5.29 Valifenalate (318)

TOXICOLOGY

Valifenalate is the ISO-approved common name for methyl-*N*-(isopropoxycarbonyl)-*L*-valyl-(3*RS*)-3-(4-chlorophenyl)-β-alaninate (IUPAC), CAS number 283159-90-0.

Valifenalate is a racemic mixture of L-(R)- and L-(S)-valifenalate. It is an antiperonosporic fungicide used to control mildew in many crops including grapes, potatoes and tomatoes. Its pesticidal mode of action is as a cellulose synthase inhibitor.

Valifenalate has not previously been evaluated by JMPR and was reviewed by the present Meeting at the request of CCPR.

All critical studies contained statements of compliance with GLP and were conducted in accordance with current test guidelines, unless otherwise stated. A literature search did not identify any toxicological information additional to that submitted for the current assessment.

Biochemical aspects

The toxicokinetics and metabolism of ^{14}C-radiolabelled valifenalate have been investigated in the rat, following oral dosing. Following a single oral dose of valifenalate, concentrations of radioactivity in whole blood increased rapidly to reach C_{max} at 1–2 hours post-dose. The maximum concentration following a single high dose of 1000 mg/kg bw was markedly lower than 10 times that seen following a low dose of 100 mg/kg bw, indicating saturation of absorption. Radioactivity was rapidly excreted, mainly in the faeces, with a lower proportion in urine. The majority of the radioactivity in tissues was found in the GI tract. The liver and kidneys also contained concentrations higher than those in the blood. Residual radioactivity declined rapidly with time and was below the limit of quantification at 72 hours post-dose.

Repeated administration of the low dose (100 mg/kg bw per day) given for 14 days with non-radiolabelled valifenalate followed by a single radiolabelled dose, did not result in any increase in tissue residues. Bioaccumulation is not predicted based on such rapid excretion. A sex difference in the excretion of radioactivity was apparent: excretion in the faeces was higher in male (83%) than in female rats (58%), with a lower proportion eliminated in the urine in males (9%) compared to females (34%). The majority of the administered radioactivity was excreted within 48 hours of dosing. In bile-cannulated rats, the majority of the administered dose was excreted in bile (65% and 49% of the dose in male and female rats, respectively). Based on these results, approximately 80% of the administered dose was absorbed. Valifenalate or its metabolites were not eliminated via expired air.

Valifenalate was found to be extensively metabolized in rats; six metabolites were identified. At the low dose level of 100 mg/kg bw only a small proportion of the administered radioactivity was eliminated as unchanged valifenalate (5–8% in faeces; not detected in urine). In high-dose groups (1000 mg/kg bw), more unchanged valifenalate was excreted compared to the low-dose groups, with females showing more extensive metabolism at this high dose compared to males (unchanged valifenalate excreted was 40% in males and 10% in females). The metabolites were the products of primary metabolism, mainly:

- *O*-demethylation - forming R2, identified as RS-β-alanine; *N*-[(1-methylethoxy)carbonyl]-L-valyl-3-(4-chlorophenyl; valifenalate acid), (found up to 36% in urine);
- hydroxylation at both carbons 2 and 3 of the chlorophenyl moieties of the parent molecule - forming R3, (only found in faeces up to 5%) and R4 (found in urine up to 0.8%);
- side-chain cleavage - forming R5, (found up to 3.6% in urine).

The diastereoisomeric ratio (S,R:S,S) of the unchanged parent compound and of R2 did not alter notably as measured in rat urine and faeces

Toxicological data

The acute oral LD_{50} of valifenalate was > 5000 mg/kg bw and the dermal LD_{50} was > 2000 mg/kg bw. The inhalation LC_{50} of valifenalate was > 3.118 mg/L. Valifenalate was not irritating to skin or eyes in rabbits and was not considered to be a skin sensitizer in the guinea pig maximization test.

In repeated-dose toxicity studies on mice (28-day and 90-day), rats (28-day and 90-day) and dogs (28-day, 90-day and one-year), the main effects were reduced body weight gain, increased liver weight and hepatocellular hypertrophy, along with changes in clinical chemistry parameters.

In a 90-day toxicity study in mice, valifenalate was administered at dietary concentrations of 0, 110, 900 and 7000 ppm (equal to 0, 15.3, 134 and 995 mg/kg bw per day for males, 0, 16.7, 148 and 1144 mg/kg per day for females). The NOAEL was 110 ppm (equal to 15.3 mg/kg bw per day), based on decreased body weight gain and liver histopathology (vacuolation in males due to fat accumulation) at 900 ppm (equal to 134 mg/kg bw per day).

In a 90-day toxicity study in rats valifenalate was administered in the diet at varying concentrations to obtain dietary doses of 0, 7, 150 or 1000 mg/kg bw per day (10 rats/sex per dose). The NOAEL for this study was 150 mg/kg bw per day based on the macroscopic change of distended caecum at 1000 mg/kg bw per day.

In a 28-day study in dogs valifenalate was administered in gelatin capsules at doses of 0, 250, 500 or 1000 mg/kg bw per day (three dogs/sex per dose). The main target organ was the liver. The NOAEL was 250 mg/kg bw per day based on increased liver weight and liver histopathology (hepatocellular hypertrophy), and clinical chemistry changes at 500 mg/kg bw per day.

In a 13-week study in dogs valifenalate was administered in gelatin capsules at dose levels of 0, 50, 250 and 750 mg/kg bw per day (four dogs/sex per dose). Similarly to the 28-day dog study, the liver was a target organ, however, effects on the thyroid were also observed after 90 days (follicular cell hypertrophy). The NOAEL was 50 mg/kg bw per day based on changes in clinical chemistry (increased alkaline phosphatase), liver (hepatocellular hypertrophy) and thyroid (follicular cell hypertrophy) at 250 mg/kg bw per day.

In a one-year dog study valifenalate was administered in gelatin capsules at dose levels of 0, 1, 7, 50 or 250 mg/kg bw per day (four dogs/sex per dose). The NOAEL was 50 mg/kg bw per day based on changes in clinical chemistry, liver effects (increased weight and hepatocellular hypertrophy) and thyroid alterations (follicular cell hypertrophy) at 250 mg/kg bw per day.

In a 78-week dietary toxicity and carcinogenicity study, mice received valifenalate at dietary levels of 0, 150, 850 or 5000 ppm (equal to 0, 16.8, 97.2 and 657 mg/kg bw per day for males, 0, 21.6, 124 and 657 mg/kg bw per day for females). The NOAEL for carcinogenicity was 150 ppm (equal to 16.8 mg/kg bw per day) with a LOAEL of 850 ppm (equal to 97.2 mg/kg bw per day) based on liver adenomas exceeding the historical control range at the mid and high dose, and at the high dose also an increase in liver carcinoma outside the historical control range was seen in males. The NOAEL for chronic toxicity was 150 ppm (equal to 16.8 mg/kg bw per day) based on increased liver weight accompanied by histopathological changes in the liver (hepatocellular hypertrophy, centrilobular hepatocellular vacuolation) at 850 ppm (equal to 97.2 mg/kg bw per day).

