

DIETARY RISK ASSESSMENT

Also see the General Report on triazoles.

Long-term intake

The evaluation of difenoconazole resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the thirteen Cluster Diets, based on estimated STMRs were 1–10% of the maximum ADI (0.01 mg/kg bw). The Meeting concluded that the long-term intake of residues of difenoconazole from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The IESTI of difenoconazole calculated on the basis of the recommendations made by the JMPR represented 0–10% of the ARfD (0.3 mg/kg bw) for children and 0–7% for the general population.

The Meeting concluded that the short-term intake of residues of difenoconazole resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

5.11 DIMETHOMORPH (225)

TOXICOLOGY

Dimethomorph is a cinnamic acid derivative for which the chemical name is (*E,Z*)-4-[3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]morpholine or (*EZ*)-4-[3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]morpholine, according to IUPAC and CAS nomenclatures respectively (CAS No. 110488-70-5). Dimethomorph is a mixture of *E*- and *Z*-isomers in the ratio of approximately 1 : 1.

Dimethomorph is a fungicide that disrupts fungal cell-wall formation. Fungicidal activity is primarily associated with the *Z*- isomer.

Dimethomorph has not been evaluated previously by the JMPR and was reviewed at the present Meeting at the request of the CCPR. All pivotal studies with dimethomorph were certified as complying with GLP.

Biochemical aspects

In most studies, the batch of dimethomorph used consisted of mixtures of the *E*- and *Z*- isomers in approximately equal amounts. It was reported that the two isomers can interconvert on exposure to light.

In several studies, the absorption, distribution, metabolism and excretion of dimethomorph were investigated in rats treated orally. After single oral doses of 10 or 500 mg/kg bw administered by gavage to male and female rats, more than 90% of the lower dose was absorbed and excreted via bile and 7% via urine. At 500 mg/kg bw, absorption decreased to 65% in males and 40% in females. Pre-treatment of the animals with nonlabelled dimethomorph at the lower dose did not influence the pattern of excretion. At 10 mg/kg bw, t_{\max} for total radioactivity was reached after 1.4–2.8 h and excretion was virtually complete after 48 h. After 24 h, up to 10% of the administered dose was found in the gastrointestinal tract (including contents, 0.4–1% in the gastrointestinal tract only). Less than 1% of the administered dose was found in the carcass and in liver, and 0.2% or less of the

administered dose was found in the kidneys, plasma and erythrocytes. In all other organs, concentrations of radioactivity were no longer quantifiable. At 500 mg/kg bw, some delay in depletion from organs was observed; residual radioactivity in tissues as a percentage of administered dose was approximately threefold that at 10 mg/kg bw. After 168 h, the pattern of distribution was very similar. Dimethomorph is extensively metabolized by demethylation of one of the methoxy groups and formation of *O*-conjugate and degradation products of morpholine ring-opening were found.

Toxicological data

Dimethomorph is of low acute toxicity in rats; the oral LD₅₀ was 350 mg/kg bw in females and 4300 mg/kg bw in males. The oral LD₅₀s for the *E*- and *Z*- isomers were similar. In studies with dimethomorph administered dermally or by inhalation, the LD₅₀ was > 2000 mg/kg bw and the LC₅₀ was > 4.24 mg/L, respectively. Dimethomorph was not a skin irritant and was not a skin sensitizer in the Magnusson & Kligman test. In a test for ocular irritation, all animals showed reddened conjunctivae and slight chemosis. These effects had resolved within 4 h after dosing.

In short- and long-term studies, the liver was consistently a target organ; increased organ weights were often accompanied by hepatocyte hypertrophy.

In short-term studies of toxicity in mice fed diets containing dimethomorph at up to 10 000 ppm, equal to 1145 mg/kg bw per day, dimethomorph was generally well tolerated, but increased liver weights were observed at all doses. In 4-week studies in rats given doses of 220 mg/kg bw per day and greater, decreased body-weight gains, liver-weight increases with increased hepatocyte hypertrophy and, at higher doses, histological changes in the intestine were observed. Generally, the same effects were also seen in two 4-week studies in rats given isolated *E*- and *Z*- isomers; NOAELs were 10 mg/kg bw per day. In a 13-week feeding study in rats allowed a recovery period after dosing, the NOAEL was 14 mg/kg bw per day on the basis of increased liver weights in females at higher doses; in males, an increase in vacuolation in adrenals was found and slightly changed haematology parameters at higher doses. In both sexes, vascular congestion of the ileum mucosa was also observed. The severity of most effects was reduced in the recovery period. In a later re-examination of histology slides, findings in the ileum of mice and rats, dilatation, mucosal hyperplasia and fibre separation in muscle layers were identified with rats being more sensitive than mice. In a 13-week feeding study in dogs, lip-licking and subdued behaviour were seen usually shortly after feeding at the highest dose of 43 mg/kg bw per day. At this dose, alkaline phosphatase activity in both sexes had nearly doubled, and males showed an increase in relative thymus weight and decreased prostate weight with increased fibrosis, while females showed an increase in liver weight. The NOAEL was 450 ppm, equal to 15 mg/kg bw per day. In the 52-week feeding study in dogs, liver weights in both sexes were increased at a dietary concentration of 450 ppm, equal to 15.2 mg/kg bw per day, and greater. At 1350 ppm, equal to 44.8 mg/kg bw per day, the highest dose, alkaline phosphatase activity was increased in males and females and, as in the 13-week study, prostate weights were decreased, with a very slightly increased severity of fibrosis. Testes weights were statistically significantly increased at the intermediate dose of 450 ppm and greater, but without a histological correlate and therefore this was not considered toxicologically relevant. The NOAEL was 450 ppm, equal to 15.2 mg/kg bw per day, on the basis of weight changes in the liver and prostate, and prostate fibrosis at 1350 ppm.

In a 24-month feeding study in mice, dimethomorph was well tolerated. Treatment-related findings were reduced absolute terminal body weight in males at 1000 mg/kg bw per day without decreased feed intake. In an interim sacrifice of animals at the highest dose at week 52, liver-weight increases and dilatations in the ileum were found; both effects were more pronounced in females. At study termination, more animals (males and females) with enlarged spleens were recorded, without a histological correlate. In females at the highest dose, an increase in the incidence of mammary adenocarcinomas was found that was within the range for historical controls. The Meeting concluded that the increased incidence in mammary adenocarcinoma was not due to a tumorigenic potential of

dimethomorph. The NOAEL was 100 mg/kg bw per day on the basis of body-weight gain decreases at the highest dose.

There were two 24 month feeding studies in rats, one of toxicity and another one of carcinogenicity. In the long-term feeding study in rats, feed intake was not affected in any group. At the highest dose (2000 ppm, equal to 99.9 mg/kg bw per day), body weight was decreased in females and an increase in relative kidney weights in females and a statistically non-significant increase in liver weights were observed in both sexes. Incidences of histological changes in the liver included ground-glass foci, periacinar hypertrophy and pigmentation, and were increased statistically significantly at the highest dose of 2000 ppm. The NOAEL was 750 ppm, equal to 36.3 mg/kg bw per day in males and 57.7 mg/kg bw per day in females, on the basis of body-weight decreases and histological changes in the liver of females at 2000 ppm. Effects observed in the study of carcinogenicity in rats were similar to those seen in the study of toxicity. Feed intake was decreased only decreased by 6% in females at the highest dose only. At the lowest dose of 200 ppm, equal to 8.8 mg/kg bw per day, body-weight gain among females was reduced by 9%, with reductions of 23% and 38% at the next higher doses. Although body-weight gain in females at 750 ppm was statistically significantly decreased, the effect was not considered to be treatment-related because there was high variability in body-weight development in the control and the dosed groups between the two 2-year studies. In males, body-weight gain was only impaired in the group at the highest dose of 2000 ppm, equal to 94.6 mg/kg bw per day. In animals at the highest dose, an increase in swollen hind feet/limbs was seen, with unknown etiology. In males, the frequency of findings of lymph node cysts and dilated blood vessels was also increased. At dietary concentrations of 2000 ppm, statistically significantly increased incidences of histological changes in the liver of males and females were seen, increased pancreatitis being observed in males at the highest dose. As in the study of toxicity, males receiving dimethomorph showed more interstitial-cell hyperplasia and adenoma of the testes than did the controls. In both studies, the incidence of adenoma at 2000 ppm, equal to 94.6 mg/kg bw per day, the highest dose, were close to the upper limit of the range for historical controls. However, there was no clear dose-response relationship and therefore adenoma was considered as part of a continuum with interstitial-cell hyperplasia. Additionally, this type of tumour is usually secondary to hormonal perturbation, an effect that is not suggested by the current toxicology database for any species. In males at the highest dose, there was also an increase in the incidence of benign medulla tumours of the adrenals when compared with concurrent controls, but this was within the range for historical controls. The Meeting concluded that dimethomorph was not tumorigenic in rats. When evaluating the two 2-year studies together, the overall NOAEL was 750 ppm, equal to 36.3 mg/kg bw per day, on the basis of reduced body-weight gain in both sexes and histological changes in the liver of females at 2000 ppm.

