lowest relevant oral NOAEL | 1500 ppm (48 mg/kg bw per day) in a 1-year study in dogs |
| Lowest relevant dermal NOAEL | < 107 mg/kg bw for local effects; 714 mg/kg bw per day for systemic effects. |
| Lowest relevant inhalation NOAEC | No data (not required) |
| *Genotoxicity* | |
| | Not genotoxic in vivo |
| *Long-term studies of toxicity and carcinogenicity* | |
| Target/critical effect | None. |
| Lowest relevant NOAEL | 7000 ppm (1021mg/kg bw per day) in mice (highest dose tested) |
| Carcinogenicity | Not carcinogenic |
| *Reproductive toxicity* | |
| Reproduction target/critical effect | None |
| Lowest relevant reproductive NOAEL | 20 000 ppm (1047 mg/kg bw per day) in rats (highest dose tested) |
| Developmental target/critical effect | None |
| Lowest relevant developmental NOAEL | 1000 mg/kg bw per day in rats and rabbits (highest dose tested) |
| *Neurotoxicity/delayed neurotoxicity* | |
| | No indications of neurotoxicity in studies of acute toxicity or repeat-doses |
| Acute neurotoxicity | NOAEL was 2000 mg/kg bw in rats (highest dose tested) |
| *Other toxicological studies* | |
| | RH-141,452<br>Rapid excretion essentially unmetabolized.<br>Oral $LD_{50}$ in mice > 5000 mg/kg bw<br>Negative in an Ames test.<br><br>RH-141,455<br>Rapid excretion essentially unmetabolized.<br>Oral $LD_{50}$ in mice > 5000 mg/kg bw<br>Negative in an Ames test |
| *Medical data* | |
| | Two reports (one case of irritation & one of flu-like symptoms) following exposure to a diluted formulation of mancozeb/zoxamide. Unlikely to be directly related to zoxamide. |

***Summary***

| | **Value** | **Study** | **Safety factor** |
|---|---|---|---|
| ADI | 0–0.5 mg/kg bw | Dog, 1-year study | 100 |
| ARfD | Unnecessary | — | — |

## RESIDUE AND ANALYTICAL ASPECTS

Zoxamide, a benzamide fungicide, was identified as a priority new compound at the 38th Session of the CCPR (ALINORM 06/29/24) for evaluation by the 2007 JMPR. The Meeting received information on physical and chemical properties, animal and plant metabolism, environmental fate, analytical methods, storage stability, use patterns, supervised trials and processing.




(*RS*)-3,5-dichloro-*N*-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide

In this appraisal, the following abbreviated names were used for metabolites.

| | |
|---|---|
| RH-127450 | 3,5-dichloro-*N*-(1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide |
| RH-129151 | 2-(3,5-dichloro-4-methylphenyl)-4-ethyl-4-methyl-4H-1,3-oxazin-5(6H)-one |
| RH-139432 | 3,5-dichloro-4-methylbenzamide |
| RH-141288 | 3,5-dichloro-*N*-(3-hydroxy-1-ethyl-1-methyl--2-oxopropyl)-4-methylbenzamide |
| RH-1452 | 3,5-dichloro-4-hydroxymethylbenzoic acid |
| RH-1455 | 3,5-dichloro-1,4-benzene-dicarboxylic acid |
| RH-149736 | 3,5-dichloro-4-hydroxymethylbenzamide |
| RH-149737 | 4-carboxy-3,5-dichlorobenzamide |
| RH-150721 | (3-amino-3-methyl-2-oxo)pentyl-(3,5-dichloro-4-methyl)benzoate |
| RH-163353 | 3,5-dichloro-*N*-(2-carboxy-1-ethyl-1-methyl-2-oxoethyl)-4-methylbenzamide |
| RH-24549 | 3,5-dichloro-4-methylbenzoic acid |

### *Animal metabolism*

The Meeting received information on the fate of orally-dosed zoxamide in a lactating goat.

When [U-$^{14}$C-phenyl]zoxamide was administered orally at a dose equivalent to a dietary concentration of 60.7 ppm to a lactating goat once a day for 7 consecutive days, 95% of the recovered radioactivity (77.5% of the administered dose) was found in urine (37.1%) and faeces (36.1%). None of individual tissues or cumulative milk sample on day 7 contained more than 3% of the administered dose. On day 4 the radioactive residues in milk was the highest at 0.24 mg/kg in parent equivalents.

