5.25 PROTHIOCONAZOLE (232)

RESIDUE AND ANALYTICAL ASPECTS

Prothioconazole was evaluated first time by the 2008 JMPR. The residue definition for plant commodities for enforcement and dietary risk assessment was prothioconazole-desthio. The residue definition for animal commodities for enforcement was prothioconazole-desthio and for dietary risk assessment was the sum of prothioconazole-desthio, prothioconazole-desthio-3-hydroxy, prothioconazole-desthio-4-hydroxy and their conjugates, expressed as prothioconazole-desthio. The residue was considered to be not fat-soluble for the purposes of residue definition.

The 2008 JMPR established, for prothioconazole-desthio, an ADI of 0–0.01 mg/kg bw and ARfD of 0.01 mg/kg bw for women of child bearing age and 1 mg/kg bw for the general population.

The Forty-fifth Session of CCPR scheduled prothioconazole for periodic re-evaluation of residues by the 2014 JMPR. For the 2014 Meeting data were provided on blueberry, corn, cranberry, cucurbits, potato, sweet corn peanut and soya bean together with current use recommendations and analytical methods used in supervised trials.

Methods of analysis

A number of validated analytical methods for the determination of residues in plant, animal tissue, milk and soils were evaluated by the 2007 and 2008 JMPR Meetings. The Meeting received the basic analytical methods with minor modifications which were validated to determine residues in crops that had been used in the residue trials. An analytical method was also provided for the determination of residues of prothioconazole in animal matrices.

The trials carried out in the USA/Canada used method RPA JA/03/01 or the modified method JA-001-P04-02 which involve extraction with methanol, hydrogen peroxide and sodium bicarbonate at an elevated temperature. This converts prothioconazole to a mixture of prothioconazole-sulfonic acid, while prothioconazole-desthio is extracted unchanged. After purification steps, the residues are analysed by LC-MS/MS. The LOQ of these methods is 0.02 mg/kg for prothioconazole-sulfonic acid and 0.02 mg/kg for prothioconazole-desthio.

The trials carried out in Brazil, EU and Australia used methods 01013, 00598/M001 and ATM-0053 in which residues of prothioconazole and prothioconazole-desthio are extracted with acetonitrile/water containing cysteine hydrochloride. After purification steps, dependent on the method, the analytes are analysed by LC-MS/MS. The LOQ of these methods is 0.01 mg/kg (or 0.05 mg/kg for forage and straw matrices) for prothioconazole and prothioconazole-desthio.

Storage stability under frozen conditions

Information relating to storage stability of residues in wheat, canola (seed, pod, straw), spinach (leaves), sugar beet (root, leaf with root collar), tomato (fruit) and field pea (dried) was evaluated at the 2008 JMPR Meeting. This showed that residues of prothioconazole-desthio were stable over a frozen storage period of up to 36 months in wheat and at least 24 months for the other crops. Residues of prothioconazole and prothioconazole-desthio were stable in wheat hay and straw, canola seeds, mustard greens, turnip root and tomato fruit over a frozen storage period of 36–42 months.

An additional freezer storage stability study for residues of prothioconazole and prothioconazole-desthio (JAU 6476-desthio) in wheat (forage, straw, grain, bran and flour), canola (seed and oil), mustard greens, tomato (fruit and paste) and turnip roots was performed.

No significant degradation of prothioconazole-desthio was observed in any matrix analysed over the 3-year frozen storage period.

The stability of parent prothioconazole varied from 57 days up to 378 days without showing any dependency on the sample matrix. However, metabolism studies indicated that after foliar

application prothioconazole rapidly degraded to prothioconazole-desthio and polar metabolites being converted to the sulfonic acid derivative, which is measured by the analytical method. Therefore the relative instability of parent compound does not affect the validity of the desthio residues measured in supervised trials.

Results of supervised residue trials on crops

Supervised trials have been conducted to support MRLs for the following crops or groups of crops: blueberry, cranberry, cucurbits (cucumber, summer squash and melon), sweet corn, soya bean, potato, maize (field corn, popcorn) and peanuts.

In trials conducted in the USA, Canada and Brazil, residues of prothioconazole sulfonic acid (JAU 6476 sulfonic acid), prothioconazole-desthio (JAU 6476 desthio) and total prothioconazole (JAU 6476) were determined and reported. In trials conducted in Australia, residues of prothioconazole (JAU 6476), prothioconazole-desthio (JAU 6476 desthio) and total prothioconazole (JAU 6476) were determined and reported. However, only the residues of prothioconazole-desthio have been used for calculation of MRL, HR and STMR values in accordance with the residue definition. The residues of prothioconazole-desthio are expressed as mg prothioconazole-desthio equivalents/kg.

