The Meeting agreed that for the residue estimation in eggs, the residues coming from the direct use of cyromazine in the feed at 5 mg/kg level, according to GAP (0 day withholding period) represents a better estimation of the likely residues.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.07 mg/kg and an HR of 0.16 mg/kg for cyromazine in eggs.

The Meeting recommends the withdrawal of the current recommendation of 0.2* mg/kg for cyromazine in eggs, of 0.01* mg/kg in milks, and of 0.05* mg/kg in poultry meat and sheep meat.

DIETARY RISK ASSESSMENT

Long-term intake

The ADI for cyromazine is 0-0.06 mg/kg bw. The International Estimated Daily Intakes (IEDI) for cyromazine was estimated for the 13 GEMS/Food cluster diets using the STMR or STMR-P values estimated by the current Meeting for 35 commodities. The results are shown in Annex 3. The IEDI ranged from 0–2% of the maximum ADI. The Meeting concluded that the long-term intake of residues of cyromazine from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The ARfD for cyromazine is 0.1 mg/kg bw. The International Estimated Short Term Intake (IESTI) for cyromazine was calculated for the plant commodities for which STMRs and HRs were estimated and for which consumption data were available. The results are shown in Annex 4. For the general population, the IESTI was higher than the ARfD for cabbage (120%) and spinach (130% ARfD). For children, the IESTI was higher than the ARfD for cabbage (280%) and spinach (390%). For all the other commodities, the intakes ranged from 0–40%.

The Meeting concluded that the short-term intake of residues of cyromazine from uses other than cabbage and spinach that had been considered by the JMPR is unlikely to present a public concern. The information provided to the JMPR precludes an estimate that the short-term intake of residues of cyromazine from the consumption of cabbage and spinach will be below the ARfD.

The ARfD established by the Meeting in 2006 was based on body-weight loss and decrease in food consumption in dams in developmental toxicity studies. The reason for these effects was unknown and there is a rapid recovery on cessation of administration. The Meeting noted that this ARfD may be conservative. Furthermore, it is possible that the short-term risk assessment conducted by the Meeting may also be conservative.

The Meeting noted that no residue data was available from an alternative GAP to estimate a lower maximum residue level for cyromazine in cabbage and spinach.

5.10 DIFENOCONAZOLE (224)

TOXICOLOGY

Difenoconazole (CAS name, 1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole, CAS No. 119446-68-3) is a systemic triazole fungicide that controls a broad spectrum of foliar, seed and soil-borne diseases caused by *Ascomycetes*, *Basidiomycetes* and

Deuteromycetes in cereals, soya, rice, grapes, pome fruit, stone fruit, potatoes, sugar beet and several vegetable and ornamental crops. It is applied by foliar spray or seed treatment and acts by interference with the synthesis of ergosterol in the target fungi by inhibition of the 14α-demethylation of sterols, which leads to morphological and functional changes in the fungal cell membrane. Difenoconazole is being reviewed for the first time by the present Meeting at the request of the CCPR. All critical studies complied with GLP.

Biochemical aspects

In rats given [^{14}C]difenoconazole labelled in either the triazole or phenyl rings as a single oral dose at 0.5 or 300 mg/kg bw, the radiolabel was rapidly and almost completely absorbed from the gastrointestinal tract, widely distributed, and eliminated from the body with excretion half-lives of about 20 h at the lower dose and about 33–48 h at the higher dose. At doses of 0.5 and 300 mg/kg bw, approximately 13–22% and 8–15%, respectively, of the applied radioactivity was excreted via the urine in rats. Excretion via the faeces accounted for 81–87% (lower dose) to 85–95% (higher dose) of the radiolabel; however, approximately 73% (males) to 76% (females) of the lower dose and approximately 39% (females) to 56% (males) of the higher dose was eliminated from the body via the bile in bile-duct cannulated rats. Thus, bioavailability decreased with increasing dose. When bile from rats given difenoconazole was introduced into the duodenum of other bile-cannulated rats, 80% of the radioactivity was re-eliminated in the bile and 4% in the urine, indicating that there was extensive enterohepatic recirculation. The greater quantities of radioactivity were distributed to the gastrointestinal tract, liver and kidneys. The initial plasma half-life was approximately 4–6 h at the lower dose and 22–24 h at the higher dose and the terminal half-life was approximately 3–4 days at both doses. In spite of these long terminal half-lives, there was no evidence for bioaccumulation of difenoconazole.

After oral administration to male and female rats, the systemically available portion of [^{14}C-phenyl]difenoconazole was rapidly and extensively metabolized to a number of biotransformation products. Three main metabolites isolated from the faeces accounted for approximately 68% of the administered doses. These were: the hydroxylated product of cleavage of the dioxolane ring; its further metabolite resulting from hydroxylation of the chlorophenoxy ring; and the product of the hydroxylation of difenoconazole, occurring directly in the chlorophenoxy ring. A minor metabolic pathway involves cleavage of the alkyl chain between the triazole and the inner phenyl ring, resulting in a hydroxy acetic acid, 2-chloro-4-(4-chlorophenoxy)-benzoic acid and free 1,2,4-triazole. Sulfate conjugates were identified for some hydroxylated metabolites.

Toxicological data

The acute toxicity of difenoconazole was low, with values for the oral LD_{50} being 1453 mg/kg bw in rats and > 2000 mg/kg bw in mice. The dermal LD_{50} in rabbits was > 2010 mg/kg bw and the inhalation LC_{50} in rats was > 3.3 mg/L. Difenoconazole is very slightly and transiently irritating to the skin and moderately and transiently irritating to the eyes of rabbits and is non-sensitizing in a modified Buehler test in guinea-pigs.

Overall, in short-term studies with orally-administered difenoconazole, the signs of toxicity observed in mice, rats and dogs were similar, with reduced body-weight gain and increased liver weights being common features. Histopathology confirmed the liver as a target organ with observation of diffuse or centrilobular hypertrophy of hepatocytes in rats and mice, although this can also be indicative of an adaptive response. Cataracts were found in dogs fed diets containing difenoconazole at a concentration of ≥ 3000 ppm, equal to 96.6 mg/kg bw per day, for 6 months, with an NOAEL of 1000 ppm, equal to 31.3 mg/kg bw per day; however, cataracts were not induced in a second study in dogs given diets containing difenoconazole at up to 1500 ppm, equal to 51.2 mg/kg bw per day, for 1 year. Increased activity of alkaline phosphatase was observed in two studies in rats and in one in dogs. No other blood chemistry changes were consistently observed, although reduced

concentrations of blood protein were observed in dogs given diets containing difenoconazole at 6000 ppm, equal to 157.8 mg/kg bw per day. Also in dogs, a reduction in erythrocyte count of almost 20% was observed in females at this high level of exposure.

For the short-term dietary studies, the NOAELs were: in studies of up to 90 days in rats, 200 ppm (equal to 17 mg/kg bw per day) on the basis of increased hepatocellular hypertrophy and liver weight; in a 90-day dietary study in mice, 200 ppm (equal to 34.2 mg/kg bw per day) on the basis of clinical signs of toxicity and changes in liver weight and increased incidence of centrilobular hepatocellular hypertrophy; in a 28-week study in dogs, 1000 ppm (equal to 31.3 mg/kg bw per day) on the basis of cataracts and liver-weight changes; in a 12-month study in dogs, 100 ppm (equal to 3.6 mg/kg bw per day) on the basis of reduced body-weight gain; in a 4-week study of dermal toxicity with difenoconazole in rats, 100 mg/kg bw per day, on the basis of minimal centrilobular hepatocellular hypertrophy, minimal to moderate thyroid follicular cell hypertrophy and skin lesions at the site of application.

Long-term feeding studies in rats and mice fed with difenoconazole confirmed that the primary target organ was the liver. There was no evidence for any carcinogenic potential in rats, in which hepatic effects were increases in liver weight and hepatocellular hypertrophy in male and female rats. In addition, there were reductions in erythrocyte parameters in female rats at the highest dose, 2500 ppm, equal to 170 mg/kg bw per day.

In mice, there was very high, treatment-related mortality at the beginning of the 18-month study. In groups of 70 mice, there were 52 deaths among females receiving difenoconazole at 4500 ppm and 16 deaths among females at 3000 ppm (reduced to 2500 ppm after 1 week) within the first 2 weeks, while, among the male mice there were 11 deaths in the group at 4500 ppm within the first 3 weeks of the study. There was an increased incidence of hepatocellular adenomas and carcinomas in the group of male and female mice fed diet containing difenoconazole at 2500 ppm, equal to 423 and 513 mg/kg bw per day, respectively, and males at 4500 ppm, equal to 819 mg/kg bw per day. No increase in the incidence of tumours was observed at 300 ppm, equal to 46.3 and 57.8 mg/kg bw per day in males and females, respectively. However, the neoplastic responses occurred at highly toxic doses that also caused the death of substantial proportions of the groups of mice. Among the survivors, biliary stasis and hepatic single-cell necrosis as well as hepatocellular hypertrophy were significantly increased in male and female mice at the tumorigenic doses. On the basis of a study of enzyme activities in male mice, difenoconazole is considered to be a reversible barbiturate-type inducer of metabolizing enzymes in the mouse liver. No peroxisome proliferation was observed. The NOEL was 10 mg/kg, there being no inductive effect on metabolizing enzymes and other parameters in the mouse liver.

The NOAEL in long-term studies in rats was 20 ppm, equal to 1.0 mg/kg bw per day, on the basis of reduced body-weight gains during the first year in males and females, reduced platelet counts in males and hepatic centrilobular hypertrophy in males and females at 500 ppm, equal to 24 mg/kg bw per day. In long-term studies in mice, the NOAEL was 30 ppm, equal to 4.7 mg/kg bw per day, on the basis of decreased body-weight gain in males, increased liver weight in females and hepatocellular hypertrophy in males at 300 ppm, equal to 46.3 mg/kg bw per day.

Difenoconazole was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence for genotoxicity was observed in any test.

The Meeting concluded that difenoconazole is unlikely to be genotoxic.

The Meeting concluded that difenoconazole caused an increase in the incidence of hepatocellular adenomas and carcinomas in mice (but not in rats) by a non-genotoxic mode of action, the nature of which has not been established but which resembles that for phenobarbital in its liver enzyme-inducing characteristics. It is therefore unlikely to pose a carcinogenic risk to humans at exposure levels that do not cause changes in the liver.

The reproductive toxicity of difenoconazole was investigated in a two-generation study of reproduction in rats and in studies of developmental toxicity in rats and rabbits.

Reproductive function was not affected in rats in the two-generation study and the NOAEL for reproductive function was 2500 ppm, equal to 132.1 mg/kg bw per day, the highest dose tested. The NOAEL for systemic toxicity in the parental animals was 250 ppm, equal to 11.5 mg/kg bw per day on the basis of reduced body-weight gain during the pre-mating period in F_0 and F_1 generations at 2500 ppm, equal to 122.7 mg/kg bw per day during these periods. In pups, lower birth weight and subsequent decreased body-weight gain at 2500 ppm, equal to 158.0 mg/kg bw per day, were the effects that defined the NOAEL for offspring toxicity at 250 ppm, equal to 14.1 mg/kg bw per day in the females.

In a study of developmental toxicity in which rats were given difenoconazole by gavage on days 6–15 of gestation, the NOAEL for maternal toxicity was 20 mg/kg bw per day on the basis of reduced body-weight gain and excess salivation first observed on day 2 of dosing in 14 out of 23 dams at 100 mg/kg bw per day. There was a statistically significant, but small increased incidence of changes in thoracic vertebral ossification centres in foetuses at 200 mg/kg bw. The NOAEL for foetal toxicity was 100 mg/kg bw per day on the basis of these skeletal anomalies.