Dimethomorph was not carcinogenic in mice or rats.

With the exception of three assays for chromosomal aberration in V79 cells and in human lymphocytes, dimethomorph gave negative results in a battery of appropriate tests for genotoxicity. A slight increase in the frequency of aberrant cells was found in V79 cells and in human lymphocytes at high doses, with reduced mitotic indices and slight precipitation of the compound.

The Meeting concluded that dimethomorph was unlikely to be genotoxic in vivo.

On the basis of the absence of carcinogenicity and genotoxicity, the Meeting concluded that dimethomorph is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity studying rats, there was a reduction in body-weight gain in dams at the highest concentration of 1000 ppm, equal to 80 mg/kg bw per day, in the pre-mating period; this was compensated for thereafter and had no impact on reproductive performance. In F₁, F_{2a} and F_{2b} pups, the only finding was a slight delay in incisor eruption, which did not affect feeding capacity. Overall, pups developed normally; no other developmental markers, such as eye-opening, pinna unfolding or hair growth, were affected. Therefore, the NOAEL for maternal and reproductive toxicity was 1000 ppm, equal to 80 mg/kg bw per day, the highest dose tested.

In studies of developmental toxicity in rats, reduced feed consumption and reduced body-weight gain were recorded at the highest dose of 160 mg/kg bw per day on days 6–10 of gestation, but not thereafter. On day 20 of gestation, the difference in absolute body weight compared with that in control animals was marginal. At the highest dose, an increase in total litter losses and an increase in post-implantation losses in females with live foetuses at terminal sacrifice were observed. There were no other effects on foetal development. The NOAEL for developmental toxicity was 160 mg/kg bw per day, the highest dose tested. The NOAEL for maternal toxicity and embryotoxicity was 60 mg/kg bw per day, on the basis of intermittent decreases in body-weight gain in dams and post-implantation losses.

In two studies of developmental toxicity in rabbits, dams lost weight or did not show an increase in body weight during days 6–12 of gestation at 600 and 650 mg/kg bw per day, respectively. At this dose, the incidence of total litter losses was increased, but there were no increases in malformations or variations. The NOAEL for maternal and developmental toxicity was 300 mg/kg bw per day.

The Meeting concluded that dimethomorph is not teratogenic.

The Meeting considered that dimethomorph is not neurotoxic on the basis of the available data.

The Meeting concluded that the existing database on dimethomorph was adequate to characterize the potential hazards to foetuses, infants and children.

No health effects related to exposure to dimethomorph were reported in personnel working in a production plant.

Toxicological evaluation

The Meeting established an ADI of 0–0.2 mg/kg bw based on a NOAEL of 15.2 mg/kg bw per day identified on the basis of the liver weight and clinical chemistry changes and prostate weight changes and prostate fibrosis observed at higher doses in the 13-week and the 1-year studies in dogs. A safety factor of 100 was applied.

The Meeting established an ARfD of 0.6 mg/kg bw based on a NOAEL of 60 mg/kg bw per day identified on the basis of post-implantation losses at higher doses in the study of developmental toxicity in rats. A safety factor of 100 was applied.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity ^a	Toxicity	100 mg/kg bw per day	1000 mg/kg bw per day
		Carcinogenicity	1000 mg/kg bw per day ^c	—
Rat	Two-year studies ^d	Toxicity	750 ppm, equal to 36.3 mg/kg bw per day	2000 ppm, equal to 99.9 mg/kg bw per day
		Carcinogenicity	2000 ppm, equal to 99.9 mg/kg bw per day ^c	—
	Two-generation study of reproductive toxicity ^a	Parental toxicity	1000 ppm, equal to 80 mg/kg bw per day ^c	—

		Offspring toxicity	1000 ppm, equal to 80 mg/kg bw per day ^c	—
	Developmental toxicity ^b	Maternal toxicity	60 mg/kg bw per day	160 mg/kg bw per day
		Embryo/fetotoxicity	60 mg/kg bw per day	160 mg/kg bw per day
Rabbit	Developmental toxicity ^b	Maternal toxicity	300 mg/kg bw per day	650 mg/kg bw per day
		Embryo/fetotoxicity	300 mg/kg bw per day	650 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity ^{ad}	Toxicity	450 ppm, equal to 15.2 mg/kg bw per day	1350 ppm, equal to 44.8 mg/kg bw per day

^a Dietary administration.^c Highest dose tested.^b Gavage administration.^d The results for two studies were combined.*Estimate of acceptable daily intake for humans*

0–0.2 mg/kg bw

Estimate of acute reference dose

0.6 mg/kg bw

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

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

Critical end-points for setting guidance values for exposure to dimethomorph*Absorption, distribution, excretion and metabolism in mammals*

Rate and extent of oral absorption	Rapid, > 90% within 24 h
Dermal absorption	4.75% after application of single dose of 7.7 mg/kg bw for 8 h
Distribution	Extensive
Potential for accumulation	Low, no evidence of accumulation
Rate and extent of excretion	Rapid, close to 100% within 48 h, mainly via faeces
Metabolism in animals	Extensive, demethylation and morpholine ring-opening
Toxicologically significant compounds in animals, plants and the environment	Dimethomorph

Acute toxicity

Rat, LD ₅₀ , oral	3900 mg/kg bw > 5000 mg/kg bw (Z-isomer) 4715 mg/kg bw (E-isomer)
Rat, LD ₅₀ , dermal	> 2000 mg/kg bw; > 5000 mg/kg bw (Z-isomer)
Rat, LC ₅₀ , inhalation	> 4.24 mg/L

Rabbit, skin irritation	Not irritating											
Rabbit, eye irritation	Initially slightly irritating											
Guinea-pig, skin sensitization (test method used)	Not a sensitizer (Magnusson & Kligman)											
<i>Short-term studies of toxicity</i>												
Target/critical effect	Prostate and liver and clinical chemistry (dogs)											
Lowest relevant oral NOAEL	15.2 mg/kg bw per day (dog)											
Lowest relevant dermal NOAEL	No data											
Lowest relevant inhalation NOAEC	No data											
<i>Genotoxicity</i>												
	Unlikely to be genotoxic in vivo											
<i>Long-term studies of toxicity and carcinogenicity</i>												
Target/critical effect	Liver histology and body-weight decrease (rats)											
Lowest relevant NOAEL	36.3 mg/kg bw per day											
Carcinogenicity	Not carcinogenic											
<i>Reproductive toxicity</i>												
Reproduction target/critical effect	No reproductive effects											
Lowest relevant reproductive NOAEL	80 mg/kg bw per day, the highest dose tested											
Developmental target/critical effect	Increased incidence of total litter losses (rats and rabbits)											
Lowest relevant developmental NOAEL	60 mg/kg bw per day (rats)											
<i>Neurotoxicity/delayed neurotoxicity</i>												
	No evidence in conventional studies											
<i>Other toxicological studies</i>												
	In pharmacological studies, evidence for an increase in phenobarbital sleeping time											
<i>Medical data</i>												
	Medical surveillance of workers in a plant producing dimethomorph did not reveal any adverse health effects.											
<i>Summary</i>												
	<table><tr><th>Value</th><th>Study</th><th>Safety factor</th></tr><tr><td>ADI</td><td>0–0.2 mg/kg bw</td><td>Dog, 13-week and 1-year study</td><td>100</td></tr><tr><td>ARfD</td><td>0.6 mg/kg bw</td><td>Rat, study of developmental toxicity</td><td>100</td></tr></table>	Value	Study	Safety factor	ADI	0–0.2 mg/kg bw	Dog, 13-week and 1-year study	100	ARfD	0.6 mg/kg bw	Rat, study of developmental toxicity	100
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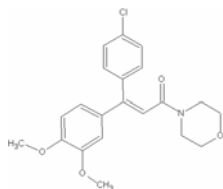
RESIDUE AND ANALYTICAL ASPECTS

Dimethomorph is a morpholine fungicide with protective action against plant pathogenic Phytophthora species and a number of downy mildew diseases of fruit, vegetables and potatoes. It was included on the schedule of new compounds for consideration by the 2007 JMPR. The Meeting received a full data package including animal and plant metabolism studies (goats, hens, grapes, potato, lettuce, tomato), soil metabolism, dissipation and photodegradation, crop rotational studies, information on analytical methods, freezer storage stability, supervised residue trial data from use as a

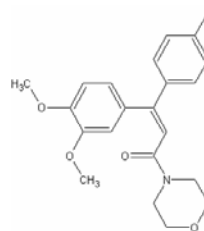
foliar spray on a range of fruit, vegetable, cereal and oil seed crops, processing studies and livestock feeding studies. GAP information was also submitted by Australia.

