5.21 MYCLOBUTANIL (181)

TOXICOLOGY

Myclobutanil is the ISO-approved common name for (*R*,*S*)-2-(4-chlorophenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl) hexanenitrile (IUPAC), with CAS number 88671-89-0. It is a broad-spectrum fungicide of the substituted triazole chemical class of compounds. It acts by inhibiting sterol biosynthesis in fungi.

Myclobutanil was evaluated by JMPR in 1992, when an ADI of 0–0.03 mg/kg bw was established. No ARfD was established, because the establishment of ARfDs by JMPR was not common practice in 1992. Myclobutanil was reviewed by the present Meeting as part of the periodic review programme of CCPR.

All critical studies contained statements of compliance with GLP. Several new studies on metabolites were submitted.

Biochemical aspects

Myclobutanil was rapidly and extensively absorbed in rats (> 89%). Peak plasma and tissue concentrations of radiolabelled myclobutanil were achieved within 1 hour after oral administration. Plasma elimination was biphasic; the half-lives were 5 hours for the rapid phase and 26 hours for the slow phase in rats exposed to a single dose. Myclobutanil was widely distributed, and no significant tissue accumulation was observed 96 hours post-dosing.

Metabolism was extensive and appeared to occur mainly through a variety of oxygenation reactions of the butyl group. The major unconjugated phenethyl triazole–containing metabolites were RH-9090 ((2*RS*,5*RS*)-2-(4-chlorophenyl)-5-hydroxy-2-(1*H*-1,2,4-triazol-1-ylmethyl) hexanenitrile) and RH-9089 ((2*RS*)-2-(4-chlorophenyl)-5-oxo-2-(1*H*-1,2,4-triazol-1-ylmethyl) hexanenitrile). Myclobutanil was rapidly and completely excreted in urine and faeces within 24–48 hours in rats.

Toxicological data

The oral LD_{50} for myclobutanil was greater than or equal to 1600 mg/kg bw in rats. The dermal LD_{50} was greater than 5000 mg/kg bw in rats and rabbits. The inhalation LC_{50} was greater than 5.1 mg/L in rats. Myclobutanil was not irritating to the skin but was moderately irritating to the eye of rabbits. Myclobutanil was not sensitizing in the guinea-pig maximization test or the mouse local lymph node assay and was mildly sensitizing using the Buehler method.

The liver was the interspecies target of myclobutanil in short- and long-term toxicity studies. The testis was also a target of myclobutanil in long-term toxicity studies in rats. Reductions of feed consumption and corresponding decreases in body weight gains at the beginning of treatment in short-term dietary studies in mice, rats and dogs and a reproductive toxicity study in rats are considered to be due to low palatability, rather than an adverse effect, as no similar change in feed consumption was observed in gavage studies and no effects on the gastrointestinal tract were observed.

In a 90-day toxicity study in mice administered myclobutanil in the diet at a concentration of 0, 3, 10, 30, 100, 300, 1000, 3000 or 10 000 ppm (equal to 0, 0.40, 1.54, 4.79, 14.1, 42.7, 132, 542 and 2035 mg/kg bw per day for males and 0, 0.62, 2.11, 6.94, 22.9, 65.5, 232, 710 and 2027 mg/kg bw per day for females, respectively), the NOAEL was 300 ppm (equal to 42.7 mg/kg bw per day), based on fatty changes and necrosis of hepatocytes at 1000 ppm (equal to 132 mg/kg bw per day).

In a 90-day oral toxicity study in rats, myclobutanil was administered in the diet at a concentration of 0, 5, 15, 50, 150, 500, 1500, 5000 or 15 000 ppm for weeks 1 and 2; at 0, 7, 21, 70, 210, 700, 2100, 7000 or 21 000 ppm for weeks 3 and 4; and at 0, 10, 30, 100, 300, 1000, 3000, 10 000 or 30 000 ppm for the remainder of the study. These dietary concentrations were equal to doses of 0, 0.52, 1.60, 5.22, 15.3, 51.5, 158, 585 and 1730 mg/kg bw per day for males and 0, 0.67,

2.03, 6.85, 19.7, 65.8, 195.2, 665 and 1811 mg/kg bw per day for females, respectively. The NOAEL was 500/700/1000 ppm (equal to 51.5 mg/kg bw per day), based on increased liver and kidney weights, hepatocellular hypertrophy, single-cell necrosis in the liver and pigmentation in tubular epithelium in the kidneys at 1500/2100/3000 ppm (equal to 158 mg/kg bw per day).

In a 90-day oral toxicity study in dogs administered myclobutanil in the diet at 0, 10, 200, 800 or 1600 ppm (equal to 0, 0.34, 7.26, 29.1 and 56.8 mg/kg bw per day for males and 0, 0.42, 7.88, 32.4 and 58.0 mg/kg bw per day for females, respectively), the NOAEL was 800 ppm (equal to 29.1 mg/kg bw per day), based on liver hypertrophy, increased alkaline phosphatase and increased platelets at 1600 ppm (equal to 56.8 mg/kg bw per day).

In a 1-year oral toxicity study in dogs administered myclobutanil in the diet at a concentration of 0, 10, 100, 400 or 1600 ppm (equal to 0, 0.34, 3.09, 14.3 and 54.2 mg/kg bw per day for males and 0, 0.40, 3.83, 15.9 and 58.2 mg/kg bw per day for females, respectively), the NOAEL was 400 ppm (equal to 14.3 mg/kg bw per day), based on ballooned hepatocytes, increased alkaline phosphatase and increased platelets in males at 1600 ppm (equal to 54.2 mg/kg bw per day).

The Meeting concluded that the overall NOAEL for oral toxicity in dogs was 800 ppm (equal to 29.1 mg/kg bw per day), and the overall LOAEL was 1600 ppm (equal to 54.2 mg/kg bw per day).

In a 2-year toxicity and carcinogenicity study in mice administered myclobutanil in the diet at a concentration of 0, 20, 100 or 500 ppm (equal to 0, 2.7, 13.7 and 70.2 mg/kg bw per day for males and 0, 3.2, 16.5 and 85.2 mg/kg bw per day for females, respectively), the NOAEL for toxicity was 100 ppm (equal to 13.7 mg/kg bw per day), based on histopathological signs of hepatotoxicity at 500 ppm (equal to 70.2 mg/kg bw per day). Myclobutanil was not carcinogenic in this study.

In a second 2-year carcinogenicity study conducted to confirm the absence of carcinogenicity at high doses, female mice were administered myclobutanil in the diet at a concentration of 2000 ppm (equal to 394 mg/kg bw per day), the maximum tolerated dose. No carcinogenicity was observed at this dose.

In a 2-year carcinogenicity study in rats administered myclobutanil in the diet at a concentration of 0, 50, 200 or 800 ppm (equal to 0, 2.5, 9.8 and 39.2 mg/kg bw per day for males and 0, 3.2, 12.8 and 52.3 mg/kg bw per day for females, respectively), the NOAEL for non-neoplastic effects was 50 ppm (equal to 2.5 mg/kg bw per day), based on testicular toxicity found after 12 months of treatment at 200 ppm (equal to 9.8 mg/kg bw per day). Myclobutanil was not carcinogenic in this study.

A second 2-year carcinogenicity study in rats confirmed the absence of carcinogenicity of myclobutanil at a higher dietary concentration, 2500 ppm (equal to 106 mg/kg bw per day for males and 136 mg/kg bw per day for females).

The Meeting concluded that myclobutanil is not carcinogenic in mice or rats.

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

The Meeting concluded that myclobutanil is unlikely to be genotoxic.

On the basis of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that myclobutanil is unlikely to pose a carcinogenic risk to humans.

