

DIETARY RISK ASSESSMENT

The current Meeting has established an ADI of 0–0.03 mg/kg bw and an ARfD of 0.1 mg/kg bw for acephate. In considering how to best approach the dietary risk assessment of mixed residues of acephate and methamidophos the 2003 JMPR decided that an appropriately conservative approach would be to sum the acephate and methamidophos residues after first scaling the methamidophos residues by a factor to account for the difference in toxicity. The current Meeting utilized the same approach, with relevant factors, for long and short-term intake, derived from the ratios of the acephate and methamidophos ADI and ARfD values; the factors are 7.5 and 10 respectively. Dietary intake estimates for the combined adjusted residues utilizing the new scaling factors were compared with the revised acephate ADI and ARfD.

Long-term intake

The International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs were in the range 1–7% of the maximum ADI of 0.03 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of acephate from uses that have been considered by the 2003 JMPR is unlikely to present a public health concern.

Short-term intake

The IESTI varied from 0% to 170% of the ARfD (0.1 mg/kg bw) for the general population and from 0% to 390% of the ARfD for children aged 6 years and below. The short-term intakes from apple, cauliflower and peppers were 110–170% of the ARfD for the general population and the short-term intakes from apple, broccoli, cauliflower, mandarin, nectarine, pear, peach and peppers were 130–390% of the ARfD for children aged 6 years and below. The information provided to the 2003 JMPR and re-evaluated in the current Meeting precluded a conclusion that the acute dietary intake of pome fruit (e.g. apple, pear) flowerhead brassicas (e.g. broccoli and cauliflower), mandarin, nectarine, peach and peppers would be below the ARfD.

The Meeting concluded that the short-term intake of residues of acephate from uses considered by the 2003 JMPR is unlikely to present a public health concern, with the exception of pome fruit (e.g. apple, pear) flowerhead brassicas (e.g. broccoli, cauliflower), mandarin, nectarine, peach and peppers.

4.2 AZOCYCLOTIN (067) AND CYHEXATIN (129)

TOXICOLOGY

Azocyclotin (tri(cyclohexyl)-1H-1,2,4-triazole-1-yltin) and cyhexatin (tricyclohexyltin hydroxide) are chemically-related organotin compounds that are used as agricultural acaricides. Azocyclotin breaks down to cyhexatin and 1,2,4-triazole. Azocyclotin has similar systemic toxicological properties to cyhexatin and may also have additional properties attributable to the 1,2,4-triazole that is formed.

Toxicological data on cyhexatin were reviewed by the JMPR in 1970, 1973, 1977, 1978, 1980, 1981, 1988, 1989, 1991 and 1994. Azocyclotin was evaluated by the JMPR in 1974, 1981, 1989 and 1991. The Meeting in 1991 considered that the ADI for cyhexatin should also cover exposure to azocyclotin. In 1994, an ADI of 0–0.007 mg/kg bw was established based on a NOAEL of 0.7 mg/kg bw per day for reduced pup survival and decreased pup body-weight gain during lactation in a multigeneration study in rats.

Azocyclotin and cyhexatin were considered by the present Meeting as part of the CCPR periodic review programme.

Several new GLP-compliant studies of cyhexatin were evaluated that had not been previously available, including investigations of absorption, distribution, metabolism and excretion, short-term studies of toxicity, tests for genotoxicity, and a long-term study of combined toxicity/carcinogenicity incorporating a neurotoxicity phase.

Biochemical aspects

Oral doses of azocyclotin and cyhexatin were absorbed to a limited extent in rats. About 12% of azocyclotin or its breakdown products were absorbed from the gut lumen in rats and 1.6–10% in the case of cyhexatin. In rabbits given oral doses of cyhexatin, less than 10% of the administered dose was absorbed from the gut. Azocyclotin was shown to completely break down in aqueous solution to form cyhexatin and 1,2,4-triazole. There were no investigations available on whether 1,2,4-triazole undergoes any metabolism in the body.

Cyhexatin is metabolized by hydroxylation, which splits off cyclohexyl rings to produce dicyclohexyltin and monocyclohexylstannic acid. The products of the initial reactions can undergo oxidation to produce unidentified polar metabolites. In addition, hydroxylated and destannylated derivatives have been identified in faeces of animals treated with cyhexatin, but it is not clear whether these were the products of bacterial and chemical breakdown in the gut lumen or the products of metabolism of absorbed material that had been excreted in bile. There was extensive distribution of metabolites of azocyclotin and cyhexatin to various organs and tissues of the body, with the highest amounts being found in the liver and the kidneys. Elevated levels of tin and ¹⁴C radiolabel were detected in fetuses, amniotic fluid and placenta in pregnant rabbits given oral doses of ¹⁴C-labelled cyhexatin.

In all species investigated (rat, rabbit and guinea-pig), excretion of the metabolites of azocyclotin and cyhexatin was mostly in the urine and to a lesser extent in the bile. As a result of poor absorption, large proportions of orally administered doses of azocyclotin and cyhexatin were found in the faeces. Minimal amounts were exhaled as carbon dioxide.

Toxicological data

Azocyclotin and cyhexatin had moderate acute toxicity by the oral route. The LD₅₀ values for azocyclotin and cyhexatin in rats were 209 mg/kg bw and 265 mg/kg bw, respectively, when administered by the oral route. Azocyclotin and cyhexatin had very low acute systemic toxicity when applied dermally, with LD₅₀ values for rats of 3600 mg/kg bw and > 2000 mg/kg bw, respectively, but high acute toxicity after exposure by inhalation, with LC₅₀ values for rats of approximately 0.02 mg/L for azocyclotin and 0.016 mg/L for cyhexatin.

Cyhexatin was a severe irritant to skin and eyes of rabbits. Azocyclotin was more irritant than cyhexatin, being corrosive to rabbit skin. Neither azocyclotin nor cyhexatin caused skin sensitization in tests in guinea-pigs.

Exposure to azocyclotin at a dose of 0.96 µg/L by inhalation caused poorly groomed appearance, impaired breathing and increased lung weight in rats exposed for 6 h per day, 5 days per week, for 3 weeks. The no-observed-adverse-effect concentration (NOAEC) for the study was 0.28 µg/L. Inhalation exposure of rabbits to cyhexatin at 0.21 mg/L or more for 6 h per day, 5 days per week, for 2 weeks, caused inflammation of the respiratory tract, pulmonary congestion and toxicity to the liver and kidneys. The NOAEC was 0.077 mg/L.