In a two-year toxicity and carcinogenicity study, rats received valifenalate in the diet at varying concentrations to obtain dietary doses of 0, 15, 150 or 1000 mg/kg bw per day. No neoplastic lesions related to treatment were observed. The NOAEL for chronic toxicity was 150 mg/kg bw per day based on thyroid (follicular cell hypertrophy) and kidney (pelvic hyperplasia) changes at 1000 mg/kg bw per day.

The meeting concluded that valifenalate is carcinogenic in mice, but not in rats.

Valifenalate was tested for genotoxicity in an adequate range of in vitro and in vivo assays. No evidence of genotoxicity was found.

The meeting concluded that valifenalate is unlikely to be genotoxic.

In view of the lack of genotoxicity, the finding of malignant liver tumours in male mice only at the highest dose, which is expected to show a threshold, and the absence of carcinogenicity in rats, the Meeting concluded that valifenalate is unlikely to pose a carcinogenic risk to humans via the diet.

In a two-generation study rats were fed diets containing valifenalate at concentrations of 0, 1250, 4300 and 15 000 ppm (equal to 0, 81, 277 and 986 mg/kg bw per day in males, 0, 93, 319 and 1146 mg/kg bw per day in females). In the absence of adverse effects, the parental NOAEL was 15 000 ppm (equal to 986 mg/kg bw per day), the highest dose tested. The NOAEL for offspring toxicity was 1250 ppm (equal to 81 mg/kg bw per day) based on decreased F_2 pup body weight gain during lactation, at 4300 ppm (equal to 277 mg/kg bw per day). The reproductive NOAEL was set at 15 000 ppm (equal to 986 mg/kg bw per day), the highest dose tested.

In a developmental toxicity study in rats valifenalate was administered via oral gavage at dose levels of 0, 100, 300 or 1000 mg/kg bw per day from GD 6–19. No signs of maternal or developmental toxicity were observed in this study, therefore the maternal and embryo/fetal NOAELs were 1000 mg/kg bw per day, the highest dose tested.

In a rabbit developmental toxicity study valifenalate was administered by oral gavage from GD 6 to GD 28 at dose levels of 0, 100, 300 or 1000 mg/kg bw per day. No signs of maternal or developmental toxicity were observed in this study, therefore the maternal and embryo/fetal NOAELs were 1000 mg/kg bw per day, the highest dose tested.

The Meeting concluded that valifenalate is not teratogenic.

No evidence of neurotoxicity was reported in routine toxicological studies with valifenalate.

The Meeting concluded that valifenalate is unlikely to be neurotoxic.

No evidence of immunotoxicity was reported in routine toxicological studies with valifenalate.

The Meeting concluded that valifenalate is unlikely to be immunotoxic.

Toxicological data on metabolites and/or degradates

Metabolite IR5839 (valifenalate acid, R2), found in plants, rats and other animals, was not acutely toxic via oral exposure (LD_{50} > 2000 mg/kg bw). Metabolite IR5839 did not induce gene mutations in an Ames test, nor did it induce mutations at the $Tk^{+/-}$ locus of mouse lymphoma L5178Y cells. Metabolite IR5839 induced structural chromosome aberrations in an in vitro assay, without any increase in polyploidy. In a follow-up in vivo micronucleus assay in mice, metabolite IR5839 did not induce micronuclei. IR5839 (R2) was one of the main metabolic products of valifenalate in rats (up to 36% in urine) and can be considered covered by studies conducted with the parent compound.

Metabolite PCBA (4-chlorobenzoic acid), found in soil, did not induce mutations at the $Tk^{+/-}$ locus of mouse lymphoma L5178Y cells. PCBA induced structural chromosome aberrations in an in vitro assay with human lymphocytes and a slight increase in polyploidy was observed. In a follow-up in vivo micronucleus assay in mice, PCBA did not induce micronuclei. It was concluded that TTC Cramer class III can be applied (value 1.5 µg/kg bw per day).

Valifenalate acid glucosyl ester is the glucosyl ester of the metabolite IR5839 (valifenalate acid, R2) and will therefore not be more toxic than R2. As R2 is covered by studies conducted with the parent compound, the Meeting concluded that this will also hold for this glucosyl ester of R2.

Metabolite β-4-chlorophenylalanine (coded R5) was found in the rat metabolism study, its level at most 3.6% of administered dose. No further data is available for this metabolite or on its conjugate β-4-chlorophenylalanine-*N*-glucoside. As no genotoxicity data has been submitted, the TTC approach could be used for both metabolites in which case TTC value is 0.0025 µg/kg bw per day.

The Meeting concluded that metabolites valifenalate acid (IR5839, R2) and valifenalate acid glucosyl ester are toxicologically relevant and of equal potency to the parent. The Meeting concluded

that a TTC approach could be used for metabolites PCBA (4-chlorobenzoic acid), β-4-chlorophenylalanine and its conjugate β-4-chlorophenylalanine-*N*-glucoside.

Microbiological data

No information is available.

Human data

No clinical cases or poisoning incidents have been recorded at pilot plant production level.

The Meeting concluded that the existing database on valifenalate was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

An ADI of 0–0.2 mg/kg bw was established on the basis of the NOAEL of 16.8 mg/kg bw per day in the 78-week study in mice and supported by the NOAEL of 15.3 mg/kg bw per day set by the 90-day study in mice, and employing a safety factor of 100. This provides a margin of 600 with respect to the LOAEL for benign liver tumours found in mice.

The Meeting concluded that it was not necessary to establish an ARfD for valifenalate in view of its low acute oral toxicity, the absence of developmental toxicity or any other toxicological effects likely to be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment of valifenalate

Species	Study	Effect	NOAEL	LOAEL
Mouse	90-day study of toxicity[a]	Toxicity	110 ppm, equal to 15.3 mg/kg bw per day	900 ppm, equal to 134 mg/kg bw per day
	Two year study of toxicity and carcinogenicity[a]	Toxicity	150 ppm, equal to 16.8 mg/kg bw per day	850 ppm, equal to 97.2 mg/kg bw per day
		Carcinogenicity	150 ppm, equal to 16.8 mg/kg bw per day	850 ppm, equal to 97.2 mg/kg bw per day
Rat	90-day study of toxicity[a]	Toxicity	150 mg/kg bw per day	1000 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	150 mg/kg bw per day	1000 mg/kg bw per day
		Carcinogenicity	1000 mg/kg bw per day[b]	-
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	15 000 ppm, equal to 986 mg/kg bw per day[b]	-
		Parental toxicity	15 000 ppm, equal to 986 mg/kg bw per day[b]	-
		Offspring toxicity	1250 ppm, equal to 81 mg/kg bw per day	4300 ppm, equal to 277 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	1000 mg/kg bw per day[b]	-
		Embryo and fetal toxicity	1000 mg/kg bw per day[b]	-
Rabbit	Developmental toxicity study[c]	Maternal toxicity	1000 mg/kg bw per day[b]	-
		Embryo and fetal toxicity	1000 mg/kg bw per day[b]	-

Dog	90-day study of toxicity[d]	Toxicity	50 mg/kg bw per day	250 mg/kg bw per day
	One-year study of toxicity[d]	Toxicity	50 mg/kg bw per day	250 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Capsule administration.