In a two-generation reproductive toxicity study in rats administered myclobutanil in the diet at a concentration of 0, 50, 200 or 1000 ppm (equal to 0, 3.67, 14.3 and 70.7 mg/kg bw per day for P_1 males, 0, 4.42, 17.2 and 85.9 mg/kg bw per day for P_1 females, 0, 3.64, 15.1 and 76.4 mg/kg bw per day for P_2 males and 0, 4.17, 17.5 and 88.0 mg/kg bw per day for P_2 females, respectively), the NOAEL for parental toxicity was 200 ppm (equal to 15.1 mg/kg bw per day), based on lower body weights, histopathological changes of vacuolation and hypertrophy of hepatocytes and testicular atrophy in P_2 males at 1000 ppm (equal to 76.4 mg/kg bw per day). The NOAEL for reproductive toxicity was 200 ppm (equal to 17.5 mg/kg bw per day), based on reduced reproductive ability,

including number of females mating, number of females giving birth, number of females weaning litters or prolonged time to mating, in P_2 females at 1000 ppm (equal to 88.0 mg/kg bw per day). The NOAEL for offspring toxicity was 200 ppm (equal to 17.2 mg/kg bw per day), based on an increased number of pups born dead for both generations at 1000 ppm (equal to 85.9 mg/kg bw per day).

In a developmental toxicity study in rats administered myclobutanil by gavage at 0, 31.3, 93.8, 313 or 469 mg/kg bw per day, the NOAEL for maternal toxicity was 93.8 mg/kg bw per day, based on clinical signs of rough hair coat, desquamation and salivation at 313 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 31.3 mg/kg bw per day, based on an increased number of early resorptions at 93.8 mg/kg bw per day.

To determine whether treatment-related early resorptions in rats were caused by chromosomal abnormalities of the spermatozoa, leading to death of conceptuses, male rats were administered a single dose of myclobutanil at 0, 10, 100 or 735 mg/kg bw and mated with untreated females. There was no evidence of treatment-related embryo death, even at a dose lethal to adults.

In a developmental toxicity study in rabbits administered myclobutanil by gavage at 0, 20, 60 or 200 mg/kg bw per day, the NOAEL for maternal toxicity was 20 mg/kg bw per day, based on decreased body weight gain on day 11 at 60 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 60 mg/kg bw per day, based on an increased number of resorptions per litter, an increased number of litters totally resorbed and lower fetal weights at 200 mg/kg bw per day.

The Meeting concluded that myclobutanil is not teratogenic.

There were no studies submitted that specifically investigated neurotoxicity or immunotoxicity.

Toxicological data on metabolites and/or degradates

The oral LD_{50} ranges for RH-9090 and RH-9089, major metabolites in plants, rats, hens and cows, were between 300 and 1000 mg/kg bw in mice.

In a 2-week oral toxicity study on myclobutanil butyric acid ((3*RS*)-3-(4-chlorophenyl)-3-cyano-4-(1*H*-1,2,4-triazol-1-yl)butanoic acid), a degradate in soil, no toxicity was observed at doses up to 1000 mg/kg bw administered by gavage to rats.

Tests of the in vitro genotoxicity of RH-9089, RH-9090 and myclobutanil butyric acid and an in vivo genotoxicity assay on myclobutanil butyric acid showed no evidence of genotoxicity.

The Meeting concluded that RH-9090 and RH-9089, which are major metabolites in rats, are covered by the reference doses for myclobutanil. Myclobutanil butyric acid is of no toxicological concern, as it is of lower toxicity than the parent.

Human data

In reports on manufacturing plant personnel, no adverse health effects were noted.

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

Toxicological evaluation

The Meeting reaffirmed the ADI of 0–0.03 mg/kg bw on the basis of the NOAEL of 2.5 mg/kg bw per day in a 2-year study in rats, based on testicular atrophy at 9.8 mg/kg bw per day. A safety factor of 100 was applied. This ADI is based on the same end-point as in 1992.

The Meeting established an ARfD of 0.3 mg/kg bw for women of childbearing age only, on the basis of the NOAEL of 31.3 mg/kg bw per day in a developmental toxicity study in rats, based on

an increased number of early resorptions at 93.8 mg/kg bw per day. A safety factor of 100 was applied. The Meeting concluded that it is not necessary to establish an ARfD for the remainder of the population in view of the low acute oral toxicity of myclobutanil and the absence of any other toxicological effects that would be likely to be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment of myclobutanil

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year studies of toxicity and carcinogenicity[a,b]	Toxicity	100 ppm, equal to 13.7 mg/kg bw per day	500 ppm, equal to 70.2 mg/kg bw per day
		Carcinogenicity	2 000 ppm, equal to 394 mg/kg bw per day[c]	–
Rat	Two-year studies of toxicity and carcinogenicity[a,b]	Toxicity	50 ppm, equal to 2.5 mg/kg bw per day	200 ppm, equal to 9.8 mg/kg bw per day
		Carcinogenicity	2 500 ppm, equal to 106 mg/kg bw per day[c]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	200 ppm, equal to 17.5 mg/kg bw per day	1 000 ppm, equal to 88.0 mg/kg bw per day
		Parental toxicity	200 ppm, equal to 15.1 mg/kg bw per day	1 000 ppm, equal to 76.4 mg/kg bw per day
		Offspring toxicity	200 ppm, equal to 17.2 mg/kg bw per day	1 000 ppm, equal to 85.9 mg/kg bw per day
	Developmental toxicity study[d]	Maternal toxicity	93.8 mg/kg bw per day	313 mg/kg bw per day
		Embryo and fetal toxicity	31.3 mg/kg bw per day	93.8 mg/kg bw per day
Rabbit	Developmental toxicity study[d]	Maternal toxicity	20 mg/kg bw per day	60 mg/kg bw per day
		Embryo and fetal toxicity	60 mg/kg bw per day	200 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity[a,b]	Toxicity	800 ppm, equal to 29.1 mg/kg bw per day	1 600 ppm, equal to 54.2 mg/kg bw per day

[a] Dietary administration.
[d] Two or more studies combined.
[c] Highest dose tested.
[b] Gavage administration.

Estimate of acceptable daily intake (ADI)

0–0.03 mg/kg bw

Estimate of acute reference dose (ARfD)

0.3 mg/kg bw (applies to women of childbearing age only)

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 myclobutanil

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapidly absorbed (> 89%)
Dermal absorption	No data
Distribution	Extensive
Potential for accumulation	No significant tissue accumulation
Rate and extent of excretion	Rapidly excreted
Metabolism in animals	Extensively metabolized, mainly through a variety of oxygenation reactions
Toxicologically significant compounds in animals and plants	Myclobutanil, unconjugated phenethyl triazole–containing metabolites (RH-9089, RH-9090) (rat, hen, cow, plants)
Acute toxicity	
Rat, LD_{50}, oral	≥ 1 600 mg/kg bw
Rat, LD_{50}, dermal	> 5 000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.1 mg/L
Rabbit, dermal irritation	Not irritating to skin
Rabbit, ocular irritation	Moderately irritating to eye
Guinea-pig, dermal sensitization	Not sensitizing (maximization test and local lymph node assay); mildly sensitizing (Buehler method)
Short-term studies of toxicity	
Target/critical effect	Liver / increases in alkaline phosphatase and platelets (dog)
Lowest relevant oral NOAEL	29.1 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	100 mg/kg bw per day (rat)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Testes/atrophy (rat)
Lowest relevant NOAEL	2.5 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic (rat and mouse); unlikely to pose a carcinogenic risk to humans
Genotoxicity	
	Unlikely to be genotoxic
Reproductive toxicity	
Target/critical effect	Testicular atrophy, increased number of pups born dead, reduced reproductive ability
Lowest relevant parental NOAEL	15.1 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	17.2 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	17.5 mg/kg bw per day (rat)

Developmental toxicity	
Target/critical effect	Fetal toxicity / increased number of early resorptions and lower fetal weights
Lowest relevant maternal NOAEL	20 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	31.3 mg/kg bw per day (rat)
Neurotoxicity	
Acute neurotoxicity NOAEL	No data
Subchronic neurotoxicity NOAEL	No data
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity	No data
Studies on toxicologically relevant metabolites	RH-9089 and RH-9090:
	Oral LD_{50}: 300–1000 mg/kg bw (mice)
	Unlikely to be genotoxic
	Myclobutanil butyric acid:
	NOAEL: 1 000 mg/kg bw, highest dose tested (2-week study in rats)
	Unlikely to be genotoxic
Studies on impurities	Studies on RH-8812 and RH-8813 not relevant for dietary risk assessment
Medical data	
	No adverse effects noted in medical surveillance reports on manufacturing plant personnel

Summary

	Value	Study	Safety factor
ADI	0–0.03 mg/kg bw	Two-year study of toxicity and carcinogenicity (rat)	100
ARfD	0.3 mg/kg bw[a]	Developmental toxicity study (rat)	100

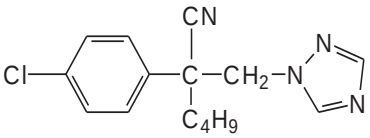
[a] Applies to women of childbearing age only.

