5.10 EMAMECTIN BENZOATE (247)

TOXICOLOGY

Emamectin benzoate is the International Organization for Standardization (ISO)–approved name for (4″*R*)-4″-deoxy-4″-(methylamino)avermectin B1 benzoate, with Chemical Abstracts Service No. 155569-91-8. It is a macrocyclic lactone insecticide derived from the avermectin series of natural products. It is a mixture of at least 90% (4″*R*)-4″-deoxy-4″-(methylamino)avermectin B1a benzoate and at most 10% ′(4 *R*)-4″-deoxy-4″-(methylamino)avermectin B1b benzoate salts. Emamectin is structurally similar to abamectin and ivermectin.

Emamectin was originally developed as the hydrochloride salt MK 243 (L-656,748-010V), but the commercial product was subsequently changed to the benzoate salt MK 244 (L-656,748-038W) and benzoate hydrate (L-656,748-052S) because of superior storage and handling characteristics. Studies were performed with emamectin benzoate, unless stated otherwise. Emamectin is being evaluated for the first time by the Joint FAO/WHO Meeting on Pesticide Residues at the request of the Codex Committee on Pesticide Residues.

All critical studies complied with good laboratory practice.

Biochemical aspects

After administration of a single oral dose (0.5 mg/kg body weight [bw]) of emamectin to rats, maximum concentrations in blood and plasma were reached after 4–12 hours, and emamectin was eliminated with plasma half-lives of 20–51 hours. Comparison of area under the curve values following oral and intravenous dosing indicated that the oral absorption of emamectin benzoate was 55–74%. There is no consistent evidence for a sex difference in oral absorption. The radiolabel was widely distributed to the tissues, with the highest levels in small intestine, caecum, spleen, liver, lung and adrenals at 3 hours and in pituitary gland, sublingual glands, Harderian glands, large intestine and lung at 24 hours. The lowest concentrations were found in the brain and spinal cord. Excretion occurred predominantly through faeces, most between 24 and 48 hours after dosing. After 2–3 days, more than 90% of the administered dose of 0.5 mg/kg bw was excreted. Following oral or intravenous administration, emamectin was excreted via bile (2–17%), and only a very small amount was excreted in urine (~1%); the major and remaining portion was excreted in the faeces through efflux transportation into the intestinal tract. Intestinal secretion of emamectin is the main route of elimination, which is consistent with the known role of p-glycoprotein as an efflux transporter of avermectins. Following a single oral dose of 20 mg/kg bw, the maximum concentrations in blood and plasma were reached after 5–8 hours and were approximately 40 times higher than those observed after a single low dose. Also in these high-dose rats, radioactivity levels in other tissues were 40–100 times higher and excretion from the body took 2 days longer in comparison with the low-dose rats. Therefore, these kinetic parameters indicate dose proportionality. Tissue distribution and the proportions eliminated by different routes were similar following the single low and high doses. Administration with a repeated low dose of 0.5 mg/kg bw per day for 14 days resulted in similar kinetics as compared with a single low dose. A steady state with a maximum concentration in plasma 2 times higher than after a single low dose was reached at the seventh dose. Tissue distribution after the repeated low dose was similar to that observed after a single low dose, but with 2 times higher radioactivity levels. Comparison of blood kinetics and excretion between the benzoate hydrate and benzoate salt and between the benzoate salt and hydrochloride salt in dogs indicates that they have similar absorption and kinetics in the blood and similar route and rates of excretion. One metabolite, AB1a, is formed by *N*-demethylation of emamectin and accounts for up to 30% of the administered dose.

Toxicological data

The median lethal dose (LD_{50}) values for emamectin benzoate dissolved in carboxymethylcellulose were 53–237 mg/kg bw in two rat studies. The LD_{50} for emamectin benzoate hydrate dissolved in carboxymethylcellulose was 58 mg/kg bw. LD_{50} values for emamectin hydrochloride, using water as vehicle, were 67–88 mg/kg bw in two rat studies. Signs of toxicity at high doses included ptosis, hypoactivity, tremors, ataxia, salivation, irritability, bradypnoea, diarrhoea, anogenital staining, reduced faecal volume and weight loss. The LD_{50} for dermal toxicity was 500–2000 mg/kg bw in rats, and the 4-hour acute inhalation median lethal concentration (LC_{50}) was 0.663 mg/L in female rats, but greater than 1.049 mg/L in male rats. Emamectin was slightly irritating to the skin and moderately irritating to the eye of rabbits. Emamectin was not a skin sensitizer in a local lymph node assay in mice.

