5.18 PENCONAZOLE (182)

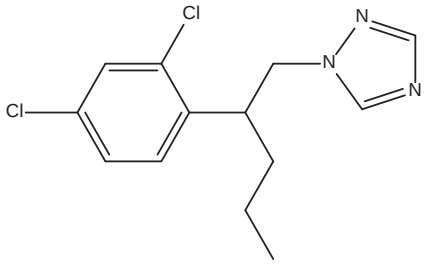
RESIDUE AND ANALYTICAL ASPECTS

Penconazole is a systemic triazole fungicide used for the control of powdery mildew, pome fruit scab and other fungal pathogens on fruit and vegetables. It belongs to the class of sterol demethylation inhibitors (DMI inhibitors), inhibiting the biosynthesis of cell membrane ergosterol.

Penconazole was first evaluated by JMPR in 1992 for toxicology and residues. In 1995, residue data for pome fruits and grapes were reviewed. In 2015, penconazole and the metabolites, 1,2,4-triazole, triazole alanine and triazole acetic acid were re-evaluated for toxicology by JMPR within the periodic review programme of CCPR. The Meeting reaffirmed the ADI of 0–0.03 mg/kg bw and established an ARfD of 0.8 mg/kg bw for penconazole. For 1,2,4-triazole, the Meeting reaffirmed the previous ADI of 0–0.2 mg/kg bw and ARfD of 0.3 mg/kg bw. For triazole alanine and triazole acetic acid, the Meeting reaffirmed the group ADI (alone or in combination) of 0–1 mg/kg bw as expressed as triazole alanine and established an ARfD of 3 mg/kg bw for triazole alanine and triazole acetic acid.

Penconazole was scheduled at the 47th Session of the CCPR (2015) for periodic re-evaluation of residues by the 2016 JMPR. The Meeting received information on physical and chemical properties, metabolism and environmental fate, residue analysis, use patterns, supervised trials, processing and animal feeding studies.

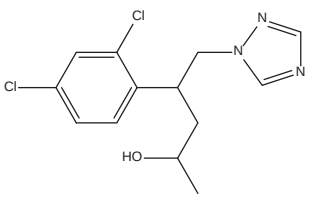
The structural formula and IUPAC name of penconazole are:

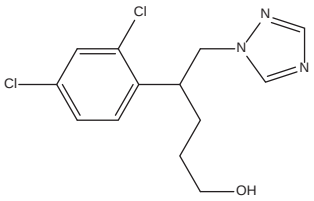
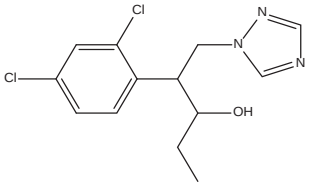
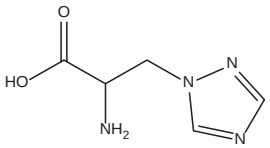
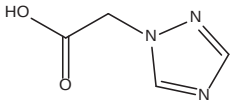
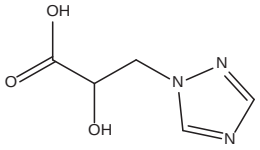
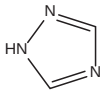
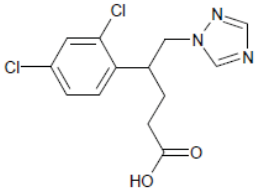


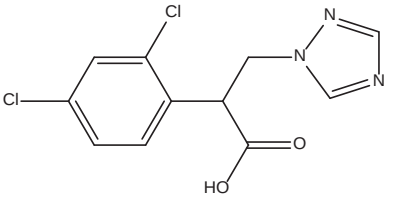
(*RS*)-1-[2-(2,4-dicholorophenyl)pentyl]-1*H*-1,2,4-triazole

Penconazole consists of a pair of enantiomers (racemic mixture). For metabolism and environmental fate studies, penconazole radio-labelled either in the phenyl or triazole-moiety was used.

The following abbreviations, along with chemical names and structures, are used for the metabolites discussed below:

Compound code	Abbreviation	Chemical name	Structure
CGA132465 (a mixture of 2 diastereoisomers CGA132465a, CGA132465b)	β-monohydroxy metabolite	4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentan-2-ol	

Compound code	Abbreviation	Chemical name	Structure
CGA127841	γ-monohydroxy metabolite	4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentan-1-ol	
CGA190503	α-monohydroxy metabolite	4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentan-3-ol	
CGA131013	TA	2-amino-3-(1H-1,2,4 triazol-1-yl)propanoic acid; 3-(1H-1,2,4-triazol-1-yl)-D,L-alanine; Triazole alanine	
CGA142856	TAA	1H-1,2,4-triazol-1-yl-acetic acid; Triazole acetic acid	
CGA205369	TLA	2-hydroxy-3-[1,2,4]triazol-1-yl-propionic acid; Triazole lactic acid	
CGA71019	1,2,4-triazole	1*H*-1,2,4-triazole	
CGA177279		4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentanoic acid	

Compound code	Abbreviation	Chemical name	Structure
CGA179944		2-(2,4-dichloro-phenyl)-3-[1,2,4]triazol-1-yl-propionic acid	

Plant metabolism

The metabolism of penconazole was studied in grapes, tomatoes and apples.

Grapes

A plot of four plants was treated four times with [14C-triazole] penconazole, with a 14–18 day interval, at rates of 5 g ai/hL by foliar spraying. Mature grapes and leaves were harvested 68 days after treatment. Total radioactive residues (TRRs) in grapes and the leaves were 0.10 mg eq/kg and 5.3 mg eq/kg, respectively. The grape TRRs were partitioned into the juice fraction (36%) and the press cake fraction (64%). Juice was partitioned with dichloromethane and the aqueous phase was hydrolysed. Press cake was extracted with 80% methanol and the extract was partitioned with dichloromethane. Then the aqueous phase was hydrolysed. Extraction with methanol recovered 84% of the TRR in juice and press cake and 95% TRR in the leaves.