RESIDUE AND ANALYTICAL ASPECTS

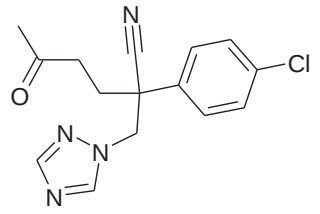
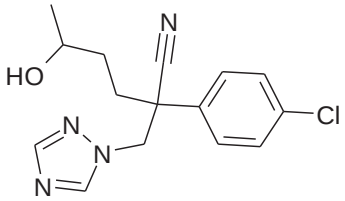
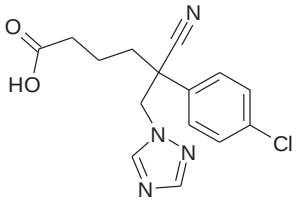
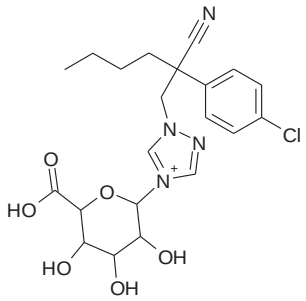
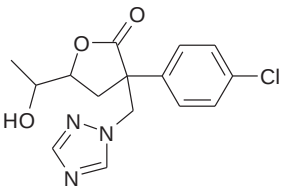
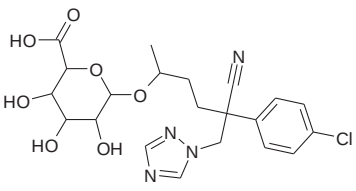
Myclobutanil was originally evaluated by the JMPR in 1992 and re-evaluated for residues in 1997 and 1998. Myclobutanil is a systemic fungicide used to control a range of economically important fungi on a variety of crops, and belongs to the steroid demethylation inhibitor (DMI) class of fungicides.

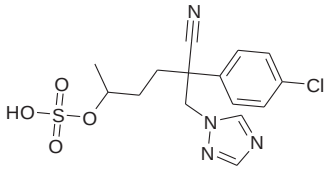
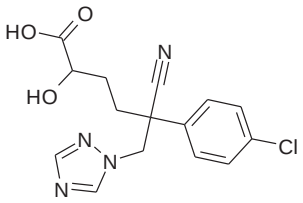
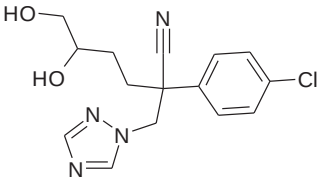
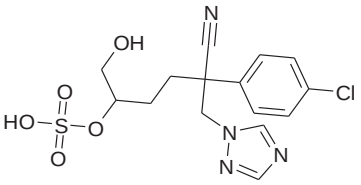
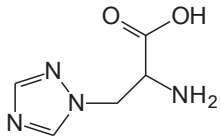
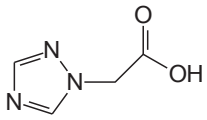
At the Forty-fifth Session of the CCPR (REP13/PR, Appendix XIV), myclobutanil was scheduled for periodic residue review by the 2014 JMPR. The Meeting received information on physical and chemical properties, metabolism, environmental fate, analytical methods and freezer storage stability, national registered use patterns, as well as supervised trials, processing studies and livestock feeding studies.

Myclobutanil is (R, S)-2-(4-chlorophenyl)-2-(1H-1, 2, 4-triazol-1-ylmethyl) hexanenitrile and exists as a racemate.



The following compound codes are used for the metabolites discussed below:

RH-9089	(2RS) -2-(4-chlorophenyl) -5-oxo-2-(1H-1,2,4-triazol-1-ylmethyl)hexanenitrile	
RH-9090	α-(4-chlorophenyl)-α-(3-hydroxybutyl)-1H-1,2,4-triazole-1-propanenitrile	
MW 318 Acid (butyl carboxylic acid of myclobutanil)	5-(4-chlorophenyl)-5-cyano-6-(1H-1,2,4-triazol-1-yl)hexanoic acid	
N-Glucuronic Acid Conjugate of Myclobutanil	1-[2-(4-chlorophenyl)-2-cyanohexyl]-4-hexopyranuronosyl-1H-1,2,4-triazol-4-ium	
Hydroxy-lactone	3-(4-chlorophenyl)-5-(1-hydroxyethyl)-3-(1H-1,2,4-triazol-1-ylmethyl)dihydrofuran-2(3H)-one	
RH-9090 Glucuronic Acid Conjugate	5-(4-chlorophenyl)-5-cyano-6-(1H-1,2,4-triazol-1-yl)hexan-2-yl hexopyranosiduronic acid	

RH-9090 Sulfate Conjugate	5-(4-chlorophenyl)-5-cyano-6-(1H-1,2,4-triazol-1-yl)hexan-2-yl hydrogen sulfate	
MW 334 Acid	5-(4-chlorophenyl)-5-cyano-2-hydroxy-6-(1H-1,2,4-triazol-1-yl)hexanoic acid	
RH-294 (Diol)	α-(-chlorophenyl)-α-(3,4-hydroxy-butyl)-1H-1,2,4-triazole-1-propane-nitrile	
RH-294 Sulfate Conjugate	5-(4-chlorophenyl)-5-cyano-1-hydroxy-6-(1H-1,2,4-triazol-1-yl)hexan-2-yl hydrogen sulfate	
RH-3968 (Triazolyl Alanine, TA)	(2*RS*)-2-amino-3-(1*H*-1,2,4-triazol-1-yl)propanoic acid	
RH-4098 (Triazolyl Acetic Acid, TAA)	1*H*-1,2,4-triazol-1-ylacetic acid	

Animal metabolism

Information was available on metabolism of myclobutanil in rats, lactating goats and laying hens.

Laboratory animals: Myclobutanil was mainly and rapidly absorbed (> 89%), extensively metabolised and rapidly and completely excreted after oral administration in rats. Peak plasma and tissue radiolabelled myclobutanil were achieved within 1 hr after oral administration and plasma elimination was biphasic. No significant tissue accumulation was observed 96 hr post-dosing. Metabolism appears to have occurred mainly through a variety of oxygenation reactions of the butyl group. The major metabolic processes involved oxygenation to the butyl group and among the metabolites formed are the RH9090 and RH9089, the major unconjugated phenethyl triazole-containing metabolites found in plants.

Lactating goats: Myclobutanil was orally dosed to lactating goats for 5 days. Individual goats were dosed separately with myclobutanil radiolabelled in either the triazole (TZ) portion or the phenyl ring (PH) at the rate of 24 ppm and 14 ppm in the diet per day, respectively. Approximately 71% and 79% of TAR was recovered in the faeces and urine for the TZ-label and PH-label dosed animal. Most of administered dose was rapidly absorbed, metabolised and rapidly eliminated via the

urine (49–58% TAR) and faeces (22% TAR). TRR levels in tissues ranged from 0.016 mg eq/kg in omental fat to 0.49 mg eq/kg in liver for the low dosed goat (PH label) and from 0.027 mg eq/kg in omental fat to 0.92 mg eq/kg in liver for the high dosed goat (TZ label). Residue levels were highest in liver and kidney and significantly lower in muscle and fat.