The primary effect of emamectin was neurotoxicity, as observed in acute neurotoxicity studies in rats and in short-term toxicity studies in rats, rabbits and dogs. In a 13-week dietary range-finding study and a 14-day dietary neurotoxicity study in mice, no signs of neurotoxicity were observed at doses up to 15 mg/kg bw per day.

In a 90-day dietary study with emamectin hydrochloride in rats, the no-observed-adverse-effect level (NOAEL) was 0.5 mg/kg bw per day, based on cytoplasmic vacuolation of neurons in the brain observed in males at 2.5 mg/kg bw per day.

In a 14-week gavage study with emamectin hydrochloride and a 1-year oral (gavage) study in dogs, the overall NOAEL was 0.25 mg/kg bw per day, based on histological changes in the brain, spinal cord and sciatic nerve and clinical signs of neurotoxicity at 0.5 mg/kg bw per day.

In several studies, changes in body weight gain and feed consumption were observed. A decrease in body weight gain was observed in mice, rats and dogs at doses equal to or greater than 5.0, 2.5 and 0.75 mg/kg bw, respectively. However, increased body weight gain was also observed in several studies in rats at 1.0–2.5 mg/kg bw per day. Such increases in body weight gain have been observed previously upon treatment with ivermectin and are generally characteristic of avermectins. As the mechanism by which avermectins increase body weight gain is unknown, the Meeting considered that this effect should be considered potentially adverse and could not be disregarded.

In a 1-year dietary study in rats, the NOAEL was 0.1 mg/kg bw per day, based on increased body weight gain observed at 1.0 mg/kg bw per day.

In a 79-week study in mice, the NOAEL was 2.5 mg/kg bw per day, based on clinical signs of toxicity and reduced body weight gain observed at 5.1 mg/kg bw per day. No effect of emamectin on tumour incidence was found at doses up to and including 7.6 mg/kg bw per day, the highest dose tested.

In a 2-year study in rats, the NOAEL was 0.25 mg/kg bw per day, based on an increase in body weight gain and increases in triglyceride concentrations in serum and relative kidney weight at 1.0 mg/kg bw per day. No increased incidence of tumours was observed at doses up to 2.5 mg/kg bw per day, the highest dose tested.

The overall NOAEL for the 1-year and 2-year dietary studies in rats was 0.25 mg/kg bw per day, based on the effects observed at 1.0 mg/kg bw per day.

The Meeting concluded that emamectin is not carcinogenic in rodents.

Emamectin was tested in an adequate range of in vitro genotoxicity tests and one in vivo test. No evidence for genotoxicity was observed in any test.

The Meeting concluded that emamectin is unlikely to be genotoxic.

In view of the lack of genotoxicity and the absence of carcinogenicity in rats and mice, the Meeting concluded that emamectin is unlikely to pose a carcinogenic risk to humans.

A two-generation study of reproductive toxicity in the rat was performed with doses of 0, 0.1, 0.6 and 3.6 mg/kg bw per day. Based on marked clinical signs of toxicity observed in F_{1a} pups, the high dose was reduced to 1.8 mg/kg bw per day during the course of the study. The NOAEL for parental toxicity was 0.6 mg/kg bw per day, based on decreased body weight gain, decreased feed consumption and neuron degeneration observed at 3.6 (reduced to 1.8) mg/kg bw per day. The NOAEL for reproductive toxicity was 0.6 mg/kg bw per day, based on decreased fecundity at 3.6 (reduced to 1.8) mg/kg bw per day. The NOAEL for offspring toxicity was 0.6 mg/kg bw per day, based on clinical signs of neurotoxicity, decreased body weight gain and neuron degeneration observed at 3.6 (reduced to 1.8) mg/kg bw per day.