In a study of developmental toxicity in which rabbits were given difenoconazole by gavage on days 7–19 of gestation, the NOAEL for maternal toxicity was 25 mg/kg bw per day on the basis of reduced body-weight gain in the first few days of dosing at 75 mg/kg bw per day. Examination of the foetuses did not reveal any treatment-related effects in soft or ossified tissues. The NOAEL for developmental toxicity was 75 mg/kg bw per day, the highest dose tested.

In a single-dose study of neurotoxicity in rats treated by gavage, the NOAEL was 25 mg/kg bw based on reduced forelimb-grip strength interpreted as a non-specific response at 200 mg/kg bw. In a 90-day study of neurotoxicity in rats given diets containing difenoconazole, the NOAEL was 40 ppm, equal to 2.8 mg/kg bw per day, on the basis of reduced hind limb-grip strength in males during the final week of the study at 250 ppm, equal to 17.3 mg/kg bw per day. These responses were considered to be non-specific effects of difenoconazole because of the absence of any changes in the multiple end-points of neurotoxicity that were measured and the absence of neuropathological findings.

The Meeting concluded that difenoconazole is unlikely to cause neurotoxicity in humans.

There were no indications of immunotoxicity in general studies of toxicity in dogs, rats and mice.

Some aspects of the toxicology of three plant metabolites of difenoconazole that are also found in rats given difenoconazole were investigated. These metabolites were: 1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanone, 1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanol and 2-chloro-4-(4-chlorophenoxy)-benzoic acid. The LD_{50} value for each of these metabolites was > 2000 mg/kg bw and none of them showed any alerts for mutagenic activity. In addition, there are three metabolites which are common to all parent triazoles: 1, 2, 4-triazole, triazole alanine and triazole acetic acid. 1,2,4-Triazole is a soil metabolite that also appears to a small extent (< 10%) in some studies in plants and is found as at least 10% of the total metabolites in rats administered difenoconazole. Triazole alanine and triazole acetic acid are plant-specific metabolites. The acute toxicity (LD_{50}) values for 1,2,4-triazole, triazole alanine and triazole acetic acid were similar to or higher than the LD_{50} values for difenoconazole. Some recent studies conducted with 1,2,4-triazole have shown certain effects at high doses, i.e., testicular atrophy in mice at ≥ 487 mg/kg bw per day; effects on the central nervous system and pathology in rats at ≥ 183 mg/kg bw per day; and a reduction in fertility in a two-generation study of reproduction in rats at 218 mg/kg bw per day. The NOAELs for 1,2,4-triazole for these effects were 90 mg/kg bw per day for testicular atrophy in mice, 33 mg/kg bw per day for neurotoxicity in rats and 16 mg/kg bw per day for effects on fertility in rats.

Repeat-dose studies in which triazole alanine was administered for up to 90 days did not show any significant effects other than reduced body-weight gains at 20 000 ppm, equivalent to 2000 mg/kg bw per day in rats and 500 mg/kg bw per day in dogs. The NOAELs in these studies were 5000 ppm,

equivalent to 500 mg/kg bw per day, in rats and 8000 ppm, equivalent to 200 mg/kg bw per day, in dogs. In a two-generation study with triazole alanine in rats, the NOAEL for parental toxicity was 10 000 ppm, equivalent to 500 mg/kg bw per day, the highest dose tested, and the NOAEL for reproductive toxicity was 2000 ppm, equivalent to 100 mg/kg bw per day, on the basis of reduced birth weights at 10 000 ppm. In a study of teratogenicity in rats, the NOAEL for maternal toxicity was 1000 mg/kg bw per day, the highest dose tested, and the NOAEL for developmental toxicity was 100 mg/kg bw per day on the basis of retarded ossification at 1000 mg/kg bw per day.

Triazole acetic acid has been tested in a 14-day dietary study in which the NOAEL was 8000 ppm, equal to 704 mg/kg bw per day, respectively, the highest dose tested.

None of these metabolites has been tested for carcinogenicity. The extent to which 1,2,4-triazole, triazole alanine and triazole acetic acid had been tested for mutagenicity varied, but no significant responses were obtained in any of the studies.

Medical surveillance of personnel has been conducted since the early 1990s at sites in several countries where difenoconazole is manufactured. Reports were available up to the end of 2002. There have been no reports of toxicity in workers during manufacture and there was only one case of allergic reaction to a formulated product. There were no reports of poisoning and no reports of sensitization during use of the formulated product.

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

Toxicological evaluation

An ADI of 0–0.01 mg/kg bw was established for difenoconazole based on the NOAEL of 1.0 mg/kg bw per day in rats, identified on the basis of reduced body-weight gains, reduced platelet counts and hepatic hypertrophy in a 24-month long-term dietary study of toxicity and carcinogenicity. A safety factor of 100 was applied. The increased incidence of hepatocellular adenomas and carcinomas observed in mice at 423 mg/kg bw per day, the NOAEL being 4.7 mg/kg bw per day, in an 18-month long-term dietary study of toxicity and carcinogenicity, was likely to be due to a mode of action without human relevance at exposure levels that do not cause changes in the liver.

An ARfD of 0.3 mg/kg bw was established for difenoconazole. This was based on the NOAEL of 25.0 mg/kg bw in rats, identified on the basis of clinical signs in a single-dose study of neurotoxicity and using a safety factor of 100. This ARfD is supported by the NOAEL of 25 mg/kg bw per day for maternal toxicity in a study of developmental toxicity in rats and rabbits on the basis of excess salivation in rats at 100 mg/kg bw per day and body-weight loss in rabbits during the first few days of treatment at 75 mg/kg bw per day.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity	Toxicity	30 ppm, equal to 4.7 mg/kg bw per day	300 ppm, equal to 46.3 mg/kg bw per day
		Carcinogenicity	300 ppm, equal to 46.3 mg/kg bw per day	2500 ppm[a], equal to 423 mg/kg bw per day

Rat	Twenty-four-month studies of toxicity and carcinogenicity	Toxicity	20 ppm, equal to 1.0 mg/kg bw per day	500 ppm, equal to 24 mg/kg bw per day
		Carcinogenicity	2500 ppm[a] equal to 124 mg/kg bw per day	—
	Two-generation study of reproductive toxicity[b]	Reproductive toxicity	2500 ppm[a] equal to 132.1 mg/kg bw per day	—
		Parental toxicity	250 ppm, equal to 11.5 mg/kg bw per day	2500 ppm[a] equal to 122.7 mg/kg bw per day
		Offspring toxicity	250 ppm, equal to 14.1 mg/kg bw per day	2500 ppm[a] equivalent to 158 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	20 mg/kg bw per day	100 mg/kg bw per day
		Embryo and foetal toxicity	100 mg/kg bw per day	200 mg/kg bw per day[a]
	Acute neurotoxicity	Toxicity	25 mg/kg bw	200 mg/kg bw per day[a]
Rabbit	Developmental toxicity[c]	Maternal toxicity	25 mg/kg bw per day	75 mg/kg bw per day[a]
		Embryo and foetal toxicity	75 mg/kg bw per day[a]	—
Dog	One-year study of toxicity	Toxicity	100 ppm, equal to 3.6 mg/kg bw per day	500 ppm, equal to 16.4 mg/kg bw per day

[a] Highest dose tested.

[b] Measurements of intake of the compound are the mean for the pre-mating phases for females.

[c] Gavage administration.

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.3 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 exposure

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

Absorption, distribution, excretion and metabolism	
Rate and extent of oral absorption	High, but incomplete (rats)
Dermal absorption	Approximately 8% (rats)
Distribution	Distributed throughout the body; higher concentrations in liver and gastrointestinal tract

Potential for accumulation	Low, no evidence of accumulation
Rate and extent of excretion	High; essentially 100% excretion in bile and urine within 7 days
Metabolism in animals	Extensive; a small number (< 10) of metabolites; little parent compound remaining
Toxicologically significant compounds in animals, plants and environment	Parent, 1,2,4-triazole
Acute toxicity	
Rat, LD_{50}, oral	1453 mg/kg bw
Rat, LC_{50}, inhalation	3.3 mg/L (4 h)
Rabbit, LD_{50}, dermal	2010 mg/kg bw
Rabbit, skin irritation	Very slightly and transiently irritating
Rabbit, eye irritation	Moderately and transiently irritating
Guinea-pig, skin sensitization	Not sensitizing (modified Buehler test)
Short-term studies of toxicity	
Target/critical effect	Liver; body weight
Lowest relevant oral NOAEL	3.6 mg/kg bw per day (12-month study in dogs)
Lowest relevant dermal NOAEL	100 mg/kg bw per day (4-week study in rats)
Lowest relevant inhalation NOAEC	No data
Genotoxicity	
	Not genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver; body weight
Lowest relevant NOAEL	1.0 mg/kg bw per day (24-month study in rats)
Carcinogenicity	Not carcinogenic at levels below those causing changes in the liver
Reproductive toxicity	
Reproductive target/critical effect	None
Lowest relevant reproductive NOAEL	132 mg/kg bw per day
Developmental target/critical effect	Not teratogenic; reduced foetal body weight, delayed ossifications in rats, but not in rabbits
Lowest relevant developmental NOAEL	100 mg/kg bw per day (rats)
Neurotoxicity/delayed neurotoxicity	
Single-dose study of neurotoxicity	No signs of neurotoxicity, NOAEL was 25 mg/kg bw (rats)
Ninety-day study of neurotoxicity	No signs of neurotoxicity, NOAEL was 2.3 mg/kg bw (rats)
Other toxicological studies	
	Induction of liver xenobiotic metabolizing enzymes
	Studies of mammalian and plant metabolites
Medical data	
	No reports of toxicity in workers exposed during

manufacture or use

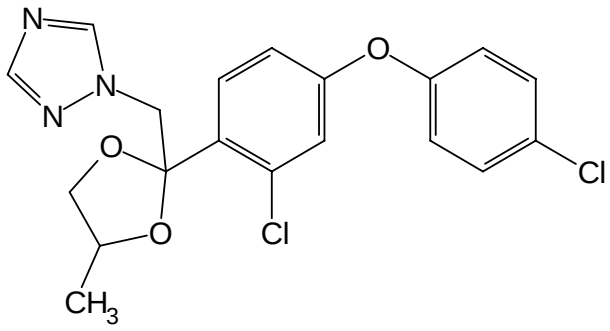
Summary

	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Rat, 2-year study of toxicity and carcinogenicity	100
ARfD	0.3 mg/kg bw	Rat, single-dose study of neurotoxicity study, supported by maternal effects in a study of developmental toxicity studying rabbits	100

RESIDUE AND ANALYTICAL ASPECTS

Difenoconazole was considered for the first time by the present meeting. It is a broad-spectrum fungicide used for disease control in many fruits, vegetables, cereals and other field crops. It has preventive and curative action. Difenoconazole acts by inhibition of demethylation during ergosterol synthesis.

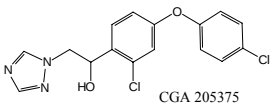
1-[2-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-4-methyl[1,3]dioxolan-2-ylmethyl]-1H-1,2,4-triazole



Animal metabolism

The Meeting received animal metabolism studies with difenoconazole in rats, lactating goats and laying hens. Difenoconazole [^{14}C] labelled in the central phenyl ring or the triazole ring was used in most of the metabolism studies. Difenoconazole [^{14}C] labelled in the chlorophenoxy ring was used in some of the studies.

Difenoconazole is rapidly metabolized, initially to 1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanol (CGA 205375) and then with cleavage of the triazole moiety from the chlorophenoxyphenyl moiety. Conjugates are formed from hydroxylated metabolites. TRR levels are higher in the liver than in other tissues. Most of the TRR is rapidly excreted.



