

5.14 ISOFETAMID (290)

RESIDUE AND ANALYTICAL ASPECTS

Isofetamid is a succinate dehydrogenase inhibitor (SDHI) fungicide with a single site of action that inhibits cellular respiration. Isofetamid was first evaluated for toxicology and residues by the JMPR in 2016. The 2016 JMPR set an ADI of 0–0.05 mg/kg bw and an ARfD of 3 mg/kg bw for isofetamid. The 2016 Meeting also concluded that the residue definition for plant commodities for compliance with the MRL and for dietary risk assessment was parent isofetamid. The residue definition for compliance with the MRL and dietary risk assessment for animal commodities was, the sum of isofetamid and 2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido) propanoyl] phenoxy] propanoic acid (PPA), expressed as isofetamid. The residue is fat-soluble.

Isofetamid was scheduled at the Forty-ninth Session of the CCPR for the evaluation of additional uses by the 2018 JMPR. The Meeting received information on use patterns, supervised residue trials and processing studies. A dairy cow feeding study was also provided to the Meeting along with an analytical method for isofetamid and PPA residues in milk and liver matrices.

Methods of analysis

The 2016 JMPR Meeting reviewed analytical methods for isofetamid in plant commodities, and for isofetamid and PPA in animal commodities. All methods were sufficiently validated and acceptable for the consideration of the residue data and enforcement. The methods for determining isofetamid residues in plant commodities including pome fruit, stone fruit, blueberry, raspberry, kiwi fruit, snap bean, lima bean, green bean, dry bean and dry pea were supported with concurrent recovery data from supervised trials submitted to the current Meeting. Analytical methods for determining isofetamid and PPA in cattle milk and liver matrices were independently validated and the methods were considered to be equivalent with the methods for animal commodities reviewed by 2016 JMPR. The methods were considered suitable for the plant and animal commodities evaluated.

Stability of pesticide residues in stored analytical samples

The 2016 JMPR indicated that isofetamid residues are stable at -20 °C for at least 12 months in almonds, rape seeds, grapes, lettuce, potatoes and dry beans.

The current Meeting received residue storage stability data for isofetamid in almonds, rape seed, grapes, lettuce, potatoes and dry beans. Residues of isofetamid in these commodities are stable for at least 24 months when stored frozen at approximately -20 °C.

The Meeting also received a residue study on the stability of isofetamid and PPA in milk, liver, kidney, muscle and fat. Isofetamid and PPA were found to be stable for at least 68 days in milk, muscle, fat, kidney and liver.

The Meeting agreed that the demonstrated storage stability in various representative plant and animal commodities covered the residue sample storage intervals used in the field trials considered by the current Meeting.

Results of supervised residue trials on crops

The Meeting received information on supervised field trials involving foliar treatments of isofetamid to pome fruits (including apple and pear), stone fruits (including peach, plum and cherry), berries, kiwi fruit, grape, legume vegetables and pulses.

Pome fruits

Results of supervised trials on apple and pear conducted in Canada and the USA were provided to the Meeting.

Apple and Pear

The critical GAP for isofetamid on pome fruits in the USA is for 6 foliar applications of 0.365 kg ai/ha with a re-treatment interval of 7 days and a PHI of 20 days.

In 16 trials on apples conducted in North America matching the GAP in the USA, the residues of isofetamid in apples (whole fruit) were (n = 16): 0.030, 0.042, 0.049, 0.066, 0.075, 0.083, 0.11, 0.14, 0.17(2), 0.18(2), 0.27(2), 0.32 and 0.38 mg/kg.

In eight trials on pears conducted in North America matching the GAP in the USA, the residues of isofetamid in pears (whole fruit) were (n = 8): 0.041, 0.043, 0.13(3), 0.14, 0.15 and 0.29 mg/kg.

The Meeting noted that residues from apples and pears were similar (Mann-Whitney test) and could be combined. The combined residue data set were (n = 24): 0.030, 0.041, 0.042, 0.043, 0.049, 0.066, 0.075, 0.083, 0.11, 0.13(3), 0.14(2), 0.15, 0.17(2), 0.18(2), 0.27(2), 0.29, 0.32 and 0.38 mg/kg.

The Meeting estimated a maximum residue level of 0.6 mg/kg, a STMR of 0.135 mg/kg and a HR of 0.42 mg/kg (highest individual value) for isofetamid on the group of pome fruits.

Stone fruits

Results from supervised trials on peach, plum and cherry conducted in Canada and the USA were provided to the Meeting.

The critical GAP for isofetamid on stone fruits in Canada and the USA is for up to 3 foliar applications of 0.365 kg ai/ha with a re-treatment interval of 7 days and a PHI of 1 day.

Peaches

In 11 trials on peach conducted in North America and matching the GAP of the USA, residues of isofetamid were (n = 11): 0.24, 0.32, 0.45, 0.54, 0.68, 0.76, 0.78, 0.83, 0.88, 1.3 and 1.7 mg/kg.