Other emamectin-like substances also induce postnatal toxicity in rats over a time period similar to that observed with emamectin. For these closely related compounds, it has been shown that these effects are a direct consequence of low p-glycoprotein levels in the neonatal rat brain and incomplete development of the blood–brain barrier. In the developing human fetus, adult levels of p-glycoprotein expression are attained by about 28 weeks of gestation, reflecting the integrity of the blood–brain barrier prior to birth. Therefore, the Meeting considered that human neonates are less susceptible than neonatal rats to neurotoxicity induced by emamectin. The NOAEL for offspring toxicity established from the study of reproductive toxicity in rats is therefore considered to be sufficiently protective for the developing human fetus and neonate.

In a developmental toxicity study in rats, the NOAEL for maternal toxicity was 2 mg/kg bw per day, based on reduced body weight gain at 4 mg/kg bw per day during gestation days 14–20. The NOAEL for fetal toxicity was 4 mg/kg bw per day, based on an increase in fetal resorptions, decreased fetal weight and an increased number of fetuses with skeletal variations and incomplete ossification at 8 mg/kg bw per day.

In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 3 mg/kg bw per day, based on clinical signs (mydriasis, decreased pupillary reaction) and decreased body weight gain from gestation days 12 to 28 at 6 mg/kg bw per day. The NOAEL for developmental toxicity in rabbits was 6 mg/kg bw per day, the highest dose tested.

The Meeting concluded that emamectin was not teratogenic in rats or rabbits.

In two acute oral (gavage) neurotoxicity studies in rats, one using emamectin hydrochloride and the other using emamectin benzoate, the overall NOAEL was 5 mg/kg bw, based on clinical signs of neurotoxicity (tremors and irritability) starting at 10 mg/kg bw. At higher doses, salivation, ataxia, bradypnoea, decreased activity, urine staining, loss of righting reflex, hypothermia, ptosis, moist stools and hyperactivity were observed. Degeneration of the white matter in the brains and spinal cord, degeneration of the sciatic nerve and decreased body weight gain were observed at single doses of 25 mg/kg bw and higher.

In a 14-week dietary neurotoxicity study in rats, emamectin induced clinical signs (body tremors, salivation, slightly soiled, urine staining) and changes in the functional observational battery test (tremors, soiled fur, decreased rearing, salivation, abnormal gait, impaired mobility, reduced limb strength or grip strength, reduced righting reflex) at a dose of 4.74 mg/kg bw per day. These signs were first observed during week 7 of treatment. Histological examination of these rats showed degeneration of neurons and white matter in the brain, spinal cord and sciatic nerve and atrophic skeletal muscles. Furthermore, body weight gain and feed consumption were decreased. The NOAEL in this study was 0.95 mg/kg bw per day.

In a developmental neurotoxicity study using emamectin benzoate hydrate, the NOAEL for maternal toxicity was 0.6 mg/kg bw per day, based on an increase in body weight gain during gestation at 2.5 mg/kg bw per day. The NOAEL for offspring toxicity was 0.6 mg/kg bw per day, based on clinical signs (head tremors, body tremors, hindlimb extension, hindlimb splay), decreased motor activity, decreased sensorimotor reflexes and decreased weight gain observed at 2.5 mg/kg bw per day. Clinical signs of toxicity were not observed until postnatal day 6.

A toxicokinetic study and a 2-week neurotoxicity study were performed with CF-1 mice, which are deficient in expression of p-glycoprotein (*Mdr1a* gene). The toxicokinetic study showed increased emamectin concentrations in the brain and slower excretion rates as compared with wild-type mice. In the 2-week neurotoxicity study, the NOAEL was 0.12 mg/kg bw per day, based on mortality and clinical signs of neurotoxicity at 0.34 mg/kg bw per day. Wild-type CD-1 mice did not show mortality or clinical signs of neurotoxicity at 1.7 mg/kg bw, the highest dose tested. The absence of p-glycoprotein has never been shown in humans, and heterozygosity still results in functional p-glycoprotein. The results from CF-1 mice are therefore considered not relevant for human risk assessment. It was previously concluded by WHO that the CF-1 polymorphic mouse is not an appropriate model for human risk assessment for avermectins.

No data on the effects of emamectin in humans were provided.

