	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 ≥ 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

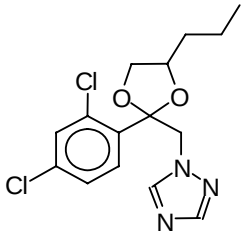
	Value	**Study**	**Safety factor**
ADI	0–0.03 mg/kg bw	Dog, studies of oral toxicity	100
ARfD	1 mg/kg bw	Rat, study of acute neurotoxicity	100

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 *β*-isomers identified in stalks and grains) and CGA-91305. O-glycosides of CGA-118244 (all four *β*-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 (3×0.029) 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 Grape presscake	1	0.05 0.95	0.05 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

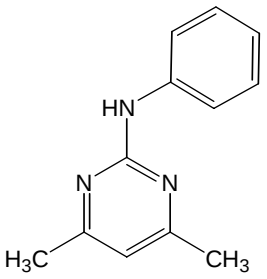
	Value	Study	Safety factor
ADI	0–0.2 mg/kg bw per day	Rats, 2-year study of toxicity	100
ARfD	Unnecessary	—	—

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

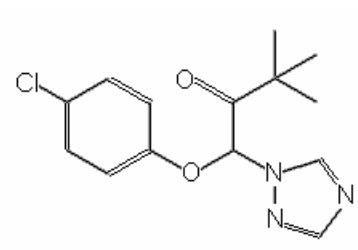
5.22 TRIADIMEFON (133)/ TRIADIMENOL (168)

RESIDUE AND ANALYTICAL ASPECTS

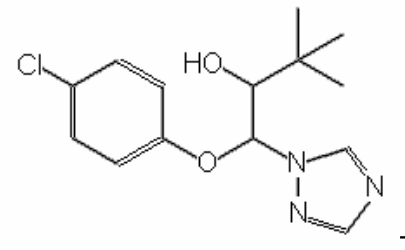
Triadimenol and triadimefon are related substances and follow the same metabolic pathways in all matrices investigated. Both compounds were evaluated by JMPR several times since 1978 and the last time in 2004, when an ADI of 0–0.03 mg/kg bw and an ARfD of 0.08 mg/kg bw were established for triadimefon 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.



ohenoxy)-3,3-dı



-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), < 0.05(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 peppers 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 tomatoes 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 peppers 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 tomatoes 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) 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

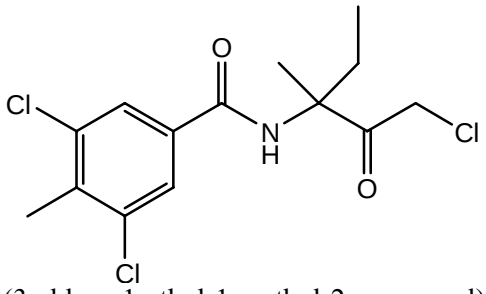
Guinea-pig, skin sensitization (test method used)	A skin sensitizer (Buehler; Magnusson & Kligman)
Short-term studies of toxicity	
Target/critical effect	Body-weight gain
Lowest relevant oral NOAEL	1500 ppm (48 mg/kg bw per day) in a 1-year study in dogs
Lowest relevant dermal NOAEL	< 107 mg/kg bw for 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 Rapid excretion essentially unmetabolized. Oral LD_{50} in mice > 5000 mg/kg bw Negative in an Ames test. RH-141,455 Rapid excretion essentially unmetabolized. Oral LD_{50} in mice > 5000 mg/kg bw 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.