CGA 205375

Parent difenoconazole has a tendency to fat-solubility, but it is always a minor component of the residue. The major component of the residue in most animal commodities is CGA 205375, which appears to be fat-soluble because residue concentrations in fat are approximately 3 times as high as those in muscle. However, it is not strong fat-solubility because residue concentrations in fat are less than those in kidney and much less than those in liver (typically residues in liver are 6–8 times as high as in the fat).

When rats were orally dosed with labelled difenoconazole it was readily absorbed followed by extensive metabolism and excretion. The following metabolites were identified in excreta: CGA 205375, 1,2,4-triazole, 2-chloro-4-(4-chlorophenoxy)-benzoic acid, 2-chloro-4-(4-

chlorophenoxy)-phenyl-hydroxyacetic acid, hydroxylated difenoconazole and hydroxylated CGA 205375. Sulphate conjugates of the hydroxylated metabolites were identified in urine. (See the toxicology report for more details of laboratory animal metabolism)

When two lactating goats were orally dosed with labelled ([^{14}C]triazole and [^{14}C]phenyl) difenoconazole for 10 consecutive days at 7.5 mg/animal/day, equivalent to 4.7 and 5.6 ppm in the feed, most of the administered [^{14}C] was excreted in the faeces (75% and 67%) and urine (31% and 21%). Residues in milk reached a plateau by day 2 (phenyl) and days 4–7 (triazole). Of the [^{14}C] in milk, 19% and 32% were distributed into the fat portion for the triazole and phenyl labels respectively (metabolite 1,2,4-triazole is water soluble). Residues of [^{14}C] were higher in liver (0.28 and 0.26 mg/kg) than in other tissues. Metabolite CGA 205375 constituted 57–58% of the TRR in liver, with parent difenoconazole at 1% or less. Triazole was the major component identified in milk, constituting 47% TRR.

When four lactating goats were orally dosed with labelled ([^{14}C]triazole and [^{14}C]phenyl) difenoconazole for 4 consecutive days at 150 mg/animal/day, equivalent to 100 ppm in the feed, [^{14}C] recovery was marginal at 40–64%. The TRR in liver (7.5 and 6.0 mg/kg) was much higher than other tissues. CGA 205375 was the major residue in each tissue, accounting for approximately 30–70% of the TRR. Difenoconazole residues in liver (0.62 and 0.40 mg/kg) were higher than in other tissues. Difenoconazole accounted for 1.5–8.3% of the TRR in each of the tissues. In milk, CGA 205375 accounted for 21% and 34% of the TRR (0.38 and 0.14 mg/kg), while difenoconazole (6–9% TRR) and triazole (6% TRR) were minor parts of the residue.

Two lactating goats were dosed orally once daily for 4 consecutive days by gelatin capsule with 150 mg/animal/day of [^{14}C-phenyl]difenoconazole, equivalent to 100 ppm in the feed and were slaughtered approximately 6 h after the final dose for tissue collection. CGA 205375 was the major component of the residue in all tissues and milk. Parent difenoconazole was present in all tissues and milk, but never exceeding 10% of the TRR. A number of metabolites resulted from hydroxylation and conjugation with glucuronic acid, sulphate and glycine. The concentration of the main component, CGA 205375, in fat was 2.3 times its concentration in muscle, but much below its concentration in liver and similar to that in kidney, suggesting borderline fat solubility.

When 4 laying hens were orally dosed with labelled ([^{14}C]triazole and [^{14}C]phenyl) difenoconazole for 14 consecutive days at 0.55 mg/bird/day, equivalent to 5 ppm in the feed, most of the administered [^{14}C] was excreted in the faeces (> 89%). Highest TRR appeared in the kidney (0.43 and 0.49 mg/kg) and liver (0.13 and 0.13 mg/kg). Apparent plateaus for TRR in egg whites and yolks were reached after approximately 4 and 7 days of dosing respectively. The plateau TRR values in egg whites were quite different for the two labels: 0.14 mg/kg for [^{14}C]triazole label and 0.011 mg/kg for [^{14}C]phenyl label, whereas the plateau levels in the yolks were essentially the same (0.28 and 0.29 mg/kg).

When 20 laying hens were orally dosed with labelled ([^{14}C]triazole and [^{14}C]phenyl) difenoconazole for 3 consecutive days at 7.5 mg/bird/day, equivalent to 68 ppm in the feed, most of the administered [^{14}C] was excreted in the faeces (76%). Highest TRR occurred in the liver (4.3 and 4.7 mg/kg) and kidney (1.9 and 2.2 mg/kg). CGA 205375 was the major identified component in each tissue: liver (30% and 34% TRR), kidney (20% and 22%), muscle (8.8% and 35%) and fat (46% and 64%). Parent difenoconazole accounted for less than 5% TRR in each tissue. For eggs from the phenyl label treatment, CGA 205375 was the main component of the residue (73–83% TRR). For the triazole label, triazole accounted for 67% of TRR in egg white and 33% TRR in egg yolk, while CGA 205375 accounted for 7.8% TRR in egg white and 36% TRR in egg yolk. Approximately 4-5% of the TRR in egg yolks was identified as parent difenoconazole.

Five laying hens were dosed orally once daily for 4 consecutive days by gelatin capsule with 12.5 mg/bird/day of [^{14}C-triazole]difenoconazole, equivalent to 121 ppm in the feed and were slaughtered approximately 6 h after the final dose for tissue collection. Significant [^{14}C] levels appeared in all tissues (liver 13 mg/kg, muscle 4.9 mg/kg, fat 10.4 mg/kg) and eggs (whites 4.0 mg/kg, yolks 4.5 mg/kg). CGA 205375 was a major component of the residue in tissues (liver 56%

TRR, muscle 24% TRR, fat 61% TRR) and egg yolk (53% TRR). Triazole was also a significant component of the residue in tissues (liver 18% TRR, muscle 55% TRR, fat 4.6% TRR) and eggs (whites 75% TRR, yolks 31% TRR). Parent difenoconazole was a minor component of the residue in liver, muscle and egg yolk (< 5%TRR) but accounted for 18% of the TRR in fat.

The metabolism of difenoconazole in rats, goats and hens is qualitatively similar.

Plant metabolism

The Meeting received plant metabolism studies with difenoconazole in tomatoes, wheat, potatoes, grapes and oilseed rape. Difenoconazole [^{14}C] labelled in the central phenyl ring, in the triazole ring or in the chlorophenoxy ring was used in the metabolism studies.

Difenoconazole is generally slowly absorbed and metabolized. In most cases, particularly for parts of the plant directly exposed to the treatment, the parent difenoconazole is the dominant part of the residue. Parts of the plant not directly exposed are more likely to contain a residue dominated by a mobile water-soluble metabolite such as triazolylalanine.

The following plant metabolites apparently do not occur as animal metabolites of difenoconazole: triazolylalanine (2-amino-3-(1,2,4]triazol)-1-yl-propionic acid), triazolyl acetic acid (1,2,4-triazol-1-yl-acetic acid) and triazolyl-lactic acid (1,2,4-triazol-1-yl-lactic acid). At least some of these metabolites are common to other fungicides containing the 1,2,4-triazole moiety.

In a tomato metabolism study in USA, tomato plants in pots in a greenhouse were foliar sprayed 6 times at 7-day intervals with [^{14}C]phenyl and [^{14}C]triazole labelled difenoconazole at the equivalent of 0.12 kg ai/ha. Parent difenoconazole was the major part of the residue on foliage. Residue levels on tomato fruits sampled 7 days after the final treatment were insufficient for identification. A field-grown tomato metabolism study produced similar results.

In another tomato metabolism study in USA, tomato plants in pots in a greenhouse were foliar sprayed 6 times at 7-day intervals with [^{14}C]triazole labelled difenoconazole at the equivalent of 0.12 kg ai/ha. In tomato fruits sampled 33 days after the final treatment, parent difenoconazole (12–51% TRR) and metabolite triazolylalanine (19–42% TRR) were major components of the residue (TRR 0.13–0.20 mg/kg). In a parallel study with phenyl labelled difenoconazole, tomato fruits, sampled 33 days after the final treatment, contained parent difenoconazole (66% TRR) as the major part of the residue (TRR 0.17 mg/kg). In both of these studies low concentrations (< 2% TRR) of metabolite CGA 205375 and its ketone (1-(2-chloro-4-(4-chloro-phenoxy)-phenyl)-2-(1,2,4-triazol)-1-yl-ethanone) occurred in the fruits.

In a wheat metabolism study, triazole and triazolylacetic acid were identified in the mature stalks and grain produced from [^{14}C]triazole labelled difenoconazole treated seed. Metabolite CGA 205375 was identified in wheat tops from a parallel wheat metabolism study with [^{14}C]phenyl labelled difenoconazole.

In a greenhouse wheat metabolism study in USA, spring wheat seeds were treated with [^{14}C]phenyl and [^{14}C]triazole labelled difenoconazole at 0.25 and 0.30 g ai/kg seed and grown to maturity. Parent difenoconazole and metabolite CGA 205375 were identified at low levels in wheat tops at 25 % maturity (40 days post sowing).

In a greenhouse wheat metabolism study in USA, spring wheat was foliar sprayed 4 times with [^{14}C]phenyl and [^{14}C]triazole labelled difenoconazole at a rate equivalent to 0.25 kg ai/ha. Mature samples of grain were harvested 29 days after the final application. In grain from the [^{14}C-triazole]difenoconazole treated crop, triazolylacetic acid and triazole accounted for 20% and 10% of the TRR (1.4 mg/kg) respectively. In grain from the [^{14}C-phenyl]difenoconazole treated crop, the TRR (0.064 mg/kg) was much lower, demonstrating that metabolic cleavage of the compound occurred before translocation to the grain. In the mature stalks, difenoconazole accounted for 50% of the TRR (54 and 47 mg/kg) for both labels.

Parent difenoconazole was not identified in mature grain from the wheat metabolism studies.

In a greenhouse potato metabolism study in USA, potato plants were foliar sprayed 6 times with [^{14}C]chlorophenoxy labelled difenoconazole at the equivalent of 0.12 kg ai/ha per application. Very little of the [^{14}C] translocated to the tubers (TRR 0.012 mg/kg) with parent difenoconazole and two primary metabolites identified as low-level components of the residue (< 10% TRR). Parent difenoconazole was the major component (76% TRR) of the foliage residue.

In a parallel study on potatoes with [^{14}C]triazole labelled difenoconazole, triazolylalanine (79% TRR) was the major part of the residue in tubers (TRR 0.087 mg/kg). Parent difenoconazole was again the major component (71% TRR) of the foliage residue.

In a field plot grape metabolism study in USA, grape vines were foliar sprayed 5 times with [^{14}C]phenyl and [^{14}C]triazole labelled difenoconazole. Parent difenoconazole was the major component (51% and 45% TRR) of the residue (TRR 0.13 and 0.12 mg/kg) in grapes harvested 20 days after 3 and 5 sprays. None of the identified metabolites exceeded 10% of the TRR in grapes. Parent difenoconazole was also the major identified component (17% TRR) of the residue (TRR 0.047 mg/kg) in grapes harvested 77 days after the second treatment.

In a field plot oilseed rape metabolism study in Switzerland, spring rape received two foliar sprays with [^{14}C]chlorophenoxy labelled difenoconazole at the equivalent of 0.13 kg ai/ha. Parent difenoconazole was the major identified component of the residue in stalks (17% TRR), seeds (15% TRR) and pods (17% TRR) taken at mature harvest 39 days after the second application and in oil (26% TRR) produced from the seed. Metabolite CGA 205375 exceeded 10% of TRR in the stalks (14%) and pods (11%).