Chemical name and structure

(E,Z) 4-[3-(4-chlorophenyl)-3-(3,4-dimethoxy-phenyl)-1-oxo-2-propenyl]-morpholine



E- isomer



Z- isomer

The following abbreviations are used for the metabolites discussed below:

- | | |
|-----------|------------------------------------------------------------------------------------------|
| Z7 | 4-Chloro-3',4'-dimethoxy-benzophenone |
| Z67 | (E/Z)-4-(3-(4-Chlorophenyl)-3-(3'-methoxy-4'-hydroxyphenyl)-1-oxo-2-propenyl)-morpholine |
| Z69 | (E/Z)-4-(3-(4-Chlorophenyl)-3-(3'-hydroxy-4'-methoxyphenyl)-1-oxo-2-propenyl)-morpholine |
| Z89 | N-[3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)-1-oxo-2-propenyl]-glycine |
| CL 411266 | 4-[(1Z)-1-(4-chlorophenyl)-3-(4-morpholinyl)-3-oxo-1-propenyl]-2-methoxyphenyl |

Animal metabolism

The Meeting received information on the fate of orally dosed dimethomorph in the lactating goat and in laying hens. Experiments were carried out with dimethomorph with the chlorophenyl ring uniformly labelled with [¹⁴C]. Metabolism in laboratory animals (rats) was summarized and evaluated by the WHO panel of this JMPR Meeting.

In rats, after oral gavage with a single dose of 10 mg/kg bw per day, dimethomorph is quantitatively absorbed and excreted to more than 90% via bile and to 7% via urine in both sexes. Following a single dose of 500 mg/kg bw per day, absorption was decreased to 65% in males and to 40% in females. At the low dose rate, excretion virtually is complete after 48 h with less than 1% of dose found in carcass and in liver and less or equal to 0.2% in kidneys. Dimethomorph is extensively metabolized by demethylation of one of the methoxy groups and formation of O-conjugate and degradation products of morpholine ring opening were found.

Two lactating goats orally treated twice daily with [¹⁴C] labelled dimethomorph at 0.55 mg/kg bw per day (equivalent to 25 ppm in feed for a day). Each animal received 15 doses over 7.5 days, the last being the morning of the 8th day, 4 h before slaughter.

Most of the applied radioactivity was excreted in urine (about 15%) and faeces (about 72%). Total Radioactive Residues (TRR) in edible tissues averaged 7.1 mg/kg in liver, 0.28 mg/kg in kidney, 0.07 mg/kg in fat and 0.03 mg/kg in muscle. In milk, residues reached a plateau of about 0.06 mg/kg after 2 days, with residues generally ranging from 0.03–0.1 mg/kg (average 0.06 mg/kg). About 80% of the TRR in milk was present in whey. The overall recovery of the radioactivity was 88–92%.

The unchanged parent was the primary residue, comprising 72% of the liver TRR, 10% of the kidney TRR, 7.5% of the muscle TRR and 75% of the fat TRR. In milk, the major identified residue

was the polar Z89 metabolite, making up approximately 48% of the milk TRR. Metabolites Z67 and Z69 were also detected in liver at levels of 3–4% of the liver TRR.

The proposed metabolic pathway for dimethomorph in the lactating goat is similar to that suggested for rats, involving the demethylation of one of the phenolic methoxy-groups, with an alternative pathway being the cleavage of the morpholine-ring.

Groups of 6–9 laying hens were orally dosed twice daily for seven consecutive days with 1 mg [^{14}C] labelled dimethomorph/kg bw per day, equivalent to 40 ppm in the feed. The hens were sacrificed 8 h, 7 days and 12 days after the last administration. Most of the administered radioactivity (85%) was found in the excreta, with edible tissues (liver, kidney, muscle and fat) containing about 0.4% and < 0.1% found in eggs. The highest radioactive residues were in liver (1.1 mg/kg dimethomorph equivalents) with lower levels found in kidney (0.3 mg/kg), fat/skin (0.04 mg/kg) and muscle (0.02 mg/kg). In egg whites, TRR reached a maximum of 0.056 mg/kg after 4 days, while in yolks, highest TRR (0.51 mg/kg) was found at day 7. At the end of the depuration period (12 days) the radioactivity levels had decreased to about the background level of 0.01 mg/kg (egg whites) and 0.02 mg/kg (yolks). The overall recovery of the radioactivity (including residues in the cage wash) was around 88%.

Dimethomorph (unchanged parent) was only found in fat and skin, at levels of < 0.02 mg/kg. Metabolites Z67 and Z69 were the major residue components identified in liver (0.13 mg/kg), egg yolks (0.07 mg/kg), kidney (0.03 mg/kg) and muscle (0.003 mg/kg). Low levels (0.02–0.05 mg/kg) of the Z43 and Z95 metabolites were reported in kidney and/or egg yolks.

In general, the metabolism of dimethomorph in farm animals is similar to that in laboratory animals, and is mostly (85–87%) excreted in urine or faeces. Most of the remaining radioactive residues are found in liver and to a much lesser extent in kidney and egg yolk, with other edible tissues and milk containing less than 0.1 mg/kg TRR. Unchanged parent is the predominant residue identified in goat liver (about 5 mg/kg) and is also present in fat, kidney (goats), poultry skin and muscle (goats), but at levels below 0.06 mg/kg. In milk, the major residue is the Z89 metabolite (0.05 mg/kg). The metabolites Z67 and Z69 are the major residue components present in poultry, mostly in liver and kidney but also at low levels in muscle (0.003 mg/kg) and in egg yolks (0.07 mg/kg).

The Meeting concluded that the major residue component in ruminant animal commodities, from the oral administration of dimethomorph, is the parent compound, with the metabolite Z89 being the major residue in milk and that the metabolites Z67 and Z69 are the predominant residues in poultry commodities.

Plant metabolism

The Meeting received information on the fate of dimethomorph in grapes, potato, lettuce and tomato, following treatment with [p-chlorophenyl- ^{14}C]dimethomorph and also on potato following treatment with [morpholine- ^{14}C]dimethomorph.

Grape vines grown outdoors under shelter in Germany were treated by syringe with an EC formulation of [^{14}C] labelled dimethomorph at a rate equivalent to 0.09 kg ai/hL or 0.9 kg ai/ha with four applications being made at 9–10 day intervals up to 35 days before harvest. Grapes and leaves were washed with acetone to remove surface residues and the washed samples were then homogenised and remaining residues were further extracted with acetone and methanol. Radioactive residues in the surface washes (leaves and grapes) accounted for 70–72% of the applied radioactivity with about 26% of the TRR in grapes (3.8 mg/kg) being found in the homogenised samples. The majority of the extractable residue was the unchanged parent (83–86% TRR).

Potato plants grown in pots in a glasshouse in Germany were sprayed with [^{14}C]-[chlorophenyl]-dimethomorph (EC) at a rate equivalent to 0.06 kg ai/hL or 0.6 kg ai/ha with four applications at 10 day intervals with the last up to 7 days before harvest. Stems, leaves and tubers

were washed with acetone to remove surface residues and the washed samples were then homogenised and remaining residues extracted with methanol. About 61% of the recovered radioactivity was present as a surface residue. The majority of the extractable residue in foliage was the unchanged parent dimethomorph (68% of the TRR). Only trace amounts of radioactivity (0.01–0.02 mg/kg) were found in tubers.

In a complimentary potato metabolism study, dimethomorph (EC) labelled with [^{14}C] in the morpholine ring was applied to greenhouse potato plants at a rate equivalent to 0.06 kg ai/hL (0.6 kg ai/ha) with four applications at 10 day intervals up to 7 days before harvest. Surface residues were removed in acetone, after which the samples were homogenised and the remaining residues extracted in methanol. In treated foliage the acetone surface wash contained about 72% of the TRR. Small amounts of radioactivity were measured in tubers from treated plants predominantly in peel where radioactive residues of < 0.03 mg/kg were found. The majority of the foliage residue was the unchanged parent (76% of the foliage TRR or 13.8 mg/kg) with the remaining extractable residue consisting of several unknown (mainly polar) metabolites at levels too low to identify.