The Meeting estimated a maximum residue level of 3 mg/kg, a STMR of 0.76 mg/kg and a HR of 1.7 mg/kg for isofetamid on the subgroup of peaches.

Plums

In eight trials on plums conducted in North America and matching the GAP of the USA, the residues of isofetamid were (n = 8): 0.03, 0.05(2), 0.14, 0.21, 0.33, 0.35 and 0.36 mg/kg.

The Meeting estimated a maximum residue level of 0.8 mg/kg, a STMR of 0.175 mg/kg and a HR of 0.39 mg/kg (highest individual) for isofetamid on the subgroup of plums.

Cherries

In 13 trials on cherry conducted in North America and matching the GAP of the USA, the residues of isofetamid were (n = 13): 0.31, 0.40, 0.66, 0.76, 0.86, 1.0, 1.1, 1.2, 1.3, 1.4, 1.7, 2.2 and 2.5 mg/kg.

The Meeting estimated a maximum residue level of 4 mg/kg, a STMR of 1.1 mg/kg and a HR of 3.4 mg/kg (highest individual) for isofetamid on the subgroup of cherries.

*Berries and other small fruits**Bush berries*

The critical GAP for isofetamid in “Berry and Small Fruit Crop Group” from Canada is for 3 foliar applications at 0.496 kg ai/ha with a re-treatment interval (RTI) of 7 days and a PHI of 7 days.

In several trials in similar locations the varietal and management differences were considered likely to result in sufficiently different residue scenarios and thus were considered to be independent.

In 10 independent trials on blueberry conducted in North America and similar to the Canadian GAP but at higher application rates of 0.650 kg ai/ha the residues of isofetamid in blueberry were (n = 10): 0.18, 0.25, 0.27, 0.30, 0.34, 0.46, 0.77, 0.89, 0.99 and 3.6 mg/kg.

Using the proportionality approach, residue were scaled with factors ranging from 0.761 to 0.839.

Scaled isofetamid residues were (n = 10): 0.14, 0.19, 0.20, 0.23, 0.27, 0.35, 0.59, 0.68, 0.77 (factor 0.781) and 3.0 mg/kg.

The Meeting estimated a maximum residue level of 5 mg/kg, a STMR of 0.31 mg/kg and a HR of 3.0 mg/kg for isofetamid on the subgroup of bush berries.

Cane berries

The critical GAP for isofetamid on cane berries included in “Berry and Small Fruit Crop Group 13-07” in Canada is for 3 foliar applications at 0.496 kg ai/ha with a re-treatment intervals of 7 days and a PHI of 7 days.

In five independent trials on raspberries conducted in North America, and similar to the Canadian GAP but at higher application rates of 0.650 kg ai/ha, the residues of isofetamid in raspberries were (n = 5): 0.20, 0.53, 0.88, 1.4 and 1.6 mg/kg.

Using the proportionality approach, residues were scaled with factors ranging from 0.762 to 0.781.

Scaled isofetamid residues were (n = 5): 0.16, 0.41, 0.68, 1.1 and 1.2 mg/kg.

The Meeting estimated a maximum residue level of 3 mg/kg, a STMR of 0.68 mg/kg and a HR of 1.2 mg/kg for isofetamid on subgroup of cane berries.

*Assorted tropical and subtropical fruits – inedible peel**Kiwi fruit*

The critical GAP for isofetamid on “Fruit, Small Vine Climbing Fruit except Grapes Subgroup 13-07E” in the USA is for 4 foliar applications at 0.448 kg ai/ha (seasonal maximum of 1.794 kg ai/ha) with re-treatment intervals of 14 days and a PHI of 7 days.

In three trials conducted in the USA, 3 foliar applications of 0.65 kg ai/ha with a PHI of 7 days resulted in isofetamid residues in kiwi fruits of (n = 3): < 0.01, 0.89 and 3.8 mg/kg.

The Meeting agreed that there were insufficient data with which to estimate a maximum residue level for kiwi fruit.

Legume vegetables

The critical GAP for isofetamid in legume vegetables in Canada and the USA is for the following foliar applications:

- beans and peas with pods: 2 × 0.5 kg ai/ha, 7-14 days RTI and a PHI of 7 days;
- Succulent beans and peas without pods: 2 × 0.5 kg ai/ha, 7–14 days RTI and a PHI of 14 days.

Beans with pods

In seven trials on snap beans conducted in Canada and the USA, matching the critical GAP the residues of isofetamid were (n = 7): 0.031, 0.057, 0.077, 0.096, 0.16, 0.16 and 0.32 mg/kg.

Peas with pods

None of the submitted trials matched the cGAP. The Meeting noted that as beans with pods is a representative crop for both the subgroup of beans with pods and the subgroup of peas with pods, the maximum residue level recommendation for beans with pods could also be applied to peas with pods.

Based on the data for snap beans the Meeting estimated a maximum residue level of 0.6 mg/kg, a STMR of 0.096 mg/kg and a HR of 0.36 mg/kg (highest individual) for isofetamid on subgroup of beans with pods and for subgroup of peas with pods.