Acceptable daily intake (ADI), applies to valifenalate, valifenalate acid and valifenalate acid glucosyl ester, expressed as valifenalate

0–0.2 mg/kg bw

Acute reference dose (ARfD), applies to valifenalate, valifenalate acid and valifenalate acid glucosyl ester, expressed as valifenalate

Unnecessary

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure.

Critical end-points for setting guidance values for exposure to valifenalate

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid absorption (T_{max} 1–2 hours) and approximately 80% absorbed at 100 mg/kg bw (based on urine, bile, cage wash and tissue/carcass)
Dermal absorption	No data
Distribution	Highest tissue levels found in GI tract, liver and kidney
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid (ca 99% within 48 hours); in bile-cannulated rats predominantly in bile (65–49%), urine (13–31%) and faeces (17–16%)
Metabolism in animals	Extensively metabolized; main metabolite R2 (valifenalate acid); oxidation and cleavage reactions
Toxicologically significant compounds in animals and plants	Valifenalate, valifenalate acid and its glucosyl ester, PCBA (4-chlorobenzoic acid), β-4-chlorophenylalanine and β-4-chlorophenylalanine-*N*-glucoside
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 3.118 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Guinea pig, dermal sensitization	Not sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	Decreased body weight gain (mice), liver weight and histopathology (mice, dog), caecum histopathology (rat), thyroid histopathology and clinical chemistry (dog)
Lowest relevant oral NOAEL	15.3 mg/kg bw per day (mouse)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rat; highest dose tested)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	

Target/critical effect	Liver (mouse); Thyroid and kidneys (rat)
Lowest relevant NOAEL	16.8 mg/kg bw per day (mouse)
Carcinogenicity	Carcinogenic in mice, not carcinogenic in rats[a]
Genotoxicity	No evidence of genotoxicity[a]
Reproductive toxicity	
Target/critical effect	Decreased pup body weight gain
Lowest relevant parental NOAEL	986 mg/kg bw per day, highest dose tested
Lowest relevant offspring NOAEL	81 mg/kg bw per day
Lowest relevant reproductive NOAEL	986 mg/kg bw per day, highest dose tested
Developmental toxicity	
Target/critical effect	None
Lowest relevant maternal NOAEL	1000 mg/kg bw per day (rat, rabbit; highest dose tested)
Lowest relevant embryo/fetal NOAEL	1000 mg/kg bw per day (rat, rabbit; highest dose tested)
Neurotoxicity	
Acute neurotoxicity NOAEL	No specific data; unlikely to be neurotoxic
Subchronic neurotoxicity NOAEL	No specific data; unlikely to be neurotoxic
Developmental neurotoxicity NOAEL	No specific data; unlikely to be neurotoxic
Immunotoxicity	No specific data; unlikely to be immunotoxic[a]
Studies on toxicologically relevant metabolites	
Acute toxicity	
IR5839 (valifenalate acid, R2), rat, oral	LD_{50} > 2000 mg/kg bw (rat)
Genotoxicity	
IR5839 (valifenalate acid, R2)	Ames: negative In vitro mammalian cell gene mutation: negative In vitro chromosome aberration: positive In vivo micronucleus: negative
PCBA (4-chlorobenzoic acid)	In vitro mammalian cell gene mutation: negative In vitro chromosome aberration: positive In vivo micronucleus: negative
Human data	No clinical cases or poisoning incidents have been recorded.

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.2 mg/kg bw[a]	78-week mouse study, supported by the 90-day mouse study	100
ARfD	Unnecessary		

[a] applies to valifenalate, valifenalate acid and valifenalate acid glucosyl ester, expressed as valifenalate

RESIDUE AND ANALYTICAL ASPECTS

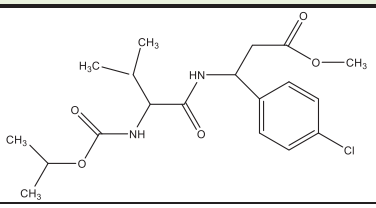
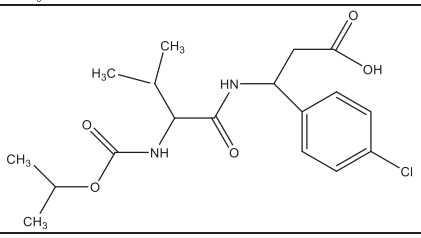
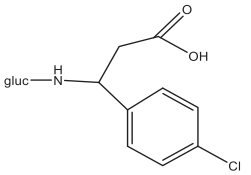
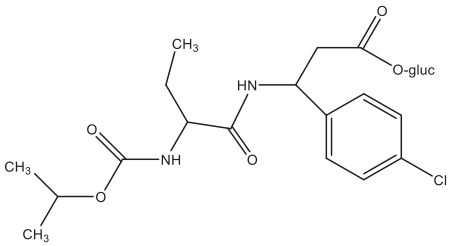
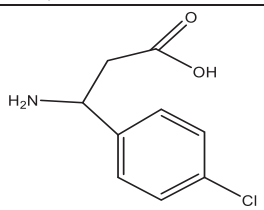
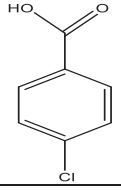
Valifenalate (methyl (3*RS*)-3-(4-chlorophenyl)-*N*-[*N*-(isopropoxycarbonyl)-L-valyl]-β-alaninate) is a fungicide belonging to the chemical group of valinamide carbamates. It interferes with cell wall synthesis affecting all the growth stages of the pathogens controlled, both outside (on the spores), or inside the plant (on the mycelium), affecting the metabolism of the fungal cell wall.

Valifenalate was scheduled at the Fiftieth Session of the CCPR as a new compound for evaluation by the 2019 JMPR.

The Meeting received information from the manufacturer on identity, physical and chemical properties, metabolism studies on plants and lactating goats, environmental fate, analytical methods and stability in stored analytical samples, use patterns, supervised residue trials and processing studies.

Valifenalate technical is an equimolar mixture of diastereomers (S,R) and (S,S).