No systemic toxicity was seen in rats given azocyclotin at doses of up to 25 mg/kg bw per day applied dermally for 7 h per day, 5 days per week, for 3 weeks. However, increased serum alkaline phosphatase activity was found when cyhexatin at a dose of 1 mg/kg bw per day was applied to the skin of rabbits for 6 h per day, 5 days per week, for 3 weeks. The NOAEL was 0.3 mg/kg bw per day.

In short-term studies with azocyclotin and cyhexatin, the main toxicological effects seen in rats were local effects on the gastric mucosa, haematological changes and hepatotoxicity. However, no treatment-related adverse effects were seen in a 90-day repeat-dose dietary toxicity study that delivered cyhexatin at doses of up to 10 mg/kg bw per day to mice. When cyhexatin was given at doses of 10 or 20 mg/kg bw per day by gavage for 14 or 28 days, erosions and/or ulcers of the glandular gastric mucosa were seen in some animals at both doses. A 28-day dietary study with cyhexatin in rats showed haematological changes related to changes in erythrocyte and blood clotting parameters at 6 mg/kg bw per day. The NOAEL was 3 mg/kg bw per day. In a 90-day study with cyhexatin in rats, there was hepatotoxicity and liver regeneration at dietary concentrations of 50 ppm or more, with a NOAEL of 10 ppm (equal to 0.68 mg/kg bw per day).

Three short-term studies of oral toxicity with azocyclotin were performed in rats, one using gavage dosing and the others using dietary administration. Low body weights were reported in treated animals in all the studies at dietary concentrations of 50 ppm (equal to 2.86 mg/kg bw per day) or more. Decreased total leukocyte counts were reported in two of the studies, with decreased lymphocyte counts in one of these. The NOAEL was 2 mg/kg bw per day. Increased liver weight and increased activities of serum enzymes, such as alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase, were reported in two of the studies. The NOAEL for these effects was 15 ppm (equal to 0.85 mg/kg bw per day).

The toxicity of dietary doses of cyhexatin in dogs was investigated in studies with durations of 90 days, 1 year and 2 years. In the 90-day and 1-year studies, no treatment-related adverse effects were seen at up to the maximum doses tested of 6 and 0.75 mg/kg bw per day, respectively. In the 2-year study, the body weights of the dogs given cyhexatin at a dose of 6 or 12 mg/kg bw per day were reduced compared with those of controls. The NOAEL was 3 mg/kg bw per day.

Feeding studies in dogs given azocyclotin for 90 days or 24 months both showed diarrhoea to be a critical end-point, with a NOAEL of 0.36 mg/kg bw per day. In the 24-month study, diarrhoea was seen in all dogs given azocyclotin at a dose of 1.09 mg/kg bw per day or more. In the 90-day study, there was also a decrease in body-weight gain at 1.73 mg/kg bw per day or more, although this effect was not seen at doses of up to 1.09 mg/kg bw per day in the 24-month study. Thus the NOAEL for decreased body-weight gain was 1.09 mg/kg bw per day. Haematological effects (decreases in erythrocyte count, erythrocyte volume fraction and haemoglobin) were seen in some of the males at 18.3 mg/kg bw per day in the 90-day study. It was considered to be likely that the decreased body weight and diarrhoea were related to the corrosiveness of azocyclotin.

The most sensitive effect seen in long-term studies of toxicity/carcinogenicity with azocyclotin in mice and rats was decreased body weight compared with that of the controls, with NOAELs of 2.12 mg/kg bw per day in mice and 50 ppm (equal to 0.26 mg/kg bw per day) in Wistar rats.

The NOAEL for cyhexatin in a long-term study in mice was 3 mg/kg bw per day on the basis of increased mortality and decreased body weight at 6 mg/kg bw per day. Three long-term studies of toxicity/carcinogenicity were performed with cyhexatin in Sprague-Dawley rats. Increased incidence of retinal atrophy was seen at dietary concentrations of 30 and 180 ppm in one of these studies, with a slight increase in severity at 180 ppm. In the same study there was an increased incidence of minimal to mild bile duct hyperplasia in treated rats. This effect was of equivocal toxicological significance

because there was no progression in severity with increasing doses. The NOAEL was 7.5 ppm (equal to 0.34 mg/kg bw per day) on the basis of retinal atrophy.

Azocyclotin did not produce any tumours in combined long-term studies of toxicity/carcinogenicity in mice and rats. With cyhexatin, no tumours were produced in a long-term study of toxicity/carcinogenicity in mice. In one out of three studies in rats, there were slightly increased incidences of hepatocellular adenomas in both sexes at 30 and 180 ppm. However, only the increased incidence in the females at 180 ppm was statistically significant. As the increased incidence of benign tumours was seen only in one sex at one dose in one of four studies with cyhexatin in rats, and as the effect was not seen in studies with azocyclotin in mice and rats, the Meeting concluded that cyhexatin and azocyclotin were unlikely to be carcinogenic in rodents.

Azocyclotin was not genotoxic in an extensive range of tests for genotoxicity in vitro and in vivo. Cyhexatin gave negative results in most tests for genotoxicity in vitro, but gave positive results in a test for mutation of the xanthine-guanine phosphoribosyl transferase (XPRT) gene in vitro in the presence of metabolic activation, and equivocal results in the absence of metabolic activation. It also gave equivocal results in a test for chromosomal effects in vitro. Cyhexatin gave negative results in a test for micronucleus formation in bone marrow of mice in vivo.

The Meeting concluded that cyhexatin and azocyclotin are unlikely to be genotoxic in vivo.

In the absence of genotoxicity in vivo and with the finding of an equivocal increase in the incidence of benign liver tumours at a high dose in female rats in only one out of four studies of carcinogenicity in rodents, the Meeting concluded that use of azocyclotin or cyhexatin as pesticides is unlikely to pose a carcinogenic risk to humans.

In a multigeneration study in rats given diets containing azocyclotin at concentrations of up to 50 ppm (equivalent to 3.7 mg/kg bw per day), there were no treatment-related adverse effects. The lowest NOAEL identified in any of three studies of reproduction in rats given cyhexatin was 0.5 mg/kg bw per day for maternal hepatotoxicity (periductal inflammation, decreased glycogen content and bile duct hyperplasia) and on the weaning weight and survival to weaning of the pups. In one of the two-generation studies of reproduction with cyhexatin there was delayed eye opening in male and female pups at a dietary concentration of 100 ppm (equal to 7.0 mg/kg bw per day), with an NOAEL of 30 ppm (equal to 2.1 mg/kg bw per day). There were associations between the delayed eye opening and low pup weight at weaning, decreased maternal body weight and decreased maternal feed intake. The Meeting concluded that the pup toxicity was secondary to maternal toxicity.