Milk and edible tissues were extracted with acetone, hexane and acetonitrile/water (80/20) and 78–101% radioactive residues were recovered. Unchanged parent compound was only observed in liver (2.1–6.0% TRR, 0.019–0.029 mg/kg). The metabolite RH-9090 and its sulphate and glucuronic acid conjugates were the primary residue in liver (total 59–60% TRR, 0.29–0.54 mg eq./kg), in kidney (total 58–61% TRR, 0.13–0.30 mg eq./kg), in muscle (total 47–80% TRR, 0.02–0.03 mg eq./kg) and in fat (total 44–46% TRR, 0.01–0.02 mg eq./kg). The hydroxy-lactone was the only other metabolite present in liver at levels in excess of 10% of the TRR (12–16% TRR, 0.08–0.11 mg eq./kg).

For both labels in milk, the residue levels reached a plateau within 4 days after the initiation of dosing at a level of approximately 0.033–0.079 mg eq./kg. The primary residue was RH-9090 which constituted about 28–58% of the TRR, while the only other two metabolites representing 10% or more of the TRR were RH-294 and the MW 318 carboxylic acid. No parent compound was detected in milk.

Laying hens: [^{14}C]-Myclobutanil was administered orally to groups of three laying hens once daily for 7 consecutive days at the nominal equivalent of 110 ppm in a diet. Over 95% of the dosed radioactivity was recovered in the excreta. Whole eggs and muscle were extracted with ethyl acetate, and then extracted with methanol. Fat and edible offal were extracted with n-hexane and methanol. The extracted radioactive residues accounted for 69% TRR in whole eggs, 79% TRR in fat, 83% TRR in thigh muscle, 97% TRR in breast muscle, 156% TRR in kidney (118% TRR as uncharacterized) and 72% TRR in liver (61% TRR as uncharacterized), respectively.

Total radioactive residues were observed in the liver (0.52 mg eq/kg) and the kidney (0.32 mg eq/kg), while lower residues were found in muscle (0.06 mg eq./kg) and fat (0.02 mg eq./kg). Parent myclobutanil was a main residue in fat (67% TRR) in kidney (12% TRR) in liver (4.8% TRR), and in muscle (up to 4% TRR). A band that co-chromatographed with RH-9090/RH9089 and lactone accounted for 15% TRR in kidney. The major component of the residue in muscle was RH-9089 (61–72% TRR). The major component of the residue in eggs was RH-9090 accounting for 36% TRR. No parent compound was observed in eggs.

In summary, the metabolism found in livestock was qualitatively comparable with that observed in laboratory animals. Characterization of the residues show myclobutanil together with RH-9090 and its conjugates are the major residues in the animal tissues, milk and eggs except RH-9089 as a major component in the muscle of laying hens.

Plant metabolism

The Meeting received plant metabolism studies with myclobutanil on grapes, apples, wheat, and sugar beets.

Grape seedlings in the greenhouse were placed in nutrient solution containing either ^{14}C-phenyl myclobutanil or ^{14}C-triazole myclobutanil. An average of 37% TRR remained as the parent compound. RH-9090 accounted for 6% TRR, with 11% TRR present as the RH-9090 glucoside and 14% TRR as an unknown polar component. In the 16-day uptake samples, parent compound accounted for an average of 53% TRR, RH-9090 8% TRR and RH-9090 glucoside 12% TRR.

Grape vines were sprayed five times weekly with myclobutanil, labelled with ^{14}C in the phenyl ring or the triazole ring each at a rate equivalent to 0.05 kg ai/ha. The overall recovery of identified radioactive residues ranged from 79% to 82%. TRR in whole grapes at harvest were 0.32 and 0.24 mg eq./kg for PH and TZ grapes, respectively. The major component of residue was the

parent compound accounting for 66% TRR, RH-9090 for 7–9% TRR, RH-9090 glucoside for 5–6% and RH-9089 for 1%, respectively.

Apple trees received ten approximately weekly sprays of myclobutanil, labelled with ^{14}C in the phenyl ring or the triazole ring, at 0.24 kg ai/ha. After extraction with chloroform or methanol, the overall recoveries of identified radioactive residues ranged from 84% to 86% TRR. TRR in whole grapes at harvest were 0.48 and 0.32 mg eq/kg for PH and TZ grapes, respectively. The major component of the terminal residue remained parent compound accounting for 49% of TRR. Conjugated RH-9090 accounted for 21–24% TRR. Free RH-9090 accounted for 12% TRR. A minor component was RH-9089 present at 1.9% TRR. There were no differences in the metabolic profile between the two radiolabelled experiments.

Wheat seedlings were exposed to ^{14}C-myclobutanil at either 42 mg/kg (PH label) or 64 mg/kg (TZ label) in nutrient solutions for an 11 day period placed in the greenhouse. After extraction with methanol, the overall recovery including the unextracted residue ranged from 90% to 96%. In the wheat seedlings, most of the radioactivity (62–71% TRR) remained as parent compound. The total conjugates constituted the complement of the total residues (accounting for 21–30% TRR). In the excised wheat shoots, more than 72% of TRR maintained as unchanged parent compound. In the excised heads of 13-day uptake samples, parent compound accounted for up to 75% TRR, free RH-9090 for 5% TRR, RH-9090 glucoside for up to 18% TRR for both labelling forms.

The metabolism of myclobutanil, using either PH or TZ labels, was studied in wheat under field conditions and greenhouse at a rate equivalent to 0.28 kg ai/ha. After extraction with methanol, the overall recovery of identified radioactive residues ranged between 77% and 102%. TRRs in wheat grain ranged from 0.07 to 3.6 mg eq./kg, and those in wheat straw were from 2.8–69 mg eq./kg. The main components of the residue in wheat straw were parent myclobutanil (under field: 29–47% TRR), RH-9090 and its conjugates (under field: 23–41% TRR). The main components of the residue in wheat grains were RH-9090 and its conjugates (35% TRR) and parent myclobutanil (11% TRR) treated with PH label under field conditions. However, the main components of the residue in wheat grains were RH-3968 (51% TRR) and RH-4098 (25% TRR), and RH-9090 and its conjugates (8.9% TRR) treated with TZ label under field conditions while unchanged myclobutanil was a minor component of residue treated with TZ label accounting for 0.4% TRR.

Foliar applications were made to sugar beet at application rates equivalent to 0.15 kg ai/ha and 1.50 kg ai/ha using two radiolabelled forms ([^{14}C]-phenyl-myclobutanil and [^{14}C]-triazole-myclobutanil) 30 days prior to maturity. After extracted with acetonitrile, the overall recovery ranged between 91% and 105%. The main components of the residue in roots were parent myclobutanil (27–33% TRR, 0.01–0.03 mg eq./kg), conjugated RH-9090 and free RH-9090 (total 8–14%TRR, 0.006–0.007 mg eq./kg). The main components of the residue in leaves at maturity were RH-9090 (50–62% TRR, 0.26–0.43 mg eq./kg) and parent myclobutanil (16–34% TRR, 0.11–0.18 mg/kg), respectively.

In summary, the metabolism of myclobutanil in crops is qualitatively consistent and considered comparable except in wheat treated with the TZ label. The conversion of myclobutanil to RH-9090 followed by conjugation with glucose is the major metabolic pathway. Minor amounts of RH-9089 are probably a result of oxidation of RH-9090. The presence of RH-3968 and RH-4098 in wheat treated with the TZ label indicates that the phenethyl triazole linkage in the parent was metabolically cleaved.

Environmental fate in soil

The Meeting received information on the environment fate of myclobutanil in confined and field crop rotational studies. A study on degradation of myclobutanil in aerobic soil showed that half-life values reached up to 574 days. Myclobutanil could be a persistent compound in some soils.