Table 1 Summary information on valifenalate and its degradation products

Code names, chemical names and structures of valifenalate and its degradation products			
Code Name/ Number	Chemical Name	Chemical Structure	Occurrence in
Valifenalate	methyl (3*RS*)-3-(4-chlorophenyl)-*N*-[*N*-(isopropoxycarbonyl)-L-valyl]-β-alaninate		Grapes, tomato, lettuce, potato, goat, rotational crops, soil
Valifenalate-acid R2	3-(4-chlorophenyl)-3-[[N-(isopropoxycarbonyl)-L-valyl]amino]propionic acid		Grapes, tomato, lettuce, potato, goat, rat, rotational crops, soil
β-4-chlorophenylalanine-N-glucoside	3-amino-3-(4-chlorophenyl)propionic acid-N-glucoside		Grapes, tomato, lettuce, potato, rotational crops
Valifenalate-acid glucosyl ester	3-(4-chlorophenyl)-3-[[N-(isopropoxycarbonyl)-L-valyl]amino]propionic-glucosyl ester		Grapes, tomato, lettuce, potato, rotational crops
β-4-chlorophenylalanine R5	3-amino-3-(4-chlorophenyl)propionic acid		Goat, rat
PCBA	4-chlorobenzoic acid		Soil

Based on the physical chemical properties, valifenalate is not very volatile, nor is it soluble in water and nonpolar solvents. Valifenalate is photochemically stable. Based on the Log K_{ow}, valifenalate has the potential to sequester to fatty matrices.

PLANT METABOLISM

The Meeting received plant metabolism studies investigating the nature of the residues following foliar application of valifenalate to grapes, lettuce, tomatoes and potatoes.

Grape - fruit

Fourteen pots of grape vine plants (variety *Trebbiano*), maintained outdoor, were sprayed four times with [^{14}C-U-phenyl]-valifenalate at a low rate of 15 g ai/hL per application (equivalent to the critical GAP) and a higher rate of 75 g ai/hL per application with re-treatment intervals of 11-14 days. Grapes were harvested at maturity, 74 days following the last application.

The total radioactive residues (TRRs) in grapes following treatment at the lower rate were 0.19 mg eq/kg, where 0.08 mg eq/kg (42% TRR) was found in the surface wash and 0.11 mg eq/kg (58% TRR) was found in the washed grapes. At the higher application rate, TRRs in grapes (1.67 mg eq/kg) were higher as were those in the surface wash (1.18 mg eq/kg; 71% TRR) and washed grapes (0.53 mg eq/kg; 32% TRR). Only the surface washes and extracts from the low treatment study were analysed.

The total radioactivity extracted following water surface wash and sequential extractions with acetone:water and acetone released 95% TRR with 5% remaining unextracted. Valifenalate accounted for all the radioactivity in the surface wash (42% TRR; 0.08 mg eq/kg) and the majority of the radioactivity in the solvent extract (24% TRR; 0.05 mg eq/kg), representing a total of 66% TRR (0.13 mg eq/kg). The valifenalate-acid metabolite was observed in the extract at 13% TRR (0.02 mg eq/kg) with the minor valifenalate-acid glucosyl ester and β-4-chlorophenylalanine-N-glucoside metabolites collectively representing approximately 10% TRR (0.016 mg eq/kg).

Grape - leaves

Vine plants (variety *Barbera*), maintained in a growth chamber under controlled environmental conditions, were sprayed once with [^{14}C-U-phenyl]-valifenalate at a rate of 15 g ai/hL. Leaves were collected 2 hours, 1, 3, 8, 14 and 30 days after treatment. At sampling times of 14, 23 and 30 days, the new leaves grown after treatment were separately analysed.

The TRRs, determined by summing the radioactivity in the washes with those of the washed leaves, remained relatively unchanged as the sampling time increased from 2 hours (56 mg eq/kg) to 30 days (51 mg eq/kg).

Greater than 88% TRR in the treated leaves was removed by surface washing with acetone. Extraction of the washed leaves with acetone:water and acetone released an additional 3–11% TRR resulting in less than 0.5% TRR unextracted at all sampling intervals. New leaves collected on sampling days 23 and 30 were extracted with the same solvents and 96–98% TRR was released with limited radioactivity remaining unextracted.

Valifenalate accounted for all the radioactivity in the surface washes at all sampling times, representing greater than 88% TRR, however, concentrations of the parent compound declined relatively slowly with increasing sampling time, from 53 mg eq/kg (2 hours following the foliar spray application) to 48 mg eq/kg (30 days post-treatment). Parent accounted for the majority of the compounds identified (> 38% radioactivity present) in the washed leaf extracts, yet concentrations of valifenalate declined at a faster rate, from 4.2 mg eq/kg to 0.75 mg eq/kg, as the duration following sampling increased. This decline was accompanied by an increase in concentration of the valifenalate-acid (0.06 mg eq/kg (1 day post-treatment) to 0.25 mg eq/kg at the end of the experiment) and the unknown metabolites (0.6 mg eq/kg (1 day post-treatment) to 1.0 mg eq/kg). In new leaves, valifenalate,

valifenalate-acid and unknown metabolites accounted for 20–27% TRR (0.03–0.06 mg eq/kg), 20% TRR (0.03–0.04 mg eq/kg) and 49–58% TRR (0.09–0.11 mg eq/kg), respectively.

Tomato - leaves

Fourteen pots of tomato plants (variety *Marmande*), maintained in growth chambers under controlled environmental conditions, were sprayed 30-40 days after sowing with a single foliar application of [^{14}C-U-phenyl]-valifenalate at a concentration of 0.25 g ai/L, equivalent to 0.625 mg ai/plant.

TRRs in treated leaves decreased from 36 mg eq/kg, 2 hours after treatment, to 8.7 mg eq/kg, 28 days after treatment. The radioactivity in the acetone surface washes and washed leaves decreased from 31 mg eq/kg and 4.6 mg eq/kg, respectively, 2 hours following application, to 7.1 mg eq/kg and 1.4 mg eq/kg, respectively, 28 days following application, demonstrating a rapid penetration of the radioactivity into the leaves and a corresponding rapid dissipation of the radioactive residues in washed leaves. A 3-fold increase in unextracted residues was observed within the same time interval (0.04 mg eq/kg to 0.12 mg eq/kg). The parent compound, valifenalate, accounted for all the radioactivity in the surface washes (> 8.0% TRR), and was identified as the major residue in the acetone:water and acetone extracts of the washed leaves (11–18% TRR; 1.0–5.2 mg eq/kg), for a total of 93–100% TRR (0.13–55.4 mg eq/kg). Three minor metabolites, valifenalate-acid, valifenalate acid glucosyl ester and β-4-chlorophenylalanine-N-glucoside were also identified in the leaf extracts, neither of which represented more than 1.5% TRR (0.22 mg eq/kg).

Analysis of new leaves, grown after the foliar spray application and sampled 21 and 28 days following treatment, showed that some of the radioactivity which penetrated the sprayed plants translocated to the new leaves. The total radioactivity in the new leaves was 0.81 mg eq/kg and 0.84 mg eq/kg at 21 and 28 days, respectively, of which up to 98% TRR was extracted with the same solvents as those used for treated leaves. Valifenalate and valifenalate-acid represented 29–45% TRR (0.23–0.38 mg eq/kg) and 20–28% TRR (0.16–0.22 mg eq/kg), respectively, accounting for the majority of the radioactivity in the solvent extracts. Valifenalate-acid glucosyl ester and β-4-chlorophenylalanine-N-glucoside were also identified, representing 6-10% TRR (0.05–0.08 mg eq/kg).