Two studies of developmental toxicity with azocyclotin in rats treated orally by gavage found no fetotoxicity or teratogenicity at any dose tested up to 30 mg/kg bw per day and no effects on embryotoxicity at doses that were not maternally toxic. The NOAELs for maternal toxicity of azocyclotin administered by gavage, as indicated by effects on body weight, were 3 and 0.3 mg/kg bw per day in rats and rabbits, respectively. Embryotoxicity (increased number of resorptions) was seen in rats given azocyclotin a dose of 30 mg/kg bw per day by gavage. Similarly with cyhexatin, a limited study of developmental toxicity in rats showed no developmental effects at doses of up to 10 mg/kg bw per day and a NOAEL for maternal toxicity of 1 mg/kg bw per day was identified. In addition, a developmental toxicity phase included in one of the two-generation studies of reproduction in rats treated with cyhexatin gave no indication of developmental toxicity at dietary concentrations of up to 100 ppm (equal to 7 mg/kg bw per day).

Six studies of developmental toxicity in rabbits have been performed with cyhexatin and two with azocyclotin. There was no embryotoxicity, fetotoxicity or teratogenicity in rabbits given azocyclotin at doses of up to 1 mg/kg bw per day by gavage. The NOAEL for maternal toxicity was 0.3 mg/kg bw per day. Maternal toxicity caused by cyhexatin, as indicated by reduced body-weight gain, was seen with an overall NOAEL of 1.5 mg/kg bw per day (in rabbits treated by gavage).

Embryotoxicity (postimplantation loss) was seen at a dose of 3 mg/kg bw per day in three of the studies in rabbits given cyhexatin by gavage. The highest NOAEL for embryotoxicity in these studies was 1.5 mg/kg bw per day (in rabbits treated by gavage). In two of the studies in rabbits (Dutchland New Zealand White rabbits from the same supplier) given cyhexatin by oral gavage, there were statistically significant increases in the incidence of hydrocephaly and/or dilated brain ventricles. Equivocal effects were recorded at 0.75 mg/kg bw per day and above in one study. Hydrocephaly was also seen in a study of dermal toxicity in Dutchland New Zealand White rabbits from the same supplier to test the same batch of cyhexatin. Other studies used other batches of cyhexatin either in Charles River New Zealand White rabbits or hybrid Hy/Cr New Zealand White rabbits. In these studies; hydrocephaly and/or dilated ventricles were either not seen at all or seen only at very low incidences at higher doses of cyhexatin. The Meeting concluded that the hydrocephaly observed in two studies was probably a consequence of the unique susceptibility of the substrain of New Zealand White rabbits and/or of a unique toxicity of the batch of cyhexatin used in the study. As a consequence, the finding of hydrocephaly was not relevant to the risk assessment. The Meeting concluded that neither azocyclotin nor cyhexatin were teratogenic or fetotoxic, and that cyhexatin was embryotoxic with a NOAEL of 1.5 mg/kg bw per day.

A 90-day study of neurotoxicity with cyhexatin showed that it was not neurotoxic in rats at dietary concentrations of up to 240 ppm (equal to 13.6 mg/kg bw per day). At the start of the study, the highest dietary concentration had been 360 ppm, but this was reduced to 240 ppm because of high mortality, feed refusal, body-weight loss and adverse clinical signs. There were adverse effects on body-weight gain, food consumption and clinical signs (emaciation, pale extremities, abnormal faeces and hypoactivity) at doses of 180 ppm (equal to 10.9 mg/kg bw per day) or more. The NOAEL for the study was 30 ppm (equal to 1.99 mg/kg bw per day).

The toxicity of the metabolite, dicyclohexyltin oxide, was tested in a 90-day dietary study in rats. No treatment-related adverse effects were seen at any dose up to the highest used, 6 mg/kg bw per day. The results of this study showed that dicyclohexyltin oxide was less toxic than either cyhexatin or azocyclotin.

No health problems were reported in most workers at a factory producing a product that contained 25% azocyclotin. However, one worker who had not worn the recommended personal protective equipment had an exposure that led to “an irritating toxic spastic bronchitis”. Recovery was complete within 3 days. Monitoring of workers at a factory manufacturing cyhexatin over a period of 10 years showed no adverse health effects.

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

Toxicological evaluation

In dogs, azocyclotin caused reduced body weight and clinical signs, including diarrhoea, at dietary concentrations of 30 ppm (equal to 1.09 mg/kg bw per day) or more. The NOAEL was 5 ppm (0.16 mg/kg bw per day). These effects were not used in the establishment of an ADI or an ARfD. The Meeting recognized that some of the reported adverse effects of both azocyclotin and cyhexatin were a secondary consequence of an irritating effect on the gastrointestinal mucosa and therefore were not relevant for establishing reference values.

The Meeting established a group ADI for azocyclotin and cyhexatin of 0–0.003 mg/kg bw based on the NOAEL of 0.34 mg/kg bw per day for retinal atrophy in a long-term study of toxicity/carcinogenicity with cyhexatin in rats and using a safety factor of 100.

The Meeting established a group ARfD for azocyclotin and cyhexatin of 0.02 mg/kg bw based on the NOAEL of 1.5 mg/kg bw per day for embryotoxicity in studies of developmental

toxicity with cyhexatin in rabbits, and using a safety factor of 100. The ARfD is applicable to women of childbearing age. No ARfD is necessary for the rest of the population, as the only other acute responses were related to dietary refusal and/or local irritation of the gut.

The Meeting recognized that the ARfD might be conservative, but it was not possible to determine whether the embryotoxicity was the result of systemic toxicity to the conceptus or the result of reduced nutrition caused by reduced maternal food intake and local adverse effects to the maternal gastrointestinal mucosa as a result of the irritant nature of the cyhexatin.

Levels relevant to risk assessment

(i) Studies with azocyclotin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Long-term study of toxicity ^c	Toxicity	15 ppm (equal to 2.12 mg/kg bw per day)	7.58 mg/kg bw per day
		Carcinogenicity	50 ppm (equal to 7.58 mg/kg bw per day) ^a	—
Rat	Long-term study of toxicity ^c	Toxicity	5 ppm (equal to 0.26 mg/kg bw per day)	15 ppm (equal to 0.79 mg/kg bw per day)
		Carcinogenicity	50 ppm (equal to 1.08 mg/kg bw per day) ^a	—
	Multigeneration study ^c	Reproductive toxicity	50 ppm (3.7 mg/kg bw per day) ^a	—
	Developmental toxicity ^b	Maternal toxicity	3 mg/kg bw per day	10 mg/kg bw per day
		Embryotoxicity	10 mg/kg bw per day	30 mg/kg bw per day
Teratogenicity and fetotoxicity		30 mg/kg bw per day ^a	—	
Rabbit	Developmental toxicity ^b	Maternal toxicity (reduced body-weight gain)	0.3 mg/kg bw per day	1.0 mg/kg bw per day
		Developmental effects	1.0 mg/kg bw per day ^a	—