Unextracted radioactivity was less than 10% of total radioactive residues (TRR) (< 0.05 mg/kg) in all samples except liver (12%).

No parent compound was found in any of tissues or milk sample. A number of metabolites were detected in milk and tissues. In fat, RH-127450 was found at 0.13 mg/kg in parent equivalent. However, as the dose administered in the study was about 14 times the highest concentration found in

any commodity after treatment of the respective crop in accordance with GAP, significant residue concentrations are unlikely to occur in milk or any tissues in practice.

Zoxamide was extensively metabolized and readily eliminated following oral administration to a lactating goat. Once administered orally, zoxamide underwent dechlorination, then oxidation of either position 4 of the benzene ring or the end of the side-chain and further hydrolysis.

The metabolism of zoxamide in the lactating goat was qualitatively similar to that described in the toxicology section (see page 282).

***Plant metabolism***

The Meeting received information on the fate of zoxamide after foliar application of [U-$^{14}$C-phenyl]zoxamide to grapes, cucumber, tomato and potato.

When grape vines were sprayed at a rate of 1.9 kg ai/ha three times at 30 day intervals, grapes harvested 1 day after the last application contained 0.74 mg/kg of radioactive residues. The parent compound was the major residue at 0.43 mg/kg (58% of TRR). RH-129151, RH-139432, RH-141288, RH-149736, RH-149737 and RH-150721 were identified but all were less than 0.021 mg/kg in parent equivalents (≤ 2.8% of TRR).

Cucumber plants were sprayed three times at the rate of 1.3 kg ai/ha at a 7 day intervals and foliage and fruit samples were harvested 1 day after the last application. While an average radioactive residue in foliage was 108 mg/kg in parent equivalent, that in fruits was 1.5 mg/kg, which indicates that translocation of zoxamide, was not significant one day after the final application. Extraction of foliage and fruit samples with acetonitrile-water mixture solubilised 100% of the total radioactivity and there were no volatile or unextracted residues. Zoxamide accounted for 87% of TRR in fruits and 89% in foliage indicating that the parent is predominant. Minor metabolites were identified in fruits and foliage. Among them, RH-150721 and RH-157450 were present at the highest concentrations but still less than 0.1 mg/kg (< 5% of TRR).

Tomato plants received three foliar applications at 0.86 mg/kg with 18 day intervals and tomato fruits were collected 1 day after the last application. The TRR was 0.29 mg/kg in green tomato and 0.50 mg/kg in red tomato. The parent was the major component of residues amounting to 0.14 mg/kg (48% of TRR) in green tomato and 0.22 mg/kg (44% of TRR) in red tomato. Minor amounts of metabolites were identified but none exceeded 3% of TRR. RH-1452 and RH-141288 were identified in two different fractions but their actual concentrations were not determined.

Three foliar applications were made at the rate of 0.9 kg ai/ha on potato plants with the first application at 39 days after planting, and the second and third made at intervals of 21 and 17 days respectively. Mature potato tubers were harvested 14 days after the last application. The TRR was 0.18 mg/kg parent equivalents. Unlike other plants tested, the parent compound was not found in the harvested commodity, i.e., the potato tuber. The metabolites RH-1455 and RH-1452 were found at 0.069 and 0.037 mg/kg accounting for 39% and 21% of the TRR, respectively.

The nature of minor metabolites suggests that zoxamide, when applied to plants, underwent dechlorination and hydrolysis or oxidation. Zoxamide was the major residue in grape, cucumber and tomato when harvested one day after the last application. However, the parent compound was not found in potato sampled 14 days after the last application.

***Environmental fate in soil***

The Meeting reviewed information on aerobic soil metabolism and rotational crop study as zoxamide was intended for protection of potatoes.

Aerobic soil metabolism studies were conducted using [U-$^{14}$C-phenyl]zoxamide applied to various soils which were then incubated under aerobic conditions at 20 or 25 °C. Under aerobic conditions, zoxamide applied to soil was rapidly degraded. After 120–122 days, only small amounts (0.6–10%) of applied zoxamide remained as the parent. Carbon dioxide was steadily evolved from all soils and accounted for 34–58% of the dose applied after 120–122 days. RH-127450, RH-129151,

RH-24549, RH-139432 and RH-163353 were formed and then degraded during the study periods. Unextracted radioactivity, 0.4-3.3% of the applied dose (3.3% in silt loam dosed at 1.5 mg/kg; for other soils tested 0.4–0.8%) on day 0, increased steadily to reach 24–38% of the applied dose on day 120–122. Several other degradates were observed at very low concentrations. These results indicate that none of zoxamide or its identified metabolites are persistent in soil.