The parent compound was found at up to 16% (0.016 mg/kg) of the TRR in grapes and 8% TRR (0.45 mg/kg) in the leaves. Hydroxylated metabolites including CGA190503, CGA132465 and CGA127841 (α-, β- and γ-monohydroxylated of the alkyl chain of parent, respectively) were the predominant residues in both grapes and leaves. In total, the monohydroxy metabolites (free or conjugated) accounted for 61% TRR (3.3 mg eq/kg) in the leaves. CGA132465, a mixture of diastereomers of CGA132465 and CGA132465 b, was the predominant residue (39% TRR, 2.1 mg eq/kg) and CGA190503 and CGA127841 were at a lesser extent (16% and 6% TRR, respectively). Polar fractions likely containing triazole-specific metabolites were not further characterized in leaves. In grapes, the monohydroxy metabolites, not characterised individually, accounted for 35% TRR (0.035 mg eq/kg). Polar fractions analysed contained TA, TAA and TLA, totalling 25% TRR (0.025 mg eq/kg), representing 10% TRR (0.01 mg eq/kg), 2.3% TRR (0.0023 mg eq/kg) and 12% TRR (0.012 mg eq/kg), respectively, in grapes.

Penconazole, radiolabelled with [^{14}C-triazole] or [^{14}C-phenyl], was applied to grape vines planted at two sites. Grape vines were treated by foliar spraying with different doses by site (3 ×0.038 kg ai/ha at 1st application, -47-day PHI, at Site 1 and 5 ×0.10 kg ai/ha, 1st application, -90-day PHI, at Site 2). At Site 1, grapes were harvested 64 (immature) and 78 (mature) days after the last application (DALA) and at Site 2, harvested 0, 14 and 22 DALA.

Overall total radioactive residues were different depending on the dose and harvest times but not related to difference with radiolabelling. In grapes (78 DALA), total radioactivity from triazole-label application was 0.08 or 0.049 mg eq/kg and was 0.05 mg eq/kg from phenyl-label application. Overall total residues in the leaves decreased over time, e.g. for Site 1 from the triazole-label, 8.1 mg eq/kg (0 DALA) to 2.5 mg eq/kg (64 DALA) and 1.9 mg eq/kg (78 DALA). Extraction of radioactive residues with methanol recovered 69–88% of the TRR in grapes. Overall metabolic fractions and distribution pattern of radioactivity were similar among the treatments.

In the mature grapes from a triazole label study (78 days, 0.049 mg eq/kg), the parent compound was found at a level of 11% TRR (0.005 mg/kg). CGA132465 (mainly), CGA127841 and

CGA190503 were the predominant residues, accounting for totalling 22% TRR mainly found after acid hydrolysis. Polar fraction (likely containing triazole-specific metabolites) making up 24% TRR (0.012 mg eq/kg) was not further characterised.

Tomatoes

[^{14}C-phenyl] penconazole was applied four times to field grown tomato plants (BBCH 71, first fruit clusters) at a 7-day interval and rates of 0.040 kg ai/ha by foliar spraying. Fruit and leaf samples were collected 7 and 40 days after treatment. Total radioactive residues decreased over time (7 to 40 DALA), 0.034 mg eq/kg to 0.014 mg eq/kg in fruit and 2.7 mg eq/kg to 0.42 mg eq/kg in the leaves. The majority (> 84%) of radioactive residues in fruit and leaves were able to be recovered by methanol extraction. Surface methanol wash of mature fruits removed only 2.4% TRR, indicating that the majority of the residue was internal to the fruits.TRR levels of the parent compound decreased over time (7 to 40 DALA), 15% TRR (0.005 mg/kg) to 7% TRR (0.001 mg/kg). In tomatoes both at 7 and 40 DALA, CGA132465 (including trace amount of CGA127841) was the predominant residues, accounting for 63–65% TRR found after acid hydrolysis (CGA132465, 62% TRR). CGA190503 was also found but at a trace level, 3–4% TRR. The metabolic patterns in the leaves were qualitatively very similar to those in fruits.

Using penconazole radiolabelled with [^{14}C-triazole], metabolism in tomatoes was investigated in the same way as the study described above, running in parallel with it.

TRRs in fruits were 0.071 mg eq/kg (7 DALA) and 0.029 mg eq/kg (40 DALA), which was two-fold higher than in fruits treated with the phenyl label. Surface wash with methanol removed 16% (7 DALA) and 3% TRR (40 DALA). The majority (> 87%) of radioactivity was able to be recovered by methanol extraction.

The results were nearly the same with those from the phenyl-label study, except for triazole specific metabolites. In mature tomatoes, the parent compound was found at 0.003 mg/kg (12% TRR). The monohydroxy metabolites, CGA132465 (55% TRR), CGA127841 (2% TRR, < 0.001) and CGA190503 (3% TRR, < 0.001) were found in total, 60% TRR level (0.017 mg eq/kg) after acid hydrolysis.

The sum of 1,2,4-triazole, TA, TAA and TLA amounted to 20% TRR (0.006 mg eq/kg). TA was most predominant, accounting for 15% TRR (0.004 mg eq/kg).

Apples

Penconazole, radio-labelled with [^{14}C-triazole], was applied ten times to two apple trees at a 8–17 day interval and rates of 2.5 g ai/hL by foliar spraying. A sample of leaves was taken at 0, 2, 5, 7 and 14 DALA. At harvest (34 DALA), all fruits, leaves, branches and roots were collected. Total radioactive residues in apple fruit were 0.10 mg eq/kg, which comprised 39% TRR in peel and 61% TRR in pulp. In leaves, branches and roots, TRR levels were 3.8, 0.61 and 0.17 mg eq/kg, respectively.