^a Highest dose tested

^b Gavage administration

^c Dietary administration

(ii) Studies with cyhexatin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Long-term study of toxicity/carcinogenicity ^d	Toxicity	3 mg/kg bw per day ^b	6 mg/kg bw per day ^b
		Carcinogenicity	6 mg/kg bw per day ^{a, b}	—
Rat	Long-term study of toxicity/carcinogenicity ^d	Toxicity (retinal atrophy)	7.5 ppm (equal to 0.34 mg/kg bw per day)	30 ppm (equal to 1.39 mg/kg bw per day)
		Multigeneration study ^d	Toxicity	0.5 mg/kg bw per day ^b
	Toxicity		0.5 mg/kg bw per day ^b	6.0 mg/kg bw per day ^b
	Developmental toxicity		7.0 mg/kg bw per day ^{a, b}	—
	Developmental toxicity ^c	Maternal toxicity	1 mg/kg bw per day	5 mg/kg bw per day
		Developmental toxicity	10 mg/kg bw per day ^a	—
Neurotoxicity ^d	Toxicity	30 ppm (equal to 1.99 mg/kg bw per day)	180 ppm (equal to 10.94 mg/kg bw per day)	
Dog	2-year study ^d	Toxicity	3 mg/kg bw per day	6 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
Rabbit	Developmental toxicity ^c	Maternal toxicity	1 mg/kg bw per day	3 mg/kg bw per day
		Developmental toxicity	1.5 mg/kg bw per day	3 mg/kg bw per day

^a Highest dose tested

^b Dietary concentrations were regularly adjusted to achieve set doses

^c Gavage administration

^d Dietary administration

Estimate of acceptable daily intake for humans

0–0.003 mg/kg bw

Estimate of acute reference dose

0.02 mg/kg bw for women of childbearing age

Unnecessary for the rest of the population

Studies that would provide information useful to the continued evaluation of the compound

The metabolic fate of the 1,2,4-triazole that splits off from azocyclotin when it breaks down to form cyhexatin is unknown.

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

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	Limited absorption in rats: about 12% absorption of azocyclotin or its breakdown products
Distribution	Extensive, with the largest amounts being found in the liver and kidneys
Potential for accumulation	Accumulation is unlikely
Rate and extent of excretion	Excreted in urine (1% of the administered ¹¹³ Sn and about 10% of the administered ¹⁴ C from radiolabelled azocyclotin) and probably also in bile. Minimal amounts were exhaled as carbon dioxide.
Metabolism in mammals	Hydrolyses rapidly in aqueous solution to cyhexatin and 1,2,4-triazole.
Toxicologically significant compounds (animals, plants and environment)	Azocyclotin and cyhexatin

Acute toxicity

Rat LD ₅₀ oral	209 mg/kg bw for males; 363 mg/kg bw for females
Rat LD ₅₀ dermal	> 2000 mg/kg bw
Rat LC ₅₀ inhalation	0.017 mg/L for males; 0.029 mg/L for females
Mouse LC ₅₀ inhalation	0.035 mg/L
Golden hamster LC ₅₀ inhalation	0.0055 mg/L for males
Rabbit, skin irritation	Corrosive
Rabbit, eye irritation	Not tested but taken to be corrosive
Skin sensitization (test method used)	No skin sensitization potential in guinea-pigs (Magnusson & Kligman test)

Short-term studies of toxicity

Target/critical effects	Reduced body-weight gain (rats, rabbits, dogs)
Lowest relevant oral NOAEL	0.3 mg/kg bw per day (rabbits)

<i>Genotoxicity</i>	
	Not genotoxic in vitro or in vivo
<i>Long-term studies of toxicity and carcinogenicity</i>	
Target/critical effects	Low body weight
Lowest relevant oral NOAEL	0.26 mg/kg bw per day (rats)
Carcinogenicity	Unlikely to pose a carcinogenic risk to humans
<i>Reproductive toxicity</i>	
Reproduction target/critical effect	No adverse effects on reproduction at any dose in the multigeneration study
Lowest relevant reproductive NOAEL	3.7 mg/kg bw per day (highest dose tested)
Developmental target/critical effect	Embryotoxicity
NOAEL for maternal toxicity	0.3 mg/kg bw per day (reduced maternal body-weight gain in rabbits)
Lowest relevant developmental NOAEL	10 mg/kg bw per day (embryotoxicity in rats)
<i>Medical data</i>	
Health monitoring of workers	An "irritating toxic spastic bronchitis" reported in one exposed worker in a factory

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

<i>Absorption, distribution, excretion and metabolism in mammals</i>	
Rate and extent of oral absorption	Limited absorption in rats (1.6–10%) and rabbits (10%)
Distribution	Extensive, with the largest amounts being found in the liver and kidneys
Potential for accumulation	Accumulation is unlikely
Rate and extent of excretion	Excretion was mainly in the urine and to a lesser extent in bile
Metabolism in mammals	Splitting off of cyclohexyl rings and oxidation to produce a variety of substances (most of which were unidentified)
Toxicologically significant compounds (animals, plants and environment)	Cyhexatin
<i>Acute toxicity</i>	
Rat LD ₅₀ oral	407 mg/kg bw for males; 265 mg/kg bw for females
Rat LD ₅₀ dermal	7600 mg/kg bw for males; 3600 mg/kg bw for females
Rabbit LD ₅₀ dermal	> 2000 mg/kg bw
Rat LC ₅₀ inhalation	0.016 mg/L
Rabbit, skin irritation	Irritant
Rabbit, eye irritation	Severely irritant
Skin sensitization (test method used)	No skin sensitization potential in guinea-pigs (Buehler test)
<i>Short-term studies of toxicity</i>	
Target/critical effect	Hepatotoxicity (rats); low body weight (dogs)
Lowest relevant oral NOAEL	0.68 mg/kg bw per day (rats)
<i>Genotoxicity</i>	
	Not genotoxic in vivo
<i>Long-term studies of toxicity and carcinogenicity</i>	
Target/critical effects	Mortality and body weight (mice); retinal atrophy (rats)
Lowest relevant oral NOAEL	0.34 mg/kg bw per day for retinal atrophy (rats)
Carcinogenicity	Unlikely pose a carcinogenic. risk to humans