Confined rotational crop

The metabolism of ^{14}C-triazole-myclobutanil in succeeding crops was investigated in wheat, radish and lettuce cultivated at three different plant back intervals for all crops (30, 120 and 365 days) at 1×0.36 kg ai/ha. Lettuce, radish and wheat were planted at rotational intervals of 30, 120 and 365 days after soil treatment, TRRs ranged from 0.07 to 2.7 mg eq/kg were found in harvested crops. Radioactive residues in immature and mature lettuce and radish tops declined over time, while residues in radish roots increased. Residues in wheat hay, straw and grain did not show consistent increase or decline. The three most abundant non-polar components in crops planted 30 days after soil application were myclobutanil at 0.43 mg/kg (55% TRR) in mature lettuce, MW 309 di-acid at 0.38 mg eq./kg (14% TRR) and RH-9090 at 0.47 mg eq./kg (17% TRR), both in wheat straw. The two most abundant polar metabolites were the triazole alanine at 0.45 mg eq./kg (30% TRR) and triazole acetic acid at 0.43 mg eq./kg (29% TRR), both in 120 DAT wheat grain. Unextracted residues exceeded both 10% of the TRR and 0.05 mg eq/kg only in wheat hay, straw and grain at all plant-backs. In wheat hay and straw, the unextracted residues ranged from 11 to 23% TRR and from 0.17 to 0.53 mg eq./kg. For wheat grain, the unextracted residues ranged from 26 to 39% TRR and from 0.21 to 0.57 mg eq./kg.

The unchanged parent molecule was found as main component in samples of immature, mature lettuce (30-day PBI), radish roots (30, 120, 365-day PBI) and wheat forage (30 day PBI). Myclobutanil was detected as minor component in other samples. Metabolites were generally detected in lower concentrations. The parent compound, RH-9090 and its conjugates were found in most parts of the four crops. The other two most abundant metabolites were MW 309 di-acid (0.4–28% TRR) and butyric acid (0.9–15% TRR), were not identified in the metabolism studies of crops. This study indicates a potential uptake of residues for myclobutanil into plant commodities.

Field rotational crops

Myclobutanil was applied at 6×0.14 kg ai/ha to zucchini in the USA (California and Georgia) approximating the estimated plateau level in soil after subsequent annual application. Within 2 days after the last application, zucchini fruit were harvested and removed from the plots. The remaining plant parts were incorporated into the soil 7–10 days after harvest and then rotational crops (soya bean, radish and wheat) were planted 30 days after the last application to the target zucchini crop. Rotational crops were sampled ranging between 71 and 258 days after final treatment. The plants were soxhlet extracted with methanol and analysed for the parent compound and RH-9090. Residues of myclobutanil and RH-9090 occurred up to 0.36 and 0.15 mg/kg in soya bean forage, 0.093 and 0.19 mg/kg in soya bean hay, 0.052 and < 0.01 mg/kg in radish root, 0.044 and 0.12 mg/kg in radish tops, 0.071 and 0.11 mg/kg in wheat forage, 0.18 and 0.63 mg/kg in wheat straw, respectively. Myclobutanil and RH-9090 residues were higher in vegetative matrices (forage, hay and straw) than the respective seed or grain crop matrix. Residue values for soya bean seeds and wheat grains were all below LOQ (0.01 mg/kg).

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for residues of myclobutanil and RH-9090 in plant and meat. Myclobutanil residues can be measured in most matrices to the LOQ range of 0.01 to 0.05 mg/kg. No stereo-selective methods were submitted for two myclobutanil enantiomers.

The crop and animal methods typically use an initial extraction with methanol or acetone or acetonitrile, and clean-up with partition and/or column steps. The final solution was analysed by GC-ECD, GC-MS or LC-MS/MS. If RH-9090 and its conjugates are determined, hydrolysis with concentrated acid and heating is applied after extraction. Myclobutanil residues can be measured in most matrices to an LOQ of 0.01 mg/kg. All methods are considered sufficiently validated. Multi-residue enforcement method DFG S19 and MRM-1 were provided and validated. The DFG S19 was

valid for RH-9090 in animal tissues except fat and MRM-1 was valid for myclobutanil in crops with the LOQ of 0.2 mg/kg. Analytical methods in the feeding studies were valid for determination of myclobutanil and total RH-9090 in milk, myclobutanil and free RH-9090 in muscle, fat, liver and kidney.

Stability of residues in stored analytical samples

The Meeting received information on the freezer storage stability of residues of myclobutanil in plant and animal commodities.

Storage stability studies were conducted on apples, radish root, soya bean, wheat forage, wheat grain, wheat hay, wheat straw, blueberry, cucurbits and snap beans. Analytical results demonstrated that myclobutanil and RH-9090 were stable in the different plant matrices for at least one year, the duration of the test period.

Storage stability studies on liver and muscle were carried out. Analytical results demonstrated that myclobutanil and its metabolite RH-9090 were stable for at least 80 days, the duration of the study.

Definition of the residue

The composition of the residue in the metabolism studies, the available residue data in the supervised trials, the toxicological significance of metabolites, the capabilities of enforcement analytical methods and the national residue definitions already operating all influence the decision on residue definition.

The metabolism studies of lactating goats showed that the unchanged parent compound was only observed in liver. RH-9090 and its conjugates were the primary residues in liver, kidney, muscle and fat. The primary residue was RH-9090, constituted about 28–58% of the TRR in milk and no parent compound was observed.

In laying hens studies, the highest ^{14}C levels were observed in liver and kidney, while fewer residues were found in muscle and fat. Parent was one of the main components detected in liver and in kidney. RH-9090-sulphate was another main residue detected in liver. A band that co-chromatographed with RH-9090/RH9089 and hydroxy-lactone accounted for 15% TRR in kidney. The major component of the residue in muscle extracts was RH-9089. The major component of residue in fat was parent compound. RH-9090 was the major component of the residue in eggs. No parent compound was observed in eggs.

RH-9090 and its conjugates are the main residues in the animal tissues, milk and eggs. Parent compound is also identified in most of tissues and as a major component in fat and kidney. Although RH-9090 and RH-9089 are found in tissues of animal metabolism study, no residues of parent compound and metabolites were expected above LOQ on the basis of dietary burden calculation and animal feeding studies. The Meeting recommended that, parent myclobutanil is the appropriate residues of concern for MRL enforcement and dietary risk assessment in animal commodities.

The octanol-water partition coefficient of myclobutanil (log K_{ow}=2.56) suggests that myclobutanil is not fat-soluble. Noting that myclobutanil residues in animal fat were less than those in muscle, the Meeting agreed that myclobutanil residue is not fat-soluble.

Metabolism studies on plants, and confined rotational crop showed that the main residues in food or feed of plant origin were myclobutanil and/or conjugated RH-9090 and free RH-9090. The Meeting decided that for plant commodities, parent myclobutanil is the appropriate residue of concern for MRL enforcement, and myclobutanil and RH-9090 and its conjugates for dietary risk assessment.

Definition of the residue (for compliance with the MRL) for plant and animal commodities: *myclobutanil.*

Definition of the residue (for estimation of dietary intake) for animal commodities: *myclobutanil.*

Definition of the residue (for estimation of dietary intake) for plant commodities: *sum of myclobutanil, α-(4-chlorophenyl)-α-(3-hydroxybutyl)-1H-1,2,4-triazole- 1-propanenitrile (RH-9090) and its conjugates, expressed as myclobutanil.*

The residue is considered not fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised trials data for myclobutanil formulations for apple, pear, peach, cherry, apricot, plum, currant, grapes, strawberry, banana, hops, tomato, squash, pepper, cucumber, melon, watermelon, snap beans and soya beans.

The method for calculation of the total residues is illustrated as follows (similar molecular weight, therefore sum residues of myclobutanil and RH-9090 as total residue).