Radioactivity in the leaves decreased over time from 5.5 mg eq/kg (0 DALA) to 3.8 mg eq/kg at harvest (34 DALA). The surface radioactivity in leaves (0 DALA) accounted for 57% TRR, but was not detected at harvest (34 DALA). Methanol extraction was able to recover > 70% of the TRRs in various matrices. Soxhlet extraction in methanol recovered an additional 3% TRR in whole fruit.

In apple fruit, the parent compound was found at 12% of the TRR (0.012 mg/kg). CGA132465 and TA were the predominant residues, accounting for 14% TRR (0.014 mg eq/kg, 5.5% TRR released after acid hydrolysis) and 23% TRR (0.023 mg eq/kg, 22% TRR from pulp), respectively. CGA127841 was present but only at 0.5% TRR (< 0.001). Other minor residues (CGA190503, CGA189659, dihydroxy metabolites, CGA179944, TAA, TLA, 1,2,4-triazole glycolic acid) were present at < 5% TRR.

In leaves, branches and roots, TRR levels of the parent compound were 7% (0.26 mg/kg), 43% (0.26 mg/kg) and 13% (0.022 mg/kg), respectively. In leaves, CGA132465 and CGA189659 were found at 38% and 14% of the TRR, while TA was not found. CGA91304 and the acetyl derivative CGA90305 were found only in the leaves at trace levels (0.03% and 0.04% TRR, respectively). For branches and roots, identification of components was not made except for parent compound.

Fractions from apple trees were collected at one and two years after last treatment. In fruits, TRR levels compared to the initial level was 92% after one year (134% in pulp and 32% in peel) and 49% after two years (68% in pulp). In both leaves and branches, TRR levels dropped to 30% and 22% after one and two years, respectively.

In one year post treatment samples, the majority of the radioactivity (82–98% TRR) was water soluble. Parent compound was not found in any part of the plants. The main metabolites found in this stage were TA, TAA and TLA, accounting for 4–65% TRR in apple, leaves and branches.

In summary, the nature of the residues was essentially the same in grape, tomato and apple. The biotransformation of penconazole results from the oxidation of penconazole at the 1, 2 and 3 positions of the alkyl chain and subsequent conjugation with sugar. Thus the monohydroxy metabolites (α-, β-, γ-monohydrxoy metabolite) were abundant in plant and acid hydrolysis or enzyme treatment was needed to release the aglycones. Among the metabolites, β-monohydroxy metabolite (CGA132465) was most predominant, accounting for 14–62% TRR (0.009–0.016 mg eq/kg). Metabolites in plants were also observed in rats.

Label-specific metabolism from the ^{14}C-triazole treatments resulted from the cleavage of the triazole moiety (1,2,4-triazole) and subsequent conjugation with serine to form TA and by catabolism to form TAA and TLA. Total triazole-specific residues amounted to 20–29% TRR in the crops (0.006–0.029 mg eq/kg), comprising TA 10–23% TRR, TAA 0.8–2.3% TRR and TLA 2.3–12% TRR. After one year following direct application on apple tree, cleavage of the triazole moiety resulted in non-detection of parent compound and abundance of triazole-specific metabolites.

Based on data from tomato and apple, penconazole remains mainly as a surface residue on fruits. However, most of radioactivity in fruits was found as conjugated monohydroxy metabolites within the fruit.

Rotational crop studies

In the two confined rotational crop studies (triazole-label and phenyl-label study), a single application was made on bare soil at a rate of 0.24 kg ai/ha. Lettuce, radish, spring wheat and winter wheat were put into the treated soil at plant-back intervals (PBIs) of 32, 126 and 358 days (only 179-day PBI for winter wheat).

TRR levels were variable with respect to increases or decreases with longer PBIs in the triazole-label study, while TRR levels consistently declined in the phenyl-label study, except in wheat fodder and grain. TRR levels demonstrated significant amounts of radioactivity transferred into the succeeding crops. The highest TRR level from the triazole-label study was 0.072 mg eq/kg in lettuce (126-day PBI), 0.084 mg eq/kg in radish tops (358-day PBI) and roots (32-day PBI), 0.24 mg eq/kg in spring wheat whole top (126-day PBI) and 3.3 mg eq/kg in wheat grain (126-day PBI) and 1.4 mg eq/kg in wheat fodder (126-day PBI). TRR levels from the phenyl-label study were lower overall.

For food commodities, TA was found at 23–87% TRR (0.013–0.057 mg eq/kg) in lettuce and radish (tops and roots). TLA was present in lettuce (76% TRR, 0.055 mg eq/kg) and wheat grain (0.6%, 0.006 mg eq/kg). 1,2,4-Triazole and TAA were present only in wheat grain (2.7% TRR, 0.029 mg eq/kg and 33% TRR, 0.87 mg eq/kg, respectively).

In wheat whole tops and wheat fodder, 1,2,4-triazole, TA, TLA and TAA were present at 4.4–6.1% TRR (0.006–0.057 mg eq/kg), 8.8–52% TRR (0.12–0.12 mg eq/kg), 26–52% TRR (0.059–0.54 mg eq/kg) and 21–30% TRR (0.057–0.30 mg eq/kg), respectively.

Two field rotational crop studies were conducted in European locations (Northern and Southern). A single application was made to bare soil with lightly sown grass at a rate of 0.20 kg ai/ha. Barley, carrots, and lettuce were planted at nominal PBIs of 30, 60 and 365 days.

The results followed the residue patterns shown in the confined studies. No parent compound was detected in the follow-on crops except carrots (< 0.01 to 0.01 mg/kg in roots and tops). The same metabolites were identified and residue levels detected were similar, except carrot tops and roots where TLA residues were found at higher levels.

For food commodities, 1,2,4-triazole was not detected in lettuce, carrot roots and barley grain. In lettuce and carrot roots, TA, TAA and TLA were detected at 0.03–0.09 mg/kg, < 0.01 mg/kg and 0.04–0.10 mg/kg, respectively. In barley grain, TA, TAA and TLA were present at 0.63 mg/kg, 0.82 mg/kg and 0.03 mg/kg, respectively.