***Residues in succeeding crops***

In an outdoor confined rotation study, mustard, radish, turnip, sorghum and soya bean were planted at 30, 137, 210, 365 days following the last of four applications of [$^{14}$C-phenyl]zoxamide. Zoxamide was applied to bare soil between mid April and early June (18 day intervals) at a rate of 0.5 kg ai/ha. Crops were harvested at an intermediate stage and when mature.

TRRs were very low for all samples at all plant back intervals. In general, the amount of extractable residues was low in all the crop samples. Between 7% and 40% of the TRR was recovered in the polar MeOH/$H_2O$ fractions for all the crops grown on treated soil. About 2 to 36% of the TRR was found in the organic extracts ($CHCl_3$, $CH_3CN$ and hexane) of all the crops. The concentrations in these samples did not exceed 0.023 mg/kg. The values of extracts for all the crop samples showed a significant fraction of unextracted residues: generally 49% or greater.

Concentrations of RH-1452 and one other metabolite were generally below 0.01 mg/kg. The second metabolite was not fully identified. Other metabolites were detected at lower concentrations in some crops.

Zoxamide residues are not expected to occur in succeeding crops.

***Methods of analysis***

Analytical methods for determination of residues of zoxamide were developed for a wide range of matrices including cucurbits, grapes, tomato, potato and their processed commodities and byproducts.

In most of the methods for determination of zoxamide only, zoxamide was extracted with organic solvent or a mixture of organic solvent and aqueous solution specific to the matrix; cleaned up with liquid-liquid partition followed by solid phase extraction using carbon, alumina, Florisil and silica singly or in combination; and analysed by gas chromatography using electron capture detection (GC/ECD) for quantitation and mass selective detection (GC/MSD) for confirmation. For detection, ELCD or NPD may also be used. These methods were validated in independent laboratories. Most of the methods were suitable as enforcement methods with the limit of quantification at 0.01 mg/kg. One method for potato and its products has an LOQ of 0.02 mg/kg.

The existing multi-residue enforcement methods, one of FDA screen methods and DFG S19 were also tested to be suitable for analysing zoxamide.

The methods for potato and its processed commodities determine zoxamide and two metabolites, RH-1452 and RH-1455. While zoxamide is extracted in the organic phase in liquid-liquid partition, these metabolites were extracted in the aqueous phase. After methylation of these metabolites using diazomethane, and further clean-up, they were analysed using GC/ECD or GC/MSD. The LOQ was 0.02 mg/kg.

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

Stability of zoxamide (0.1–2 mg/kg) in homogenized samples of grapes (433 days), cucumbers (868 days), tomatoes (810 days), and potatoes (708 days); grape juice (858 days); dried grapes (789 days); wine (8 months); tomato juice (832 days); tomato paste (237 days); and tomato puree (228 days) stored in deep freezer at a temperature below -10 ˚C was investigated.

No decrease of zoxamide was observed in all samples of cucumbers, tomatoes and its processed products and potatoes during the test periods.

In the case of grapes and its products, in particular grape juice, relatively large fluctuations were observed in the percentage of remaining zoxamide during the test period. However, the Meeting

concluded that zoxamide was sufficiently stable for 14 months in grapes, 28 months in grape juice, 26 months in dried grapes and 8 months in wine.

RH-1452 and RH-1455 were shown to be stable for 29 months of storage while frozen.

***Definition of the residue***

In grapes, zoxamide represented 58% of the TRR with no metabolite exceeding 5% of the TRR. Also in cucumber and tomato, zoxamide is the major residue component: 87% of TRR in cucumber, 48% of TRR in green tomatoes and 44% of TRR in red tomatoes. No metabolite was found to be more than 10% of the TRR in all cucumber and tomato samples. Most metabolite residues were present at less than 5% of the total residues. These indicate that the residue of concern in grapes, cucurbit and tomato be defined as parent although samples analysed were taken only one day after the last application.