<i>Reproductive toxicity</i>	
Reproduction target/critical effect	Decreased pup weight at weaning and decreased survival to weaning at parentally toxic doses
Lowest relevant reproductive NOAEL	Parents and offspring: 0.5 mg/kg bw per day Reproductive toxicity: 7.5 mg/kg bw per day, highest dose tested (rats)
<i>Developmental toxicity</i>	
Developmental target/critical effect	Embryotoxicity (postimplantation loss) in rabbits
NOAEL for maternal toxicity	1.5 mg/kg bw per day in studies of developmental toxicity in rabbits (low body-weight gain). 0.5 mg/kg bw per day in a two-generation study in rats (hepatotoxicity)
Lowest relevant developmental NOAEL	1.5 mg/kg bw per day for embryotoxicity in rabbits.
<i>Medical data</i>	
Health monitoring of workers	No adverse effects seen

Summary for azocyclotin and cyhexatin

	Value	Study	Safety factor
Group ADI	0–0.003 mg/kg bw	Rat, 2-year study, NOAEL	100
Group ARfD*	0.02 mg/kg bw	Rabbit, developmental toxicity, NOAEL	100

* For women of childbearing age, unnecessary for the rest of the population

RESIDUE AND ANALYTICAL ASPECTS

Azocyclotin and cyhexatin are organotin acaricides effective against phytophagous mites. The compounds have been reviewed by the JMPR many times since 1970, the last residue evaluation of azocyclotin being in 1991 and of cyhexatin in 1992. In 2005, the Meeting established a group ADI of 0–0.003 mg/kg bw and a group ARfD of 0.02 for women of child-bearing age for cyhexatin and azocyclotin.

At the 22nd Session of CCPR, the Committee decided to harmonize the residue definition of azocyclotin and cyhexatin as the sum of both compounds, expressed as cyhexatin. The Committee also decided to have two separate but identical lists of CXLs. At the 33rd Session of CCPR, all CXLs were withdrawn, with the exception of apple, citrus fruits, grapes, meat (from mammals other than marine mammals), milk products, milks and pear for cyhexatin, and citrus fruits, grapes, meat (from mammals other than marine mammals), milk products and milks for azocyclotin. The compounds were listed in the Periodic Re-Evaluation Programme at the 36th Session of CCPR for periodic review by the 2005 JMPR.

The present Meeting received and evaluated information on the identity and physical chemical properties of the compounds, metabolism in farm animals and plants, methods of residue analysis and freezer storage stability for cyhexatin, national use patterns, supervised residue trials and processing studies.

Animal metabolism

Three metabolism studies conducted in farm animals were submitted. One study was conducted in dairy cows dosed with cyclohexyl UL-¹⁴C-azocyclotin (gelatin capsule with β -lactose) for 5 consecutive days at a rate of 0.5 mg/kg bw. Kidney, liver, heart, brain, muscle, omental, renal and back fat samples were excised and analysed. More than 98% of the radioactivity present in the tissues

was extracted. Liver, kidney and heart contained the greatest concentration of radioactive residues (0.34, 0.25 and 0.12 mg/kg azocyclotin equivalents (eq), respectively). Muscle, fat and brain contained 0.09, 0.10 and 0.04 mg/kg azocyclotin eq, respectively. Milk collected once or twice a day during the dosing period, reached a maximum residue level at day 4 (0.02 mg/kg azocyclotin eq). Most of the extracted radioactivity (43% TRR in fat, 84% in muscle, and 92% in milk) was assigned as azocyclotin/cyhexatin, as it was stated that no distinction could be made between the compounds in the TLC plate. No cyhexatin standard was, however, applied to the TLC. Dicyclohexyl tin oxide (DCTO) was responsible for up to 23% TRR in fat and up to 15% in loin muscle. From 4% TRR (milk) to 33% (fat) was identified as cyclohexyl stannic acid (MCTA), which was not detected in heart or muscle.

One study conducted in two lactating goats dosed with ^{119}Sn -cyhexatin for 4 days at 100 ppm in the feed was submitted. On average, 68.5% of the administered radioactivity was recovered from the animals, from which 44% was found in the faeces, 24% in the gastrointestinal (GI) tract and 0.15% in the liver (mean of 1.1 mg/kg cyhexatin eq). Less than 0.1% was found in the other tissues and milk, corresponding, on average, to 0.56 mg/kg cyhexatin eq in kidney, 0.08 mg/kg cyhexatin eq in muscle and up to 0.02 mg/kg eq in milk. Most of the radioactivity found in tissues was cyhexatin (from 70 to 84% TRR in the organic extract), with less than 10% of DCTO and MCTA. Only the parent compound was found in milk.

In one study conducted with laying hens (two groups of six) dosed with ^{119}Sn -cyhexatin for 5 days at 100 ppm in the feed, most of the administered radioactivity (mean of 66.3%) was found in the excreta (63.5%). Liver and kidney had the highest residues (mean of 3.0 and 2.8 mg/kg cyhexatin eq, respectively), followed by muscle (mean of 0.42 mg/kg cyhexatin eq) and fat (0.36 mg/kg cyhexatin eq). Residues in eggs increased during the dose period and were concentrated in the yolk. On day 2, mean residues in the yolk were 0.2 mg/kg cyhexatin eq and in egg white, 0.055 mg/kg. On day 5, residues reached 3.6 and 0.22 mg/kg cyhexatin eq in yolk and white respectively. The organic tissue extracts showed mostly cyhexatin (up to 50% TRR), DCTO (up to 30% TRR) and MCTA (up to 16% TRR). Egg white contained less than 10% TRR of cyhexatin, while only the parent compound was found in the yolk.

Metabolism studies conducted in rats with cyhexatin and azocyclotin and evaluated by the present Meeting (Toxicological evaluation) showed a similar metabolic pathway described for farm animals.

Plant metabolism

Three studies conducted in plants were submitted. Apples, treated with cyclohexyl $\text{U-}^{14}\text{C}$ -azocyclotin applied at a rate of 0.03 kg ai/hL, had most of the applied radioactivity in the organic fraction of the acetone wash of the fruits (from 96% at day 0 to 29% at day 21). On average, 78% TRR was azocyclotin/cyhexatin, 9% DCTO and 2% MCTA. On day 21, 11% of the applied radioactivity was found in the peel and < 1% in the pulp. Only 70% TRR found in the peel was characterized, being approximately 9% azocyclotin/cyhexatin and 27% DCTO and MCTA (11% stayed at the TLC origin and 17% remained in the aqueous phase).

In one study conducted with ^{119}Sn cyhexatin on apples at 3.8 kg ai/ha rate, the applied radioactivity was recovered after successive extractions with water, HCl and organic solvents. Most of the radioactivity at 14 days PHI was found in the peel (96% TRR) and whole fruit contained 4% TRR. Peel organic extracts showed approximately 45% TRR as cyhexatin, 25% as inorganic tin, 14% as MCTA and 12% as DCTO.