Succulent beans without pods

The critical GAP for isofetamid in “Legume Vegetables, Edible podded” in Canada is for 2 foliar applications at 0.5 kg ai/ha with a re-treatment interval of 7 days and a PHI 14 days.

In two trials on lima beans conducted in the USA and matching the critical GAP the residues of isofetamid were (n = 2): < 0.01 (2) mg/kg.

The Meeting agreed that there was insufficient data to estimate a maximum residue level for succulent beans without pods.

Succulent peas without pods

In three trials on peas conducted in Canada and the USA, and matching the cGAP the residues of isofetamid were (n = 3): < 0.01 (2) and 0.023 mg/kg.

The Meeting agreed that there was insufficient data to estimate a maximum residue level for succulent peas without pods.

Pulses

The critical GAP for isofetamid on pulses including dry beans and dry peas in the USA and Canada is for 2 foliar applications of 0.5 kg ai/ha with a 7 day re-treatment interval and a PHI of 30 days.

Dry beans

In eight trials on dry beans conducted in North America and matching the critical GAP the residues of isofetamid were (n = 8): < 0.01 (7), 0.036 mg/kg.

Dry peas

In 11 trials on dry peas conducted in North America and matching the critical GAP the residues of isofetamid were (n = 11): < 0.01 (9), 0.02, 0.08 mg/kg.

The Meeting noted that residues from dry beans and dry peas were similar (Mann-Whitney test) and could be combined. The combined residue data were (n = 19): < 0.01 (16), 0.02, 0.036 and 0.08 mg/kg

The Meeting estimated a maximum residue level of 0.05 mg/kg, and a STMR of 0.01 mg/kg for isofetamid on subgroup of dry beans except soya bean, and subgroup of dry peas.

Fate of residues during processing

The Meeting received studies on the effect of processing on isofetamid residues in apple and plum.

Summary of isofetamid processing factors and STMR-P values in apple and plum processed commodities

Matrix	Isofetamid		RAC STMR (mg/kg)	STMR-P (mg/kg)
	Calculated processing factors	PF		
Apple juice	0.31	0.31	0.13	0.04
Apple wet pomace	4.1	4.1		0.53
Dried prune	4.1, 3.8	4.0 (mean)	0.14	0.56

The Meeting estimated a maximum residue level of $4 \times 0.8 = 3$ mg/kg for dried prune, along with a STMR-P of $4 \times 0.14 = 0.56$ mg/kg and a HR of $4 \times 0.38 = 1.5$ mg/kg.

Residues in animal commodities

Farm animal feeding studies

An isofetamid feeding study in dairy cow was provided to the Meeting. Isofetamid was administered orally once daily in the diet to dairy cows for 28 days at levels of 0.5 (low), 1.5 (mid) and 5.01 (high) ppm diet (dry wt/day). The metabolite PPA was not detected in milk, muscle, fat, kidney or liver. Isofetamid residues were below the LOQ (0.01 mg/kg) in all animal matrices.

Estimation of livestock dietary burdens

The current Meeting noted that residues in apple (pomace), dry beans and dry peas may contribute to the livestock dietary burden. The dietary burdens were estimated using the OECD diets listed in Appendix IX of the 2016 edition of the FAO manual. The dietary burden for dairy cattle and beef cattle remained unchanged. The slight increase in estimated maximum and mean dietary burdens for poultry layers (0.008 ppm) were not expected to add significantly to residues in poultry. The meeting confirmed the previous recommendations for animal commodities.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI and IESTI assessment.

Definition of the residue for compliance with the MRL and dietary risk assessment for plant commodities: *Isofetamid*.

Definition of the residue for compliance with the MRL and dietary risk assessment for animal commodities: *the sum of isofetamid and 2-[3-methyl-4-[2-methyl-2-(3-methylthiophene-2-carboxamido)propanoyl]phenoxy]propanoic acid (PPA), expressed as isofetamid*.

The residue is fat-soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for isofetamid is 0–0.05 mg/kg bw. The International Estimated Daily Intakes (IEDIs) for isofetamid were estimated for the 17 GEMS/Food Consumption Cluster Diets using the STMR or STMR-P values estimated by the JMPR. The results are shown in Annex 3 of the 2018 JMPR Report. The IEDIs ranged from 0–6% of the maximum ADI.

The Meeting concluded that long-term dietary exposure to residues of isofetamid from uses considered by the JMPR is unlikely to present a public health concern.

Acute dietary exposure

The ARfD for isofetamid is 3 mg/kg bw. The International Estimate of Short Term Intakes (IESTIs) for isofetamid were calculated for the food commodities and their processed commodities for which HRs/HR-Ps or STMRs/STMR-Ps were estimated by the current JMPR and for which consumption data were available. The results are shown in Annex 4 of the 2018 JMPR Report. The IESTIs varied from 0–3% of the ARfD for children and 0% for the general population.

The Meeting concluded that acute dietary exposure to residues of isofetamid from uses considered by the the current JMPR is unlikely to present a public health concern.