In an additional study on potato plants grown in a lysimeter, [^{14}C]-[chlorophenyl]-dimethomorph (DC) was applied at a rate equivalent to 0.3 kg ai/ha as a foliar spray three times, 10 days apart, up to 28 days before harvest. About 98% of the recovered radioactivity was found in the foliage, with about 1.5% TRR being found in the tubers, 0.8% (0.12 mg/kg) in the peel and 0.7% (0.025 mg/kg) in the peeled potatoes. Further investigation of the tuber residues identified the unchanged parent compound to be the major residue, predominantly in the peel (about 46% or 0.06 mg/kg), with the metabolites Z67 and Z69 comprising < 10% of the peel TRR.

In field grown lettuce, chlorophenyl ring labelled [^{14}C]dimethomorph (DC) was applied in four successive foliar applications at a rate equivalent to 1.14 kg ai/ha. Applications were made 8 days after transplanting and at intervals of 9, 10 and 11 days, with plants (without roots) being sampled four days after the final application. Close to 99% of the TRR was extracted from macerated samples with acetone or acetone:water with most of this (93%) being the unchanged parent. Trace levels of the metabolites Z7 and Z67 were also reported, each accounting for 0.5% TRR (0.5 mg/kg). The remaining extractable residue (4.5% TRR) consisted of several minor unknown polar components, which were not further characterized.

Tomatoes (young plants) were treated with [^{14}C]-[chlorophenyl]-dimethomorph by the addition of 8 mg ai/L to the hydroponic nutrient solution for 7 days. Plant samples (without roots) were taken 0, 14 and 28 days after termination of the application. Total radioactive residues in leaves and stems, at the end of the 7 day exposure period were 24.5 mg/kg dimethomorph equivalents, reducing to 12.5 mg/kg after 14 days and to 7 mg/kg after 28 days. Dimethomorph was the predominant residue, initially comprising 66% of the TRR and reducing to 28% after 14 days and to 16% after 28 days. The calculated half-life of the parent compound was about 13 days. The demethylated metabolite Z69 (including conjugates) was the major metabolite found (13–34% TRR), with metabolites Z93 (8–17% TRR), Z95 (4–8% TRR) and Z98 (1–7% TRR) also being found.

The Meeting concluded that the metabolic pathways of dimethomorph in plants show a common pattern, with the unchanged parent being the only significant residue in plant commodities. Residues are mostly found on the plant surface, i.e., negligible systemic translocation, with only low residues being found in potato tubers (almost all in the peel). However, when young tomato plants are exposed to dimethomorph in a hydroponic nutrient solution, residues can be taken up by the roots and translocated to leaves and stems. The primary metabolic pathway involves the demethylation of the dimethoxyphenyl ring to produce the metabolites Z67 and Z69, with the probable formation of the associated glucose conjugates. A secondary pathway involves the hydrolysis of dimethomorph to form the Z7 metabolite.

Environmental fate in soil

The Meeting received information on the environmental fate of dimethomorph in soil, including aerobic soil metabolism, soil photodegradation and also confined and field rotational crop studies.

Aerobic soil metabolism

In six laboratory studies the degradation of dimethomorph in soil under aerobic conditions was investigated in sand, loamy sand, sandy loam and silty clay loam, using [^{14}C] labelled dimethomorph (labelled in either the chlorophenyl or the morpholine ring). Under sterile conditions, dimethomorph was stable, with about 90% of the applied radioactivity identified as the parent compound after four months (compared with 36% remaining in a comparable unsterile soil), indicating microbial action was the major source of degradation. As the levels of extractable dimethomorph decreased over time, there was a corresponding increase in unextracted residues, the nature of which was not investigated. The shift in the ratio of *E*- and *Z*-isomers of dimethomorph was investigated in most of these studies, with the initial *E*:*Z* ratio of about 50:50 shifting to about 40:60 after 60–90 days and 30:70 after 180 days. Half-lives in the laboratory studies ranged from 47 days to 90 days except in one atypical acidic sandy soil (pH 3.5, 99% sand), where 86% of the applied dimethomorph remained after 120 days.

In field studies, where dimethomorph was applied at rates of 0.43–0.6 kg ai/ha to a range of different soil types (sand, loamy sand, sandy loam, clay), dimethomorph residues were only detected in the top 10 cm, with trace amounts of the metabolites Z67 and Z69 being found in the top 20 cm, but only within the first two months after treatment. Half-lives for dimethomorph in these studies ranged from 10–61 days.

Photodegradation in soil

In a soil photolysis study where [^{14}C] labelled dimethomorph was added to sterile sandy-loam soil and exposed to light continuously for 15 days, less than a 10% decrease in dimethomorph residues was observed, with two minor (unidentified) metabolites found at levels up to 4.2% of the applied radioactivity. During the study period, the *E*/*Z*-isomer ratio shifted from about 40:60 to 34:66.

Residues in rotational crops

In two confined rotational crop studies, [^{14}C] labelled dimethomorph was applied to bare soil at rates equivalent to 4 kg ai/ha and 1.7 kg ai/ha.

In the first study, lettuce, carrots and wheat were planted in soil treated with dimethomorph to simulate the application of 4 kg ai/ha followed by incorporation to a depth of 15 cm and aged for 29, 120 and 361 days. Total radioactive residues of 4.8 mg/kg were found in wheat straw, 1 mg/kg in wheat forage and 0.14–0.2 mg/kg in carrot tops and lettuce planted in the 29 day aged soil. Dimethomorph residues in soil at the time of planting were about 0.8 mg/kg. In the soil aged for 120 days, dimethomorph residues at planting were about 0.05 mg/kg and total radioactive residues in all subsequent crops were < 0.1 mg/kg except wheat foliage (0.24 mg/kg) and wheat straw (0.78 mg/kg).

In the second study, wheat, lettuce, soya beans and radish were planted in soil treated with the equivalent of 1.7 kg ai/ha and aged for 30–394 days. In soil aged for 30 days, total radioactive residues were < 0.1 mg/kg in all crops except wheat straw (0.15 mg/kg). Dimethomorph residues were 0.01 mg/kg or less in all crops and the only metabolite found was CL 411266, at 0.04 mg/kg in wheat straw and 0.01 mg/kg in radish tops and wheat forage. In soil aged for 60 days, total radioactive residues were < 0.05 mg/kg in all crops except wheat straw (0.13 mg/kg). Dimethomorph residues were not found in any crops and the metabolite CL 411266 was measured in wheat straw (0.03 mg/kg) and lettuce (0.02 mg/kg). Radioactive residues did not exceed 0.05 mg/kg in any samples from crops grown in soil aged for 394 days.

Rotational crop field studies were conducted in Germany, where carrots, spinach and beans were planted immediately after harvest of a potato crop treated with 3 applications of 0.18 kg ai/ha dimethomorph (PHIs of 2–6 weeks). At the time of planting the rotational crops, dimethomorph residues in soil were 0.08–0.14 mg/kg. Dimethomorph residues in subsequent crops were all 0.02 mg/kg or less, except in spinach sampled 72–76 days after the last soil treatment, where residues of 0.09 mg/kg and 0.21 mg/kg were found. Residues were below the limit of quantification in all three crops at maturity.

The Meeting concluded that dimethomorph is stable to hydrolysis and photolysis and is moderately persistent in soil with field half-lives of 10–61 days. In rotational crops, dimethomorph can be taken up by the roots and dimethomorph residues may occur in early harvest crops (e.g., spinach) planted within 44 days of the last application.

Methods of analysis

The Meeting received data on analytical methods for enforcement and monitoring of dimethomorph and its major metabolites in plant and animal commodities. A number of these methods are capable of determining the individual dimethomorph isomers but in most cases these residues have been combined in the supervised field trial reports, as to minimise isomerization reactions during preparation and analysis, the analytical work needs to be conducted in the absence of light. However these isomerization reactions do not influence the measurement of total residues.