In a parallel oilseed rape study with [^{14}C]triazole labelled difenoconazole, parent difenoconazole was a major identified component of the residue in stalks (17% TRR), pods (14% TRR) from samples taken at mature harvest, 39 days after the second application, and in oil (84% TRR) produced from the seed. Metabolite CGA 205375 exceeded 10% of TRR in the stalks (17%) and pods (13%). Triazolylalanine, the major residue component in the seed (56% TRR) also exceeded 10 % in pods (12%). Triazolylalanine was also the major residue component in the meal (56% TRR). Other identified components of the residue in the meal were triazolylacetic acid, CGA 205375 and difenoconazole.

Parent difenoconazole is the main component of the residues in those parts of the crop directly exposed to treatment. For other parts of the crop, e.g., the grain of cereals and the tubers of potatoes, the main components of the residue are translocatable metabolites, e.g., triazolylalanine, which are common to other fungicides containing the 1,2,4-triazole moiety.

Environmental fate in soil

The Meeting received information on soil aerobic metabolism and soil photolysis properties of difenoconazole as well as studies on the behaviour of difenoconazole residues in crop rotations. Difenoconazole residues are reasonably persistent in soils and are expected to be present in the soil at harvest time for treated root and tuber crops. Difenoconazole residues are also expected to persist in the soil until the sowing of rotational crops. The confined rotational crops studies demonstrate that difenoconazole itself does not appear as a residue in the rotational crop. The water-soluble and mobile metabolites triazolylalanine, triazolylacetic acid and triazolyl-lactic acid have been identified in the rotational crops.

Aerobic soil degradation rates were influenced by the nature of the soil, temperature, moisture status of the soil and dose when [^{14}C]difenoconazole was subjected to laboratory soil incubation. Estimated aerobic soil metabolism half-lives for difenoconazole at 20 °C ranged from 63 to 700 days (n=12) with a median of 181 days. After 220–300 days, mineralization and unextractable residues (20–54% of dose) were major sinks for the [^{14}C] label. The degree of mineralization was different for

the phenyl and triazole label positions, e.g., 0.8–4.6 % of the dose for the triazole label and 3.4–33 % for the phenyl label.

CGA 205375 and 1,2,4-triazole were identified as soil metabolites. Metabolite CGA 205375 consistently reached a maximum (expressed as parent) of 5–10% of the dose and had begun to decline by the end of the observation period. Metabolite 1,2,4-triazole typically reached a maximum (expressed as parent) around 20% of the dose during the observation period. The aerobic soil metabolism of the metabolites, CGA 205375 and 1,2,4-triazole, was studied separately. The major metabolite of CGA 205375 was 1,2,4-Triazole.

Difenoconazole on a soil surface was stable to photolysis during the test period of 30 days.

In rotational crops with the [^{14}C] label in the phenyl moiety, the level of carry-over residues in rotational crops was too low for characterization or identification. With the [^{14}C] label in the triazole moiety and application to bare ground at 0.13 kg ai/ha, metabolites triazolylalanine, triazolylacetic acid and triazolyl-lactic acid were identified in rotational crops: maize grain TRR 0.21 mg/kg (66% triazolylalanine 66%); wheat grain 0.34 mg/kg (44% triazolylalanine, 26% triazolylacetic acid); lettuce heads 0.017 mg/kg (31% triazolylalanine, 43% triazolyl-lactic acid; and sugar beet tops 0.029 mg/kg (25% triazolylalanine, 54% triazolyl-lactic acid).

In outdoor non-confined rotational crop studies in Germany, bare ground was treated directly with difenoconazole at a rate equivalent to 0.75 kg ai/ha and the upper 10 cm soil layer was turned over to mix in the applied material. Carrots or spinach were sown 30–31 days after the difenoconazole application and harvested for analysis 97–136 days (carrots) and 62–77 days (spinach) after the application. Residues of difenoconazole (LOQ 0.02 mg/kg) and triazolylalanine (LOQ 0.05 mg/kg) in the carrots and spinach did not exceed the LOQs. Difenoconazole residue levels in the soil were in the range 0.15-0.23 mg/kg during rotational crop samplings.

Methods of residue analysis

The Meeting received descriptions and validation data for analytical methods for residues of parent difenoconazole in raw agricultural commodities, processed commodities, feed commodities, animal tissues, milk and eggs. Methods were provided also for metabolite CGA 205375 in animal tissues, milk and eggs.

In the methods for plant commodities, macerated samples are typically extracted with methanol or acetonitrile and the extract is cleaned up by solvent partitions and solid phase column chromatography. The final residue may be determined by GLC with ECD or NPD or alternatively by LC-MS-MS. LOQs are typically in the 0.01–0.05 mg/kg range. The analytical methods for animal commodities are similar, but with extraction methods tailored for milk, eggs or animal tissues. The LOQ for milk is 0.005 mg/kg and eggs and tissues 0.01–0.05 mg/kg.

Analytical recovery data were satisfactory for difenoconazole and CGA 205375 (in animal commodities) for numerous commodities.

Residue methods were tested by independent laboratories unfamiliar with the analysis and were found to have satisfactory recoveries and no background interferences.

DFG Method S19 (revision) was demonstrated to be suitable for analysis of difenoconazole residues in a number of crop commodities.

The acetonitrile-water extraction of poultry tissues and eggs, as in the analytical method, was applied to liver, fat, muscle and egg yolk samples from a [^{14}C-triazole]difenoconazole metabolism study and was shown to provide comparable extraction for difenoconazole, CGA 205375 and 1,2,4-triazole with the exhaustive extraction of the metabolism study.

Stability of residues in stored analytical samples

Information was received on the freezer storage stability of parent difenoconazole residues in plant and animal commodities, and of residues of CGA 205375 in animal commodities.

Difenoconazole residues were stable in the following crop commodities for the intervals tested, some for 1 year, but most for 2 years: banana, cotton seed, cotton seed meal, cotton seed oil, lettuce, potatoes, soya beans, tomatoes, wheat forage, wheat grain and wheat straw.

Difenoconazole and metabolite CGA 205375 spiked into animal tissues (0.2 mg/kg) and milk (0.05 mg/kg) were stable when stored at or below -18 °C for approximately 10 months.

Definition of the residue

Parent difenoconazole is the dominant component of the residue in crop commodities and is a suitable analyte for enforcement purposes.

Parent difenoconazole is generally no more than a minor component in animal commodities. The major component of the residue in most animal commodities is metabolite CGA 205375 (1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanol).

In the goat metabolism studies, the concentration of CGA 205375 in the fat was approximately 3 times as high as in the muscle, but much lower than in the liver. In the dairy cow feeding studies, the concentration of CGA 205375 in the fat was approximately 3 times as high as in the muscle, but much lower than in the liver. In the laying hen metabolism studies, the concentration of CGA 205375 in the fat was approximately 5–8 times as high as in the muscle, but also much lower than in the liver. The octanol-water partition coefficient of CGA 205375 (log P_{OW}=3.8) suggests fat-solubility.

The Meeting decided the residue would be defined as fat-soluble.

The Meeting recommended a residue definition for difenoconazole.

Definition of the residue (for compliance with the MRL and for estimation of dietary intake) for plant commodities: difenoconazole.

Definition of the residue (for compliance with the MRL and for estimation of dietary intake) for animal commodities: sum of difenoconazole and 1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanol), expressed as difenoconazole.

The residue is fat soluble.

Results of supervised residue trial on crops

The Meeting received supervised trials data for difenoconazole uses on oranges, pome fruits (apple, pear), stone fruits (cherries, peach, plum), grapes, olives, tropical fruits (banana, mango, papaya), bulb vegetables (garlic, leek), Brassica vegetables (broccoli, Brussels sprouts, cabbages, cauliflower), watermelon, fruiting vegetables (chilli peppers, tomatoes), lettuce, soya beans, root and tuber vegetables (carrot, potato, sugar beet), stalk and stem vegetables (asparagus, celeriac, celery), cereal grains (rice, wheat) and oilseeds (rape seed, sunflower seed). Residue data were also provided on wheat straw and fodder, rice straw and fodder, sugar beet leaves and tops, oilseed rape fodder and sunflower plant and stubble.

In trials where duplicate field samples from an unreplicated plot were taken at each sampling time and analysed separately, the mean of the two results was taken as the best estimate of the residue from the plot.

Labels (or translations of labels) were available from Australia, Belgium, Brazil, Central America (Belize, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua,

Panama), France, Germany, Indonesia, Italy, Poland, Spain, Switzerland and UK describing the registered uses of difenoconazole.

Citrus fruits

In Brazil, difenoconazole may be applied to citrus trees twice at a spray concentration of 0.005 kg ai/hL with a 30 days PHI. In two trials in Brazil matching GAP and two others with a spray concentration of 0.01 kg ai/ha, difenoconazole residue levels were < 0.05 mg/kg.

The number of trials was insufficient for an orange MRL recommendation.

Pome fruit

Spanish GAP allows five applications of difenoconazole to apple or pear trees at 0.075 kg ai/ha with a PHI of 14 days. In three trials from Spain, matching GAP, difenoconazole residues in apples were 0.10, 0.14 and 0.15 mg/kg.

In two apple trials from France with application parameters matching Spanish GAP, difenoconazole residues were 0.11 and 0.28 mg/kg.

In two trials from Greece, also with application parameters matching Spanish GAP, difenoconazole residues were 0.05 and 0.13 mg/kg.

In two trials from Italy also with application conditions matching Spanish GAP, difenoconazole residues were 0.06 and 0.08 mg/kg.

In one pear trial from France and one from Greece, matching Spanish GAP, difenoconazole residues in pears were 0.07 and 0.16 mg/kg, respectively.

The Meeting decided to combine the apple and pear data to support a pome fruit MRL. Residues in the 11 trials in ranked order (median underlined) were: 0.05, 0.06, 0.07, 0.08, 0.10, <u>0.11</u>, 0.13, 0.14, 0.15, 0.16 and 0.28 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in pome fruit of 0.5, 0.11 and 0.28 mg/kg respectively.

Stone fruits

Polish GAP allows 3 applications of difenoconazole to cherry trees at 0.05 kg ai/ha with a PHI of 14 days.

In a cherry trial from France and two from Germany, with application conditions matching Polish GAP, difenoconazole residues in cherries were 0.08, 0.06 and 0.10 mg/kg, respectively.

Italian GAP allows 3 applications of difenoconazole to peach trees with a spray concentration of 0.0075 kg ai/hL with a PHI of 7 days. In five Italian trials matching Italian GAP, difenoconazole residues on peaches were 0.07, 0.11, 0.14, 0.14 and 0.19 mg/kg.

In a peach trial from France and two from Greece with application conditions matching Italian GAP, difenoconazole residues in peaches were 0.18, 0.16 and 0.26 mg/kg, respectively.

In summary, the difenoconazole residues on peaches from eight trials (in ranked order, median underlined) were: 0.07, 0.11, 0.14, <u>0.14</u>, <u>0.16</u>, 0.18, 0.19 and 0.26 mg/kg.

French GAP allows 3 applications of difenoconazole to plum trees with a spray concentration of 0.005 kg ai/hL with a PHI of 14 days. In four French trials matching GAP (accepted variation on spray concentration 0.0035–0.0065 kg ai/hL) difenoconazole residues on plums were 0.02, 0.03, 0.07 and 0.10 mg/kg.

In four German trials on plums with application conditions matching French GAP (accepted variation on spray concentration 0.0035–0.0065 kg ai/hL), difenoconazole residues were < 0.01, 0.01, 0.02 and 0.04 mg/kg.

In two Spanish trials on plums with application parameters matched French GAP, difenoconazole residues were 0.03 and 0.08 mg/kg.

In summary, the difenoconazole residues on plums from 10 trials were: < 0.01, 0.01, 0.02, 0.02, 0.03, 0.03, 0.04, 0.07, 0.08 and 0.10 mg/kg.