In carrot tops and barley (whole plant and straw), 1,2,4-triazole was not detected and TA, TAA and TLA were present at 0.02–0.32 mg/kg, < 0.01–0.39 mg/kg and 0.32–0.80 mg/kg, respectively.

Based on the findings, the Meeting concluded that residues of the parent compound and monohydroxy metabolites found in plant metabolism study are not expected in rotational crops following treatments according to the GAPs under consideration. Conversely, the triazole-specific metabolites may be detected in rotational crops.

Animal metabolism

Laboratory animals

The toxicological evaluation for penconazole was performed by the 2015 JMPR. Absorption by rats was rapid and extensive, and maximum blood concentrations were reached in 4–6 hours. Over a 6-day period, the highest tissue concentrations of radioactivity were observed in liver, lungs and kidneys. Radioactivity administered was excreted mainly in urine (62–85% of the dose). 14–39% of the dose was excreted in faeces.

Primary metabolic reactions involved cleavage of the triazole ring (estimated 15% of the dose), oxidation of the ω-position of the alkane chain to form the respective carboxylic acid (CGA177279, 30% of the dose), oxidation of the 3- or 4-position of the alkane chain to form monohydroxy and dihydroxy derivatives (2.5% of the dose) and oxidation of the triazole ring in the 3- or 5-position (0.7% of the dose). Furthermore, secondary metabolic reactions produced various metabolites, CGA177281, CGA177280, CGA179944, 3- or 4-keto derivatives produced from oxidation of 3,4-dihydroxy derivatives and conjugates of all alkanol derivatives with glucuronic acid. A small amount of parent compound was identified in faeces, representing unabsorbed dose.

Lactating goats

Two lactating goats were administered [^{14}C-phenyl] penconazole at a rate of 5.1 mg/kg body weight corresponding to 112 ppm in the feed for 4 consecutive days by capsule dosing. Milk and excreta were collected daily at 0-78 hour intervals. Radioactive residues in milk reached plateau by 24 hr. The goats were sacrificed 6 hours after the last dose. The majority of the AR (64%) was excreted in urine. Excretion in faces accounted for 6.4% of the AR. Only 0.06% of the AR was eliminated in milk.

The mean residue concentration in milk was 0.11 mg eq/kg. The radioactive residues in edible tissues were 0.16 mg eq/kg in muscle, 0.74 mg eq/kg in fat, 5.3 mg eq/kg in kidney and 5.3 mg eq/kg in liver. Unchanged penconazole was found in milk and in all tissues, forming the most abundant component in liver (43% TRR, 2.3 mg/kg) and to a lesser extent in fat (16% TRR,

0.11 mg/kg), kidney (9.4% TRR, 0.50 mg/kg), muscle (4.6% TRR, 0.007 mg/kg) and milk (0.7% TRR, 0.0008 mg/kg).

In tissues and milk, CGA132465 (diastereomers, a and b), found in free or conjugated form (sulfate or glucuronide), was the predominant residue, and followed by the metabolite CGA177279. The N10 metabolite (glucuronic acid conjugate of penconazole) found only in kidney, liver and urine was minor, accounting for less than 8% TRR (0.42 mg eq/kg TRR) in kidney and liver each.

In muscle, fat, liver, kidney and milk, the metabolite found and the radioactivity level were as follows:

In muscle, CGA132465 (41%, 0.066 mg eq/kg), CGA132465 glucuronide (17% TRR, 0.027 mg eq/kg), CGA132465 sulfate (7% TRR, 0.01 mg eq/kg) and CGA177279 (24% TRR, 0.039 mg eq/kg).

In fat, CGA132465 (31% TRR, 0.23 mg eq/kg), CGA132465 glucuronide (13% TRR, 0.097 mg eq/kg), CGA132465 sulfate (ca. 4% TRR, 0.030 mg eq/kg) and CGA177279 (24% TRR, 0.18 mg eq/kg).

In liver, CGA132465 (25% TRR, 1.3 mg eq/kg), CGA132465 glucuronide (10% TRR, 0.53 mg eq/kg), CGA132465 sulfate (ca. 1.5% TRR, 0.082 mg eq/kg) and CGA177279 (4% TRR, 0.21 mg eq/kg).

In kidney, CGA132465 (11% TRR, 0.43 mg eq/kg), CGA132465 glucuronide (32% TRR, 1.7 mg eq/kg), CGA132465 sulfate (13% TRR, 0.67 mg eq/kg) and CGA177279 (23% TRR, 1.2 mg eq/kg).

In milk, CGA132465 (14% TRR, 0.015 mg eq/kg), CGA132465 glucuronide (not detectected), CGA132465 sulfate (69% TRR, 0.072 mg eq/kg) and CGA177279 (7.9% TRR, 0.008 mg eq/kg).

Laying hens

Two hens were fed [3, 5-^{14}C-triazole] penconazole, and two with [^{14}C-phenyl] penconazole for 16 consecutive days at 5 ppm in the feed. Twenty-four hours after the last dose, the hens were sacrificed and samples of the tissues were collected. 99% of administered radioactivity was excreted within 24 hours after the first dose in both labels. From the triazole and phenyl-label, radioactive residue levels were up to 0.025 mg eq/kg in tissues (liver, kidney, lean meat, skin/fat and peritoneal fat), 0.029 mg eq/kg in egg yolks and 0.010 mg eq/kg in egg whites, respectively. Regardless of label, radioactivity in eggs plateaued within 11 days (0.022 mg eq/kg). Identification of radioactive residues in edible tissues was not performed.

In summary, the principal residues in goat tissues and milk are the parent compound, CGA132465 (free and conjugated) and CGA177279. The main metabolic pathways of penconazole processed in goats are hydroxylation of penconazole to form CGA132465, conjugation of CGA132465 with glucuronic acid or sulfuric acid, and oxidation of penconazole to form the carboxylic acid CGA177279.