The Meeting concluded that the existing database on emamectin is sufficient to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) for emamectin benzoate of 0–0.0005 mg/kg bw on the basis of an overall NOAEL of 0.25 mg/kg bw per day in the 1-year and 2-year rat studies, for increased body weight gain, triglyceride concentrations in serum and relative kidney weight at 1.0 mg/kg bw per day, and on the basis of an overall NOAEL of 0.25 mg/kg bw per day in 14- and 53-week toxicity studies in dogs, for histological changes in the brain, spinal cord and sciatic nerve and clinical signs of neurotoxicity at 0.5 mg/kg bw per day, using a safety factor of 500. An additional safety factor of 5 was applied to the default safety factor of 100, as a number of studies in mice, rats and dogs show steep dose–response curves and irreversible histopathological effects in neural tissue at the lowest-observed-adverse-effect level (LOAEL). A NOAEL based predominantly on such histopathological changes is considered to be less sensitive than the observation of clinical signs. Moreover, in the 1-year dog study, animals were killed in extremis at doses that were only 3 times higher than the NOAEL in this study.

The Meeting established an acute reference dose (ARfD) of 0.03 mg/kg bw for emamectin benzoate, based on a NOAEL of 5 mg/kg bw for clinical signs of neurotoxicity (tremors and irritability) observed in an acute neurotoxicity study in rats at 10 mg/kg bw. A safety factor of 200 was applied, which includes a 2-fold factor based on serious histopathological observations of degeneration of neurons in brain, spinal cord and sciatic nerve at 25 mg/kg bw. Observations of toxicity observed in neonatal rats in reproductive toxicity studies and a developmental neurotoxicity study were considered not relevant for setting an ARfD, as these effects are a direct consequence of low p-glycoprotein levels in the neonatal rat brain and incomplete development of the blood–brain barrier. In the developing human fetus, adult levels of p-glycoprotein expression are attained by about 28 weeks of gestation, reflecting the integrity of the blood–brain barrier prior to birth.

A toxicological monograph was prepared.

Levels relevant for risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Seventy-nine-week study of toxicity and carcinogenicity[a]	Toxicity	2.5 mg/kg bw per day	5.1 mg/kg bw per day
		Carcinogenicity	5.1 mg/kg bw per day[b]	—
Rat	Fourteen-week study of toxicity[a]	Toxicity	0.5 mg/kg bw per day	2.5 mg/kg bw per day
	One-year study of toxicity and 2-year study of toxicity	Toxicity[c]	0.25 mg/kg bw per day	1.0 mg/kg bw per day
		Carcinogenicity	2.5 mg/kg bw per day[b]	—

Species	Study	Effect	NOAEL	LOAEL
	and carcinogenicity[a]			
	Two-generation study of reproductive toxicity[a]	Parental toxicity	0.6 mg/kg bw per day	1.8/3.6 mg/kg bw per day[c]
		Offspring toxicity	0.6 mg/kg bw per day	1.8/3.6 mg/kg bw per day[c]
		Reproductive toxicity	0.6 mg/kg bw per day	1.8/3.6 mg/kg bw per day[c]
	Developmental toxicity study[d]	Maternal toxicity	2 mg/kg bw per day	4 mg/kg bw per day
		Embryo and fetal toxicity	4 mg/kg bw per day	8 mg/kg bw per day
	Acute neurotoxicity studies[e]	Neurotoxicity	5 mg/kg bw	10 mg/kg bw
	Developmental neurotoxicity study[a]	Maternal toxicity	0.6 mg/kg bw per day	2.5 mg/kg bw per day
		Offspring toxicity	0.6 mg/kg bw per day	2.5 mg/kg bw per day
Rabbit	Developmental toxicity study[d]	Maternal toxicity	3 mg/kg bw per day	6 mg/kg bw per day
		Embryo and fetal toxicity	6 mg/kg bw per day[b]	—
Dog	Fourteen-week and 1-year studies of toxicity[d,e]	Toxicity	0.25 mg/kg bw per day	0.5 mg/kg bw per day

[a] Dietary administration. Dietary concentrations of emamectin were adjusted over the course of the study in order to obtain the required daily doses (mg/kg bw per day) for the different dose groups and sexes. Therefore, ppm values are not presented.

[b] Highest dose tested.