The data from the peaches and plums were apparently of different populations and could not be combined.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in peaches of 0.5, 0.15 and 0.26 mg/kg respectively. These values may also be used for nectarines.

The data from plums and cherries were combined for mutual support, residues in 13 trials in ranked order (median underlined) were: < 0.01, 0.01, 0.02, 0.02, 0.03, 0.03, 0.04, 0.06, 0.07, 0.08, 0.08, 0.10 and 0.10 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in plums and cherries of 0.2, 0.04 and 0.10 mg/kg respectively.

Grapes

Italian GAP allows 4 applications of difenoconazole to grape vines with a spray concentration of 0.005 kg ai/hL with a PHI of 21 days. In six Italian trials from 2003–2004 matching GAP, difenoconazole residues on grapes were 0.01, 0.02, 0.02, 0.03, 0.03 and 0.04 mg/kg. In two French trials matching Italian GAP, residues in grapes were 0.04 and 0.07 mg/kg.

In summary, the difenoconazole residues on grapes from eight trials in ranked order (median underlined) were: 0.01, 0.02, 0.02, 0.03, 0.03, 0.04, 0.04 and 0.07 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in grapes of 0.1, 0.03 and 0.07 mg/kg respectively.

Olives

In Spain, difenoconazole may be applied to olive trees three times at a spray concentration of 0.015 kg ai/hL with a 30 days PHI. In seven trials in Spain in 2003–2005 matching GAP, difenoconazole residue levels were 0.22, 0.29, 0.40, 0.42, 0.51, 0.90 and 1.2 mg/kg.

In an olive trial in France with application conditions matching Spanish GAP, difenoconazole residues on olives were 0.76 mg/kg.

In summary, difenoconazole residues in olives from eight trials in ranked order (median underlined) were: 0.22, 0.29, 0.40, 0.42, 0.51, 0.76, 0.90 and 1.2 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in olives of 2, 0.465 and 1.2 mg/kg respectively.

Bananas

In Costa Rica, Guatemala and Honduras difenoconazole may be applied 8 times to bananas at 0.1 kg ai/ha with harvest permitted on the day of application. The use pattern includes aerial application.

In the banana trials in 1997 in Ecuador, Colombia and Honduras, unbagged fruit were chosen for study although these cropping conditions, approved as GAP, rarely occur in commercial banana

production. The trials of 1993 in Costa Rica and Guatemala included both bagged and unbagged fruits. For the purposes of estimating an MRL, only data from unbagged fruit are considered in this case.

In three banana trials in Colombia with conditions matching the GAP of Costa Rica, residues of difenoconazole in whole fruit were < 0.02, 0.02 and 0.04 mg/kg, with residues in pulp all at < 0.02 mg/kg.

In two banana trials in Costa Rica with conditions matching GAP, difenoconazole in whole fruit were 0.03 and 0.04 mg/kg, with residues in pulp both at < 0.02 mg/kg.

In three banana trials in Ecuador with conditions matching the GAP of Costa Rica, difenoconazole in whole fruit were all < 0.02 mg/kg, with residues in pulp also all at < 0.02 mg/kg.

In one banana trial from Guatemala with conditions matching the GAP of Costa Rica, difenoconazole in whole fruit were 0.07 mg/kg, with residues in pulp at < 0.02 mg/kg.

In three banana trials in Honduras with conditions matching the GAP of Costa Rica, difenoconazole in whole fruit were < 0.02, < 0.02 and 0.03 mg/kg, with residues in pulp also all at < 0.02 mg/kg.

In summary, difenoconazole residues in whole bananas from the 12 unbagged trials were: < 0.02 (5), 0.02, 0.02, 0.03, 0.03, 0.04, 0.04 and 0.07 mg/kg. Residues in banana pulp were all < 0.02 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in bananas of 0.1, 0.02 and 0.02 mg/kg respectively.

Mango

In Brazil, difenoconazole may be applied to mango trees three times at a spray concentration of 0.0125 kg ai/hL with a 7 days PHI. In four trials in Brazil in 2003 matching GAP, difenoconazole residues in mango whole fruits were 0.025, 0.025, 0.035 and 0.04 mg/kg. No data were available for residues in edible portion.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in mangos of 0.07, 0.03 and 0.04 mg/kg respectively.

Papaya

In Brazil, difenoconazole may be applied to papayas four times at a spray concentration of 0.0075 kg ai/hL with a 14 days PHI. In four trials in Brazil in 2002 matching GAP, difenoconazole residues in papaya whole fruits were 0.02, 0.03, 0.07 and 0.10 mg/kg and residues in edible portion were all < 0.01 mg/kg. In four trials where the spray concentration was 0.015 kg ai/hL (2 × label) residues in whole papaya fruit were 0.09, 0.09 0.12 and 0.20 mg/kg and residues in edible portion were < 0.01 (3) and 0.02 mg/kg, suggesting residues could occur in the edible portion, i.e., not a nil residue.

The double rate trials provided additional support, particularly in cases such as this for difenoconazole where the residue is generally external and essentially non-systemic.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in papaya of 0.2, 0.01 and 0.02 mg/kg respectively.

Garlic

In Brazil, difenoconazole may be applied to garlic crops six times at a rate of 0.13 kg ai/ha with a 14 days PHI. In four trials in Brazil in 1995 with 6 applications of 0.19 or 0.38 kg ai/ha (1.5 × and 3 ×

label rates), difenoconazole residues in bulbs of garlic were all < 0.02 mg/kg at PHIs of approximately 0, 7, 14 and 21 days.

Data from the exaggerated rates and various sampling intervals suggest that difenoconazole residues do not reach garlic bulbs.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in garlic of 0.02*, 0 and 0 mg/kg respectively.

Leeks

In Germany, difenoconazole may be applied to leek crops 3 times at a rate of 0.1 kg ai/ha with a 21 days PHI. In four trials in Germany with application in line with GAP, difenoconazole residues in whole plants with roots removed were 0.02, 0.07, 0.09 and 0.12 mg/kg.

In four leek trials in France with conditions matching German GAP, difenoconazole residues in whole plants were 0.03, 0.05, 0.13 and 0.21 mg/kg.

In two leek trials from Italy with conditions matching German GAP, difenoconazole residues in whole plants were 0.14 and 0.17 mg/kg.

In two leek trials from Switzerland with conditions matching German GAP, difenoconazole residues in edible portions were 0.02 and 0.04 mg/kg.

The Meeting accepted that the three descriptions of the commodity analysed, i.e., (1) whole plants with roots removed, (2) whole plants and (3) edible parts, were all intended to agree with the Codex description of the commodity for analysis: *Whole vegetable after removal of roots and adhering soil*.

In summary, difenoconazole residue in leeks from the 12 trials, in rank order (median underlined), were: 0.02, 0.02, 0.03, 0.04, 0.05, <u>0.07</u>, <u>0.09</u>, 0.12, 0.13, 0.14, 0.17 and 0.21 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in leeks of 0.3, 0.08 and 0.21 mg/kg respectively.

Broccoli

In Belgium, difenoconazole may be applied twice to broccoli at a rate of 0.13 kg ai/ha with a 14 days PHI. In trials in France, Netherlands and Spain, difenoconazole was applied 3 times rather than twice. Difenoconazole is a reasonably persistent residue as found in the decline trials with residue remaining on the whole plant just prior to the final application. However, carryover on the flower heads is not expected as they were unlikely to be formed at the time of the first application.

In four broccoli trials in France with conditions matching Belgian GAP, except for 3 applications instead of 2, difenoconazole residues in flower heads on days 13–15 after the final application were 0.02, 0.05, 0.08 and 0.10 mg/kg.

In two broccoli trials from The Netherlands, with conditions matching Belgian GAP except for 3 applications instead of 2, difenoconazole residues in flower heads on day 14 after the final application were < 0.02 and 0.03 mg/kg.

In two broccoli trials in Spain, with conditions matching Belgian GAP except for 3 applications instead of 2, difenoconazole residues in flower heads on day 14 and day 21 (higher residues than on day 14) after the final application were 0.41 and 0.15 mg/kg.

In summary, difenoconazole residue in broccoli flower heads from the eight trials, in ranked order (median underlined), were: 0.02, 0.02, 0.03, <u>0.05</u>, <u>0.08</u>, 0.10, 0.15 and 0.41 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in broccoli of 0.5, 0.065 and 0.41 mg/kg respectively.

Brussels sprouts

In France, difenoconazole may be applied to Brussels sprouts 3 times at a rate of 0.13 kg ai/ha with a 21 days PHI.

In four Brussels sprouts trials from Belgium in 1999, with conditions in line with French GAP, difenoconazole residues in buttons on days 20–21 and 28 (higher residues than on day 21) after the final application were 0.02, 0.05, 0.07 and 0.09 mg/kg.

In eight Brussels sprouts trials in the UK, with conditions matching French GAP, difenoconazole residues in buttons on days 21–22 after the final application were 0.04, 0.05, 0.05, 0.06, 0.07, 0.08, 0.10 and 0.14 mg/kg.

In summary, difenoconazole residues in Brussels sprouts buttons from the 12 trials, in ranked order (median underlined), were: 0.02, 0.04, 0.05, 0.05, 0.05, 0.06, 0.07, 0.07, 0.08, 0.09, 0.10 and 0.14 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in Brussels sprouts of 0.2, 0.065 and 0.14 mg/kg respectively.

Cabbage

In France, difenoconazole may be applied to cabbage 3 times at a rate of 0.13 kg ai/ha with a 21 days PHI. In six trials from France, with application parameters in line with GAP, difenoconazole residues in cabbage heads were < 0.01 (2), 0.01, < 0.02 and < 0.05 (2) mg/kg.

In Germany, difenoconazole may be applied to cabbage 3 times at a rate of 0.1 kg ai/ha with a 21 days PHI. In two trials in Germany, with trial parameters in line with GAP, difenoconazole residues in cabbage heads were < 0.02 (2) mg/kg.

In five cabbage trials in Belgium in 1999, with conditions in line with French GAP, difenoconazole residues in cabbage heads on day 21 after the final application were < 0.02 (5) mg/kg.

In two cabbage trials in Germany in 2003, with conditions in line with French GAP, difenoconazole residues in cabbage heads on day 21 after the final application were < 0.02 and 0.19 mg/kg.

In two cabbage trials in The Netherlands in 2002, with conditions in line with French GAP, difenoconazole residues in cabbage heads on day 21 after the final application were < 0.02 (2) mg/kg.

In three cabbage trials in UK in 1990 with conditions in line with French GAP, difenoconazole residues in cabbage hearts on day 21 after the final application were 0.06, 0.10 and 0.13 mg/kg. The Meeting accepted that cabbage "hearts" meant the same as cabbage "heads".

In summary, difenoconazole residues in cabbages from the 20 trials, in rank order (median underlined), were: < 0.01 (3), 0.01, < 0.02 (10), < 0.05 (2), 0.06, 0.10, 0.13 and 0.19 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in head cabbage of 0.2, 0.035 and 0.19 mg/kg respectively.

Cauliflowers

In France, difenoconazole may be applied to cauliflowers 3 times at a rate of 0.13 kg ai/ha with a 14 days PHI. In 12 trials from France matching GAP, difenoconazole residues in the flower heads were 0.01, < 0.02 (9), 0.03 and 0.10 mg/kg.

In a cauliflower trial in Switzerland in 2005, with conditions in line with French GAP, difenoconazole residues in flower heads on day 14 after the final application were < 0.01 mg/kg.

In two cauliflower trials in the UK in 1999 and 2005, with conditions matching French GAP, difenoconazole residues in flower heads on day 14 after the final application were < 0.02 and 0.02 mg/kg.