Analytical methods for enforcement and monitoring

The multi-residue analytical method DFG S19, with a modification to use ethyl acetate:cyclohexane instead of dichloromethane in the partition clean-up step, has been validated in a range of commodities as an enforcement-monitoring method for the determination of dimethomorph in plant commodities. With an alternative extraction procedure for fat (DFG Method 5), this method can be used to measure dimethomorph residues in animal matrices. Reported LoQs are 0.01 mg/kg for animal matrices and 0.02 mg/kg for plant matrices.

Analytical methods used in study reports

Analytical methods used in the supervised residue trials and in the animal residue studies generally involve extraction with acetone, acetonitrile or acidified methanol with residues being partitioned into dichloromethane, ethyl acetate or cyclohexane and cleaned-up by gel permeation chromatography prior to analysis. An additional silica gel column clean-up step is included in some methods, and for some matrices, an additional partition step with hexane (to remove fatty constituents) is included. Analysis can be by HPLC-UV, GC-NPD, GC-MS or HPLC-MS/MS. In most of the commonly used methods, LOQs of 0.01 mg/kg or 0.02 mg/kg have been reported. The methods used in the animal studies were capable of measuring the parent compound, the Z89 metabolite and the sum of the Z67 and Z69 metabolite residues.

Validation studies on the more commonly used analytical methods generally reported mean recovery rates of 73–116% when a wide range of plant and animal matrices were fortified with dimethomorph at concentrations of 0.01–5 mg/kg and with 0.1 mg/kg of the metabolites Z89, Z67 and Z69 in the case of cattle matrices.

The Meeting concluded that adequate analytical methods exist for the determination of dimethomorph in crops and livestock commodities both for data collection and MRL enforcement purposes.

Stability of residues in stored analytical samples

The Meeting received information on the frozen storage stability of residues in cattle milk and edible tissues, grapes, rape seed, hops, tomato, broccoli, spinach, potato and processed grape, hops, tomato

and potato matrices. In all cases, residues were stable in the macerated matrices under conditions of frozen storage for an interval at least as great as the storage interval of supervised field trial or livestock feeding samples.

Dimethomorph residues were stable under conditions of frozen storage for the intervals tested: 24 months in broccoli, grapes, spinach, tomato, 21 months in processed tomato matrices, 18 months in soil, rape seed, hops, beer, spent hops and brewer's yeast, 16 months in processed grape commodities, 14 months in raisins and 6 months in potatoes and processed potato commodities. In cattle meat, milk, liver and kidney, residues of dimethomorph and its metabolites Z67 and Z69 were stable for the 16 month frozen storage interval. The predominant residue in milk (the Z89 metabolite) was also stable over the 16 month test interval.

The Meeting concluded that dimethomorph is stable (less than 10% loss of residues) in most crop, processed commodity, and livestock commodity samples under frozen storage conditions.

Definition of the residue

In plants, dimethomorph is stable to hydrolysis and occurs mostly as surface residue with no significant metabolism. The major residue resulting from foliar applications of dimethomorph is the parent compound, present as a mixture of the *E*- and *Z*-isomers, the ratio of which can change over time as a result of isomerisation reactions stimulated by light.

In animals, while metabolism studies indicate that the parent compound is the major residue in cattle liver and fat, residues of the metabolites Z67 and Z69 are also present in significant amounts and metabolite Z89 is the largest single component in milk. In poultry commodities, the parent compound is only found in fat and skin, with metabolites Z67 and Z69 being the major residues. However the Meeting noted that these results were from feeding studies involving exaggerated dosing regimes, and that under practical conditions, residues are not expected in animal commodities.

A validated multi-residue method is available to measure dimethomorph, as the sum of the *E*- and *Z*-isomers in both plant and animal matrices.

Based on the above, the Meeting agreed:

Definition of the residue in plant commodities for estimation of dietary intake and for compliance with MRLs: dimethomorph (sum of isomers).

Definition of the residue in animal commodities for estimation of dietary intake and for compliance with MRLs: dimethomorph (sum of isomers).

The results of the animal metabolism studies indicate that dimethomorph is not fat-soluble.

Results of supervised trials on crops

Supervised trials were available for the use of dimethomorph as a foliar spray on citrus (oranges), strawberries, grapes, pineapples, onions, green onions, brassica vegetables (cabbage, broccoli, kohlrabi), cucumber, courgettes (zucchini), melons, tomatoes, peppers (sweet), lettuce, spinach and hops.

Supervised trials involving dimethomorph seed-piece treatment on pineapples and as a seed treatment on oil seed rape were also made available.

In many countries, dimethomorph is available in formulations with and without other complimentary fungicides such as mancozeb, chlorothalonil, copper and folpet. For the purpose of this evaluation, the PHIs defined as GAP for each crop are those established for dimethomorph when formulated without other active ingredients. Where dimethomorph is available only as combination products with different PHIs, the shortest PHI has been selected when defining GAP.

Oranges, sweet, sour

The results of residue trials in Spain involving foliar applications on oranges were made available to the Meeting.

The only GAP provided to the Meeting was for stem paint treatments in Thailand and Vietnam.

The Meeting agreed the data was not sufficient to estimate a maximum residue limit for oranges.

Strawberries

In Belgium, GAP is for three root drench applications of 0.05 g ai/plant, just after planting, one month later and again at the start of spring growth (about 2 months before harvest). In trials from Belgium, matching this GAP, residues found were 0.01, 0.01, 0.02 and 0.02 mg/kg.

In Netherlands, GAP for protected strawberries is to apply 0.05 g ai/plant with the nutrient solution as a root drench up to 35 days before harvest. In three outdoor trials match Netherlands GAP, residues found were 0.01, 0.01 and 0.02 mg/kg.

GAP for outdoor strawberries in Netherlands is for a single foliar spray (0.15 kg ai/ha) just after planting and in four trials in Netherlands matching this GAP, residues were all < 0.01 mg/kg.

The Meeting agreed to use the data from the root drench trials in Belgium and Netherlands to give a combined data set of: 0.01 (4), 0.02 and 0.02 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg for dimethomorph in strawberries and estimated an STMR of 0.01 mg/kg and an HR of 0.02 mg/kg.

Grapes

The results of residue trials in grapes from France, Germany, Greece, Italy, Spain, Australia, New Zealand and Brazil were made available to the Meeting.

Residues in trials in Brazil matching the GAP in Columbia (0.3–0.4 kg ai/ha, PHI 19 days) were: 0.24, 0.31, 0.99 and 1.1 mg/kg.

Residues in trials from Germany matching the GAP of Belgium (0.3 kg ai/ha, up to 3 applications per season, with a PHI of 28 days) were: 0.26, 0.36, 0.6, 0.71, 1.2 and 1.3 mg/kg.

Residues in trials from Spain matching the GAP of Spain (0.03 kg ai/hL, with a PHI of 28 days) were: 0.09, 0.11, 0.14, 0.24 and 0.25 mg/kg.

Residues in trials from France, matching the GAP of Spain (0.03 kg ai/hL, PHI 28 days), were: 0.16, 0.20, 0.27, 0.38, 0.38, 0.39, 0.39, 0.46, 0.47, 0.51, 0.51, 0.61, 0.62, and 1.7 mg/kg.

Residues in trials from Italy, matching the GAP of Spain (0.03 kg ai/hL, PHI 28 days), were: 0.1, 0.18, 0.19, 0.21, 0.42, 0.85, 0.94, and 1.2 mg/kg.

Residues from a single trial from Greece, matching the GAP of Spain (0.03 kg ai/hL, PHI 28 days), were: 0.39 mg/kg.

The Meeting agreed to use the trials in Spain, France, Italy and Greece matching the GAP of Spain. Residues in ranked order (median underlined) were: 0.09, 0.1, 0.11, 0.14, 0.16, 0.18, 0.19, 0.20, 0.21, 0.24, 0.25, 0.27, 0.38, 0.38, 0.39, 0.39, 0.39, 0.42, 0.46, 0.47, 0.51, 0.51, 0.61, 0.62, 0.85, 0.94, 1.2 and 1.7 mg/kg (n=27).

The Meeting estimated a maximum residue level of 2 mg/kg for dimethomorph in grapes and estimated an STMR of 0.39 mg/kg and an HR of 1.7 mg/kg.

Pineapple

GAP for pineapples in Philippines is for pre-plant dip treatments of seed-pieces (0.19 kg ai/hL dipping solution) and up to 3 post-planting foliar spray applications (1.8 kg ai/ha), 4, 7 and 10 months after planting. Pineapples are commonly harvested about 16–17 months after planting, about 6 months after the last foliar spray.