Bush berries

Blueberry

Eleven supervised trials were conducted in 2010 in the USA and Canada matching the US GAP (2 × 200 g ai/ha nominal rate at 6–7 days intervals, 7-day PHI) for the bush berry subgroup.

Prothioconazole-desthio residues from trials on blueberries were: 0.15, 0.22, 0.26, 0.28, 0.42, 0.52, 0.56, 0.60, 0.65, 0.70 and 0.87 mg/kg.

Taking into account that blueberry is the representative commodity for the subgroup; the Meeting estimated a maximum residue level of 1.5 mg/kg, a HR of 0.87 mg/kg and a STMR of 0.52 mg/kg for prothioconazole-desthio residues for the bush berry subgroup.

Low growing berries

Cranberry

Six supervised trials were conducted in 2010 in the USA according to the US GAP (2 × 186 g ai/ha nominal rate at 7-10 days intervals, 45-day PHI)

Prothioconazole-desthio residues from trials on cranberries were: < 0.02 (3), 0.03 (2) and 0.09 mg/kg.

The Meeting estimated maximum residue level of 0.15 mg/kg, HR of 0.09 mg/kg and STMR of 0.025 mg/kg for prothioconazole-desthio residues for cranberry.

Fruiting vegetables, Cucurbits

Eight supervised trials were conducted in 2010 on *cucumber*, eight trials on *musk melon* and eight trials on *summer squash* in the USA according to US GAP (one soil +2 × 200 g ai/kg nominal rate at 7-10 days intervals, max 600 g ai/season,, 7-day PHI).

Prothioconazole-desthio residues from trials on cucumber were: 0.02, 0.02, 0.03, 0.03, 0.04, 0.05, 0.05, 0.06 mg/kg.

Prothioconazole-desthio residue concentrations from trials on musk melon were: 0.03, 0.06, 0.06, 0.06, 0.06, 0.07, 0.15, 0.15 mg/kg.

Prothioconazole-desthio residue concentrations from trials on summer squash were: < 0.02 (5), 0.03, 0.05 and 0.06 mg/kg.

The Meeting noted that the GAP in USA is for cucurbit vegetables, the residue populations were not significantly different and the median residues were within the 5 times range, and agreed to combine the datasets. Residues in the 24 trials were: < 0.02 (5), 0.02 (2), 0.03 (4), 0.04, 0.05 (3), 0.06 (6), 0.07 and 0.15 (2) mg/kg.

The Meeting noted that the ARfD would be exceeded by 150% for watermelon. As no alternative GAP for fruiting vegetables was available, watermelon was not included in the recommendation for the crop group fruiting vegetables, cucurbits.

The Meeting estimated a maximum residue level of 0.2 mg/kg, HR of 0.15 mg/kg and STMR of 0.045 mg/kg prothioconazole-desthio residues for fruiting vegetables, cucurbits (except watermelon).

Fruiting vegetables, other than Cucurbits

Sweet corn

Twelve supervised trials were conducted on sweet corn in the USA at 4 × 200 g ai/ha matching the current US GAP. The PHI for sweet corn forage and ears is 0 days and 14 days for fodder.

Prothioconazole-desthio residue concentrations in corn ears were: < 0.018 in all samples.

The Meeting estimated a maximum residue level of 0.02 mg/kg, and HR and STMR values of 0.018 mg/kg for sweet corn.

Pulses

Soya beans

Residue data on soya beans, from 19 trials conducted in the USA, were previously evaluated by the 2008 and 2009 JMPR Meetings. The current US GAP for soya beans permit 3 applications at 88–175 g ai/ha rate at 10–21 day intervals with a PHI of 21 days.

The average prothioconazole-desthio residues in soya bean samples derived from trials corresponding to the current US GAP were: < 0.05 (16), 0.051, 0.055 and 0.105 mg/kg

Ten supervised trials were conducted in 2012–2013 season on soya bean in Brazil matching the GAP for Brazil (4 × 87.5 g ai/ha, PHI 30 days). The prothioconazole-desthio residues were reported as the parent compound. Applying the conversion factor of 0.907 (312.20/344.26) the residues expressed as prothioconazole-desthio were: < 0.009 × 4, 0.009 × 2, 0.018, 0.027, 0.036 and 0.091 mg/kg.