In one study conducted in grapes treated with $\text{U-}^{14}\text{C}$ -cyhexatin at 0.3 kg ai/ha, a mean of 86% TRR was found on the fruit surface and 14% in the grape homogenate (acid methanol extraction) at 10 or 28 days after application. Cyhexatin accounted for 77.6 and 59% TRR in the

grape surface after 10 and 28 days, respectively, while DCTO accounted for 7.7 and 14.8%. In the fruit homogenate, only cyhexatin was detected (5% TRR).

In summary, the metabolism of azocyclotin and cyhexatin in animal and plants appears to be similar, and occurs through the loss of the triazole moiety (from azocyclotin) to produce cyhexatin, with subsequent hydrolysis of the cyclohexyl ring to yield DCTO and MCTA.

Environmental fate

One hydrolysis study was conducted in water with [triazole-3,5-¹⁴C]azocyclotin and [cyclohexyl-UL-¹⁴C]azocyclotin, at a concentration of about 30 µg ai./L in 0.01 M buffer solutions at pH 4, 7 and 9 and in drinking water. The buffer solutions were incubated for 10, 30, and 60 minutes under sterile conditions and the drinking water solution for 10 minutes in the dark at 20°C. Azocyclotin was completely hydrolysed within 10 min ($DT_{90} \leq 10$ min), and cyhexatin and 1,2, 4 triazole were the degradation products identified.

Degradation studies with cyhexatin in soil, field dissipation studies, adsorption/desorption studies in soil and degradation studies in water/sediment system were provided to the Meeting. However, these studies are not relevant to the present evaluation.

Method of analysis

As only cyhexatin and DCTO residues are detected in plants treated with azocyclotin, no analytical method to analyse azocyclotin was submitted.

Complete method validation studies to analyse residues of cyhexatin and DCTO in various crops were submitted. The methodology involves extraction with a mixture of hexane and ethyl acetate in the presence of acetic acid and water, followed by methylation with methyl magnesium chloride to form tricyclohexylmethyltin (TCMT) from cyhexatin and dicyclohexyldimethyltin (DCMT) from DCTO. The extract with the methylated compounds was cleaned-up with florisil, and quantification was performed by gas chromatography with flame photometric detection (GC-FPD) using a sulfur filter or using a tin filter as a primary methodology followed by confirmation using a sulfur filter. No matrix effects were found in the method, regardless of the filter used. The methylated compounds were found to be stable after 7 days stored in the dark at 4°C.

For grapes, oranges, fresh orange juice, peel and molasses, apples, apple pomace (wet) and apple juice, the LOQ for both cyhexatin and DCTO was set at 0.01 mg/kg. The LOQ was 0.02 mg/kg for orange dry pulp, 0.05 mg/kg for apple pomace and 0.10 mg/kg for peel oil and juice concentrate. The limits of detection ranged from 0.005 to 0.013 mg/kg. Recovery at the LOQ level and at 0.1 mg/kg ranged from 71 to 128% for cyhexatin and from 61 to 83% for DCTO.

In some residue trials, a method to analyse only cyhexatin was used. The method involves extraction of the residues with chloroform, clean up with silica gel and quantification by reverse phase high-performance liquid chromatography (HPLC-UV at 215–225 nm. In this methodology, LOQs of 0.05 or 0.1 mg/kg were reported, and recoveries at these levels presented in the trial reports were normally within the 70 to 120% range.

Stability of pesticide residues in stored analytical samples

The stability of stored analytical samples fortified with cyhexatin and DCTO was studied in apples, grapes, raisins and wine. Samples fortified at 0.5 mg/kg were stored up to 12 months at -20° C in the dark. In most cases, residues were stable for up to a year ($\geq 70\%$ remained), except for cyhexatin and DCTO in grapes and raisins (approximately 50% remained) and DCTO in apples (62% remained).

Definition of the residue

The hydrolysis study conducted with azocyclotin showed that 90% of this compound degrades to cyhexatin in less than 10 min. Therefore, no residues of azocyclotin are expected to be present in the application solution, and consequently, in treated plants. Metabolism studies conducted in animal and plants with azocyclotin and cyhexatin have shown that cyhexatin is the major residue to be found. Residues of the dicyclohexyltin oxide metabolite (DCTO) can be higher than 10% TRR in some cases, but this metabolite is not considered of toxicological concern.

The log P_{ow} of cyhexatin (6.1 at pH 7) suggests that the compound is fat soluble. However, metabolism studies conducted in cows, goats and hens indicated that cyhexatin does not concentrate in fat.

The Meeting agreed that the residue definition for azocyclotin and cyhexatin in plants and animal products for both enforcement and dietary intake assessment purposes is cyhexatin. The residue definition applies to residues coming from the use of azocyclotin and/or cyhexatin.

Results of supervised trials on crops

Orange and clementine

Thirty four trials were conducted with cyhexatin in oranges in Brazil from 1993 to 1995 using 1 or 2 applications at 0.025 or 0.05 kg ai/hL (GAP is 0.025 kg ai/hL). Residues found, of cyhexatin in whole fruit with a 30 day PHI, in 16 trials conducted according to Brazilian GAP were < 0.01, 0.01 (2), 0.02, 0.03 (2), 0.04 (2), 0.05 (4), 0.06 (2) and 0.07 (2) mg/kg. Residues from trials conducted at double rates reached a maximum of 0.18 mg/kg with a 30 day PHI.

In twenty nine trials (see processing studies), residues were also analysed in peel. On average, residues of cyhexatin in the peel at PHI represented 30% of the residues in the whole fruit.

Three trials were conducted in Spain in 1997 with oranges and three with clementines at 0.36 kg ai/ha (GAP is 0.25 to 0.31 kg ai/hL, 15 days PHI). Residues of cyhexatin from trials conducted according to GAP were < 0.1 mg/kg (0.05 mg/kg) in orange and < 0.1 mg/kg (0.02 and 0.07 mg/kg) in clementine. The LOQ was 0.1 mg/kg, but values below the limit of quantification were reported.

Residues of cyhexatin coming from 17 trials conducted according to GAP in Brazil and Spain in orange were < 0.01, 0.01 (2), 0.02, 0.03 (2), 0.04 (2), 0.05 (4), 0.06 (2) and 0.07 (2) and < 0.1 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg for azocyclotin and cyhexatin in oranges. Considering that 70% of cyhexatin residues in oranges are present in the pulp, and the supervised trial median and highest residue in whole fruit were 0.05 mg/kg and 0.07 mg/kg, respectively, the Meeting estimated an STMR of 0.035 mg/kg and an HR of 0.049 mg/kg in orange pulp.