In potato, however, no parent zoxamide was detected. RH-1452 and RH-1455, comprising 21% and 39% of the total residue, respectively, were the major components of the residue. Another 16% of the residue was identified as glucose and/or other sugars. No other metabolites were present at or higher than 10% of TRR. In supervised field trials in Northern and Southern Europe, the United States, Canada and Mexico, samples were analysed for zoxamide, RH-1452 and RH-1455. In all trials, residues of parent were below the LOQ and concentrations of the metabolites were also below the LOQ in all but two trials where zoxamide was found at 0.02 mg/kg.

Methods of analysis are available for determination of zoxamide in grapes, cucurbits, tomatoes and potatoes and their processed products. A method is available also for determination of RH-1452 and RH-1455 in potatoes.

The current Meeting concluded that only zoxamide is toxicologically significant.

In the lactating goat study, the main components of residues were RH-127450 in milk and fat, glucuronic acid conjugates of 4-hydroxymethyl-RH-141288 in liver, with the highest concentration of 0.13 mg/kg parent equivalents of RH-12740 in liver. However, as the administered dose was 14 times higher than the highest residue concentration found in the reported trials, no residue was expected to be found in animals given feed with incurred residues of zoxamide. No method of analysis is currently available for these metabolites. For these reasons, the Meeting concluded that it was not in a position to recommend a residue definition for animal commodities.

In the lactating goat study, the concentration of radioactive residues expressed in parent equivalent in fat was about 4 times that in muscle but about one half of that in kidney or liver. Therefore, the Meeting considered residues not fat-soluble.

In countries where there are MRLs for zoxamide, the residue definition was mostly “zoxamide” except in the USA where it is zoxamide including its metabolites RH-1452 and RH-1455 for potato and its products.

The Meeting recommended the following residue definition for zoxamide in plant commodities.

*For plants: Definition of the residue (for compliance with the MRL and for estimation of dietary intake):* zoxamide

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

The Meeting received supervised trial data for zoxamide uses on grapes, cucurbits, tomato and potato.

*Grapes*

Numerous residue trials were conducted on grapes in Brazil, Canada, Germany, France, Greece, Italy, Republic of Korea, Spain and the USA.

The trials conducted in Germany used six applications rather than four as on the label. The Meeting decided to use the results of these trials for MRL estimation as the last applications contribute most to the residue concentration at harvest. In 12 German trials in accordance with German GAP

(maximum rate of 0.24 kg ai/ha in 800-1600 L/ha, 4 applications, with a PHI of 56 days) (except application number), zoxamide residues in rank order were: 0.34, 0.38, 0.39, 0.41, 0.41, 0.45, 0.49, 0.55, 0.59, 0.60, 0.66 and 0.72 mg/kg.

The trials conducted in France used ten applications rather than three on the label. The Meeting decided to use the results of these trials for MRL estimation as it is the last applications that contribute the most to the residue concentration at the harvest. In 21 Northern French trials in accordance with French GAP (0.12 kg ai/ha, 3 applications, PHI 28 days)(except application number), zoxamide residues in rank order were: 0.09, 0.17, 0.19, 0.19, 0.33, 0.35, 0.45, 0.47, 0.48, 0.50, 0.50, 0.51, 0.55, 0.56, 0.67, 0.77, 0.77, 0.81, 0.88, 1.31, 1.55 mg/kg. In 15 Southern French trials conducted in accordance with French GAP, zoxamide residues in rank order were: 0.21, 0.21, 0.33, 0.42, 0.42, 0.46, 0.49, 0.54, 0.58, 0.61, 0.63, 1.07, 1.11, 1.53 and 2.84 mg/kg. Since the residue populations in the Northern and Southern France are similar and there is a uniform GAP for the whole of France, the Meeting considered it appropriate to combine the results from 36 trials in France: 0.09, 0.17, 0.19, 0.19, 0.21, 0.21, 0.33, 0.33, 0.35, 0.42, 0.42, 0.45, 0.46, 0.47, 0.48, 0.49, 0.50, 0.50, 0.51, 0.54, 0.55, 0.56, 0.58, 0.61, 0.63, 0.67, 0.77, 0.77, 0.81, 0.88, 1.07, 1.11, 1.31, 1.53, 1.55 and 2.84 mg/kg.