The Meeting noted that the US trials resulted in higher residues and used those values. The meeting estimated a maximum residue level of 0.2 mg/kg and STMR value of 0.05 mg/kg.

Root and tuber vegetables

Potato

A total of twenty supervised trials were conducted in 2005 and 2010 as potato seed-piece treatments in Belgium, France, Germany, Italy, the Netherlands, Spain and the UK at maximum GAP (up to

0.64 g ai/100 kg seed, equivalent to 16 g ai/ha) or higher rate. The potatoes were harvested at maturity. The prothioconazole-desthio residues were < 0.01 mg/kg in all samples take 90–136 days after seed treatment.

Taking into account that the LOQ of the enforcement method is 0.02 mg/kg, the Meeting estimated a maximum residue level of 0.02* mg/kg, HR and STMR values of 0.01 mg/kg for potato.

Cereal grains

Maize

Twenty supervised trials were conducted in 2006 on field corn and three trials on popcorn in the USA (4 × 200 g ai/ha at 7–14 days apart, 0 day PHI for forage and 14 days for grain and fodder).

The prothioconazole-desthio residues in maze grain samples collected at 14 days after last application were: < 0.018 (17), and 0.05 mg/kg,

Ten supervised trials were conducted in 2011-2012 on corn in Brazil according to the GAP (2 × 70-87.5 g ai/ha, at minimum 15 days, 15 days PHI).

The prothioconazole-desthio residues in maize grain samples collected at 14-15 days after last application were: < 0.01 (10) mg/kg.

A total of twenty supervised trials were conducted in 2007, 2008 and 2011 on maize/corn in Europe matching the GAP of the Czech Republic (2 × 125 g ai/ha, PHI 35 days) and Italy (2 × 125 g ai/ha, retreatment at a minimum of 14 days, 35 days or non-specified PHI).

The prothioconazole-desthio residues in all of immature and mature maize grain samples collected from 17 days onward were: < 0.01 (20) mg/kg.

The Meeting considered that all maize grain/seed samples (47) contained non-detectable resides regardless of maturity and time between last application and sampling, except in one trial where residues of up to 0.05 mg/kg residue was measured.

The Meeting estimated a maximum residue level of 0.1 mg/kg and STMR value of 0.018 mg/kg for maize and popcorn.

Oilseeds

Peanuts

Residue data on peanuts from trials conducted in the USA had been evaluated by the 2009 JMPR. Residues of prothioconazole-desthio were < 0.02 mg/kg in 12 trials matching the USA GAP (4 × 200 g ai/ha, PHI 14 days).

Eight supervised trials were conducted in 2011–2012 in Australia. Four trials included plots which were treated according to the GAP for peanut in Australia (4 times 120–192 g ai/ha at 10–14 days apart, 28-day PHI), and four trials included plots which were treated with higher number of applications and a shorter PHI (up to 21 days). Samples were taken immediately before the last application and 0, 7, 14–15 and 20–21 days after.

The prothioconazole-desthio residues in all samples collected from Day 0 to day 29 days were: < 0.01 mg/kg.

The Meeting confirmed its previous recommendations of 0.01* mg/kg.

Primary feed commodities

Descriptions of trial conditions and residues are described under relevant food commodities. The residue data relevant to the feed commodities are summarized below.

Maize and sweet corn forage and fodder

Prothioconazole-desthio residue concentrations in sweet corn forage from trials conducted at 4 × 200 g ai/ha were: 1.31, 1.50, 1.89, 1.94, 1.98, 2.08, 2.12, 2.37, 2.82, 3.20, 3.75 and 4.08 mg/kg.

Prothioconazole-desthio residue concentrations in field corn forage from trials based on the USA GAP for corn are: 0.71, 1.67, 1.75, 1.84, 1.90, 1.96, 2.14, 2.15, 2.19, 2.20, 2.27, 2.41, 2.58, 2.62, 2.65, 2.99 (2), 3.06, 3.44 and 3.60 mg/kg.

The Meeting noted that the GAP in USA for sweet corn and maize is the same and that the residue populations were not significantly different, and agreed to combine the datasets.

Residues in the trials were: 0.71, 1.31, 1.50, 1.67, 1.75, 1.84, 1.89, 1.90, 1.94, 1.96, 1.98, 2.08, 2.12, 2.14, 2.15, 2.19, 2.20, 2.27, 2.37, 2.41, 2.58, 2.62, 2.65, 2.82, 2.99 (2), 3.06, 3.44, 3.60, 3.75 and 4.08 mg/kg.