Lettuce

Six lettuce plants (variety *Romana*), grown in one pot maintained outdoors, received three foliar spray applications of [^{14}C-U-phenyl]-valifenalate formulated as a wettable powder, at a rate of 150 g ai/ha per application. The applications were performed at intervals of seven days. TRRs in mature lettuce plants harvested 7 days following the last application were 3.6 mg eq/kg.

Analysis of the water surface wash (32% TRR) and the combined acetone:water and acetone extracts (70% TRR) showed that the parent compound was the main component of these fractions, representing all the radioactivity in the surface wash and 64% TRR in the extracts, for a total of 96% TRR (3.55 mg eq/kg). Once valifenalate penetrated into the lettuce leaves, it was metabolized into the valifenalate-acid (1.8% TRR; 0.07 mg eq/kg), the valifenalate-acid glucosyl ester (1.1% TRR; 0.04 mg eq/kg) and the β-4-chlorophenylalanine-N-glucoside (2.6% TRR; 0.09 mg eq/kg).

Potato - leaves

Fourteen pots of potato plants (variety *Primura*), maintained outdoors, were sprayed with a single foliar application of [^{14}C-U-phenyl]-valifenalate at a concentration of 0.25 g ai/L, equivalent to 0.625 mg ai/plant.

The radioactivity in the leaves dissipated from 10 mg eq/kg, 2 hours after treatment, to 5.6 mg eq/kg, 28 days following treatment. In a similar manner, TRRs in the acetone surface wash declined from 9.4 mg eq/kg to 4.5 mg eq/kg within the same sampling interval, with a corresponding increase in extracted (acetone:water and acetone) radioactivity, from 5% TRR (0.55 mg eq/kg) to 19% TRR (1.0 mg eq/kg).

Analysis of the leaf surface wash solutions demonstrated that the entire radioactivity on the leaf surface corresponded to the parent compound, valifenalate. Some of the parent compound that had

penetrated into the leaves appeared to undergo O-demethylation to the valifenalate-acid, which accounted for 0.06–0.87% TRR (0.006-0.05 mg eq/kg), followed by conjugation to valifenalate-acid glucosyl ester and β-4-chlorophenylalanine-N-glucoside, both of which increased from 0.10 to 0.61% TRR (0.01 to 0.04 mg eq/kg), with the increase in sampling time.

Potato tubers

Four pots of potato plants (variety *Primura*), maintained outdoors, received three applications of [^{14}C-U-phenyl]-valifenalate at 150 g ai/ha per application. The applications were performed at intervals of 7 days. The plants were harvested at maturity, 21 days following the last application.

The majority of the radioactive residue (98% TRR) in tubers was extracted with acetone:water and acetone, with unextracted residues accounting for ≤10% TRR. The TRRs in the leaves (58.3 mg eq/kg, radioactivity not further investigated) were significantly higher than those in tubers (0.013 mg eq/kg) demonstrating minimal translocation from the leaves to the tubers.

While chromatographic analysis of the potato tuber extracts revealed that the parent compound was not detected in tubers, four metabolites were identified, valifenalate-acid (15% TRR; 0.002 mg eq/kg), valifenalate-acid glucosyl ester (16% TRR; 0.002 mg eq/kg), β-4-chlorophenylalanine (32% TRR; 0.004 mg eq/kg) and β-4-chlorophenylalanine-N-glucoside (0.75% TRR; 0.0001 mg eq/kg).

In summary, the metabolism of valifenalate is adequately understood in grapes, tomato (leaves), lettuce and potato, representing fruit, a root and tuber vegetable and a leafy crop. In all crops, except potato tuber, the major component of the residue is valifenalate (66–99% TRR). Metabolites identified were the valifenalate-acid, valifenalate-acid glucosyl ester and β-4-chlorophenylalanine-N-glucoside. In all metabolism studies, there was evidence of limited translocation of the radioactivity from the site of application.

The degradation of ^{14}C-valifenalate proceeds predominantly via O-demethylation to the valifenalate-acid followed by conjugation to valifenalate-acid glucosyl ester and β-4-chlorophenylalanine-N-glucoside. The major plant metabolite, valifenalate-acid, was identified as a major metabolite in rats.

Surface washes and extracts of all crops tested were further analysed by HPLC to determine the ratio of S,R and S,S diastereomers of valifenalate and the valifenalate-acid metabolite (grape leaves only). Valifenalate and the valifenalate-acid metabolite in both surface washes and extracts were made up of S,R and S,S diastereomers in similar ratios (approximately 50%). Therefore, no changes in the isomeric ratio were observed in any of the plant metabolism studies.

ANIMAL METABOLISM

The Meeting received animal metabolism studies with valifenalate in goats and rats. A metabolism study in laying hen was not provided to the Meeting. Evaluation of the rat metabolism study was carried out by the WHO Core Assessment Group.

Lactating Goat

[^{14}C-U-phenyl]-valifenalate was orally administered to a lactating goat (*Saanan*, weighing 60 kg) by gelatine capsules, twice daily for 5 consecutive days. The average daily dose level was equivalent to 13 ppm in the feed (dry matter). The goat was sacrificed 23 hours after administration of the last dose.

The majority of the administered dose (AD) was excreta-related (83.1% AD). Limited radioactivity was eliminated in the milk (0.02% AD) and the tissue burden was low (0.13% AD). The remainder of the radioactivity was recovered in the GI tract, accounting for 15% AD. The overall recovered radioactivity accounted for 98% AD.

Radioactivity in milk remained low throughout the study duration with no plateau observed (≤ 0.003 mg eq/kg). In the tissues, TRRs were highest in liver (0.11 mg eq/kg) followed by kidney (0.045 mg eq/kg), fat (omental and renal; 0.011 mg eq/kg) and muscle (hind and fore quarter;

0.003 mg eq/kg). Due to the low levels of radioactivity in muscle, no further analysis was undertaken to elucidate the nature of the residues.

Successive extractions of milk and tissues using various organic solvents released more than 83% TRR. The unextracted residues ranged from 4–8% TRR.

Valifenalate accounted for the majority of the radioactivity in milk (53% TRR). The minor metabolites, valifenalate-acid and β-4-chlorophenylalanine were also observed, however, neither accounted for more than 3% TRR (0.0001 mg eq/kg).

Valifenalate accounted for approximately 2% TRR (0.002 mg eq/kg) in both liver and kidney. The valifenalate-acid was the predominant metabolite detected in both tissues accounting for 51% TRR (0.023 mg eq/kg) in kidney and 61% TRR (0.066 mg eq/kg) in liver. The only other identified metabolite was β-4-chlorophenylalanine, representing 9% TRR (0.004 mg eq/kg) in kidney and 2% TRR (0.002 mg eq/kg) in liver.

In renal and omental fat, valifenalate accounted for the majority of the radioactivity (64% TRR; 0.002 mg/kg), and the valifenalate-acid was the only metabolite identified, representing 9–18% TRR (≤ 0.002 mg eq/kg).