In summary, difenoconazole residues in cauliflowers from the 15 trials, in ranked order (median underlined), were: < 0.01, 0.01, < 0.02 (10), 0.02, 0.03 and 0.10 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in cauliflowers of 0.2, 0.02 and 0.10 mg/kg respectively.

Watermelons

Residue data were available only on the edible portion of the watermelons in the four trials provided, so estimation of an MRL was not possible.

Chilli peppers

In Indonesia, difenoconazole may be applied at 7 day intervals to chilli pepper crops at a spray concentration of 0.0063–0.013 kg ai/hL with no required PHI.

One trial from Indonesia matched GAP for maximum spray concentration with harvest on day 6 after treatment. A second Indonesian trial used a spray concentration of 0.025 kg ai/hL (2 × label rate). One trial from Malaysia matched Indonesian GAP for maximum spray concentration and harvest on the day of treatment. A second Malaysian trial used a spray concentration of 0.025 kg ai/hL (2 × label rate).

The Meeting agreed that, for a minor use, a minimum of three trials matching GAP conditions is needed. The Meeting was not able to recommend a maximum residue level for difenoconazole residues in chilli peppers.

Tomatoes

In Italy, difenoconazole may be applied to tomato crops 4 times at a rate of 0.13 kg ai/ha with a 7 days PHI.

In two tomato trials (glasshouse and polytunnel) in France in 2005, with conditions in line with Italian GAP, difenoconazole residues in tomatoes on day 7 after the final application were 0.04 and 0.05 mg/kg.

In five tomato trials (field) in Greece in 2001–2003, with conditions in line with Italian GAP, difenoconazole residues in tomatoes on day 7 and 10 (higher residues than on day 10) after the final application were 0.10, 0.13, 0.18, 0.28 and 0.36 mg/kg.

In a tomato trial (glasshouse) in UK in 2005, with conditions in line with Italian GAP, difenoconazole residues in tomatoes on day 7 after the final application were 0.10 mg/kg.

In two tomato trials (field) in Spain in 2003, with conditions in line with Italian GAP, difenoconazole residues in tomatoes on day 7 after the final application were 0.03 and 0.09 mg/kg.

In a tomato trial (polytunnel) in Spain in 2005, with conditions in line with Italian GAP, difenoconazole residues in tomatoes on day 7 after the final application were 0.12 mg/kg.

In summary, difenoconazole residues in tomatoes from the field trials were: 0.03, 0.09, 0.10, 0.13, 0.18, 0.28 and 0.36 mg/kg; and from protected trials were: 0.04, 0.05, 0.10, and 0.12 mg/kg. The data appear to be from similar populations and can be combined.

In summary, difenoconazole residues in tomatoes from the 11 trials, in ranked order (median underlined), were: 0.03, 0.04, 0.05, 0.09, 0.10, 0.10, 0.12, 0.13, 0.18, 0.28 and 0.36 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in tomatoes of 0.5, 0.10 and 0.36 mg/kg respectively.

Lettuce

In Spain, the registration document states that difenoconazole is registered for use on lettuce at a rate of 0.13–0.20 kg ai/ha with a 14 days PHI. The maximum application rate on the available label was 0.13 kg ai/ha. The Meeting agreed to use the GAP from the registration document.

In eight lettuce trials from Spain in 1991 and 2003 with application rates of 0.17–0.18 kg ai/ha (within 30% of GAP rate) the residues 13–14 days after the final application, in ranked order (median underlined), were: 0.07, 0.08, 0.29, 0.31, 0.51, 0.56, 0.65 and 1.0 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in head lettuce and leaf lettuce of 2, 0.41 and 1.0 mg/kg respectively.

Soya beans

In Brazil, difenoconazole may be applied to soya bean crops once at a rate of 0.075 kg ai/ha with a 30 days PHI. In six soya bean trials in 2000 and 2003 in Brazil with conditions in line with GAP, except that there were 2 applications in place of 1, difenoconazole residues in the dry beans on day 30 and 31 after the final application were < 0.01 (3) and < 0.02 (3) mg/kg.

The Meeting estimated a maximum residue level and an STMR value for difenoconazole in soya beans of 0.02* and 0.02 mg/kg respectively.

Carrots

In France, difenoconazole may be applied to carrot crops 3 times at a rate of 0.13 kg ai/ha with a 14 days PHI. In nine carrot trials in 1991–1993, 1996 and 2000 in France, with conditions in line with GAP, difenoconazole residues in the carrots on days 14 or 15 after the final application were 0.02, 0.02, 0.03, 0.03, 0.04, 0.05, 0.07, 0.11 and 0.13 mg/kg.

In two carrot trials in 1987 in Switzerland, with conditions in line with French GAP, difenoconazole residues in carrots on day 14 after the final application were 0.07 and 0.12 mg/kg.

In summary, difenoconazole residues in carrots from the 11 trials, in rank order (median underlined), were: 0.02, 0.02, 0.03, 0.03, 0.04, 0.05, 0.07, 0.07, 0.11, 0.12 and 0.13 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in carrots of 0.2, 0.05 and 0.13 mg/kg respectively.

Potatoes

In Spain, difenoconazole may be applied to potato crops 4 times at a rate of 0.2 kg ai/ha with a 30 days PHI. In seven potato trials in 2003 and 2005 in Spain with conditions in line with GAP except that only 2 applications were made, difenoconazole residues in the potato tubers on days 27–31 after the second and final application were < 0.01 (6) and 0.01 mg/kg.

In a trial in 2005 in Italy with the application rate in line with Spanish GAP, difenoconazole residues in potato tubers on day 29 after the second application were < 0.01 mg/kg.

The potato metabolism studies suggest that parent difenoconazole residues in tubers should be below LOQ. However, residues might be occasionally expected in tubers with surface exposure to spray application.

In summary, difenoconazole residues in potatoes from the eight trials, in rank order (median underlined), were: < 0.01 (7), 0.01 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in potatoes of 0.02, 0.01 and 0.01 mg/kg respectively.

Sugar beet

In Germany, difenoconazole may be applied to sugar beet crops twice at a rate of 0.1 kg ai/ha with a 28 days PHI. In 14 sugar beet trials in 1987–88 and 1995-96 in Germany with conditions in line with GAP except that in some trials 3 applications were made, difenoconazole residues in the sugar beet roots on days 27–30, or later if higher residues, after the second application were < 0.02 (4), 0.02 (4), 0.03, 0.03, 0.06, 0.08, 0.08 and 0.10 mg/kg.

In three sugar beet trials in 1985 and 1991 in France, with conditions in line with German GAP, difenoconazole residues in sugar beet tubers on days 25, 29 and 33 after the second application were all < 0.02 mg/kg.

In a sugar beet trial in Denmark with conditions matching German GAP, difenoconazole residue in sugar beet root 37 days after the second application was 0.08 mg/kg.

In a sugar beet trial in the UK with conditions matching German GAP, difenoconazole residue in sugar beet root 35 days after the second application was 0.08 mg/kg.

In summary, difenoconazole residues in sugar beet from the 19 trials, in ranked order (median underlined), were: 0.01, < 0.02 (7), <u>0.02</u> (4), 0.03, 0.033, 0.06, 0.08, 0.08, 0.08 and 0.10 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for difenoconazole in sugar beet of 0.2 and 0.02 mg/kg respectively.

Asparagus

In France, difenoconazole may be applied to asparagus crops 3 times at 0.13 kg ai/ha. In asparagus crops protected by 6 to 8 applications of fungicide per year, the difenoconazole product should be used for the first three treatments and other products that act in a different way should be used to complete the season.

In four asparagus trials in France, two in Italy and two in Switzerland where difenoconazole was applied 4–8 times at 0.13 kg ai/ha and asparagus shoots were harvested for analysis 179–290 days later (approximating French GAP), the resulting difenoconazole residues were < 0.02 (7) and 0.02 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in asparagus of 0.03, 0.02 and 0.02 mg/kg respectively.

Celeriac

In Belgium, difenoconazole may be applied to celeriac 4 times at a rate of 0.13 kg ai/ha with a 14 days PHI. In three Belgian trials matching GAP, difenoconazole residues in celeriac roots 15 days after the final treatment were 0.08, 0.12 and 0.22 mg/kg.

The Meeting acknowledged that celeriac is a minor crop and decided to estimate an MRL based on the three trials. The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in celeriac of 0.5, 0.12 and 0.22 mg/kg respectively.

Celery

In France, difenoconazole may be applied to celery crops 4 times at a rate of 0.13 kg ai/ha with a 14 days PHI.

The Codex description of the sample to be analysed is: "*Whole commodity as marketed after removal of obviously decomposed or withered leaves."* For celery, the commodity marketed is usually

trimmed celery, i.e., most foliage removed. In a number of the celery trials, leaf and stems had been detached and analysed separately. The Meeting agreed to use the stem data where stems and leaf were analysed separately.

In four celery trials in 2003–04 in France, with conditions in line with GAP, difenoconazole residues in celery stems on day 14 after the final application were 0.03, 0.04, 0.14 and 0.26 mg/kg.

In two celery trials in 1990 in Italy, with conditions in line with French GAP, difenoconazole residues in celery edible parts and celery stems on day 14 after the final application were 1.2 and 2.0 mg/kg respectively.

In two celery trials in 2004 in Spain and one in Switzerland in 1988, with conditions in line with French GAP, difenoconazole residues in celery stems on day 14 after the final application were 0.04, 0.05 and 0.17 mg/kg. Data from a second trial in Switzerland were not used because difenoconazole residues (0.02 mg/kg) in a sample from the control plot were significant with respect to the residue (0.058 mg/kg) in the treated plot.

In summary, difenoconazole residues in celery from the nine trials, in ranked order (median underlined), were: 0.03, 0.04, 0.04, 0.05, <u>0.14</u>, 0.17, 0.26, 1.2 and 2.0 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in celery of 3, 0.14 and 2.0 mg/kg respectively.

Rice

In Indonesia, difenoconazole may be applied to rice at 0.050 to 0.10 kg ai/ha, with one application at the mid booting stage (45 days after sowing) and one at the 75% flowering stage (approximately 60 days after sowing). These growth stages are interpreted as equivalent to BBCH 43–45 and BBCH 63–67 growth stages.

In two rice trials in Indonesia with application rates of 0.063 kg ai/ha (37% below maximum GAP) and with timing to match GAP, residues in rice grain were 1.3 and 0.75 mg/kg.

In three rice trials in Malaysia with application rates of 0.064–0.075 kg ai/ha and timing to match Indonesian GAP, difenoconazole residues in rice grain harvested 28–30 days after the second application were 0.15, 0.16 and 0.37 mg/kg. In another trial in Malaysia at 0.12 kg ai/ha and with similar timing, residues of difenoconazole in rice grain were 0.76 mg/kg.

In summary, difenoconazole residues in rice grain from the six trials were: 0.15, 0.16, 0.37, 0.75, 0.76 and 1.3 mg/kg.

The Meeting decided that six trials (some at application rates not close enough to maximum GAP) were insufficient for a major commodity such as rice and did not estimate a maximum residue level.

Wheat

In Switzerland, difenoconazole may be applied once to wheat crops at a rate of 0.13 kg ai/ha up to growth stage BBCH 61.

In three wheat trials in Denmark, three in France and one in Switzerland where the difenoconazole was applied at 0.13 kg ai/ha up to growth stage BBCH 61, residues of difenoconazole in wheat grain were all < 0.02 mg/kg.

In nine wheat trials in France and seven in the UK, where the difenoconazole was applied at 0.12–0.15 kg ai/ha from growth stages BBCH 61 to 87, residues of difenoconazole in wheat grain were also all < 0.02 mg/kg.

In summary, difenoconazole residues in wheat grain from the 23 trials were all < 0.02 mg/kg.