Residues in forage from the European trials were much lower (< 0.2 mg/kg) than from the trials conducted according to the USA GAP, and therefore the Meeting used the US trial data for the estimation of residue levels.

The Meeting estimated highest residue of 4.08 mg/kg and median residue of 2.15 mg/kg for sweet corn and filed maize forage.

Prothioconazole-desthio residue concentrations in sweet corn stover from trials conducted at 4 × 200 g ai/ha were: 0.67 (2), 0.71, 0.82, 0.90, 0.98, 1.45, 1.68 (2), 1.70, 3.61 and 5.88 mg/kg.

Prothioconazole-desthio residue concentrations in field corn stover from trials based on the USA GAP for corn were: 0.67 (2), 0.71, 0.82, 0.90, 0.98, 0.99, 1.09, 1.45, 1.68 (2), 1.70, 2.22, 2.32, 2.35, 2.42, 2.90, 3.18, 3.22, 3.42, 3.48, 3.59, 3.61, 3.68, 3.78, 3.89, 4.05, 4.47, 4.66, 5.88, 6.16 and 6.70 mg/kg.

Prothioconazole-desthio residue concentrations in popcorn stover from trials based on the USA GAP for corn were: 2.46, 2.51 and 4.43 mg/kg.

The Meeting noted that the GAP in the USA is for sweet corn and maize is the same and the residue populations were not significantly different, and agreed to combine the datasets. Residues in the trials were: 0.99, 1.09, 2.22, 2.32, 2.35, 2.42, 2.46, 2.51, 2.90, 3.18, 3.22, 3.42, 3.48, 3.59, 3.68, 3.78, 3.89, 4.05, 4.43, 4.47, 4.66, 6.16 and 6.70 mg/kg.

The Meeting estimated a maximum residue level of 15 mg/kg (dry weight basis) highest residue of 6.7 mg/kg and median residue of 3.48 mg/kg for sweet corn and field maize stover.

Soya bean forage and hay

The Meeting received information on residues in soya bean forage and hay. However, the samples were taken at 7 days PHI, which did not correspond to the current US GAP and therefore could not be used for the estimation of residue levels.

Peanut fodder

Prothioconazole-desthio residue concentrations in peanut hay from trials based on the Australian GAP for peanuts were: 1.14, 1.15, 7.00 and 11.60 mg/kg.

The Meeting estimated highest and median residues of 11.6 mg/kg and 4.08 mg/kg, respectively, for peanut hay.

Fate of residue during processing

Processing Corn

Field corn was treated at 5× total seasonal rate. Subsamples of corn grain were removed for analysis, aspirated grain fractions were generated, and the remaining grain was used to generate the required processed commodities of starch, oil (wet and dry milled, refined, bleached, and deodorized), grits, flour, meal and bran. Processing was performed using procedures that simulated commercial practices.

The processing factors calculated from total prothioconazole residues were: starch (< 0.28), oil, wet milled (< 0.28, grits (< 0.28), flour (0.57), meal (0.43), bran (1.31), oil, dry milled (< 0.28).

The Meeting noted that the major part of the residue is prothioconazole-desthio and concluded that the results of processing study can be used for estimation of the processing factors for prothioconazole-desthio. The Meeting estimated STMR values (mg/kg) for maize starch (0.0050), maize flour (0.010), and refined maize oil (0.0050).

Processing rape seed

Rape seed was sampled following treatment with prothioconazole, 2 × 120 g/ha. The conditioned and cleaned rape seeds were pressed in a screw press, yielding screw pressed oil, and pomace. An aliquot of pomace was extracted twice with hexane. The screw pressed oil and extracted oil were combined to obtain crude oil, which was neutralized and processed to obtain refined oil.

The processing factors calculated were: screw pressed oil (1), pomace (1), meal (< 1), solvent extracted oil (2), crude oil (2), pre-clarified crude oil (2), neutralized crude oil (1) and refined oil (< 1)

The Meeting estimated STMR-P values for rape seed oil, edible of 0.02 mg/kg based on the STMR of 0.02 estimated by the 2009 JMPR

Residues in animal commodities

The following commodities evaluated by the present and previous Meetings could result in residues in animal tissues, milk, and eggs: sweet corn forage and stover, field corn forage and stover, popcorn forage and stover, soya bean hay and peanut fodder (dry), grains, straw and fodder (dry) of cereal grains.