In 15 Italian trials conducted in accordance with Italian GAP (maximum rate of 0.17 kg ai/ha, 0.017 kg ai/hL, 5 applications, PHI 28 days), zoxamide residues in rank order were: 0.24, 0.28, 0.29, 0.30, 0.33, 0.48, 0.48, 0.54, 0.59, 0.65, 0.66, 0.81, 0.82, 1.37 and 1.56 mg/kg.

In six Spanish trials conducted in accordance with Italian GAP, zoxamide residues in rank order were: 0.36, 0.53, 1.17, 1.21, 1.42 and 1.92 mg/kg.

In four Greek trials conducted in accordance with Italian GAP, zoxamide residues in rank order were: 0.27, 0.32, 0.34 and 0.64 mg/kg.

Combined residues from Italian, Spanish and Greek trials in accordance with Italian GAP in rank order were: 0.24, 0.27, 0.28, 0.29, 0.30, 0.32, 0.33, 0.34, 0.36, 0.48, 0.48, 0.53, 0.54, 0.59, 0.64, 0.65, 0.66, 0.81, 0.82, 1.17, 1.21, 1.37, 1.42, 1.56 and 1.92 mg/kg.

Six trials were conducted in Canada but none was in accordance with Canadian GAP (0.19 kg ai/ha, 6 applications, PHI 66 days). However, four trials were in accordance with US GAP (maximum rate of 0.22 kg ai/ha, 8 applications, PHI 14 days). Residues in rank order were: 1.12, 1.46, 1.52 and 1.69 mg/kg.

Among numerous US trials, 17 trials were conducted in accordance with US GAP. Zoxamide residues in rank order were: 0.22, 0.31, 0.34, 0.34, 0.42, 0.46, 0.49, 0.52, 0.61, 0.66, 0.83, 0.91, 1.08, 1.18, 1.61, 1.65 and 4.34 mg/kg.

Combined residues from the US and Canadian trials conducted in accordance with US GAP (ranked order, median underlined) were: 0.22, 0.31, 0.34, 0.34, 0.42, 0.46, 0.49, 0.52, 0.61, 0.66, <u>0.83,</u> 0.91, 1.08, 1.12, 1.18, 1.46, 1.52, 1.61, 1.65, 1.69 and 4.34 mg/kg.

In seven Brazilian trials conducted in accordance with Brazilian GAP (maximum rate of 0.13 kg ai/ha, 600–1000 L/ha, PHI 7 days), zoxamide residues in rank order were: 0.07, 0.08, 0.14, 0.14, 0.15, 0.16 and 0.36 mg/kg.

Three trials conducted in the Republic of Korea seemed to be in accordance with Korean GAP (0.01 kg ai/ha, three applications, PHI 7 days). The residues were: 0.05, 0.06 and 0.08 mg/kg.

Among results of these trials, residues from US trials would lead to the highest maximum residue level. Based on the results from US and Canadian trials, the Meeting estimated a maximum residue level and an STMR for zoxamide in grapes of 5 and 0.83 mg/kg respectively.

*Fruiting Vegetables, cucurbits*

Protected supervised trials were conducted on cucumber in France and Spain and field trials in the Republic of Korea and the USA. Supervised trials were also conducted in the USA for cantaloupe and squash.

Six supervised indoor trials on cucumber in France were in accordance with Polish GAP (maximum rate of 0.15 kg ai/ha, 700–800 L/ha, 3 applications, PHI 4 days) although five applications were made. Residues from these trials in rank order were: 0.01, 0.03, 0.04, 0.06, 0.06 and 0.48 mg/kg. In three Spanish trials conducted in accordance with Polish GAP, zoxamide residues in rank order were: 0.25, 0.44 and 0.45 mg/kg. Combined residues in rank order (median underlined) were: 0.01, 0.03, 0.04, 0.06, 0.06, 0.25, 0.44, 0.45 and 0.48 mg/kg.

Seven outdoor trials were conducted in the USA but only one trial was in accordance with the current US GAP for cucurbits (maximum rate of 0.19 kg ai/ha, 8 applications, PHI 5 days). The residues were: 0.04 mg/kg.

Four trials were conducted in the Republic of Korea on cucumber but none were in accordance with Korean GAP.

Seven trials on cantaloupe and six on summer squash were conducted in the USA but only one each was in accordance with the current US GAP. The residue level in one cantaloupe trial was 0.04 mg/kg and that in one squash trial was 0.09 mg/kg.

On the basis of indoor trials in Europe, the Meeting estimated a maximum residue level and an STMR for zoxamide in cucumber at 1 and 0.06 mg/kg respectively.