RH-9090 less than LOQ (0.01 mg/kg) and more than LOD (0.0025 mg/kg)

Myclobutanil, mg/kg	RH-9090, mg/kg	Total, mg/kg
< 0.01	< 0.01	< 0.02
0.08	< 0.01	0.09

RH-9090 less LOD (0.0025 mg/kg)

Myclobutanil, mg/kg	RH-9090, mg/kg	Total, mg/kg
< 0.01	< 0.0025	< 0.01
0.08	< 0.0025	0.08

RH-9090 equal to or more than LOQ (0.01 mg/kg)

Myclobutanil, mg/kg	RH-9090, mg/kg	Total, mg/kg
0.21	0.03	0.24

Pome fruits

The critical GAP for myclobutanil on pome fruits is in Czech Republic, 3×0.09 kg ai/ha, 14-day PHI. Seven trials were available from Europe on apple against Czech GAP with myclobutanil residue of 0.03(2), 0.05, 0.07, 0.11, 0.20 and 0.34 mg/kg, with total residue of 0.03, 0.04, 0.05, 0.08, 0.12, 0.22 and 0.35 mg/kg.

Eight trials were available from Europe on pear against Czech GAP with myclobutanil residue of 0.03(2), 0.04, 0.05, 0.06, 0.10, 0.28 and 0.32 mg/kg, and with total residue of 0.05(3), 0.06, 0.07, 0.11, 0.29 and 0.35 mg/kg.

Noting the similar data population from apple and pear and medians of the datasets differed less than 5-fold, The Meeting agree to combined the residues, expressed in terms of myclobutanil, which were: 0.03(4), 0.04, 0.05(2), 0.06, 0.07, 0.10, 0.11, 0.20, 0.28, 0.32 and 0.34 mg/kg. The residues expressed in terms of total myclobutanil residues were: 0.03, 0.04, 0.05(4), 0.06, 0.07, 0.08, 0.11, 0.12, 0.22, 0.29 and 0.35(2) mg/kg. On the basis of myclobutanil residues, the Meeting estimated a maximum residue level of 0.6 mg/kg pome fruits to replace the previous recommendation of 0.5 mg/kg. The Meeting also agreed to combine two datasets to estimate an HR of 0.35 mg/kg, an STMR of 0.07 mg/kg based on the total residue.

Stone fruits

The critical GAP for myclobutanil on peach, nectarine and cherry is in the USA, 8× 0.18 kg ai/ha with PHI of 0 day. Nine trials were conducted with application number from 7 to 11 within ± 25% GAP rate in the USA. No significant contribution should be expected from the treatments more than 3 half-lives to the final residue. Myclobutanil residues with 0 day PHI on peach were: 0.34, 0.38, 0.62, 0.66, 0.75, 0.84, 0.85 and 1.23 mg/kg and the total residues were: 0.37, 0.55, 0.76, 0.82, 0.91, 1.06, 1.12 and 1.54 mg/kg.

Eight trials were available from the USA on cherries with myclobutanil residue 0.20, 0.28, 0.75, 0.85, 0.92, 1.04, 1.12 and 1.44 mg/kg, and with total residue 0.22, 0.32, 0.82, 1.05, 1.07, 1.52, 1.61 and 2.05 mg/kg.

The Meeting estimated an HR of 2.05 mg/kg, an STMR 1.06 mg/kg, and maximum residue level of 3 mg/kg for cherry.

The critical GAP for myclobutanil on apricot, plum and prune is from the USA, 7×0.18 kg ai/ha with a PHI of 0 days. Seven trials were available from the USA and Europe on apricot against US GAP, myclobutanil residues were: 0.11, 0.12, 0.17, 0.18, 0.23, 0.34 and 0.62 mg/kg, and total residues were: 0.13, 0.14, 0.21, 0.25, 0.29, 0.38 and 0.70 mg/kg.

Eight trials were available from the USA on plum against US GAP, myclobutanil residues were: 0.09, 0.13, 0.20, 0.25, 0.28, 0.59, 0.97 and 1.12 mg/kg, and total residues were: 0.11, 0.36, 0.40, 0.73 and 1.45 mg/kg.

The Meeting estimated an HR of 1.45 mg/kg, an STMR 0.40 mg/kg, and maximum residue level of 2 mg/kg and agreed to replace the previous recommendation of 0.2 mg/kg for plums.

Considering the higher residues came from peach, the Meeting decided not to combine datasets of peach and apricot, and estimated an HR of 1.54 mg/kg, STMR 0.865 mg/kg, and maximum residue level of 3 mg/kg for peach, nectarine and apricot on the basis of residues of peach. The Meeting agreed to withdraw the previous recommendation of 2 mg/kg for stone fruits (except plums) and 0.5 mg/kg for prunes.

Currants

The critical GAP for myclobutanil on currants is from the UK, 6×0.09 kg ai/ha with a PHI of 14 days. Twelve trials were available from the UK on black currants matching GAP with myclobutanil residue 0.19, 0.24(2), 0.26(2), 0.29, 0.30(2), 0.31, 0.35, 0.42 and 0.43 mg/kg, and with total residue 0.21, 0.28(2), 0.31(2), 0.34(2), 0.35, 0.37, 0.39, 0.46 and 0.47 mg/kg.

The Meeting agreed to estimate an HR 0.47 mg/kg, an STMR 0.34 mg/kg, and maximum residue level of 0.9 mg/kg for currants to replace the previous recommendation of 0.5 mg/kg on currants, black.

Grapes

The critical GAP for myclobutanil on grapes is in the USA, 5×0.15 kg ai/ha with PHI of 14 days. Nine trials were available from the USA on grapes against US GAP. Myclobutanil residues in grapes were: 0.13, 0.14(2), 0.25, 0.31, 0.32(2), 0.48 and 0.53 mg/kg, and total residues in grapes were: 0.17, 0.19(2), 0.29, 0.34, 0.40(2), 0.58 and 0.60 mg/kg.

The Meeting estimated an HR of 0.60 mg/kg, an STMR 0.34 mg/kg, and maximum residue level of 0.9 mg/kg for to replace the previous recommendation of 1 mg/kg for grapes.

Strawberry

The critical GAP for myclobutanil on strawberry is from the USA, 6×0.14 kg ai/ha with a PHI of 0 days. Seven outdoor trials from the USA against US GAP gave residues of: 0.03, 0.04, 0.10, 0.15, 0.20, 0.23 and 0.31 mg/kg.

The critical GAP for myclobutanil on strawberry is from the UK, 6×0.09 kg ai/ha with PHI of 3 days. In 19 outdoor trials from Europe at UK GAP, myclobutanil residues were 0.08, 0.10, 0.14, 0.15, 0.17, 0.18(2), 0.19(4), 0.20(2), 0.22, 0.24, 0.30, 0.48, 0.50 and 0.69 mg/kg, and total residues were 0.09, 0.10, 0.15(2), 0.17, 0.18(2), 0.19(4), 0.20(2), 0.22, 0.24, 0.31, 0.48, 0.50 and 0.69 mg/kg. Eight indoor trials were available from Europe on strawberry matching the GAP of the UK with myclobutanil residues of 0.13, 0.16, 0.18, 0.19, 0.20, 0.24, 0.37and 0.46 mg/kg, and with total residues of 0.14, 0.17, 0.19, 0.20, 0.21, 0.25, 0.38 and 0.47 mg/kg.

Considering the higher residues came from Europe, and residue populations from indoor and outdoor European trials were similar, the Meeting decided to combine the two datasets. The residues from 27 trials were: 0.08, 0.10, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18(3), 0.19(5), 0.20(3), 0.22, 0.24(2), 0.30, 0.37, 0.46, 0.48, 0.50 and 0.69 mg/kg for myclobutanil and 0.09, 0.10, 0.14, 0.15(2), 0.17(2), 0.18(2), 0.19(5), 0.20(3), 0.21, 0.22, 0.24, 0.25, 0.31, 0.38, 0.47, 0.48, 0.50 and 0.69 mg/kg for myclobutanil and RH-9090 and its conjugates. The Meeting estimated a maximum residue level of 0.8 mg/kg on the basis of parent residues for strawberry to replace the previous recommendation of 1 mg/kg on strawberry. The Meeting also estimated an HR of 0.69 mg/kg and an STMR of 0.19 mg/kg on the basis of total residues.