Livestock dietary burden

The maximum and mean dietary burdens were calculated using the highest residues or median residues of prothioconazole-desthio estimated by the current Meeting on a basis of the OECD Animal Feeding Table. The calculated maximum and mean animal burdens are summarized below

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	4.04	3.32	12.36	5.47	21.6[a]	5.50[c]	3.15	3.15
Dairy cattle	10.63	4.85	10.89	4.94	18.42[b]	5.50[d]	7.66	5.25
Broilers	2.86	2.86	1.17	1.17	1.18	1.18	0.29	0.29
Layers	2.86	2.86[f]	3.33[e]	1.71	1.18	1.18	1.72	1.72

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat

[b] Highest maximum dairy cattle dietary burden suitable for MRL estimates for mammalian milk

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

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

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

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

Animal commodity maximum residue levels

The 2009 JMPR summarized the total prothioconazole desthio residues (mg/kg) in edible tissues of dairy cattle after 28 days of dosing with prothioconazole-desthio:

Tissue	4 ppm dose		25 ppm dose		100 ppm dose	
	Range	Mean	Range	Mean	Range	Mean
Liver	0.02-0.05	0.04	0.18-0.26	0.22	0.61-1.6	0.95
Kidney	0.01-0.04	0.02	0.11-0.17	0.14	0.41-1.1	0.65
Muscle	< 0.01	< 0.01	< 0.01	< 0.01	0.01-0.03	0.02
Fat	< 0.01	< 0.01	0.01-0.02	0.01	0.03-0.14	0.07
Milk	< 0.004	< 0.004	< 0.004	< 0.004	0.013-0.02	0.017

The maximum dietary burden for beef cattle remained the same as was estimated by the 2009 JMPR. The maximum dietary burden for dairy cattle is 18.42 ppm which is smaller than the 25 ppm dose and no detectable residue can be expected in milk.

The mean dietary burden for beef and dairy cattle is 5.5 ppm, which is higher than the 4.8 ppm estimated by the 2009 JMPR. However the STMR values estimated by the 2009 JMPR cover the likely median residues.

The Meeting confirmed its previous recommendations for maximum residue levels, HR and median residues for mammalian meat, and edible offal and milk.

The 2008 Meeting concluded that the feeding study on poultry did not reflect the residue composition in feed and could not be used for estimation of residue levels.

RECOMMENDATIONS

On the basis of the data from supervised trials and farm animal feeding studies reported by the 2006 JMPR, the Meeting concluded that the residue levels listed below are appropriate for establishing maximum residue limits and for IEDI assessment.

Definition of the residue (for enforcement and dietary risk assessment) for plant commodities: *prothioconazole-desthio.*

Definition of the residue (for enforcement and dietary risk assessment) for animal commodities: *the sum of prothioconazole-desthio. (M04), prothioconazole-desthio-3-hydroxy (M14), prothioconazole-desthio-4-hydroxy (M15), expressed as prothioconazole-desthio after correction for molecular weight.*

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intake (IEDI) for prothioconazole-desthio was calculated from the recommendations for STMR-s for raw agricultural commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 3 to the 2014 Report.

The IEDI of the 17 GEMS/Food cluster diets were in the range of 0–3 % of the maximum ADI of 0.01 mg/kg bw. The Meeting concluded that the long-term intake of residues from uses of prothioconazole considered by the Meeting is unlikely to present a public health concern.

Short-term intake

The International Estimated Short-term Intake (IESTI) for prothioconazole-desthio was calculated from the recommendations for HR and STMR-s for raw agricultural commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 4 to the 2014 Report.

The IESTI for women of child bearing age is 0–100% of the ARfD of 0.01 mg/kg bw. The IESTI for children and general populations is 0–1 % of the ARfD of 1 mg/kg bw.

For watermelon the IESTI represented 150% of the ARfD of 0.01 mg-kg bw. No alternative GAP was available. On the basis of information provided to the JMPR it was not possible to conclude that the estimate of short-term intake of prothioconazole, from the consumption of watermelon was less than the ARfD. The Meeting did not estimate MRL for watermelon.

The other commodities considered by the JMPR were within 0–100% of ARfD for women of child bearing age and 1% of general population. The Meeting concluded that the short-term intake of prothioconazole when used in ways that have been considered by the MPR is unlikely to present public health concern.