In a set of trials in Philippines, residues in pineapples following pre-plant seed-piece dipping treatments at 2 × and 4 × the recommended rate were < 0.01 (2) mg/kg in both flesh and peel. Residues were also < 0.01 (2) mg/kg in flesh and peel of pineapples following the pre-plant seed-piece dip treatments (2 × and 4 ×) combined with three foliar sprays matching the recommended application rate and timing. Similarly, pineapples treated with a combination of pre-plant seed-piece dipping (2 × and 4 ×) and three foliar sprays (2 ×), residues were also < 0.01 (2) mg/kg in both flesh and peel.

Since residues were all < 0.01 mg/kg in all four trials involving exaggerated (2 × and 4 ×) pre-plant dipping treatment combined with foliar treatments (1 × and 2 ×), the Meeting agreed to use the results of these trials to give a combined data set of < 0.01, < 0.01, < 0.01 and < 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.01* mg/kg for dimethomorph in pineapple and estimated an STMR of 0 mg/kg and an HR of 0 mg/kg.

Onions, bulb

In Australia, GAP for onions is up to 0.18 kg ai/ha (maximum 3–4 applications per season), with a PHI of 7 days and in one trial in Australia matching this GAP (but with 7 applications), residues were < 0.02 mg/kg.

Residues in two trials from Germany, matching the German GAP of 4 × 0.3 kg ai/ha, with a PHI of 14 days for bulb vegetables, were < 0.01 and < 0.01 mg/kg.

In one trial in France, matching the German GAP, residues were 0.02 mg/kg.

The Meeting agreed the data was not sufficient to estimate a maximum residue limit for onions, bulb.

Green onions

The Meeting received results of residue trials in Australia on green onions (spring onions).

GAP for bulb vegetables in USA is 0.22 kg ai/ha, PHI 0 days, in Australia GAP for onions is 0.18 kg ai/ha, PHI 7 days, maximum 4 applications/season and in Germany, GAP for bulb vegetables is 0.3 kg ai/ha, PHI 14 days.

No trials matching these GAPs were available and the Meeting agreed the data was not sufficient to estimate a maximum residue limit for green onions.

Cabbage, head

The Meeting received results of residue trials in USA on cabbage.

In trials in USA matching the GAP of Cuba (0.2–0.23 kg ai/ha, PHI 7 days for vegetables) residues of dimethomorph in cabbages (including wrapper leaves) were < 0.05, 0.14, 0.25, 0.4, 0.69, 1.1 and 1.4 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg for dimethomorph in cabbage and estimated an STMR of 0.4 mg/kg and an HR of 1.4 mg/kg.

Broccoli

The Meeting received results of residue trials in the USA on broccoli.

In trials in USA matching the GAP of Cuba (0.2–0.23 kg ai/ha, PHI 7 days for vegetables), residues of dimethomorph in broccoli were: < 0.05, 0.12, 0.17, 0.2, 0.25 and 0.52 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg for dimethomorph in broccoli and estimated an STMR of 0.19 mg/kg and an HR of 0.52 mg/kg.

Kohlrabi

GAP in Germany for kohlrabi is 0.3 kg ai/ha (maximum 2 applications per season), PHI 14 days and in two outdoor trials and three indoor trials in Germany matching this GAP, residues in kohlrabi were: < 0.02, < 0.02, < 0.02, < 0.02 and < 0.02 mg/kg.

The Meeting estimated a maximum residue level of 0.02 mg/kg for dimethomorph in kohlrabi and estimated an STMR of 0.02 mg/kg and an HR of 0.02 mg/kg.

*Fruiting vegetables, cucurbits**Cucumber*

The Meeting received results of residue trials in outdoor cucumbers in Hungary and Germany. No GAP matched these trials.

The Meeting received results of residue trials on protected cucumbers from France, Greece, Italy and Spain.

GAP for cucurbits in the USA is 0.22 kg ai/ha (maximum 5 applications/season), PHI 0 days. In protected cucumber trials, matching the GAP of USA, residues were: 0.02, 0.05 and 0.08 mg/kg in trials in Spain, 0.03 mg/kg in one trial in France, 0.05 mg/kg in one trial in Italy and 0.07 and 0.07 mg/kg in trials in Greece.

The Meeting noted that these trials involved 3–4 applications per season but agreed to use these results because 1–2 additional treatments applied more than 3–4 weeks before harvest would not contribute significantly to the final residue in rapidly growing protected cucumbers. Residues were: 0.02, 0.03, 0.05, 0.05, 0.07, 0.07 and 0.08 mg/kg.

Squash, summer:

The Meeting received results of residue trials on protected summer squash (courgettes) in Greece, Italy and Spain and on outdoor summer squash (zucchini) in Australia.

Residues from five protected summer squash trials in Greece, Italy and Spain, matching the GAP for cucurbits in the USA (0.22 kg ai/ha, maximum of 5 applications per season, PHI 0 days) were: 0.2 and 0.24 mg/kg (Greece), 0.07, 0.13 and 0.17 mg/kg (Italy) and 0.02 mg/kg (Spain).

The Meeting noted that these trials involved 3 applications per season and agreed that the contribution of 2 additional treatments applied more than 3–4 weeks before harvest would not contribute significantly to the final residue.

In one outdoor summer squash trial in Australia matching the Australian GAP (0.18 kg ai/ha, maximum 4 applications per season, PHI 7 days), residues were < 0.02 mg/kg.

The Meeting noted that the residues in protected summer squash trials matching the USA GAP were higher than those from the outdoor summer squash trial in Australia and agreed to use the data on protected summer squash. Residues found were: 0.02, 0.07, 0.13, 0.17, 0.2 and 0.24 mg/kg.

Melons, except watermelons

The Meeting received results of residue trials from Australia, Brazil, France, Italy and Spain.

Residues in trials in France matching the GAP of Israel (0.18 kg ai/ha, PHI 3 days) were: 0.03 and 0.04 mg/kg (whole fruit).

In two trials in Italy matching the GAP of Israel, whole fruit residues were 0.04 and 0.11 mg/kg.

In trials in Spain matching the GAP of Israel, whole fruit residues were: 0.02, 0.02, 0.2 and 0.24 mg/kg and in a further four trials, residues in melon flesh were: < 0.02, < 0.02, < 0.02 and 0.05 mg/kg.

The Meeting agreed to combine the results of the trials in France, Italy and Spain matching the GAP in Israel. Whole fruit residues were: 0.02, 0.02, 0.03, 0.04, 0.04, 0.11, 0.2 and 0.24 mg/kg and residues in melon flesh were: < 0.02, < 0.02, < 0.02 and 0.05 mg/kg.

The Meeting agreed that the data on cucumbers, summer squash and melons were sufficient to support a group MRL and estimated a maximum residue level of 0.5 mg/kg for dimethomorph in fruiting vegetables (cucurbits).

The Meeting estimated an STMR of 0.15 mg/kg and an HR of 0.24 mg/kg for cucurbits with an edible peel (based on the summer squash data) and an STMR of 0.02 mg/kg and an HR of 0.05 mg/kg for cucurbits with an inedible peel (based on the melon data).

*Fruiting vegetables, other than cucurbits**Tomato*

In protected tomato trials from France, Greece, Italy and Spain, matching the GAP of Japan (0.025 kg ai/hL, maximum 3 applications per season, PHI 1 day), residues were: 0.03, 0.05, 0.06, 0.07, 0.1, 0.1, 0.1, 0.11, 0.11, 0.13, 0.16, 0.16, 0.19 and 0.26 mg/kg.

Residues in outdoor tomato trials in USA matching the USA GAP (0.22 kg ai/ha, maximum 5 applications per season, PHI 4 days) were: 0.06, 0.08, 0.21, 0.26 and 0.41 mg/kg (n=5).

Residues in a further seven trials from the USA matching this GAP but with 6–7 applications per season were: < 0.05, < 0.05, < 0.05, 0.05, 0.14, 0.14, and 0.51 mg/kg (n=7).

The Meeting agreed that the contribution of 1–2 additional treatments applied more than 4 weeks before harvest would not contribute significantly to the final residue and agreed to use these results to give a combined data set of: < 0.05, < 0.05, < 0.05, 0.05, 0.06, 0.08, 0.14, 0.14, 0.21, 0.26, 0.41 and 0.51 mg/kg (n=12) for outdoor tomatoes.

The Meeting noted that the residues from the protected tomato trials matching the GAP of Japan and the outdoor tomato trials matching the GAP of the USA were from similar populations and agreed to combine the results. Residues in ranked order (median underlined) were: 0.03, < 0.05, < 0.05, < 0.05, 0.05, 0.05, 0.06, 0.06, 0.07, 0.08, 0.1, 0.1, 0.1, 0.11, 0.11, 0.13, 0.14, 0.14, 0.16, 0.16, 0.19, 0.21, 0.26, 0.26, 0.41 and 0.51 mg/kg (n=26).