[c] Based on marked clinical signs of toxicity observed in F_{1a} pups, the high dose of 3.6 mg/kg bw per day was reduced to 1.8 mg/kg bw per day during the course of the study.

[d] Gavage administration.

[e] Two studies combined.

Estimate of acceptable daily intake for humans

0–0.0005 mg/kg bw

Estimate of acute reference dose

0.03 mg/kg bw

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

Results from epidemiological, occupational health and other such observational studies of exposures in humans

Critical end-points for setting guidance values for exposure to emamectin benzoate

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	55–74% (female rats)
Distribution	Widely distributed (rats)

Potential for accumulation	Low
Rate and extent of excretion	At 0.5 mg/kg bw, > 90% excretion within 72 h, mainly via faeces through efflux transportation from the blood to the intestine; ~1% excretion in urine (rats)
	Plasma half-lives (0.5 mg/kg bw): 20–51 h
	Plasma half-lives (20 mg/kg bw): 35–36 h
Bioequivalence	Emamectin benzoate hydrate, benzoate salt and hydrochloride salt have similar oral absorption, blood kinetics and excretion (dogs)
Metabolism in animals	Limited, metabolism via N-demethylation to form the metabolite AB1 (rat)
Toxicologically significant compounds (animals, plants and the environment)	Emamectin benzoate
Acute toxicity	
Rat, LD50, oral	Emamectin benzoate dissolved in carboxymethylcellulose: 53–237 mg/kg bw
	Emamectin benzoate hydrate dissolved in carboxymethylcellulose: 58 mg/kg bw
	Emamectin hydrochloride dissolved in water: 67–88 mg/kg bw
Rat, LD50, dermal	500–1000 mg/kg bw (males), 1893 mg/kg bw (females)
Rat, LC50, inhalation	> 1.049 mg/L (males), 0.663 mg/L (females)
Rabbit, dermal irritation	Slightly irritating to the skin
Rabbit, ocular irritation	Moderately irritating to the eye
Mice, dermal sensitization (local lymph node assay)	Not sensitizing
Short-term studies of toxicity	
Target/critical effect	Nervous system (clinical signs, lesions in brain, spinal cord, sciatic nerve) (rat, rabbit, dog)
	Body weight increase (rat)
Lowest relevant oral NOAEL	0.25 mg/kg bw per day (dog), 0.1 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalatory NOAEC	No data
Genotoxicity	
	Not genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Increased body weight gain (both sexes), increased relative kidney weight in males, increased serum triglyceride levels in females (rats)
Lowest relevant NOAEL	0.25 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic (mouse, rat)
Reproductive toxicity	
Reproduction target/critical effect	Decreased fecundity
Lowest relevant reproductive NOAEL	0.6 mg/kg bw per day (rat)

Developmental target / critical effect	Decreased fetal weight, increased number of skeletal variations and delayed ossification
Lowest relevant developmental NOAEL	4 mg/kg bw per day (rat)
Neurotoxicity/delayed neurotoxicity	
Acute oral neurotoxicity, NOAEL	5.0 mg/kg bw (rat); tremors, irritability
Acute dermal neurotoxicity, NOAEL	< 500 mg/kg bw (rabbit, lowest dose tested); degeneration of brain, spinal cord, peripheral nerve, tremors, mydriasis
Ninety-day neurotoxicity, NOAEL	0.95 mg/kg bw per day (rat); tremors, degeneration and vacuolation in brain, spinal cord, sciatic nerve
Developmental neurotoxicity, NOAEL	0.6 mg/kg bw per day (rat, offspring); reduced weight gain, tremors, hindlimb extension/splay, decreased motor activity, delayed development of sex organs
Medical data	
	No data

Summary

	Value	Study	Safety factor
ADI	0–0.0005 mg/kg bw	One-year and 2-year studies of toxicity in rat; 14-week and 1-year studies of toxicity in dogs	500
ARfD	0.03 mg/kg bw	Acute neurotoxicity study in rats	200

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of emamectin benzoate were considered for the first time by the present Meeting. The toxicological and residue evaluation was scheduled for the 2011 JMPR by the Forty-second Session of the 2010 CCPR (ALINORM 10/33/24).