Banana

Myclobutanil is registered in Costa Rica for use as a post-harvest run-off or dip application at 84.8 g ai/hL, application prior to the packing of fruit. Three trials from Costa Rica on banana matching GAP gave myclobutanil residues in whole fruits of 0.028(2) and 0.29 mg/kg. Total residues in banana pulp were 0.06, 0.07 and 0.09 mg/kg.

The Meeting considered three trials to be insufficient for the estimation of a maximum residue level, an STMR and an HR for banana. The Meeting agreed to withdraw the previous recommendation of 2 mg/kg for banana.

Fruiting vegetables, other than Cucurbits

Tomatoes

The critical GAP for myclobutanil on tomatoes is from the USA, 4×0.11 kg ai/ha with a PHI of 0 days. Seventeen outdoor trials were available from the USA on tomatoes matching US GAP with myclobutanil residues of 0.02, 0.03(2), 0.04(2), 0.06, 0.07(5), 0.08(2), 0.09, 0.10, 0.11 and 0.22 mg/kg, and with total residues of 0.02, 0.03, 0.04(2), 0.05, 0.06, 0.07(4), 0.08, 0.09, 0.10(2), 0.11, 0.12 and 0.25 mg/kg.

The Meeting decided to estimate an HR of 0.25 mg/kg, an STMR of 0.07 mg/kg based on total residues, and a maximum residue level of 0.3 mg/kg based on myclobutanil residues for tomatoes, confirming the previous recommendation.

Peppers

The critical GAP for myclobutanil on peppers is from the USA, 4×0.14 kg ai/ha with a PHI of 0 days. Two outdoor trials were available from the USA on sweet pepper matching US GAP with myclobutanil residue 0.03 and 0.47 mg/kg, and with total residue 0.05 and 0.64 mg/kg. Four outdoor trials were available from the USA on chilli pepper against US GAP with myclobutanil residue 0.09, 0.18, 1.19 and 2.03 mg/kg, and with total residue 0.12, 0.23, 1.39, 2.40 mg/kg.

Considering the residues from sweet and chilli peppers to be similar, the Meeting decided to combine the two datasets. The residues in six trials were 0.03, 0.09, 0.18, 0.47, 1.19 and 2.03 mg/kg for myclobutanil and 0.05, 0.12, 0.23, 0.64, 1.39, 2.40 mg/kg for myclobutanil and RH-9090 and its conjugates. The Meeting estimated an HR 2.40 mg/kg, an STMR 0.435 mg/kg based on total residues, and maximum residue level of 3 mg/kg based on myclobutanil residues for peppers.

On the basis of residues in peppers and dehydration factor of 7, the Meeting estimated an HR of 16.8 mg/kg, an STMR of 2.45 mg/kg and recommended a maximum residue level of 40 mg/kg for myclobutanil on peppers chilli, dried.

Fruiting vegetables, Cucurbits

The critical GAP for myclobutanil on cucurbits is from the USA, 5 applications at 0.14 kg ai/ha with a PHI of 0 days.

Summer Squash

Nine outdoor trials were available from the USA on summer squash matching US GAP. Myclobutanil residues in squash were: 0.01(2), 0.02(2), 0.04, 0.05, 0.06, 0.10 and 0.16 mg/kg, and with total residues of 0.01, 0.02, 0.03(2), 0.04, 0.05, 0.07, 0.11 and 0.16 mg/kg.

Cucumber

Seven outdoor trials were available from the USA on cucumbers matching US GAP. Myclobutanil residues were: 0.02, 0.03(2), 0.04(2) and 0.07 mg/kg, and with total residue of 0.03(2), 0.04 (3) and 0.07 mg/kg.

Melons

Four outdoor trials were available from the USA on melons matching US GAP with myclobutanil residues of 0.02, 0.05, 0.07 and 0.08 mg/kg, and with total residues of 0.02, 0.05, 0.07 and 0.08 mg/kg. Two outdoor trials were available from Southern Europe on melon matching US GAP with myclobutanil residues of 0.09 and 0.10 mg/kg, and total residue of 0.10 and 0.11 mg/kg.

The US GAP is the same for cucumbers, melons and squash. The Meeting considered that the residues from trials with the foliar application on cucumber, melon and squash were similar. The Meeting agreed to propose a group maximum residue level for fruiting vegetables, cucurbits. The residues expressed in terms of myclobutanil were: 0.01(2), 0.02(4), 0.03(2), 0.04(3), 0.05(2), 0.06, 0.07(2), 0.08, 0.09, 0.10(2) and 0.16 mg/kg. The residues expressed in terms of myclobutanil and RH-9090 and its conjugates were: 0.01, 0.02(2), 0.03(4), 0.04(4), 0.05(2), 0.07(3), 0.08, 0.10, 0.11(2) and 0.16 mg/kg

Based on the trials for cucumbers, melons and squash in the USA and Southern Europe, the Meeting estimated an HR of 0.16 mg/kg, an STMR of 0.04 mg/kg and a maximum residue level of 0.2 mg/kg for fruiting vegetables, cucurbits respectively.

Legume vegetables

Common bean

The critical GAP for myclobutanil on snap beans is from the USA, i.e., 4×0.14 kg ai/ha with a PHI of 0 days. Nine trials were available from the USA on snap beans matching US GAP. Myclobutanil residues found were: 0.04, 0.09, 0.14, 0.19, 0.20, 0.22, 0.30, 0.37 and 0.47 mg/kg, and total residues were: 0.06, 0.11, 0.16, 0.21, 0.22, 0.24, 0.32, 0.39 and 0.49 mg/kg.

On the basis of the trials on snap beans, the Meeting estimated an HR of 0.49 mg/kg, an STMR 0.22 mg/kg based on the total residues dataset, and a maximum residue level of 0.8 mg/kg for beans, except broad bean and soya bean (green pods and immature seeds), respectively.

Soya bean (dry)

The critical GAP for myclobutanil on soya beans is from Brazil, 2×0.125 kg ai/ha with a PHI of 24 days. Nine trials were available from Brazil on soya bean matching the Brazilian GAP with parent residues of < 0.01(5), < 0.02(2), 0.02 and 0.03 mg/kg.

Noting that total residues were not available from the Brazilian trials, the Meeting did not estimate a maximum residue level for soya bean.

Hops

The critical GAP for myclobutanil on hops is from the USA, 4×0.28 kg ai/ha with a PHI of 14 days. Ten trials were available from Germany on hops matching US GAP, myclobutanil residues in dried hops were: < 0.50, 0.53, 0.63, 0.73, 1.02, 1.06, 1.14, 1.54, 1.80 and 3.50 mg/kg, and with total residues of 0.53, < 1.00, 1.13, 1.23, 1.52, 1.56, 2.04, 3.20 and 5.60 mg/kg.

The Meeting estimated an HR of 5.60 mg/kg, a STMR 1.52 mg/kg based on the total residue dataset, and a maximum residue level of 5 mg/kg for dry hops based on myclobutanil residues to replace the previous recommendation of 2 mg/kg on dry hops.

Animal feedstuffs

The critical GAP for myclobutanil on soya bean is from the USA, 2×0.14 kg ai/ha with a PHI of 28 days.

Soya bean forage

Two trials were available from the USA on soya bean forage matching US GAP with residues of 0.67 and 1.01 mg/kg.

Two trials on soya bean forage were considered insufficient for the estimation of median and highest residues.

Soya bean hay (dry)

Noting no trials on soya bean hay were available from the USA against US GAP, the Meeting did not make recommendations for soya bean hay.