The Meeting also recommends the withdrawal of the current MRL of 2 mg/kg for azocyclotin and cyhexatin in citrus fruit. The number of trials conducted in clementines according to GAP were not considered sufficient to make any recommendation for this commodity.

Apple and pears

Eight trials were conducted with azocyclotin in apples. In one trial conducted in Brazil (GAP of a maximum of 2 applications at 0.02 to 0.025 kg ai/hL, 30 day PHI) residues of cyhexatin at the 30 day PHI were 0.16 mg/kg. One trial was conducted in Chile (no GAP) and six in Israel. Although azocyclotin is registered in Israel, the trials conducted in this country could not be evaluated as a translated label was not submitted.

Fifty three trials were conducted with cyhexatin in apples in Europe from 1991 to 2001, of which 24 were in France, 21 in Italy and eight in the Netherlands. In 13 trials conducted in France at GAP (0.03 kg ai/hL), residues of cyhexatin at a 30 day PHI were 0.03 (3), 0.04 (4), 0.06 (3), 0.08 (2) and 0.11 mg/kg. In 12 trials conducted at the same GAP in Italy, residues at the 30 day PHI were < 0.1 (4), 0.02 (6) and 0.03 (2) mg/kg.

In six trials conducted in the Netherlands according to Italian and French GAP, residues at the 30 day PHI were 0.02 (5) and 0.03 mg/kg. Currently, there is no GAP for cyhexatin in apple in the Netherlands.

Twenty trials were conducted with cyhexatin in pears in Italy. In 16 trials conducted according to GAP (0.03 kg ai/hL), residues at 30 a day PHI were, < 0.01 (7), < 0.05 (2), 0.01 (2) and 0.02 (3) 0.07 and 0.16 mg/kg.

The Meeting agreed that residues of cyhexatin from the 48 trials conducted according to GAP (apple and pears conducted with cyhexatin in Europe and one trial conducted with azocyclotin in apples in Brazil) can be grouped together as reflecting the use of cyhexatin and azocyclotin. They were, in ranked order < 0.01 (7), 0.01 (2), 0.02 (14), 0.03 (6), 0.04 (4), < 0.05 (2), 0.06 (3), 0.07, 0.08 (2), < 0.1 (4), 0.11 and 0.16 (2) mg/kg.

The Meeting recommended a maximum residue level of 0.2 mg/kg for azocyclotin and cyhexatin in apples and pears. The Meeting also estimated an STMR of 0.025 mg/kg and an HR of 0.16 mg/kg.

The Meeting recommended withdrawal of the current MRLs of 2 mg/kg for cyhexatin in apples and pears.

Grapes

Forty nine trials were conducted with cyhexatin in France (31), Italy (11) and Spain (7) on grapes from 1990 to 2002. GAP rate in France and Spain is similar (0.3 kg ai/ha). In 19 trials conducted at 0.3 kg ai/ha in France, residues of cyhexatin within 30 days PHI were, in rank order, 0.02, 0.04, 0.05, 0.06 (2), 0.07, 0.08, 0.09 (2), 0.10, 0.11 (2), 0.12 (2), 0.15 (2), 0.17 (2) and 0.19, mg/kg. In Spain, residues in the 6 trials conducted according to GAP were 0.02, 0.05, 0.06, 0.08, 0.12 and 0.14 mg/kg.

Cyhexatin is not registered in Italy, but the trials conducted in this country were evaluated against the Spanish GAP. Eleven trials conducted at GAP gave residues at a 30 day PHI of 0.02 (2), 0.04, 0.05, 0.07 (3), 0.08, 0.09 (2) and 0.11 mg/kg

Residues of cyhexatin from 36 trials conducted in Europe according to GAP were grouped as 0.02 (4), 0.04 (2), 0.05 (3), 0.06 (3), 0.07 (4), 0.08 (3), 0.09 (4), 0.10, 0.11 (3), 0.12 (3), 0.14, 0.15 (2), 0.17 (2) and 0.19, mg/kg.

The Meeting recommended a maximum residue level of 0.3 mg/kg, an STMR of 0.085 mg/kg and an HR of 0.19 mg/kg for cyhexatin and azocyclotin in grapes.

The Meeting also recommended the withdrawal of the current MRLs of 0.2 mg/kg for cyhexatin and azocyclotin in grapes.

Stone fruit

Sixteen trials were conducted with cyhexatin in peaches in France and Italy and 6 trials were conducted in plums in France at rates of 0.03 to 0.09 kg ai/hL. GAP rate in France is 0.03 kg ai/hL (30 days PHI) and in Spain is 0.025–0.037 kg ai/hL. There is no registered use of cyhexatin on peaches in Italy. In three trials conducted at 0.03 kg ai/hL in peaches in Italy, residues of cyhexatin

27 days after application were 0.09, 0.21 and 0.41 mg/kg. In 10 French trials conducted at 0.075 kg ai/hL in peaches and at 0.09 kg ai/hL in plums, residues reached a maximum of 0.14 mg/kg at the 30 day PHI.

The number of trials conducted according to GAP was not considered sufficient to recommend maximum residue levels for cyhexatin and azocyclotin in peaches or plums.

Currants, red, black, white

Three trials were conducted with blackcurrants according to French GAP (0.3 kg ai/ha, 28 day PHI). Residues of cyhexatin found 30 days after application were < 0.05 (2) and 0.05 mg/kg. The Meeting recommended a maximum residue level of 0.1 mg/kg and an STMR of 0.05 mg/kg for cyhexatin and azocyclotin in currants, red, black, white.

Dried hops

Nineteen trials were conducted in hops in the United Kingdom and Germany at rates from 0.6 to 1.1 kg ai/ha. Residues of cyhexatin ranged from 63 mg/kg (0 days) to 2.9 (28 days). Cyhexatin has no registered use in UK or Germany, nor is this compound registered for dried hops in other countries in Europe. The Meeting made no recommendation for dried hops.

Fate of residues during processing

Nineteen processing studies were conducted in oranges treated with cyhexatin (0.025 or 0.50 kg ai/ha). Residues of cyhexatin in concentrated juice were all < 0.1 mg/kg. No residues were found in any of the fresh or pasteurized juice samples (< 0.01 mg/kg) produced from orange samples containing from 0.02 to 0.23 mg/kg cyhexatin. A processing factor (PF) of 0.04 (0.01/0.23) was applied to an STMR of 0.05 mg/kg in oranges and the Meeting recommended an STMR of 0.002 mg/kg in orange juice.

Residues of cyhexatin in the peel represented, on average, 30% of residues in the whole fruit. In four trials where molasses samples were analysed, residues of cyhexatin were at or below the LOQ.