Environmental fate in soil

Soil photolysis

Penconazole was relatively stable with a half-life of 148 days. No photodegradation products greater than 5% of the AR were observed after 30 days.

Hydrolysis

Penconazole, CGA 179944 and 1,2,4-triazole were stable in aqueous solutions representative of environmental conditions (pH 4, 5, 7 and 9 during one week at 50 °C or 30 days at 25 °C).

Aerobic degradation in soil

Penconazole was stable in aerobic sterile soil, accounting for 86% of the AR at day 84. Penconazole in soil was degraded under aerobic and unsterile conditions with a half-life of 178 days (61–238 days).

Degradation of penconazole proceeds principally via oxidation of the alkyl chain of the parent compound yielding CGA179944. Bridge cleavage in CGA179944 leads either directly or via the intermediate TAA to 1, 2, 4-triazole. Finally, the last metabolic steps generate carbon dioxide and bound residues. CGA179944 and 1,2,4-triazole were degraded with a half-life of 17 days (7.3–25. days) and 9.2 days (6.3–12 days), respectively.

Penconazole was moderately persistent in soil. However, following subsequent annual application, accumulation of penconazole in soil is not expected.

Methods of analysis

The basic method for analysis of penconazole in plants and animal matrices employs extraction with methanol (plant) or acetonitrile (animal), partitioning with hexane or dichloromethane, a clean-up step and GC-ECD/NPD analysis. This method achieves LOQ levels of 0.01–0.02 mg/kg in fruit plant matrices, 0.01 mg/kg in milk and 0.05 mg/kg in animal tissues. In addition, LC-MS/MS may be used, omitting a clean-up step and achieving a LOQ level of 0.01 mg/kg in various plant matrices (m/z 284→159 for quantification, m/z 284→70 for confirmation).

An analysis method for residues convertible to 2,4-dichlorobenzoic acid (DCBA; total residues) in plants and animal commodities is available. In grape and apple samples, mean recovery of penconazole was 63% (42–91%, RSD, < 20%). In addition, recoveries for the metabolites from grape were 62%, 56%, 30% for CGA132465, CGA127841 and CGA177280, respectively. In animal commodities, 39–83% of penconazole was recovered. This method is not considered as suitable due to low recoveries for penconazole and its metabolites.

The application of multi-residue methods was tested with DFG S19 for analysis of penconazole in plant and animal matrices. The method was shown suitable with a LOQ of 0.01 mg/kg in plant matrices and animal matrices (milk, meat, eggs and fat). For liver and kidney, LOQ is 0.1 mg/kg due to matrix interference.

Stability of pesticide residues in stored analytical samples

Penconazole was stable for at least 24 months in cucumber and apple (high water) and grape (high acid) samples stored at -18 °C. Other matrices were not tested. No storage stability data were provided for animal matrices.

Definition of the residue

In plants (grape, tomato, apple), major residues were parent penconazole (7–16% TRR), free and conjugated CGA132465 (14–62% TRR), and triazole-specific metabolites (TA, TAA, TLA; in total, 20–25% TRR).

In determining residues suitable for monitoring compliance with MRLs in plant commodities, the Meeting noted that parent penconazole was found in all plants investigated and that suitable methods are available for its analysis. Analytical methods are not available for CGA132465 (free or conjugated), and the triazole-specific metabolites are not unique to penconazole; therefore neither of

these compounds is suitable for compliance purposes. The Meeting concluded that the residue definition for compliance with MRLs for residues of penconazole in plant commodities is penconazole.

For evaluation of dietary risk assessment from residues in plants, the Meeting noted that all metabolites found in plants were also identified in rats. Dietary exposure to residues in plants is likely to be to penconazole, CGA132465 (free and conjugated), and the triazole-specific metabolites. The toxicity of CGA132465 is considered to be addressed by the toxicity of parent penconazole based on structural similarity. In the absence of data specific to CGA132465, it is assumed to be no more toxic than penconazole. The triazole-specific metabolites have toxicities known to be different from penconazole and are assessed separately. Therefore, the Meeting determined that the residue definition for assessing dietary intake from plants is the combined residues of penconazole and CGA132465 (free and conjugated), expressed as penconazole.

In goats, the principal residues were parent penconazole (0.7–43% TRR), CGA177279 (4–24% TRR), and free and conjugated CGA132465 (37–83% TRR). In laying hens, components of residues were not identified, as total radioactive residues were too low.

For monitoring compliance with MRLs in livestock commodities, residues of penconazole were observed in all commodities and there is a method available for analysis. Analytical methods are not available for either CGA177279 or CGA132465. Therefore, the Meeting concluded that the residue definition for compliance with MRLs for residues of penconazole in livestock commodities is penconazole.

In goat, penconazole concentrations in fat tissues were at least one order of magnitude higher than in muscle tissues. The log P_{ow} of penconazole is 3.1. The Meeting decided that residues of penconazole are fat soluble.

For evaluation of dietary risk assessment from residues in livestock commodities, exposures are likely to be to penconazole and the metabolites CGA177279 and CGA132465 (free and conjugated). In the absence of metabolite-specific data, these two metabolites are assumed to be no more toxic than penconazole. The Meeting determined that the residue definition for assessing dietary intake from livestock commodities is the combined residues of penconazole, CGA177279, and CGA132465 (free and conjugated), expressed as penconazole.

Definition of the residue for compliance with MRL for plant and animal commodities: *penconazole*

Definition of the residue for estimation of dietary intake for plant commodities: *sum of penconazole and 4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentan-2-ol (free and conjugated), expressed as penconazole*

Definition of the residue for estimation of dietary intake for animal commodities: *sum of penconazole, 4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentan-2-ol (free and conjugated) and 4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentanoic acid, expressed as penconazole*

The residue is fat soluble.

Results of supervised residue trials on crops

The Meeting received supervised residue trial data for pome fruits (apple, pear), stone fruits (peach, cherry), berries and other small fruits (blackcurrant, grape, strawberry), fruiting vegetables (melon, cucumber, tomato, sweet pepper) and globe artichoke. All residue trials were conducted in European countries.