*Tomato*

Protected supervised trials were conducted on tomato in Greece and Spain; and field trials in Brazil, Italy, Spain and the USA.

In 10 Spanish indoor trials conducted in accordance with Italian GAP (maximum rate of 0.17 kg ai/ha, 0.017 kg ai/hL, 5 applications, PHI 3 days), zoxamide residues in rank order were: 0.07, 0.08, 0.09, 0.09, 0.10, 0.12, 0.12, 0.15, 0.24 and 0.29 mg/kg.

In two French indoor trials conducted in accordance with Italian GAP, zoxamide residues in rank order were: 0.28 and 0.31 mg/kg.

In three Greek indoor trials conducted in accordance with Italian GAP, zoxamide residues in rank order were: 0.15, 0.30 and 0.30 mg/kg.

Combined residues from the indoor trials in Spain, France and Greece in accordance with Italian GAP were: 0.07, 0.08, 0.09, 0.09, 0.10, 0.12, 0.12, 0.15, 0.15, 0.24, 0.28, 0.29, 0.30, 0.30 and 0.31 mg/kg.

In 12 Italian outdoor trials conducted in accordance with Italian GAP, zoxamide residues in rank order were: 0.12, 0.13, 0.14, 0.15, 0.16, 0.18, 0.18, 0.20, 0.22, 0.24, 0.24 and 0.30 mg/kg. In five Spanish outdoor trials conducted in accordance with Italian GAP, zoxamide residues in rank order were: 0.03, 0.04, 0.04, 0.05 and 0.05 mg/kg. Combined residues were: 0.03, 0.04, 0.04, 0.05, 0.05, 0.12, 0.13, 0.14, 0.15, 0.16, 0.18, 0.18, 0.20, 0.22, 0.24, 0.24 and 0.30 mg/kg.

Eighteen US outdoor trials were considered to have been conducted in accordance with US GAP (maximum rate of 0.19 kg ai/ha, 8 applications, PHI 5 days) although application number was mostly 10 up to 13 despite the label specification of 8 applications; however the Meeting concluded that the last applications contribute the most to residue concentrations at harvest. Zoxamide residues in ranked order (median underlined) were: 0.07, 0.10, 0.11, 0.12, 0.13, 0.16, 0.18, 0.18, 0.19, 0.20, 0.21, 0.21, 0.22, 0.23, 0.32, 0.38, 0.40 and 1.0 mg/kg.

In five Brazilian outdoor trials conducted in accordance with Brazilian GAP (maximum rate of 0.13 kg ai/ha, applied in 800 L/ha, with a PHI of 7 days), zoxamide residues in rank order were: 0.01, 0.02, 0.02, 0.03 and 0.14 mg/kg.

Among results from the above trials, those from US trials would lead to the highest maximum residue level. Based on the US data, the Meeting estimated a maximum residue level and an STMR for zoxamide in tomato of 2 and 0.195 mg/kg respectively.

*Potato*

Supervised trials were conducted on potato in Argentina, Brazil, Canada, France, Germany, Greece, Italy, Republic of Korea, Mexico, the Netherlands, Spain, the UK and the USA.

In six trials in Northern France, seven in Germany, one in the Netherlands and 11 from the UK conducted in accordance with GAP in Ireland, the Netherlands and the UK (maximum rate of 0.15 kg ai/ha, 200–600 L/ha, 10 applications, PHI 7 days), zoxamide residues were all < 0.02 mg/kg (25).

In six trials in Southern France, four in Greece, seven in Italy and six in Spain conducted in accordance with Italian GAP (maximum rate of 0.17 kg ai/ha (0.017 kg ai/hL), 5 applications, PHI 7 days), zoxamide residues were all < 0.02 mg/kg (23).

Twelve Canadian trials were considered to have been conducted in accordance with Canadian GAP (0.19 kg ai/ha, 6 applications, PHI 3 days) although 10 applications were made; however the Meeting concluded that the later applications contribute the most to residue concentrations at harvest. The residues were all < 0.02 mg/kg (12). A total of 27 USA trials were considered to be in compliance with US GAP (0.19 kg ai/ha, 6 applications, PHI 3 days) although 10 applications were made. The residues were all below the LOQ (0.02 mg/kg) (4) or LOD (0.006 mg/kg) (22) and hence < 0.02 mg/kg (27). Even with double rate applications, residues were below the LOQ.