Rotational crops

The Meeting noted that myclobutanil may accumulate in soil and be taken up by following crops in significant amounts. Residues were reported in field rotational crop studies following application to zucchini at rates of 6×0.14 kg ai/ha. Since the foliage of the crop was incorporated into soil after harvest of the fruits, this application rate can be assumed to approximate the estimated soil plateau level following annual treatment according to the GAPs considered by the Meeting.

Residues for parent myclobutanil in respective field studies were < 0.003 mg/kg for soya bean seeds, 0.03 mg/kg to 0.36 mg/kg for soya bean forage and 0.017 mg/kg to 0.093 mg/kg for soya bean straw. The Meeting concluded that for pulses no significant transfer into seeds is expected. Median and highest residues were estimated at levels of 0.195 mg/kg and 0.36 mg/kg for legume forages and of 0.055 and 0.093 mg/kg for legume fodders.

Based on the average dry-matter content of 85% for soya bean hay, the Meeting estimated a maximum residue level of 0.2 mg/kg (DM) for legume animal feeds.

In leaves of radish grown as rotational crops myclobutanil residues were 0.015 mg/kg to 0.044 mg/kg. Extrapolating the residues found in radish leaves to all Brassica vegetables and leafy vegetables (including Brassica leafy vegetables), the Meeting estimated maximum residue levels of 0.05 mg/kg and HR and STMR values of 0.044 mg/kg and 0.030 mg/kg for Brassica vegetables and leafy vegetables (including leafy Brassica vegetables), respectively.

The roots of radish grown as a rotational crop contained myclobutanil residues of 0.026 mg/kg to 0.052 mg/kg. The Meeting decided to extrapolate the results to all bulb vegetables and all root and tuberous vegetables. The Meeting estimated a maximum residue level of 0.06 mg/kg and HR and STMR values of 0.039 mg/kg and 0.052 mg/kg for bulb vegetables and root and tuber vegetables, respectively.

Residues in wheat matrices obtained from field rotational crop studies contained myclobutanil residues < 0.003 mg/kg in the grain, 0.023 mg/kg to 0.071 mg/kg in forage and 0.015 mg/kg to 0.18 mg/kg in hay and straw. The Meeting concluded that for cereal grains no significant transfer of residues into seeds is expected. Median and highest residues were estimated at levels of 0.047 mg/kg and 0.071 mg/kg for cereal forages and of 0.098 and 0.18 mg/kg for cereal straw and fodder.

Based on the average dry-matter content of 88% for wheat straw, the Meeting estimated a maximum residue level of 0.3 mg/kg (DM) for straw and fodder (dry) of cereal grains.

The Meeting also concluded that the contribution of residues by uptake of myclobutanil from soil is insignificant compared to direct treatment for the uses evaluated.

Fate of residues during processing

The Meeting received information on the hydrolysis of myclobutanil as well as processing studies during the food processing of apples, grapes, tomatoes, soya beans and hops.

No degradation of myclobutanil was observed in a hydrolysis study at pH 4, 7 and 9 held at 50 °C, over a 5 day period.

In the following table all processing factors based on parent residues relevant for recommendation of maximum residue levels and estimation of animal dietary burden for processed commodities are summarized.

Portion Analysed		Median Processing Factor	Median resiudes	
			Raw commoditeis	Processed commodities
Apple			0.06	
	Wet pomace	1.61		0.097
	Dry pomace	12.1		0.726
Grapes			0.295	
	Wet pomace	0.90		0.266
	Dry pomace	3.94		1.16
	Raisin	6.31		1.86
Tomato			0.07	
	Dry pomace	20.05		1.40
	Wet pomace	4.54		0.318
Soya bean			0	
	Hulls	1.14		0
	Meal	0.43		0
	Oil, refined	2.14		0
Hops			1.04	
	Beer	0.0145		0.015

Based on the median processing factor of 6.31, the Meeting estimated a maximum residue level of 6 mg/kg for raisins.

In the following table all processing factors based on total residues relevant for the estimation of the dietary intake for processed commodities are summarized.

Raw and processed commodity		Median Processing Factor	STMR (mg/kg)	STMR-P (mg/kg)	HR (mg/kg)	HR-P (mg/kg)
Apple			0.07			
	Juice	0.17		0.012		
	Puree	0.30		0.021		
Grapes			0.34		0.60	
	Juice	0.20		0.068		
	Wine after half year	0.17		0.058		
	Wine at bottling	0.14		0.048		
	Raisin	6.29		2.14		3.77
Tomato			0.07			
	Juice	0.50		0.031		
	Purée	1.33		0.093		
	Preserve	0.29		0.020		
	Paste	3.92		0.27		
Hops	Beer	0.015	1.52	0.023		

Residues in animal commodities

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, broilers and layers are provided in Annex 6 to the 2014 Report. The calculations were made according to the animal diets from US-Canada, EU, Australia and Japan in the OECD Feed Table 2009.

The calculations are then summarised and the highest dietary burdens are selected for MRL and STMR estimates on animal commodities.

	Animal dietary burden, myclobutanil, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle	0.046	0.26	1.22	0.83	1.47 [a]	0.96 [b]	0.096	0.055
Dairy cattle	0.63	0.45	0.86	0.58	1.31 [c]	0.88 [d]	0.18	0.10
Poultry-broiler	0	0	0.035	0.026	0	0	0.051	0.028
Poultry-layer	0	0	0.22 [e]	0.13 [f]	0	0	0	0

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat.
[b] Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.
[c] Highest maximum dairy cattle dietary burden suitable for MRL estimates for mammalian milk.
[d] Highest mean dairy cattle dietary burden suitable for STMR estimates for mammalian milk.
[e] Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.
[f] Highest mean poultry dietary burden suitable for STMR estimates for meat and eggs.

Lactating cows were orally administered myclobutanil equivalent to 0 ppm, 1.6 ppm, 4.8 ppm and 16 ppm in the feed, respectively. Residues of myclobutanil and RH-9090 in whole milk and tissues of the cows in all groups were < 0.01 mg/kg.

Dietary burden calculations showed the highest dietary burdens were less than the lowest feeding level. The Meeting decided to estimate maximum residue levels of 0.01*, and STMRs and HRs of 0 mg/kg for all milk, eggs and animal tissues. Confirming the previous recommendations of 0.01* mg/kg for cattle meat, milk and edible offal, and eggs, poultry meat and edible offal of the 1992 JMPR.

RECOMMENDATIONS

On the basis of the data from supervised trials, the Meeting concluded that the residue concentrations listed below are suitable for establishing MRLs and for assessing IEDIs and/or IESTIs.

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

Definition of the residue (for estimation of dietary intake for plant commodities): *sum of myclobutanil, α-(4-chlorophenyl)-α-(3-hydroxybutyl)-1H- 1,2,4-triazole-1-propanenitrile (RH-9090) and its conjugates, expressed as myclobutanil*.

DIETARY RISK ASSESSMENT

Long term intake

The evaluation of myclobutanil resulted in recommendations for MRLs and STMR values for raw and processed commodities. Data on consumption were available for 33 food commodities and were used to calculate dietary intake. The results are shown in Annex 3 to the 2014 Report.

The International Estimated Daily Intakes (IEDIs) of myclobutanil, based on the STMRs estimated, represented 1–6% of the upper bound of the maximum ADI of 0.03 mg/kg bw for the 17 GEMS/Food cluster diets. The Meeting concluded that the long-term intake of residues of myclobutanil resulting from its uses that have been considered by the JMPR was unlikely present a public health concern.

Short-term intake

The 2014 Meeting established an ARfD of 0.3 mg/kg bw for women of childbearing age only; ARfD was unnecessary for the general population.

The International Estimated Short Term Intake (IESTI) for myclobutanil was calculated for the food commodities for which STMRs, HRs and maximum residue levels were estimated by the current Meeting and for which consumption data were available. The results are shown in Annex 4 to the 2014 Report. The IESTI represented up to 10% (peach) for women of childbearing age only. The Meeting concluded that the short-term intake of residues of myclobutanil resulting from uses considered by the current Meeting was unlikely to present a public health concern.