The Meeting withdraws its previous recommendations for hops, dry, as the residue trial data were not provided.

Data depicting residues of free and conjugated CGA132465 were not provided for residue trials conducted with penconazole. In order to estimate residues for dietary intake from plants, the Meeting examined metabolism data from grapes, tomato, and apple. Comparison of residues in analytical fractions, containing CGA132465 (following hydrolysis) with residues of parent penconazole, resulted in conversion factors [(penconazole + CGA132465) ÷ penconazole] of 2.8 for mature grapes, 4.5 and 5.4 for tomato 7 DALA (approximating the registered GAP for tomato), and 2.2 for apples sampled 34 days after the last application. As a conservative estimate of residues for dietary risk assessment, the Meeting used the mean conversion factor, 5, obtained from tomato for all crops.

Pome fruits

Apple, pear

Penconazole is registered in Italy for apple and pear at rates of 3 ×0.060-0.068 kg ai/ha on a 7-day interval and with a 14 day-PHI. Independent residue trials from France, Germany and Spain matching the Italian GAP were submitted.

The residues in apple were (n = 14): < 0.02 (4), 0.01, 0.01, 0.02 (3), 0.030, 0.038, 0.048, 0.05, and 0.079 mg/kg.

The residues in pear were (n = 4): < 0.01, 0.01, 0.01 and 0.04 mg/kg.

As residue values of apple and pear were comparable and not different significantly, the values were combined for mutual support.

The combined data set for apple and pear was (n = 18): < 0.01, < 0.02 (4), 0.01 (4), 0.02 (3), 0.030, 0.038, 0.04, 0.048, 0.05 and 0.079 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg, an STMR of 0.10 (0.02 × 5) mg/kg and an HR of 0.40 (0.079 × 5) mg/kg for apple and pear, noting that the GAP in Italy is not for the pome fruit crop group. Furthermore, the Meeting withdrew its previous recommendations for pome fruits.

Stone fruits

Peach

Penconazole is registered in Italy for peach at rates of 3 × 0.075 kg ai/ha on a 7-day interval and with a 14-day PHI. Twelve independent trials from Germany, France, Italy and Spain were submitted. One trial matched the GAP, having a residue of 0.03 mg/kg in whole peach (no flesh data).

Eleven trials were conducted at rates of 0.1 kg ai/ha, which is higher than the GAP. The residues in whole peach were (n = 11): < 0.02, 0.02, 0.025, 0.029, 0.03 (3), 0.033, 0.04, 0.06 and 0.08 mg/kg. Using the factor of 0.75, the scaled residues in whole peach were (n = 11): < 0.02, 0.015, 0.019, 0.022, 0.023 (3), 0.025, 0.03 , 0.045 and 0.06 mg/kg.

Combined residues in whole peach were (n = 12): < 0.02, 0.015, 0.019, 0.022, 0.023 (3), 0.025, 0.03 (2), 0.045 and 0.06 mg/kg.

The residues in flesh of peach from the trials conducted at the higher rate were (n = 10): 0.021, 0.027, 0.03, 0.036 (2), 0.04 (3), 0.08 and 0.09 mg/kg. Using the scaling factor of 0.75, the scaled residue values in peach flesh were (n = 10): 0.016, 0.020, 0.023, 0.027 (2), 0.03 (3), 0.06 and 0.068 mg/kg.

The Meeting estimated a maximum residue level of 0.08 mg/kg for peach subgroup and an STMR of 0.14 (0.028 ×5) mg/kg and an HR of 0.34 (0.068 ×5) mg/kg. The Meeting, therefore, withdraws its previous recommendations for peach.

Cherry

Penconazole is registered in Lithuania for use in cherries at rates of 2 × 0.050 kg ai/ha on a 10 or 14-day interval and with a 20-day PHI. Eight residue trials from France and Germany were conducted at 5 or 9-day intervals and at 14-day PHI. The Meeting noted that as the trials did not match GAP no maximum residue level, STMR or HR values could be estimated.

Berries and other small fruits

Blackcurrants

Penconazole is registered in the UK for blackcurrants at rates of 4 × 0.05 kg ai/ha on a 10 or 14-day interval with a 28-day PHI. Five independent trials from the UK matching GAP were submitted.

The residues in blackcurrants were (n = 5): 0.11, 0.13, 0.30, 0.76 and 0.88 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg, an STMR of 1.5 (0.30 × 5) mg/kg and an HR of 4.4 (0.88 × 5) mg/kg for blackcurrants.

Grapes

Penconazole is registered in Spain for grape vines, trellised vines at rates of 3 × 0.040 kg ai/ha on a 7 or 14-day interval with a 14-day PHI. Fourteen independent trials from Italy, France, Hungary, the UK, Poland and Germany matching the Spanish GAP were submitted.

The residues in grapes were (n = 14): < 0.01, 0.01, 0.02 (3) 0.03 (4), 0.04, 0.05, 0.08, 0.17 and 0.32 mg/kg.

The Meeting estimated a maximum residue level of 0.4 mg/kg, an STMR of 0.15 (0.03 × 5) mg/kg and an HR of 1.6 (0.32 × 5) mg/kg for grapes. Furthermore, the Meeting withdrew its previous recommendation for grapes.

Strawberry

Penconazole is registered in Belgium for strawberry, protected and unprotected, at rates of 4 × 0.050 kg ai/ha on a 10-day interval with a 3-day PHI. Residue trials (protected and outdoor) from France, Germany, Italy, Spain and Greece matching Belgian GAP were submitted.

The residues in strawberry (outdoor) were (n = 17): 0.03, 0.03, 0.04, 0.043, 0.045, 0.06, 0.06, 0.1 (3), 0.11, 0.12, 0.14, 0.14, 0.17, 0.38 and 0.43 mg/kg

The residues in strawberry (protected) were (n = 8): 0.03, 0.04, 0.07, 0.07, 0.08, 0.087, 0.15 and 0.19 mg/kg.