Eight trials were conducted in Mexico but samples were taken 13 or 14 days after the last application instead of the PHI of 7 days as specified on the label.

In two Argentine trials, conducted in accordance with Argentine GAP (0.15 kg ai/ha, 400–1000 L/ha, PHI 7 days), zoxamide residues were < 0.05 mg/kg (2).

In six Brazilian trials, conducted in accordance with Brazilian GAP (maximum rate of 0.13 kg ai/ha, 650 L/ha, PHI 7 days), zoxamide residues (ranked order, median underlined) were: < 0.<u>01</u> (4) (two were below the LOD) and 0.02 mg/kg (2).

Six trials were conducted in the Republic of Korea but none were in compliance with Korean GAP.

On the basis of the Brazilian trials and the fact that, other than two Brazilian trials, residues from trials done in accordance with respective GAP were all below the LOQ, the Meeting estimated a maximum residue level and an STMR at 0.02 and 0.02 mg/kg.

***Fate of residues during processing***

The Meeting received information on processing of grapes to dried grapes, juice, wine and pomace, tomatoes to puree and paste, and potatoes into flakes, chips and peel.

Processing factors were calculated for grapes (dried grapes, juice, wine and pomace), tomato (puree and paste) and potato (peel) and are shown in the Table below. Processing factors could not be calculated for potato flakes or chips because the residue concentrations were below the LOQ in both potatoes and processed products.

Mean processing factors and STMR-P for food and feed.

| Commodity | Processing factor | Median or best estimate | STMR-P mg/kg |
|---|---|---|---|
| Grapes | | | 0.83 |
| Unclarified juice | 0.10, 0.16 | 0.13 | 0.11 |
| Dried grapes | 2.2, 3.5 | 2.9 | 2.4 |
| Wine | < 0.01, < 0.01, < 0.01, < 0.01, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.03, < 0.03, < 0.04 | < 0.02 | 0.02 |
| Pomace, wet | 0.01, 0.02, 0.05, 0.05, 0.13, 0.79, 1.1, 1.5, 3.1 | 1.3 [1] | 1.1 |
| Tomato | | | 0.195 |
| Puree | 0.43 | 0.43 | 0.08 |
| Paste | 0.97 | 0.97 | 0.19 |
| Potato | | | 0.02 |
| Peel | > 3.0 | 3.0 | 0.06 |

[1] As the spread of processing factors of wet pomace calculated from trial results is very large, the Meeting decided to take a conservative approach and use four values at the higher end to provide the best estimate of the processing factor.

Dried grapes are expected to contain higher residues than grapes. Multiplying the highest residue concentration found in the supervised trials (4.34 mg/kg) by the processing factor of 2.9, resulted in an estimate of 12.6 mg/kg, the Meeting estimated a maximum residue level at 15 mg/kg.

### *Residues in animal commodities*

Potato wet peel and wet grape pomace may be fed to dairy cattle and beef cattle but not as major feed ingredients. The calculated maximum and mean livestock animal burden was 0.03–1.50 ppm.

In the metabolism study, in which zoxamide equivalent to 60.7 ppm in the diet was orally administered to a lactating goat for 7 consecutive days, no parent compound was found in any tissue or milk. A number of metabolites were present in tissues and milk but mostly below 0.1 mg/kg parent equivalents. Given the low estimated animal burden, about one fortieth of the administered level, no zoxamide or its metabolite is expected to be present at detectable levels in tissues or milk.

The Meeting agreed that no maximum residue level was necessary for commodities derived from mammals.

The livestock dietary burden was also calculated for layers and broilers with potato wet peel and wet grape pomace and were 0–0.73 ppm. No information was available on the fate of zoxamide in poultry. In addition, no method of analysis was submitted for zoxamide or metabolites in commodities derived from poultry.

The Meeting agreed that no maximum residue level could be estimated for commodities of poultry origin.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

The International Estimated Dietary Intakes (IEDIs) of zoxamide were calculated for the 13 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.5 mg/kg bw and the calculated IEDIs were all 0% of the maximum ADI. The Meeting concluded that the long-term intakes of residues of zoxamide, resulting from the uses considered by the current JMPR, are unlikely to present a public health concern.

### *Short-term intake*

The 2007 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of residues of zoxamide is unlikely to present a public health concern.