The metabolism studies suggest that parent difenoconazole residues should not occur in the grain. The Meeting agreed that the evidence supported an STMR of nil residues in wheat.

The Meeting estimated a maximum residue level and an STMR value for difenoconazole in wheat of 0.02* and 0 mg/kg respectively.

Rapeseed

In the UK, difenoconazole may be applied twice to oilseed rape crops at a rate of 0.13 kg ai/ha up to the end of flowering (growth stage BBCH 69).

In four oilseed rape trials in 1996 in Germany, with conditions in line with GAP of the UK, difenoconazole residues in rape seed on days 56–80 after the second application were all < 0.02 mg/kg.

In three oilseed rape trials in 1997 in Germany with the second of two applications of difenoconazole of 0.13 kg ai/ha at growth stages BBCH 69–75, i.e., later than approved in UK GAP, difenoconazole residues in rape seed on days 55–56 after the second application were all < 0.02 mg/kg.

In two oilseed rape trials in 1988 in France with two applications of difenoconazole of 0.13 kg ai/ha and harvest 83 days after the second application (probably before end of flowering), i.e., within the conditions of UK GAP, difenoconazole residues in rape seed were both 0.04 mg/kg.

In summary, difenoconazole residues in rape seed from the nine trials, in ranked order (median underlined), were: < 0.02 (7), 0.04 and 0.04 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for difenoconazole in rape seed of 0.05 and 0.02 mg/kg respectively.

Sunflower seed

In Switzerland, difenoconazole may be applied once to sunflower crops at a rate of 0.13 kg ai/ha up to growth stage BBCH 51. In three trials on sunflower in 2004–2005 in Switzerland according to the conditions of GAP, except that 2 applications were made instead of 1, difenoconazole residues in sunflower seed, harvested 68–73 days after the second application were all < 0.01 mg/kg.

In six sunflower trials in 2004–05 in France, with conditions matching Swiss GAP, except for 2 applications instead of 1, difenoconazole residues in sunflower seed harvested 59–101 days after the second application were < 0.01 (5) and 0.01 mg/kg.

In two sunflower trials in 2005 in Spain with conditions matching Swiss GAP, except for 2 applications instead of 1, difenoconazole residues in sunflower seed harvested 74 and 87 days after the second application were both < 0.01 mg/kg.

In summary, difenoconazole residues in sunflower seed from the 11 trials, in ranked order (median underlined), were: < 0.01 (10), 0.01 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for difenoconazole in sunflower seed of 0.02 and 0.01 mg/kg respectively.

Wheat straw and fodder

In Switzerland, difenoconazole may be applied once to wheat crops at a rate of 0.13 kg ai/ha up to growth stage BBCH 61. In a Swiss trial on wheat in 1989 with conditions matching GAP, difenoconazole residues in wheat straw harvested 45 days after the single application were 1.2 mg/kg.

In three wheat trials in 1989–1990 in Denmark with conditions in line with Swiss GAP, difenoconazole residues in wheat straw on days 57, 58 and 75 after the single application were 0.26, 0.64 and 0.31 mg/kg.

In two wheat trials in 1989 in France, with conditions in line with Swiss GAP, difenoconazole residues in wheat straw on days 57 and 63 after the single application were 0.73 and 0.82 mg/kg.

In summary, difenoconazole residues in wheat straw from the six trials, in ranked order (median underlined), were: 0.26, 0.31, 0.64, 0.73, 0.82 and 1.2 mg/kg.

The Meeting estimated a maximum residue level, an STMR value and a highest residue value for difenoconazole in wheat straw and fodder of 3, 0.685 and 1.2 mg/kg respectively.

Sugar beet leaves or tops

In Germany, difenoconazole may be applied to sugar beet crops twice at a rate of 0.1 kg ai/ha with a 28 days PHI. In 14 sugar beet trials in 1987–1988 and 1995–1996 in Germany with conditions in line with GAP except that in some trials 3 applications were made, difenoconazole residues in the sugar beet leaves or tops on days 27–30 after the second application were 0.084, 0.087, 0.09, 0.11, 0.20, 0.25, 0.25, 0.26, 0.43, 0.43, 0.47, 0.53, 0.62 and 0.95 mg/kg.

In a sugar beet trial in 1985 in France, with conditions in line with German GAP, difenoconazole residues in sugar beet leaves 24 days after the second application were 0.17 mg/kg.

In a sugar beet trial in Denmark with conditions matching German GAP, difenoconazole residues in sugar beet leaves 37 days after the second application were 0.45 mg/kg.

In a sugar beet trial in the UK, with conditions matching German GAP, difenoconazole residues in sugar beet leaves 27 days after the second application were 0.09 mg/kg.

In summary, difenoconazole residues in sugar beet leaves or tops from the 17 trials in ranked order (median underlined), were: 0.084, 0.087, 0.09, 0.09, 0.11, 0.17, 0.20, 0.25, 0.25, 0.26, 0.43, 0.43, 0.45, 0.47, 0.53, 0.62 and 0.95 mg/kg.

The Meeting estimated an STMR value and a highest residue value for difenoconazole in sugar beet leaves or tops of 0.25 and 0.95 mg/kg (fresh weight), respectively.

Fate of residues during processing

The Meeting received information on the fate of difenoconazole residues during the processing of apples for juice, carrots for juice and canning, grapes for wine and dried grapes, olives for oil, rape seed for oil, sugar beet for sugar and molasses, and tomatoes for juice and puree. Also information was provided on hydrolysis studies of difenoconazole to assist with identification of the nature of the residue during processing.

Processing factors have been calculated for difenoconazole residues in apples, carrots, grapes, olives and tomatoes. The data for rape seed and sugar beet could not be used as residue levels in the raw commodity did not exceed the LOQ.

Difenoconazole was stable under the hydrolysis conditions (pH, temperature, time) representing the food processes pasteurisation, baking, brewing and boiling and sterilisation.

Apples from difenoconazole field trials at exaggerated application rates were washed, sliced and pressed to separate pomace from juice. The juice was pasteurised at 80–82 °C for 30 minutes. Puree was produced by boiling washed apples until the puree passed through a sieve. Sugar, citric acid and ascorbic acid were added until the puree reached a pH of 3.0–4.5 and then was heated at 95 °C for 20 minutes.

In a grape drying trial in Chile, grapes were harvested 63 days after the third of 3 applications of difenoconazole at 1 × and 5 × the label rate. The grapes were washed for about one minute and then placed in wooden trays with mesh bottoms and subjected to sulphur dioxide fumigation for 12 h. The trays of grapes were then dried in ovens at 65 °C for about 36–40 h losing approximately two-thirds of their weight, 30 kg grapes producing 10 kg dried grapes.

Wine was produced from grapes in a series of supervised field trials in France and Spain. Difenoconazole residues appeared in the pomace, but not in the wine. In grape trials in Chile, difenoconazole residues appeared in the pomace, but not in the juice.

Olives from a difenoconazole field trial at an exaggerated rate (2 ×) were processed into virgin oil and refined oil. The virgin oil was separated by centrifuging the mixture of olive pulp (from milling) and added water. The oil was refined by a sodium hydroxide process to produce soap from free acids. Residue levels in virgin and refined oil were essentially the same.

In a tomato processing trial in France, tomatoes were harvested 7 days after the final of 3 applications of difenoconazole at 0.37 kg ai/ha. In processing to juice, unwashed tomatoes were crushed and sieved to produce juice and pomace. Finished juice was produced by pasteurization for 1 minute at 82–85 °C after citric acid and salt were added to raw juice. In the production of puree, unwashed tomatoes were crushed and concentrated in a saucepan and then sieved. Salt and citric acid were added and the puree, in glass jars, was sterilised for 10 minutes at 115 °C. In the simulation of canning, unwashed tomatoes were blanched and then immediately plunged into cold water to split and loosen the peel which was removed with a knife. The peeled tomatoes, in glass jars, were covered with tomato juice and sterilised for 10 minutes at 115–120 °C.

In a carrot processing trial in France, carrots were harvested 7 days after the final of 3 difenoconazole applications at 0.50 kg ai/ha. In the simulation of canning, carrots were sorted and peeled with both ends removed. The peeled carrots were washed thoroughly and blanched in boiling water for 1 minute and placed in jars with brine and added citric acid to produce a pH of 3.5 and then sealed and sterilized for 10 minutes at 115–120 °C. For cooked carrots, the washed carrots were cooked in boiling water for 15 minutes and packaged in plastic bags under vacuum. For juicing, carrots were washed thoroughly after sorting, peeling and end removal and were then processed in a juice extractor which separated juice from pulp in a centrifugal filter. After the pH of the juice was adjusted to 3.5 with citric acid, the juice was pasteurized at approximately 85 °C and packaged in glass jars.

Calculated processing factors and the median or best estimate are summarized in the following table.

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors.	Median or best estimate
Apple	juice	< 0.02, < 1.0. < 1.0	< 0.02
Apple	dry pomace	15.4	15
Apple	puree	0.14	0.14
Carrot	canned	0.02, 0.03, 0.05, 0.12	0.04
Carrot	juice	0.02, 0.05, 0.06, 0.12	0.055
Grapes	juice	< 0.5	< 0.5
Grapes	dry pomace	9.3, 10.3, 14.0, 15.4	12
Grapes	dried grapes	1.01, 1.4	1.2
Grapes	wine	< 0.18, < 0.20, < 0.20, < 0.29, < 0.33, < 0.33, < 0.33, < 0.50, < 0.50, < 0.50, < 0.50	< 0.18
Olives	refined oil	1.19, 1.40, 1.50, 1.51	1.4
Olives	virgin oil	1.47, 1.50, 1.50, 1.63	1.5
Tomatoes	canned tomato	< 0.05, 0.06, 0.07, 0.08	0.065
Tomatoes	juice	0.14, 0.15, 0.28, 0.32	0.22
Tomatoes	puree	0.54, 0.58, 0.74, 1.00	0.66

The processing factors for dry apple pomace (15), apple juice (< 0.02) and apple puree (0.14) were applied to the estimated STMR for pome fruits (0.11 mg/kg) to produce STMR-P values for dry apple pomace (1.65 mg/kg), apple juice (0.0022 mg/kg) and apple puree (0.015 mg/kg).

The processing factors for dry grape pomace (12), grape juice (< 0.5) and wine (< 0.18) were applied to the estimated STMR for grapes (0.03 mg/kg) to produce STMR-P values for dry grape pomace (0.36 mg/kg), grape juice (0.015 mg/kg) and wine (0.0054 mg/kg).

The processing factor for dried grapes (1.2) was applied to the estimated STMR and HR for grapes (0.03 and 0.07 mg/kg) to produce STMR-P and HR-P values for dried grapes (raisins) of 0.036 and 0.084 mg/kg respectively.

The Meeting estimated a maximum residue level for difenoconazole in dried grapes (= currants, raisins, sultanas) of 0.1 mg/kg. The estimated maximum residue level is the same as for grapes, so no separate MRL recommendation is necessary.

The processing factors for canned carrots (0.04) and carrot juice (0.055) were applied to the estimated STMR for carrots (0.05 mg/kg) to produce STMR-P values for canned carrots (0.002 mg/kg) and carrot juice (0.0028 mg/kg).

The processing factors for tomato puree (0.66), tomato juice (0.22) and canned tomato (0.065) were applied to the estimated STMR for tomatoes (0.10 mg/kg) to produce STMR-P values for tomato puree (0.066 mg/kg), tomato juice (0.022 mg/kg) and canned tomato (0.0065 mg/kg).

The processing factors for virgin olive oil (1.5) and refined olive oil (1.4) were applied to the estimated STMR for olives (0.465 mg/kg) to produce STMR-P values for virgin olive oil (0.70 mg/kg) and refined olive oil (0.65 mg/kg)

Residues in animal commodities

Livestock feeding

The meeting received lactating dairy cow feeding studies and a laying hen feeding study, which provided information on likely residues resulting in animal commodities, milk and eggs from difenoconazole residues in the animal diet.