Emamectin benzoate is a foliar insecticide derivative of abamectin, which is isolated from fermentation of *Streptomyces avermitilis*, a naturally occurring soil actinomycete. It acts by stimulating the release of γ-aminobutyric acid, an inhibitory neurotransmitter, thus causing insect paralysis within hours of ingestion, and subsequent insect death 2–4 days later. It has registered uses in many countries on fruits, vegetables, cereals, tree nuts, oilseeds, herbs and tea.

Other related avermectins are abamectin, ivermectin, doramectin and eprinomectin of which abamectin has been evaluated before by JMPR and abamectin and the other avermectins have been evaluated by JECFA.

The manufacturer supplied information on identity, metabolism, storage stability, residue analysis, use pattern, residues resulting from supervised trials on pome fruit, stone fruit, grapes, brassica vegetables, fruiting vegetables, leafy vegetables, legume vegetables, cottonseed, fate of residues during processing, and livestock feeding studies. In addition, Japan supplied information on use patterns.

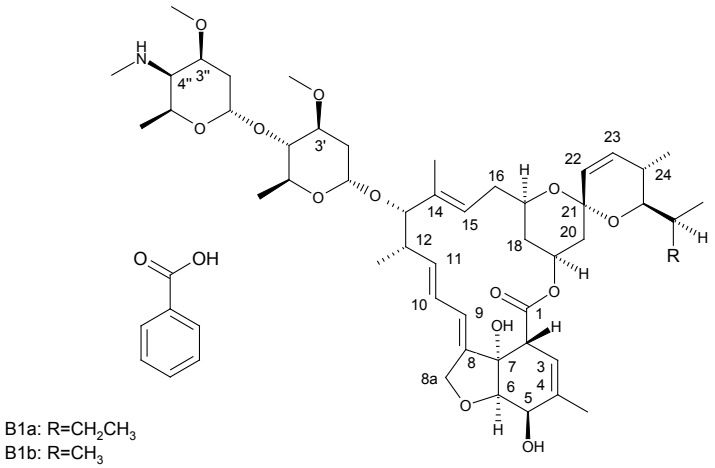
Chemical name

Emamectin exists in various forms: as emamectin (free base), as emamectin benzoate salt (MK244) and as emamectin hydrochloride (MK243). Emamectin benzoate exists as the anhydrous and various hydrated forms having different crystal morphologies. The amount of water is nonstoichiometric.

Experiments described in this evaluation were carried out with a non-specified hydrate form of the emamectin benzoate salt.

Emamectin benzoate (MK-0244) is the common name for 4"-deoxy-4"-epi-methylamino-avermectin B1 (MAB1), which is a mixture of 4"-deoxy-4"-epi-methylamino-avermectin B1a benzoate (MAB1a or emamectin B1a benzoate) and 4"-deoxy-4"-epi-methylamino-avermectin B1b benzoate (MAB1b or emamectin B1b benzoate). The avermectins in emamectin benzoate are specified as a ratio MAB1a:MAB1b=90:10 (w/w) and differ by a methylene group at the C26 alkyl substituent: $–CH_2CH_3$ for MAB1a and $-CH_3$ for MAB1b.

Structural formula:



R = CH_2CH_3 for emamectin B1a benzoate; R = CH_3 for emamectin B1b benzoate

Metabolites referred to in the appraisal by codes:

8,9-ZMa/b	8,9-Z isomer of emamectin B1a or B1b
AB1a/b	des-N-methyl derivative of emamectin B1a or B1b
MFB1a/b	N-formyl derivative of emamectin B1a or B1b
8,9-ZMFB1a/b	8,9-Z isomer of MFB1a/b
FAB1a/b	N-formyl-des-N-methyl derivative of emamectin B1a or B1b
8a-OHMAB1a/b	8a-hydroxy derivative of emamectin B1a or B1b
8a-OHMFB1a/b	8a-hydroxy derivative of MFB1a/b
8a-OXOMAB1a/b	8a-oxo derivative of emamectin B1a or B1b
8a-OXOMFB1a/b	8a-oxo derivative of MFB1a/b
15-OHB1a/b	15OH derivative of emamectin B1a or B1b
24-OH MAB1a/b	24-hydroxymethyl derivative of emamectin B1a or B1b
24-OH AB1a/b	24-hydroxymethyl derivative of AB1a/b
MSB1a/b	monosaccharide B1a or B1b;
OXIB1a/b	4"-oxime-avermectin B1a or B1b
ACROB1a/b	4"-deoxy-4"-epi-(N-propenal-N-methyl)-avermectin B1a or B1b
di-epoxide	10,11-14,15-di-epoxide derivative of emamectin B1a or B1b
milbemectin B	aglycone of B1a or B1b