The Meeting concluded that, in the species investigated (goats and rats), the total administered radioactivity was predominantly eliminated in excreta. Qualitatively there are no major differences among the metabolic profiles with the exception that the metabolism in rats was more extensive than in goats. The routes and products of metabolism were similar across both animals, resulting from O-demethylation to form the valifenalate-acid metabolite followed by hydrolysis of the amide bond to form β-4-chlorophenylalanine.

ENVIRONMENTAL FATE IN SOIL

The Meeting received information on hydrolysis, soil photolysis, aerobic degradation and the behaviour of [^{14}C]-valifenalate in confined rotational crops..

Hydrolysis

Valifenalate was hydrolytically stable at pH4. Its hydrolytic degradation increased with increasing pH. The DT_{50} at pH 7 (25 °C) was estimated to be 91 days and at pH 9 (25 °C) was 4.2 days. The major hydrolytic degradation product identified was the valifenalate-acid which was demonstrated to be stable to hydrolysis at all tested pH.

Photolysis - Soil

Valifenalate is stable to photolysis.

Aerobic degradation in soil

The degradation of [^{14}C-U-phenyl]-valifenalate was investigated in various soil types (including sandy loam, loamy sand, loam, silty clay loam) under aerobic laboratory conditions (20 °C for up to 96 days).

Following first order kinetics or first-order multi-compartment (FOMC) kinetics, the resulting DT_{50} values for valifenalate ranged from 0.04–0.36 days while those for its major degradation product, valifenalate-acid, ranged from 0.33–0.93 days.

The resulting DT_{50} values for the soil metabolite PCBA ranged from 2–3 days.

The Meeting concluded that valifenalate, valifenalate-acid and PCBA are not persistent in soil.

Confined rotational crop

Bare sandy loam soil was treated with an aqueous solution of [^{14}C-U-phenyl]-valifenalate at a rate of 1440 g ai/ha, equivalent to almost 10-fold the highest annual rate. The treated soil was aged for 30, 120 and 365 days prior to sowing winter wheat, carrot and lettuce. Crops were harvested at maturity. Winter

wheat was also harvested at an intermediate growth stage (forage).

In carrot, TRRs were ≤ 0.008 mg eq/kg at all plant-back intervals (PBI), while TRRs in carrot leaves decreased from 0.056 mg eq/kg at the 30-day PBI to 0.018 mg eq/kg at the 365-day PBI. In lettuce, TRRs at the 30-day PBI were 0.017 mg eq/kg and remained at 0.09 mg eq/kg at PBIs of 120 and 365 days. In wheat forage, straw and grain, TRRs consistently declined with increasing PBI (forage: 0.018 mg eq/kg (30-day PBI) to 0.008 mg eq/kg (120-day PBI) to < 0.006 mg eq/kg (365-day PBI); straw: 0.098 mg eq/kg (30-day PBI) to 0.051 mg eq/kg (120-day PBI) to 0.030 mg eq/kg (365-day PBI); grain: 0.030 mg eq/kg (30-day PBI) to 0.013 mg eq/kg (120-day PBI) to 0.005 mg eq/kg (365-day PBI)).

The radioactivity released following acetone:water extraction ranged from 33 to 73% TRR. The unextracted residue ranged between 29 and 67% of TRR (< 0.01 to 0.05 mg eq/kg) for all crops at all PBIs. A high proportion of this radioactivity was incorporated into the cellulose (5–38% TRR; < 0.01 to 0.03 mg eq/kg) and lignin fractions (1–22% of TRR; ≤ 0.01 mg eq/kg).

Valifenalate appeared to be taken up from the soil into the crops where it was metabolized into three compounds, valifenalate-acid, valifenalate-acid glucosyl ester and β-4-chlorophenylalanine-N-glucoside. The main residue found in all crops was the unchanged parent, valifenalate. The amount of valifenalate detected in raw commodities destined for human consumption was very low (lettuce: 19% of TRR, 0.003 mg eq/kg; wheat grain: 19% of TRR; 0.006 mg eq/kg) while that in feed commodities (carrot leaves, wheat forage and wheat straw) was ≤4 8% TRR (≤ 0.03 mg eq/kg). Valifenalate-acid was not observed in wheat forage at any PBI, however, it was present in almost all other tested matrices, accounting for 6–11% TRR (0.001–0.006 mg eq/kg) in carrot leaves, 5% TRR (0.0009 mg eq/kg) in lettuce (30-day PBI), 17% TRR (0.002 mg eq/kg) in wheat straw (365-day PBI) and < 1% TRR (0.002 mg eq/kg) in wheat grain (30-day PBI). Both valifenalate-acid glucosyl ester and β-4-chlorophenylalanine-N-glucoside were present but at concentrations lower than those of the acid metabolite.

The Meeting concluded that, considering the residues of valifenalate and its associated metabolites in follow crops were low following application to bare soil at 10-fold the highest annual rate, no significant residues of the parent compound or the metabolites are anticipated following treatment at the maximum annual rate.

METHODS OF ANALYSIS

The Meeting received descriptions and validation data for an analytical method capable of quantifying residues of valifenalate and valifenalate-acid in diverse plant matrices. Sequential extractions were carried out with acetonitrile: 0.02 M triethylamine or dichloromethane. After clean-up the final extracts were quantified for residues of valifenalate and/or valifenalate-acid using liquid chromatography with tandem mass spectrometric detection (LC-MS/MS). The LOQ was reported to be 0.01 mg/kg for each analyte for all plant matrices. Recoveries of valifenalate and valifenalate-acid were typically within the acceptable range of 70–120% with relative standard deviations below 20%.

The Meeting also received descriptions and validation data for several analytical methods for analysis of residues of valifenalate and the valifenalate-acid metabolite in milk, eggs and livestock matrices. Extraction solvents used were acetonitrile: 0.02 M triethylamine, hexane pre-saturated with acetonitrile in combination with acetonitrile pre-saturated with hexane, hexane:acetone and acetonitrile. Clean-up of the extracts was performed using liquid partitioning. For all methods, residues of valifenalate and valifenalate-acid were quantified using LC-MS/MS. The LOQs achieved for all animal commodities were 0.01 mg/kg for each analyte. Recoveries of valifenalate and the valifenalate-acid were typically within the acceptable range of 70–120% with relative standard deviations below 20%.

Many of the methods, capable of analysing valifenalate and/or valifenalate-acid in plant and animal matrices, were successfully validated by independent laboratories, demonstrating good reproducibility. Some of the methods were also subjected to radiovalidation, where 73–109% of the valifenalate residues were recovered from samples collected from the metabolism studies, demonstrating the efficiency of the data collection analytical methods to extract incurred residues of valifenalate.

STABILITY OF PESTICIDE RESIDUES IN STORED ANALYTICAL SAMPLES

The stability of valifenalate and valifenalate-acid was investigated in lettuce, tomatoes, onions, potatoes, grapes and wine. Samples were fortified with each analyte at various concentrations, stored frozen at -20 ºC and taken for analysis at intervals up to 24 months.