Lactating dairy cows

Groups of 3 lactating Holstein dairy cows were dosed once daily via gelatin capsule with difenoconazole at 1 ppm (1 ×), 3 ppm (3 ×) and 10 ppm (10 ×) in the dry-weight diet for 29–30 consecutive days. Parent difenoconazole residues did not occur above LOQ in muscle, kidney or fat tissues or milk for any of the test doses, but were present in liver from the 10 ppm feeding-level group. Metabolite CGA 205375 was present in each of the tissues from the 3 and 10 ppm feeding-level groups and in the liver and fat from the 1 ppm feeding-level animals. The concentration of metabolite CGA 205375 in fat was approximately 3.3 times its concentration in muscle. The average concentrations of metabolite CGA 205375 in the tissues from the 10 ppm feeding-level animals were: muscle 0.020 mg/kg; liver 0.30 mg/kg; kidney 0.044 mg/kg; fat 0.072 mg/kg. For metabolite CGA 205375 in liver, the transfer factors for the 3 feeding levels were reasonably consistent. For fat, the transfer factors for metabolite CGA 205375 apparently decreased as the feeding level increased. For the 10 ppm feeding-level animals, metabolite CGA 205375 was consistently present in the milk from day 2 onwards at 0.005–0.009 mg/kg.

In a second study, groups of 3 lactating Holstein dairy cows were dosed once daily via gelatin capsule with difenoconazole at 1 ppm (1 ×), 5 ppm (5 ×) and 15 ppm (15 ×) in the dry-weight diet for 29–30 consecutive days. Parent difenoconazole residues did not occur above LOQ in muscle, kidney or fat tissues or milk for any of the test doses. Parent difenoconazole residues were present in liver from the 5 and 15 ppm feeding-level groups. Metabolite CGA 205375, the major part of the residue, was present in each of the tissues from the 5 and 15 ppm feeding-level animals and in the liver, kidney and fat from the 1 ppm feeding-level group. In the 15 ppm feeding-level group, the concentration of metabolite CGA 205375 in fat was approximately 3.1 times its concentration in muscle. The average concentrations of metabolite CGA 205375 in the tissues from the 15 ppm feeding-level animals were: muscle 0.04 mg/kg; liver 0.57 mg/kg; kidney 0.11 mg/kg; fat 0.12 mg/kg. For metabolite CGA 205375 in liver, the transfer factors for the 5 ppm and 15ppm feeding levels were close. For fat, the transfer factors for metabolite CGA 205375 were also consistent for the 5 ppm and

15 ppm feeding levels. Metabolite CGA 205375 reached a plateau level in milk of approximately 0.012 mg/kg within 2 days from the 15 ppm feeding-level animals. Metabolite 1,2,4-triazole (not included in the difenoconazole residue definition) was consistently present in the milk from the 5 and 15 ppm feeding levels groups where plateau concentrations in milk of approximately 0.017 mg/kg and 0.04 mg/kg respectively were quickly reached.

The two feeding studies were generally in good agreement of transfer factors. The Meeting decided to use the study with the 1 and 3 ppm feeding levels as most closely bracketing the dietary burdens.

Laying hens

Laying white leghorn hens were fed rations treated with difenoconazole at 0.3 ppm, 1 ppm, 3 ppm and 10 ppm for 28 consecutive days. Parent difenoconazole residues did not occur above LOQ (0.01 mg/kg) in muscle, fat, liver or eggs for any of the test doses. Metabolite CGA 205375 also was not present in the tissues above LOQ (0.01 mg/kg). Average levels of 1,2,4-triazole in the tissues from the 10 ppm feeding-level birds were: skin plus attached fat 0.012 mg/kg; peritoneal fat < 0.005 mg/kg; liver 0.02 mg/kg; muscle 0.022 mg/kg. Metabolite CGA 205375 occurred in eggs from the 1, 3 and 10 ppm feeding-level groups reaching a plateau after approximately 9 days with levels of 0.037 mg/kg and 0.13 mg/kg in eggs from the 3 and 10 ppm feeding-level groups respectively. At the 1 ppm feeding level, CGA 205375 was present in eggs at close to the LOQ (0.01 mg/kg). Metabolite 1,2,4-triazole occurred in eggs from the 1, 3 and 10 ppm feeding-level birds. It reached a plateau after approximately 6 days with plateau levels of 0.007, 0.020 and 0.060 mg/kg in eggs from the 1, 3 and 10 ppm feeding-level birds respectively.

Livestock dietary burden

The Meeting estimated the dietary burden of difenoconazole in livestock 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.

Estimated maximum and mean dietary burdens of livestock

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

	Livestock dietary burden, difenoconazole, ppm of dry matter diet					
	US-Canada		EU		Australia	
	max	mean	max	mean	max	mean
Beef cattle	0.62	0.48	1.85	0.81	1.42	0.9 [2]
Dairy cattle	0.44	0.30	2.10 [1]	0.76 [3]	0.59	0.44
Poultry - broiler	0.01	0.01	0.12	0.05	0.01	0.01
Poultry - layer	0.01	0.01	0.54 [4]	0.20 [5]	0.01	0.01

[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.

Animal commodities, MRL estimation

For MRL estimation, the residues in the animal commodities are the sum of difenoconazole and CGA 205375 (1-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-2-(1,2,4-triazol)-1-yl-ethanol)) expressed as difenoconazole.

Cattle

For MRL estimation, the high residues in the tissues were calculated by interpolating the maximum dietary burden (2.10 ppm) between the relevant feeding levels (1 and 3 ppm) from the dairy cow feeding study and using the highest tissue concentrations from individual animals within those feeding groups.

The STMR values for the tissues were calculated by taking the STMR dietary burden (0.95 ppm) as a proportion of the lowest feeding level (1 ppm) multiplied by the feeding-level residue (mean of the 3 animals).

Residues in the milk were below LOQ (0.005 mg/kg) for all samples from the 1 ppm and 3 ppm feeding groups, so the dietary burdens (2.10 and 0.95 ppm) were taken as a proportion of the 3 ppm to calculate the residues resulting from the dietary burdens.

In the table below, dietary burdens are shown in round brackets (), feeding levels and residue concentrations from the feeding study are shown in square brackets [] and estimated concentrations related to the dietary burdens are shown without brackets.

Dietary burden (ppm) Feeding level [ppm]	Milk	Muscle	Liver	Kidney	Fat
MRL					
	mean	highest	highest	highest	highest
MRL dairy cattle (2.10) [1, 3]	< 0.004 [< 0.005, < 0.005]	0.019 [< 0.01, 0.026]	0.11 [0.051, 0.15]	0.016 [< 0.01, 0.021]	0.028 [0.015, 0.038]
STMR					
	mean	mean	mean	mean	mean
STMR beef cattle (0.95) [0, 1]		< 0.01 [0, < 0.01]	0.043 [0, 0.045]	< 0.01 [0, < 0.01]	0.012 [0, 0.013]
STMR dairy cattle (0.76) [0, 1, 3]	< 0.001 [0, < 0.005, < 0.005)]				

The data from the cattle feeding studies were used to support mammalian meat and milk MRLs.

The Meeting estimated a maximum residue level and an STMR value for difenoconazole in milks of 0.005* and 0.001 mg/kg, respectively. No information was available on the distribution of residue between the fat and non-fat milk fractions.

For muscle, the residue arising from a dietary burden of 2.10 ppm was 0.019 mg/kg, while the residue resulting from a dietary burden of 0.95 ppm was < 0.01 mg/kg. For fat, the residue arising from a dietary burden of 2.10 ppm was 0.028 mg/kg, while the residue resulting from a dietary burden of 0.95 ppm was 0.012 mg/kg.

The Meeting estimated a maximum residue level for difenoconazole in mammalian meat (fat) of 0.05 mg/kg. The Meeting estimated STMR and HR values for meat (fat) of 0.012 and 0.028 mg/kg respectively. The Meeting estimated STMR and HR values for meat (muscle) of 0.01 and 0.019 mg/kg respectively.

For liver, the residue arising from a dietary burden of 2.10 ppm was 0.11 mg/kg, while the residue resulting from a dietary burden of 0.95 ppm was 0.043 mg/kg. The Meeting estimated a

maximum residue level, an STMR value and an HR value for difenoconazole in liver of 0.2, 0.043 and 0.11 mg/kg, respectively.

For kidney, the residue arising from a dietary burden of 2.10 ppm was 0.016 mg/kg, while the residue resulting from a dietary burden of 0.95 ppm was < 0.01 mg/kg. Although the residue levels in kidney were somewhat below those in liver, the Meeting decided that it was preferable to have an offal MRL which would be supported by the liver data.

The Meeting estimated a maximum residue level, an STMR value and an HR value for difenoconazole in mammalian edible offal of 0.2, 0.043 and 0.11 mg/kg, respectively.

Poultry

In the table, dietary burdens are shown in round brackets (), feeding levels and residue concentrations from the feeding study are shown in square brackets [] and estimated concentrations related to the dietary burdens are shown without brackets.

Dietary burden (ppm) Feeding level [ppm]	Eggs	Muscle	Liver	Fat	Skin + attached fat
MRL					
	highest	highest	highest	highest	highest
MRL laying hens (0.54) [0, 1]	0.0054 [0, 0.01]				
MRL laying hens (0.54) [0, 3, 10]		< 0.00054 [0, < 0.01, < 0.01]	< 0.00054 [0, < 0.01, < 0.01]	< 0.00054 [0, < 0.01, < 0.01]	< 0.00054 [0, < 0.01, < 0.01]
STMR					
	mean	mean	mean	mean	mean
STMR laying hens (0.20) [0, 1]	< 0.0020 [0, < 0.01]				
STMR laying hens (0.20) [0, 3, 10]		< 0.0002 [0, < 0.01, < 0.01]	< 0.0002 [0, < 0.01, < 0.01]	< 0.0002 [0, < 0.01, < 0.01]	< 0.0002 [0, < 0.01, < 0.01]

The data from the laying hen feeding studies were used to support poultry meat and egg MRLs.

The residue levels of difenoconazole + CGA 205375, expressed as difenoconazole, in poultry tissues and eggs arising from the dietary burdens (0.54 and 0.20 ppm difenoconazole in feed, dry weight) were all less than the analytical method LOQ (0.01 mg/kg).

For poultry tissues, residues were below LOQ (0.01 mg/kg) even at the 10 ppm feeding level, so an estimate of the STMRs was made by dividing the dietary burden (0.20 ppm) by 10 ppm and multiplying by the LOQ (0.01 mg/kg) to produce a value of 0.00020 mg/kg. An estimate of the HRs was made by dividing the dietary burden (0.54 ppm) by 10 ppm and multiplying by the LOQ (0.01 mg/kg) to produce a value of 0.00054 mg/kg.

For eggs, residues were below LOQ (0.01 mg/kg) at the 1 ppm feeding level, so an estimate of the STMR was made by dividing the dietary burden (0.20 ppm) by 1 ppm and multiplying by the LOQ (0.01 mg/kg) to produce a value of 0.0020 mg/kg. Similarly, a calculation for the HR for eggs produced a value of 0.0054 mg/kg.

The Meeting estimated maximum residue levels of 0.01* mg/kg for poultry eggs, poultry meat (fat) and poultry edible offal.

The Meeting estimated STMRs of 0.0020 mg/kg for eggs and 0.00020 mg/kg for poultry meat and poultry edible offal.

The Meeting estimated HRs of 0.0054 mg/kg for eggs and 0.00054 mg/kg for poultry meat and poultry edible offal.

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