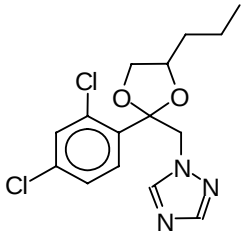
5.20 PROPICONAZOLE (160)

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).