As the median residues from outdoor and protected strawberry are within a 5-fold range and the residues are not significantly different by the Kruskal-Wallis test, the residues were combined for more robust estimation.

The combined data set for strawberry (outdoor and protected) were (n = 25): 0.03 (3) 0.04 (2), 0.043, 0.045, 0.06 (2), 0.07 (2), 0.08, 0.087, 0.1 (3) 0.11, 0.12, 0.14 (2), 0.15, 0.17, 0.19, 0.38 and 0.43 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg, an STMR of 0.44 (0.087 × 5) mg/kg and an HR of 2.2 (0.43 × 5) mg/kg for strawberries. The Meeting withdrew its previous recommendations for strawberry.

Fruiting vegetables, Cucurbits

Melons, except Watermelon

Penconazole is registered in Germany for greenhouse melon at rates of 4 × 0.050 kg ai/ha on a 7-day interval and with a 3-day PHI. Nine residue trials from Germany, Italy and Spain according to this GAP were submitted. Two trials, in which melon seeds were removed and discarded, could not be used for estimation of a maximum residue level.

The residues in melons (greenhouse) were (n = 7): 0.01, 0.01, 0.02, 0.04, 0.04, 0.05 and 0.06 mg/kg.

The Meeting estimated a maximum residue level of 0.15 mg/kg, an STMR of 0.20 (0.04 × 5) mg/kg and an HR of 0.30 (0.06 × 5) mg/kg for melons, except watermelon. The Meeting withdraws its previous recommendations for melons.

Cucumber

Penconazole is registered in Germany for cucumber, protected and pâtisson squash, protected and outdoor, at rates of 4 × 0.050 kg ai/ha on a 7-day interval and with a 3-day PHI. Residue trials from France, Greece, Italy and Spain according to this GAP were submitted.

The residues in cucumber, protected, were (n = 8): < 0.01, < 0.02, < 0.02, 0.01, 0.01, 0.02, 0.03 and 0.03 mg/kg.

The Meeting estimated a maximum residue level of 0.06 mg/kg, an STMR of 0.05 (0.01 × 5) mg/kg and an HR of 0.15 (0.03 × 5) mg/kg for cucumber, withdrawing its previous recommendations. Further the Meeting extrapolated the residue values for cucumber to summer squash and gherkin based on the same German GAP, and estimated maximum residue levels of 0.06 mg/kg, STMRs of 0.05 mg/kg and an HRs of 0.15 mg/kg for summer squash and gherkin.

Fruiting vegetables, other than Cucurbits

Tomato

Penconazole is registered in Germany for tomato and eggplant, greenhouse, at rates of 4 × 0.050 kg ai/ha on a 7-day interval and with a 3-day PHI. Residue trials from Germany, France, Netherlands, Spain and Greece according to this GAP were submitted.

The residues in tomato and cherry tomato, greenhouse, were (n = 14): < 0.01 (3), < 0.02 (3), 0.02 (4), 0.03, 0.03, 0.04 and 0.07 mg/kg.

The Meeting estimated a maximum residue level of 0.09 mg/kg, an STMR of 0.10 (0.02 × 5) mg/kg and an HR of 0.35 (0.07 ×5) mg/kg for tomato, withdrawing its previous recommendations. The Meeting also estimated a maximum residue level of 0.09 mg/kg, an STMR of 0.10 mg/kg and an HR of 0.35 mg/kg for egg plant, extrapolating tomato residues to egg plant under the same German GAP.

Pepper, Sweet

Penconazole is registered in Germany for sweet pepper, greenhouse, at rates of 4 × 0.050 kg ai/ha, on a 7-day interval with a 3-day PHI. Residue trials from France, Netherlands, Spain and Italy according to this GAP were submitted.

The residues in sweet pepper, greenhouse, were (n = 8): < 0.02, < 0.02, 0.02, 0.02, 0.036, 0.04, 0.041 and 0.12 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg, an STMR of 0.14 (0.028 × 5) mg/kg and an HR of 0.60 (0.12 × 5) mg/kg for sweet pepper.

Stalk and stem vegetables

Artichoke, globe

Penconazole is registered in Italy for globe artichoke, at rates of 4 × 0.050 kg ai/ha, on a 14- or 16-day interval with a 14-day PHI. Residue trials from Italy, Germany, France and Spain according to this GAP were submitted.

The residues in globe artichoke were (n = 7): < 0.01, < 0.02 (4), 0.02 and 0.04 mg/kg.

The Meeting estimated a maximum residue level of 0.06 mg/kg, an STMR of 0.10 (0.02 × 5) mg/kg and an HR of 0.20 (0.04 × 5) mg/kg for globe artichoke.

Fate of residues during processing

High-temperature hydrolysis

Using [^{14}C-triazole] penconazole, typical processing conditions were simulated (pH 4, 5 and 6 with 90 °C, 100 °C and 120 °C for 20, 60 and 20 minutes). Penconazole was stable in all conditions of temperature, pH and reaction time that mimic pasteurisation, baking, brewing, boiling and sterilisation.

Residue after processing

The fate of penconazole residues has been examined simulating household and commercial processing of grape, apple, strawberry and blackcurrants. Estimated processing factors for the commodities considered at this Meeting are summarized below.

The meeting noted that residues of free and conjugated CGA132465 are likely to be considerably more water soluble than penconazole, *per se*. As such, it is not appropriate to use processing factors based solely on residues of penconazole when estimating residues in processed commodities such as juice and wine. The Meeting noted that the grape metabolism study included residue analysis for whole grapes as well as grape juice. The sum of residues in analytical fractions containing CGA132465 and penconazole in grape berries was 0.051 mg/kg. The sum of those residues in grape juice was 0.013 mg/kg, resulting in a processing factor of 0.25. This processing factor was also used for other juices and wine.