Peppers sweet

In trials on protected sweet peppers in Greece, Italy and Spain matching the GAP of the USA for fruiting vegetables, except tomatoes (0.22 kg ai/ha, maximum 5 applications per season, PHI 0 days), residues in ranked order (median underlined) were: 0.13, 0.13, 0.16, 0.17, 0.18, 0.21, 0.21, 0.26, 0.31, 0.38, 0.48 and 0.56 mg/kg (n=12).

The Meeting noted that these trials involved 3 applications per season but agreed to use this data because the contribution of 2 additional treatments applied more than 3 weeks before harvest would not contribute significantly to the final residue in rapidly growing protected peppers.

Peppers, chilli

The GAP for peppers in the Republic of Korea is 0.3 kg ai/hL with a maximum of 4 applications per season with a PHI of 3 days. In three outdoor chilli pepper trials in Korea, matching this GAP, residues were 0.22, 0.31 and 0.53 mg/kg.

The Meeting noted that the results of the trials on peppers, sweet and peppers, chilli were from similar populations and agreed to combine the results. Residues in ranked order (median underlined) were: 0.13, 0.13, 0.16, 0.17, 0.18, 0.21, 0.21, 0.22, 0.26, 0.31, 0.31, 0.38, 0.48, 0.53 and 0.56 mg/kg.

The Meeting noted that GAP existed in the USA for the fruiting vegetable group and based on the data for peppers and tomatoes, agreed to establish a group MRL for 'fruiting vegetables, other than cucurbits' except mushrooms and sweet corn of 1 mg/kg and estimated an STMR of 0.22 mg/kg and an HR of 0.56 mg/kg.

Lettuce, head

In protected head lettuce trials in Germany, Greece, Italy and Spain matching the GAP in the USA (0.22 kg ai/ha, maximum 5 applications per season, PHI 0 days), residues were: 1.5, 2.2, 2.2, 2.3, 2.7, 2.9, 3.1, 3.6, 3.9, 3.9, 4.2, 4.3, 4.6, 7.1 and 7.2 mg/kg (n=15).

The Meeting noted that these trials involved 2–3 applications per season and agreed to use these results because the contribution of 2–3 additional treatments applied more than 3 weeks before harvest would not contribute significantly to the final residue in rapidly growing protected lettuce.

In outdoor lettuce trials in Spain, matching the GAP of Spain (0.23 kg ai/ha, PHI 7 days), residues found were: 0.05, 0.06, 0.07, 0.1, 0.16, 0.38, 0.39 and 0.43 mg/kg.

The Meeting noted that the residues from the protected lettuce trials and the outdoor lettuce trials were from different populations and agreed to use the data from the protected lettuce trials.

The Meeting estimated a maximum residue level of 10 mg/kg for dimethomorph in lettuce, head and estimated an STMR of 3.6 mg/kg and an HR of 7.2 mg/kg.

Corn salad

The Meeting received results of residue trials in protected corn salad (Lambs lettuce) from Italy and Spain. Residues in trials matching the GAP for lettuce (including Lambs lettuce) in Spain (0.23 kg ai/ha, PHI 7 days) were: 0.79, 0.79, 1.9, 4.8, 5.3 and 7.1 mg/kg.

The Meeting estimated a maximum residue limit of 10 mg/kg for dimethomorph in corn salad and estimated an STMR of 3.4 mg/kg and an HR of 7.1 mg/kg.

Spinach

The Meeting received results of residue trials in spinach in USA.

No GAP matching these USA trials was available and the Meeting agreed the data was not sufficient to estimate a maximum residue limit for spinach.

Potatoes

The Meeting received results of residue trials from Argentina, Australia, Belgium, Brazil, Canada, Denmark, France, Greece, Germany, Italy, New Zealand, Spain, UK and USA on potatoes.

In trials in Brazil matching the GAP of Brazil (0.4 kg ai/ha, maximum 4 applications per season, PHI 14 days), residues were: < 0.03 (9) and 0.03 mg/kg (n=10).

In trials in USA matching USA GAP (0.22 kg ai/ha, maximum 8 applications per season, PHI 4 days), residues were: < 0.01 (6) and 0.02 mg/kg (n=7).

Residues in trials in UK matching the GAP of the UK (0.15 kg ai/ha, maximum 8 applications per season, PHI 7 days), were: < 0.01 (12), < 0.02 (18), 0.02 and 0.04 mg/kg (n=32).

Residues in trials in France matching the GAP of France (0.18 kg ai/ha, maximum 4 applications per season, PHI 7 days) were: < 0.01 (4) and < 0.05 mg/kg (n=5).

The Meeting agreed to combine the results to give a total data set of: < 0.01(22), < 0.02(18), 0.02(2), < 0.03(9), 0.03, 0.04, < 0.05 mg/kg (n=54).

The Meeting estimated a maximum residue level of 0.05 mg/kg for dimethomorph in potatoes and estimated an STMR of 0.02 mg/kg and an HR of 0.05 mg/kg.

Rape seed

GAP in Germany for rape seed is for a pre-plant seed treatment using 5 g ai/kg of seed and in two trials from Germany matching this GAP, residues in rape seed from plants grown from treated seed were both < 0.02 mg/kg. In two related trials, residues of < 0.02 mg/kg were reported in rape seed from treated plots. However the presence of residues of 0.02 mg/kg in control samples suggested that the samples had been mislabelled.

The Meeting agreed that while residues would not be expected in rape seed following a pre-plant seed treatment, there was insufficient data to estimate a maximum residue level for dimethomorph in rape seed.

Hops

In Austria and Germany, GAP on hops is 0.015 kg ai/hL (maximum 6 applications per season in two sets of three applications), PHI 10 days.

One trial in Germany matched the GAP in Germany, with residues of 28 mg/kg in dried hops. A further eight trials in Germany matching GAP but with 4 applications per season reported residues of 8.3, 8.7, 9.3, 24, 26, 26, 29 and 42 mg/kg.

The Meeting agreed that the final 3 applications in these trials would contribute most to the final residue and agreed to use these results to give a combined data set: 8.3, 8.7, 9.3, 24, 26, 28, 26, 29 and 42 mg/kg for dried hops.

The Meeting estimated a maximum residue level of 80 mg/kg for dimethomorph in hops, dry and estimated an STMR of 26 mg/kg.

Fate of residues during processing

Dimethomorph is stable under the standard hydrolysis conditions used to simulate food processing.

The Meeting received information on the fate of incurred residues of dimethomorph during the processing of grapes, tomatoes, potatoes and hops. The processing factors (PF) shown below were calculated from the residues for the commodities for which MRLs, STMRs and HRs were estimated.

Raw commodity (RAC)	Processed commodity	Calculated processing factors.	Median or best estimate	
Grapes	Red wine	0.06, 0.12, 0.16, 0.17, 0.17, 0.17, 0.17, 0.22, 0.24, 0.24, 0.25, 0.25, 0.27, 0.28, 0.29, 0.29, 0.30, 0.31, 0.34, 0.34, 0.35, 0.36, 0.38, 0.38, 0.47, 0.53, 0.58, 0.67, 0.69, 0.70, 0.8	0.29	0.29
	White wine	0.10, 0.12, 0.13, 0.14, 0.17, 0.18, 0.31, 0.43, 0.50, 0.51, 0.61, 1.24	0.24	
	Pomace, wet (red wine)	1.6, 2.4, 2.7, 2.8, 3.1, 3.3, 4.1, 7.3	3.0	2.75
	Pomace, wet (white wine)	1.7, 2.3	2.0	

Raw commodity (RAC)	Processed commodity	Calculated processing factors.	Median or best estimate
	Raisins	1.5, 2.1	1.8
Tomatoes	Juice	0.5	0.5
	Paste	2.4	2.4
Potatoes	Wet peel	6.4	6.4
Hops	Beer	0.0011, < 0.0012, 0.0025, 0.0035	0.002

Grapes were processed into wine and dried grapes (raisins). Processing factors were 0.29 (wine), 1.8 (raisins) and 2.75 (grape pomace). Based on the STMR value of 0.39 mg/kg for grapes and the median processing factors of 0.29 (red and white wine combined) 1.8 for raisins and 2.75 for wet pomace, the STMR-Ps for dimethomorph residues were 0.11 mg/kg in wine, 0.7 mg/kg in dried grapes and 1.07 mg/kg in grape pomace, wet.