Residues of valifenalate and valifenalate-acid were determined to be stable at -20 ºC for at least 24 months in high water content commodities (lettuce, tomatoes and onions), grapes (high acid), potatoes (high starch) and wine.

Studies on storage stability of valifenalate in milk and animal tissues were not provided to the Meeting.

DEFINITION OF THE RESIDUE

The nature of the valifenalate residues was investigated in grapes (leaves and fruit), lettuce, tomatoes (leaves) and potatoes (leaves and tubers) following foliar treatment.

As valifenalate was, in most cases, the major analyte in all tested plant matrices (66–99% TRR; 0.13–5.5 mg eq/kg) and suitable analytical methods are available to analyse the parent compound, the Meeting considered that valifenalate was a suitable marker for enforcement of MRLs for plants.

In deciding which compounds should be included in the residue definition for risk assessment, the Meeting considered the likely occurrence of the valifenalate-acid and its conjugate valifenalate-acid glucosyl ester and β-4-chlorophenylalanine and its conjugate β-4-chlorophenylalanine-N-glucoside.

In the metabolism studies, the ratios of the combined levels of valifenalate-acid (free and conjugated) to the parent compound were up to 0.23. In a few of the supervised residue trials conducted on grapes, where residues of free valifenalate-acid were reported, the ratios of valifenalate-acid to the parent ranged from 0.085–0.83. The median of all ratios was 0.25.

In the metabolism studies where β-4-chlorophenylalanine and/or its conjugate β-4-chlorophenylalanine-N-glucoside were measured, the ratios of these metabolites to the parent compound ranged from 0.0018–0.026 (median = 0.0046).

The toxicological properties of these metabolties were considered. Valifenalate-acid is not likely to be more potent than the parent compound, given its toxicity profile as well as its detection in rats at significant levels. While the valifenalate-acid-glucosyl-ester was not observed in the rat, considering it is a conjugate of the valifenalate-acid, the metabolite valifenalate-acid glucosyl ester was also considered to be covered by the parent compound.

β-4-chlorophenylalanine-N-glucoside was not detected in the rat metabolism study. This metabolite is the glucoside conjugate of β-4-chlorophenylalanine which was observed as a minor metabolite (< 10%) in the rat metabolism study but no conclusion on its toxicological relevance could be drawn. Therefore, the Meeting noted that the TTC for potential genotoxicity (0.0025 µg/kg bw per day) should be applied for β-4-chlorophenylalanine (free and conjugated). The estimated maximum long-term dietary exposure to β-4-chlorophenylalanine (free and conjugated) is 0.001 µg/kg bw per day and below the TTC. It is therefore unlikely to present a public health concern based on the uses considered by the current Meeting.

Noting the above, the Meeting decided the residue definition for dietary risk assessment for plant commodities should be valifenalate and the valifenalate-acid (free and conjugated), expressed as valifenalate equivalents.

As residues of valifenalate-acid (free and conjugated) were not measured in field trials approximating GAP, an adjustment factor of 1.25 was derived from the metabolism studies and a select number of grape residue trials. This factor will be used to convert residues of valifenalate to total residues of valifenalate and the valifenalate-acid (free and conjugated). The Meeting considered the factor would only be applied to supervised trial median residues (STMRs) to estimate the relevant values required for dietary risk assessment.

The nature of the valifenalate residues was investigated in lactating goat. Following oral administration of the test substance to a lactating goat (13 ppm feed), valifenalate was the predominant analyte in milk and fat (renal and omental) accounting for 53–63% TRR (0.002–0.007 mg eq/kg). In kidney and liver, the parent accounted for < 3% TRR (< 0.003 mg eq/kg), with valifenalate-acid representing the majority of the radioactivity in these tissues (51–61% TRR; 0.02–0.07 mg eq/kg). Due to the low levels of radioactivity in muscle (0.01% AD; 0.003 mg eq/kg), no further analysis was undertaken to elucidate the nature of the residues.

No farm animal feeding studies were provided to the Meeting.

As the livestock dietary burden is anticipated to be zero, based on the uses considered by the current Meeting, residues of valifenalate and valifanalate-acid in animal matrices are not anticipated. Based on the available information, the Meeting decided that the parent was a suitable marker for all animal matrices. Suitable methods are available for valifenalate in animal commodities.

Noting the above, the Meeting concluded that for enforcement of MRLs for livestock matrices, the residue definition should be valifenalate.

In deciding which compounds should be included in the residue definition for risk assessment, the Meeting considered the likely occurrence of the metabolites valifenalate-acid and β-4-chlorophenylalanine.

Valifenalate-acid may contribute significantly to the consumer exposure as it is present in liver and kidney at levels 25–30 fold higher than that of the parent compound in the goat metabolism study. In these same tissues, β-4-chlorophenylalanine was present at levels 4-fold higher than that of the parent.

The valifenalate-acid was detected as a major metabolite in the rat metabolism study and not likely to be more potent than the parent. Therefore, the valifenalate-acid is considered to be toxicologically covered by the parent compound.

β-4-chlorophenylalanine was observed as a minor metabolite (< 10%) in the rat metabolism study but no conclusion on its toxicological relevance could be drawn. Therefore, similar to plant commodities, the Meeting noted that the TTC for potential genotoxicity (0.0025 µg/kg bw per day) should be applied for β-4-chlorophenylalanine. The long-term dietary exposure to β-4-chlorophenylalanine residues in animal matrices is not likely to contribute to the estimated exposure for plants above, considering the current livestock dietary burden of 0.

Noting the above, the Meeting concluded that the residue definition for dietary risk assessment for animal commodities should be valifenalate and valifenalate-acid, expressed as valifenalate.

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

Definition of the residue for risk assessment for plant commodities: *valifenalate and* 3-(4-chlorophenyl)-3-[[N-(isopropoxycarbonyl)-L-valyl]amino]propionic acid (valifenalate-acid), free and conjugated, expressed as valifenalate.

Definition of the residue for risk assessment for animal commodities: *valifenalate and* 3-(4-chlorophenyl)-3-[[N-(isopropoxycarbonyl)-L-valyl]amino]propionic acid (valifenalate-acid), expressed as valifenalate.

There is insufficient data to characterize whether the sum of residues in the residue definition (sum of valifenalate and valifenalate-acid) is fat-soluble. The nature of the residues in muscle was not investigated. The log K_{ow} for valifenalate is 3.11 and the log K_{ow} value of valifenalate acid is expected to be lower, suggesting the residue does not preferentially partition into fatty matrices.

On the weight of evidence, the Meeting decided the residue is not *fat-soluble*.

Results of supervised residue trials in crops

Grapes

The critical GAP for grapes is from the Ukraine; 4 × 120 g ai/ha, 10-day RTI and 30-day PHI.

As there were no supervised residue trials conducted in accordance with the Ukrainian GAP, the GAP from Italy was considered; 3 × 120 g ai/ha, 10–14 day RTI and 28-day PHI for wine grape and 70-day PHI for table grape.