For raisin, a maximum residue level of 1.5 mg/kg was estimated based on a maximum residue level 0.4 mg/kg for grapes and a processing factor of 3.8.

Crop	STMR	HR	Commodity	Processing factor		STMR-P (mg/kg)	HR-P (mg/kg)
				Individual values	Best estimate		
Grapes	0.15	1.6	Raisin	2.2, 3.6, 4.0, 4.0	3.8	0.57	6.1
			Wet pomace	1.1, 2.5, 2.8, 2.8, 3.0, 3.2, 5.2, 7.5	2.9	0.44	
			Dry pomace	10, 13, 21, 26	17	2.6	
			Juice		0.25[a]	0.038	0.40
			Wine		0.25[a]	0.038	0.40
Apple	0.10	0.40	Wet pomace	2.0, 2.1, 2.2, 3.1	2.2	0.22	
			Dry pomace	7.3, 8.7, 9.3, 9.3	9.0	0.9	
			Juice		0.25[a]	0.025	0.10

Crop	STMR	HR	Commodity	Processing factor		STMR-P (mg/kg)	HR-P (mg/kg)
				Individual values	Best estimate		
			Sauce	0.13, 0.13, 0.20, 0.20	0.17	0.017	0.068
Strawberry	0.44	2.2	Jam, sterilized	0.73, 0.77, 0.90, 1.0	0.84	0.37	1.8
			Canned, pasteurized	0.50, 0.50, 0.60, 0.60	0.55	0.24	1.2
Blackcurrant	1.5	4.4	Juice		0.25[a]	0.38	1.1

[a] The processing factor for juices and wine were derived from the grape metabolism study.

Residues in animal commodities

Estimation of dietary burden

The maximum and mean dietary burdens were calculated using the highest residues or median residues of penconazole (combined residues of parent and CGA132465) estimated at the current Meeting on the basis of the OECD Animal Feeding Table. Apple and grape pomace data were used for estimation of dietary burdens. The calculated maximum and mean animal burdens are summarised below. For broiler poultry and laying poultry, no feed items were applicable in this evaluation.

Summary of livestock dietary burdens (ppm of dry matter diet)

	US-Canada		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle			0.11	0.11	0.11	0.11	-	-
Dairy cattle	0.055	0.055	0.055	0.055	0.099	0.099	-	-

Farm animal feeding studies

Lactating cows were fed diets containing 10, 50 and 100 ppm penconazole, for up to 28 days. Parent penconazole was analysed for milk and tissue samples. Parent compound was found at only the highest does only in liver, 0.26 mg/kg (milk, < 0.01 mg/kg; other tissues, < 0.05 mg/kg). All samples were also analysed for residues convertible to DCBN (total residues; including metabolites CGA132465 and CGA177279), however, the analytical method was not considered sufficiently reliable.

Laying hens were fed diets containing 1.25, 6.25 and 12.5 ppm penconazole, for up to 29 days. Only total residues (as DCBN) were analysed. No total residues (< 0.05 mg/kg) were found in any samples at any of the feeding levels, except liver sample at the highest dose, determined at 0.09 mg/kg.

Animal commodity maximum residue levels

In the feeding studies, no residues of total residues were found in milk and tissues, except liver. For liver, when a dose level of 100 ppm (0.26 mg/kg at the dose) was compared with the dietary burden, 0.11 ppm, no significant residue is expected. The Meeting estimated a maximum residue level of 0.01* mg/kg for milk and 0.05* mg/kg for meat, fat, liver and kidney.

From a goat metabolism study (112 ppm), sum of the residues of parent, CGA132465 and CGA177279 were muscle 0.15 mg eq/kg (92% TRR), fat 0.65 mg eq/kg (88% TRR), liver 4.4 mg eq/kg (83% TRR), kidney 4.5 mg eq/kg (88% TRR) and milk 0.096 mg eq/kg (92% TRR). Comparing with 1018-times lower dietary burden, residue levels would be expected < 0.001 mg/kg in

muscle, milk and fat, and 0.004 mg/kg in liver and kidney. The Meeting estimated 0 mg/kg for STMR and HR for muscle, fat and milk; 0.004 mg/kg for STMR and HR for liver and kidney.

For poultry, no relevant feed item was identified. The Meeting estimated a maximum residue level of 0.05* mg/kg, an STMR of 0 mg/kg and an HR of 0 mg/kg for poultry and eggs.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex I are appropriate for establishing maximum residue limits and for IEDI and IESTI assessment.

Definition of the residue for compliance with MRL for plant and animal commodities: *penconazole*

Definition of the residue for estimation of dietary intake for plant commodities: sum of penconazole and *4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentan-2-ol (free and conjugated), expressed as penconazole*

Definition of the residue for estimation of dietary intake for animal commodities: sum of *penconazole, 4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentan-2-ol (free and conjugated) and 4-(2,4-dichloro-phenyl)-5-[1,2,4]triazol-1-yl-pentanoic acid , expressed as penconazole.*

The residue is fat soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The International Estimated Daily Intakes (IEDIs) of penconazole were calculated for the 17 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current and previous Meetings. The results are shown in Annex 3 in the 2016 JMPR Report.

The ADI is 0–0.03 mg/kg bw and the calculated IEDIs were 0–3% of the maximum ADI. The Meeting concluded that the long-term exposure to residues of penconazole resulting from the uses considered by the JMPR is unlikely to present a public health concern.

Short-term dietary exposure

The International Estimated Short Term Intakes (IESTIs) of penconazole were calculated for the food commodities using HRs and STMR/STMR-Ps estimated by the current Meeting. The results are shown in Annex 4 to the 2016 JMPR Report.

The ARfD is 0.8 mg/kg bw and the calculated IESTIs were 0–6% of the ARfD for the general population and 0–10% of the ARfD for children. The Meeting concluded that the short-term dietary exposure to penconazole residues, resulting from uses that have been estimated by the 2016 JMPR, is unlikely to present a public health concern when penconazole is used in ways that were considered by the Meeting.