Residues of cyhexatin concentrated in dried pulp and in peel oil had mean PFs of 1.6 and 102, respectively. Based on the estimates for oranges, the Meeting estimated a median residue of 0.08 mg/kg for citrus dried pulp.

Twenty three processing studies were conducted in apples. Residues in apples ranged from < 0.01 to 0.12 mg/kg, but none of the juice samples analysed had detectable residues of cyhexatin. A PF of 0.08 (0.01/0.12) was applied to an STMR of 0.025 mg/kg for apple, and the Meeting estimated an STMR of 0.002 mg/kg in apple juice.

Residues of cyhexatin concentrated in wet pomace, with PFs ranging from 1 to > 5 (median of 1.7). The Meeting estimated a median residue of 0.272 mg/kg for cyhexatin in wet pomace. The processing factor for dry pomace ranged from < 0.05 to 4.

Twenty eight processing trials were conducted in grapes. Residues decreased in juice and wine, and were not detected in most of the samples. Median PFs were 0.8 and 0.7 for juice and wine, respectively. These PFs were applied to the STMR on grapes of 0.085 mg/kg. The Meeting recommended STMRs of 0.068 mg/kg for juice and of 0.060 mg/kg for wine.

Processing factors for raisins ranged from 0.3 to 2 (median of 0.9). The Meeting recommended an STMR of 0.076 mg/kg for cyhexatin in grapes, dried (= currants, raisins and sultanas).

Residues of cyhexatin concentrated in all samples of wet and dry pomace with a mean PF of 2.6 and 4.8, respectively.

In three processing studies conducted in dried hops, residues of cyhexatin ranged from 1.9 to 18.2 mg/kg, but no residues of any compound were found in beer.

Farm animal dietary burden

The Meeting estimated the dietary burden of cyhexatin coming from the use of azocyclotin and cyhexatin, in cattle and poultry on the basis of the diets listed in Appendix IX of the *FAO Manual* and the highest and median residues estimated at this Meeting.

Calculation of the dietary burden for maximum residue level and STMR estimation

Commodity	Median residue	Group	% DM	Residues dw	Diet content (%)			Residue contribution, mg/kg		
					Beef cattle	Dairy cows	Poultry	Beef cattle	Dairy cows	Poultry
Apple wet pomace	0.04	AB	40	0.067	40	20	-	0.027		0
Citrus dried pulp	0.08	AB	91	0.08	20	20	-		0.016	0
				Total	40	20	-	0.027	0.016	0

Farm animal feeding studies

No animal feeding studies were provided to the Meeting. The calculated cyhexatin dietary burden was 0.027 ppm for mammals and 0 ppm for poultry. No registered direct use of azocyclotin or cyhexatin on animals was provided to the Meeting.

Metabolism studies in goats and hens were conducted at a dose of 100 ppm of ¹¹⁹Sn cyhexatin, approximately 3700 times the calculated dietary burden in goats. In these studies, only total radioactivity was quantified in milk and tissues. Residues in goats were 0.02 mg/kg cyhexatin equivalents in milk, 0.13 mg/kg in muscle, 0.91 mg/kg in kidney and 1.83 mg/kg in liver. In the metabolism study conducted with hens, maximum total radioactivity in tissues and eggs was found in liver (3.0 mg/kg cyhexatin equivalents).

The Meeting concluded that no residues of cyhexatin are expected in animal commodities. No recommendations could be made as no analytical methods for animal commodities were submitted to the Meeting.

DIETARY RISK ASSESSMENT

Long-term intake

The 2005 JMPR established a group ADI of 0–0.003 mg/kg bw for cyhexatin and azocyclotin. The IEDIs were calculated for the five GEMS/Food regional diets from the STMR and STMR-P values for fruits and processed products as estimated by the present Meeting (Annex 3). The group ADI for cyhexatin and azocyclotin is 0.003 mg/kg bw, and the calculated IEDIs ranged from 0 to 5% of the ADI.

The Meeting concluded that these uses of cyhexatin and/or that of azocyclotin resulting in long-term intake of residues of cyhexatin as considered by the JMPR are unlikely to present a public health concern.

Short-term intake

The 2005 JMPR established a group ARfD of 0.02 mg/kg bw for women of childbearing age for cyhexatin and azocyclotin. The IESTI was calculated based on consumption data generated for the general population as no consumption data is available for this group of the population. The IESTI ranged from 3 to 20% ARfD.

An ARfD for the rest of the population was considered unnecessary and no intake calculations were performed for the general population and for children.

The Meeting concluded that the short-term intake of residues of cyhexatin, from uses of cyhexatin and azocyclotin, on commodities that have been considered by the JMPR, is unlikely to present a public health concern.

4.3 BENALAXYL (155)

TOXICOLOGY

Benalaxyl, the ISO approved name for methyl *N*-(2,6-dimethylphenyl)-*N*-(phenylacetyl)-DL-alaninate (a racemic mixture), is a broad-spectrum phenylamide fungicide that inhibits mycelial growth of fungi and germination of zoospores. Benalaxyl was first evaluated by the 1987 JMPR (Annex 1, reference 52), when an ADI of 0–0.05 mg/kg bw was established on the basis of a NOEL of 5.0 mg/kg bw per day for hepatic enlargement in a 13-week dietary study in rats and a safety factor of 100.

Benalaxyl was considered by the present Meeting within the periodic review programme of the CCPR. The Meeting reviewed new data on benalaxyl (studies of toxicokinetics, metabolism, acute toxicity after inhalation, eye irritation, mutagenesis and several studies of toxicity with the two main soil metabolites) that had not been reviewed previously, as well as relevant data from the previous evaluation.

All pivotal studies with benalaxyl were certified as complying with GLP.

Biochemical aspects

Several toxicokinetic studies in rats given ¹⁴C-labelled benalaxyl as single and repeated oral doses showed that the active substance is rapidly and extensively absorbed and distributed by all organs and tissues, with the greatest proportion of radioactivity remaining in the intestine and its contents, and in the liver and kidneys (minor quantities). Seven days after treatment, only approximately 0.3% of the administered radiolabelled dose remained in the rat and was distributed among organs and tissues. The half-life of elimination was about 30 h after administration of single doses and 36 h after administration of repeated doses. The pattern of elimination in the urine and faeces was also similar in all situations (administration of single and repeated oral doses) and was not sex-dependent. At 48 h after dosing, the radioactivity was mainly excreted in the faeces (at least 80%), via the bile and in the urine (approximately 8%).

The metabolites of benalaxyl that appeared in the faeces and urine were similar, irrespective of dose and type of administration (single or repeated doses). Unchanged benalaxyl was not detected