Based on the HR of 1.7 mg/kg estimated for grapes and the processing factor of 1.8 for raisins, the Meeting estimated a maximum residue level of 5 mg/kg for dimethomorph in dried grapes.

Tomatoes were processed into juice, puree and paste with processing factors of 0.5, 1.2 and 2.4 respectively. Based on the STMR value of 0.11 mg/kg for tomato, the STMR-Ps for dimethomorph residues were 0.055 mg/kg (tomato juice) and 0.264 mg/kg (tomato paste).

Potatoes, based on a processing factor of 6.4 for wet peel and an STMR of 0.02 mg/kg, the Meeting estimated an STMR-P for dimethomorph residues in potato process waste of 0.128 mg/kg.

Hops were processed into beer with a processing factor of 0.002. Based on the STMR value of 26 mg/kg for hops, dry, the STMR-P for dimethomorph residues in beer was 0.052 mg/kg.

Peppers, chilli dried. Based on the HR value of 0.56 mg/kg and the STMR value of 0.22 mg/kg for fresh peppers (including chilli peppers) and using the new generic processing factor of 7 for dried chilli peppers, the Meeting estimated a maximum residue level of 5 mg/kg and an STMR-P of 1.54 mg/kg for dimethomorph in peppers, chilli dried.

Estimated maximum and mean dietary burdens of farm animals

The Meeting estimated the dietary burden of dimethomorph in farm animals on the basis of the diets listed in Annex 6 of the 2006 JMPR Report (OECD Feedstuffs Derived from Field Crops). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex VI. The calculations were made according to the animal diets from US-Canada, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report).

	Animal dietary burden, dimethomorph, ppm of dry matter diet					
	US-Canada		EU		Australia	
	max	mean	max	mean	max	mean
Beef cattle	0.32	0.32	2.3 ¹	0.96	1.48	1.48 ²
Dairy cattle	0.11	0.11	2.19	0.85	1.43	1.43 ³
Poultry - broiler	0	0	0.03	0.01	0	0
Poultry - layer	0	0	0.5 ⁴	0.14 ⁵	0	0

¹ Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat and milk.

² Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.

³ Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

⁴ Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.

⁵ Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs.

Farm animal feeding studies

The Meeting received information on feeding studies with lactating cows.

A residue transfer study in livestock was conducted with 4 groups of 3 Friesian cows that were fed for 28 to 35 days with diets containing dimethomorph, administered (in corn oil) in the diet, corresponding to feeding levels of 0–12.5–37.5–125 ppm. Milk was collected daily at morning and afternoon milking and pooled for analysis. Sub-samples of milk were separated into cream and skim milk on days 14 and 28, with the day 28 milk also being pasteurised, separated into cream (35% butterfat) and skimmed milk (fat content about 0.1%) or treated and centrifuged to obtain acid whey. Liver, kidney muscle, and fat (subcutaneous and peritoneal) were taken within 24 h of the final administration for analysis. Residues in whole milk, pasteurised milk, skimmed milk, acid whey and cream were all below the limits of quantitation (0.01 mg/kg for dimethomorph and metabolite Z89) and 0.02 mg/kg for metabolites Z67/Z69) except in the 125 ppm dose group, where trace residues of dimethomorph (0.01 mg/kg) were found in cream samples.

In animals from the 12.5ppm dose group, residues of dimethomorph and metabolites Z69 and Z67 were not detectable or below the limit of quantification (0.01 mg/kg) in all tissues analysed. Residues were also all below the limit of quantification for all tissues from the 37.5 ppm dose group except for liver, where residues of up to 0.02 mg/kg of the Z69 metabolite were found. Only in the highest dose group (125 ppm) were significant residues found, mostly in liver and kidney, where residues of the Z69 metabolite were measured at levels up to 0.15 mg/kg and 0.14 mg/kg respectively and residues of the parent compound were found in liver (up to 0.05 mg/kg), and in fat (up to 0.03–0.04 mg/kg).

Residues in animal commodities

The maximum calculated animal burden estimated for dairy and beef cattle is 2.3 ppm. In the cattle feeding study, where lactating cows were dosed at 12.5 ppm (more than 5 times higher than the calculated animal burden), no dimethomorph residues were detected in tissues and milk. Therefore, the Meeting concluded that no residues are to be expected at the maximum calculated dietary burden.

The maximum animal burden estimated for poultry (layers) is 0.5 ppm. In the metabolism study where laying hens were fed the equivalent of 40 ppm in feed for seven days, dimethomorph residues in fat and skin were < 0.02 mg/kg and were not detected in eggs or other edible tissues. Metabolites Z67 and Z69 were the major residue components identified in liver (0.13 mg/kg), egg yolks (0.07 mg/kg), kidney (0.032 mg/kg) and muscle (0.003 mg/kg). Low levels (0.02–0.05 mg/kg) of the Z43 and Z95 metabolites were reported in kidney and/or egg yolks.

On the basis that the maximum calculated dietary burden is about 80 times lower than the dose rate in the metabolism study, the Meeting concluded that no residues of dimethomorph, or its primary metabolites, are to be expected at the maximum calculated dietary burden of 0.5 ppm.

The Meeting estimated a maximum residue level of 0.01* mg/kg in meat (from mammals except marine mammals) and estimated HRs and STMRs of 0 mg/kg.

The Meeting also estimated a maximum residue level of 0.01* mg/kg in edible offal (mammalian) and estimated HRs and STMRs of 0 mg/kg.

For milks, the Meeting estimated a maximum residue level of 0.01* mg/kg and estimated an STMR of 0 mg/kg.

The Meeting estimated a maximum residue level of 0.01* mg/kg in poultry meat, poultry offal and eggs and estimated HRs and STMRs of 0 mg/kg.

DIETARY RISK ASSESSMENT

Long term intake

The evaluation of dimethomorph has resulted in recommendations for MRLs and STMRs for raw and processed commodities. Consumption data was available for 31 food commodities and was used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 0–1% of the maximum ADI of 0.2 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of dimethomorph from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The international estimated short-term intake (IESTI) for dimethomorph was calculated for the food commodities (and their processing fractions) for which maximum residue levels and HRs were estimated and for which consumption data was available. The results are shown in Annex 4.

The IESTI varied from 0–10% of the ARfD (0.6 mg/kg bw) for the general population. The IESTI varied from 0–20% of the ARfD for children 6 years and below. The Meeting concluded that the short-term intake of residues of dimethomorph from uses considered by the Meeting was unlikely to present a public health concern.

5.12 FENITROTHION (037)

TOXICOLOGY

Fenitrothion is the ISO approved name for O,O-dimethyl O-4-nitro-m-tolyl phosphorothioate (IUPAC) (CAS No. 122-14-5), a broad-spectrum organophosphorus pesticide. Its toxicity was first evaluated by the JMPR in 1969, and re-evaluated in 1974, 1977, 1982, 1984, 1986, and 1988. The 2000 JMPR confirmed the ADI of 0–0.005 mg/kg bw based on a NOAEL of 0.5 mg/kg bw per day in a 2-year study of toxicity in rats, that had been established by the 1988 JMPR. Also at the 2000 JMPR, an ARfD of 0.04 mg/kg bw was established based on a NOAEL of 0.36 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in a study in human volunteers.

The 2004 JMPR noted that some estimations of long-term and short-term intake exceeded the ADI or ARfD that had been established by the 2000 JMPR. The 2004 JMPR concluded that a review of the toxicological database of fenitrothion might enable a refinement of the ADI or ARfD, particularly when concepts such as setting of an overall NOAEL or deriving compound-specific adjustment factors, were taken into account. Owing to the intake concerns identified, the CCPR at its 38th Session in 2006²⁸ asked JMPR to consider possible refinement of the ADI and ARfD for fenitrothion. Since no relevant new toxicological data had been submitted for evaluation, the data from previous evaluations conducted by the JMPR were reconsidered by the present Meeting.

For technical fenitrothion, specifications have been published as *WHO specification and evaluation for public health pesticides: technical fenitrothion* (1999).²⁹ Specifications have also been established for other formulations of fenitrothion.

Toxicological evaluation

²⁸ Codex Alimentarius Commission. *Report of the 38th Session of the Codex Committee on Pesticide Residues, 3–8 April 2006, Fortaleza, Brazil* (ALINORM06/29/24).

²⁹ Available from: <http://www.who.int/whopes/quality/en/Fenitrothion.pdf>