In trials from Europe, matching the GAP from Italy, residues of valifenalate in grapes in ranked order were (n = 16): < 0.010, 0.013, 0.014, 0.019, 0.040, 0.045, 0.051, 0.058, 0.067, 0.073, 0.086, 0.087, 0.095, 0.11, 0.12 and 0.13 mg/kg.

The Meeting estimated a maximum residue level and STMR of 0.3 and 0.079 (1.25 × 0.0625) mg/kg, respectively, for grapes.

Onion, Bulb

The critical GAP for bulb onions/shallots is from Bulgaria; 3 × 150 g ai/ha, 7-day RTI and 3-day PHI.

In trials from Europe matching the critical GAP, valifenalate residues in bulb onions in ranked order were (n = 12): < 0.01 (4), 0.014, 0.018, 0.042, 0.079, 0.087, 0.18 (2) and 0.26 mg/kg

The Meeting estimated a maximum residue level and STMR of 0.5 and 0.0375 (1.25 × 0.030) mg/kg, respectively, for onion, bulb.

The critical GAP from Bulgaria also includes shallots. The Meeting decided the data could be used to extrapolate the maximum residue level and the STMR values for onion to shallot.

Tomatoes

The critical GAP for field tomato/eggplant is from France; 3 × 150 g ai/ha, minimum 7-day RTI and 3-day PHI.

In trials from Europe matching the critical GAP, valifenalate residues in field tomatoes in ranked order were (n = 9): < 0.01 (2), 0.014, 0.021, 0.039, 0.051, 0.055, 0.088 and 0.27 mg/kg.

The Meeting estimated a maximum residue level and STMR of 0.4 and 0.049 (1.25 × 0.039) mg/kg, respectively, for tomatoes.

The critical GAP from France for field tomato also covers eggplants. The Meeting decided the data could be used to extrapolate the maximum residue level and the STMR values of tomato to eggplants.

FATE OF RESIDUES DURING PROCESSING

Processing

The Meeting did not receive information on the nature of residues under conditions simulating pasteurisation, baking/brewing/boiling and sterilisation. However, the Meeting received information on the fate of valifenalate and valifenalate-acid residues during the processing of grapes and information on the fate of valifenalate residues during the processing of tomatoes. For estimation of maximum residue levels, processing factors calculated for valifenalate for the processed commodities of grapes and tomatoes are shown in the table below.

For dietary risk assessment, processing factors, best estimates, STMR-Ps and HR-Ps (canned tomatoes only) were calculated for valifenalate and valifenalate-acid. In the case of the tomato processed commodities, residues of valifenalate-acid were not reported in the study, therefore, the ratio of 1.25 was applied to each of the individual valifenalate residues, to calculate the total residues of

valifenalate and valifenalate acid (free and conjugated), from which the processing factors were then derived.

Table 2 Derivation of maximum residue levels for processed commodities

Commodity	Calculated Processing Factors	Best Estimate	Maximum Residue Level, mg/kg
Grapes (maximum residue level = 0.3 mg/kg)			
Must	0.93, 0.86	0.90 (mean)	-
Wet pomace (wine making)	3.6, 2.2	2.9 (mean)	-
Bottled wine	0.56, 0.46, 0.70	0.56 (median)	-
Wet pomace (juice)	2.7, 1.5	2.1 (mean)	-
Juice, pasteurized	0.45, 0.50	0.48 (mean)	-
Tomatoes (maximum residue level = 0.4 mg/kg)			
Juice	0.32	0.32 (n = 1)	-
Ketchup	0.27	0.27 (n = 1)	-
Canned, peeled	< 0.1	0.1 (n = 1)	-
Puree (13% dry matter)	0.51	0.51 (n = 1)	-
Paste (33% dry matter)	0.83	0.83 (n = 1)	-

Table 3 Derivation of STMR-Ps for processed commodities

Commodity	Calculated Processing Factors [a]	Best Estimate	RAC STMR (mg/kg)	STMR-P [b] (mg/kg)
Grapes				
Must	0.94, 1.1	1.0 (mean)	0.079	0.079
Wet pomace (wine making)	3.4, 2.8	3.1 (mean)		0.24
Bottled wine	0.52, 0.65, 0.76	0.65 (median)		0.051
Wet pomace (juice)	2.5, 1.9	2.2 (mean)		0.16
Juice, pasteurized	0.54, 0.54	0.54 (mean)		0.043
Tomatoes				
Juice	0.32	0.32 (n = 1)	0.049	0.016
Ketchup	0.28	0.28 (n = 1)		0.014
Canned, peeled	< 0.1	< 0.1 (n = 1)		0.005
Puree (13% dry matter)	0.51	0.51 (n = 1)		0.025
Paste (33% dry matter)	0.82	0.82 (n = 1)		0.040

[a] PF based on total residues of valifenalate and valifenalate-acid (free and conjugated), determined by multiplying all valifenalate residues in all processed commodities by 1.25, expressed as parent equivalents.

[b] STMR-P is used for the dietary exposure estimates and are based on the residue definition for dietary risk assessment: valifenalate and valifenalate-acid (free and conjugated), expressed as parent equivalents

RESIDUES IN ANIMAL COMMODITIES

Farm animal feeding studies

The Meeting did not receive farm animal feeding studies.

Estimated dietary burdens of farm animals

For the uses considered by the current Meeting, grape pomace and tomato pomace are only potential feed items in Australia where they can be fed to beef or dairy cattle. However, valifenalate is not registered for use in Australia and neither of these feed items is traded. Therefore, the Meeting concluded that the dietary burdens for beef and dairy cattle are 0. Based on the uses considered by the current Meeting, there are no poultry feed items.

Thus, the Meeting estimated maximum residue levels of 0.01(*) mg/kg for milks, meat (from mammals other than marine mammals), mammalian fats (except milk fats), edible offal (mammalian), eggs and poultry edible offal, fat and meat and STMRs of 0 mg/kg for milks, meat (from mammals other than marine mammals), mammalian fats (except milk fats), edible offal (mammalian), eggs and poultry edible offal, fat and meat.

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 assessment.

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

Definition of the residue for risk assessment for plant commodities: *valifenalate and* 3-(4-chlorophenyl)-3-[[N-(isopropoxycarbonyl)-L-valyl]amino]propionic acid (valifenalate-acid), free and conjugated, expressed as valifenalate.

Definition of the residue for risk assessment for animal commodities: *valifenalate and* 3-(4-chlorophenyl)-3-[[N-(isopropoxycarbonyl)-L-valyl]amino]propionic acid (valifenalate-acid), expressed as valifenalate.

The residue is not fat-soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for valifenalate is 0–0.2 mg/kg bw. The International Estimated Daily Intakes (IEDIs) for valifenalate 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 2019 JMPR Report. The IEDIs were 0% of the maximum ADI.

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

Acute dietary exposure

The Meeting determined that establishment of an acute reference dose is unnecessary for valifenalate. The Meeting therefore concluded that acute dietary exposure to residues of valifenalate, resulting from uses that have been considered by the JMPR, is unlikely to present a public health concern.