Animal metabolism

The Meeting received results of animal metabolism studies in lactating goats and in laying hens. Experiments were carried out with the emamectin B1a benzoate variant only, labelled as [5-^{3}H] emamectin B1a benzoate and [25-^{14}C] emamectin B1a benzoate. Residues are expressed as emamectin B1a benzoate equivalents.

Metabolism in laboratory animals was summarized and evaluated by the WHO panel of the JMPR in 2011.

Lactating goats, orally treated once daily for 7 consecutive days with radio-labelled emamectin B1a benzoate, were sacrificed 10 hours after the last dose. Three goats received an actual dose rate of 8.5 ± 1.1 mg ai/kg feed (0.50 mg ai/kg bw) of [5-^{3}H]emamectin benzoate daily. One goat received 9.6 mg ai/kg feed (0.66 mg ai/kg bw) of a mixture of 5-^{3}H-emamectin benzoate plus [25-^{14}C]emamectin benzoate daily. Nearly all radioactivity (94–105% of the total administered radioactivity, TAR) was accounted for in the faeces and GI tract contents of all four goats. The contribution from urine, milk and tissues was 1% TAR. The average radioactivity levels from the ^{3}H dosed goats were 1.0 mg/kg eq (liver), 0.50 mg/kg eq (kidney), 0.12 mg/kg eq (leg muscle), 0.096 mg/kg eq (loin muscle), 0.28 mg/kg eq (omental fat) and 0.28 mg/kg eq (renal fat), respectively. There was no significant difference in tissue radioactivity levels from ^{3}H-and ^{14}C-emamectin benzoate treated goats. Radioactivity levels in whole milk during days 1–7 ranged from 0.007–0.057 mg/kg eq in the [^{3}H] and]^{3}H/^{14}C] dosed goats. Radioactivity levels in afternoon milk were higher than residue levels in morning milk (just before the next dosing). Average radioactivity levels in combined afternoon/morning milk increased slightly (factor 2.4) during the treatment period and a plateau was not reached within 7 days of treatment. Radioactivity levels in skim milk ranged from 0.006–0.040 mg/kg eq for ^{3}H and ^{3}H/^{14}C dosed goats, while radioactivity levels in cream ranged from 0.040–0.35 mg/kg eq for ^{3}H and ^{3}H/^{14}C dosed goats. Total radioactive residues in cream were on average 6.3 fold higher than in whole milk for the ^{3}H and ^{3}H/^{14}C treated goats.

Radioactivity was characterized in all tissues and milk. A total of 70–83% and 56–82% of the total radioactivity (TRR) could be identified in tissues and milk. Parent emamectin B1a benzoate was the major compound found at 76–78% (liver), 75–77% (kidney), 64–80% (muscle), 73–82% (fat) and 54–79% (milk) of the total radioactivity, respectively. A single metabolite (AB1a) was consistently identified in tissues and milk (0.74–7.8% TRR). Two minor metabolites (each < 3% TRR) of unknown identity, one very polar and one less polar than emamectin B1a benzoate, were inconsistently detected in liver and milk. Part of the extractable residue in tissues and milk remained unidentified (6.2–18% TRR in tissues and 16–38% TRR in milk). Up to 12% TRR remained unextracted.

Ten laying hens, orally treated once daily for 7 consecutive days with radio-labelled emamectin B1a benzoate were sacrificed 20 hours after the last dose. Hens were treated with a mixture of radio-labelled [5-^{3}H] emamectin B1a benzoate and [25-^{14}C] emamectin B1a benzoate at an actual dose rate of 12.8 mg/kg ai in feed/day (equivalent to 1 mg ai/kg bw/day). Total recovery of the applied dose was 78/72% for [^{3}H] and [^{14}C] treatments. The majority of the radioactivity was found in the excreta, GI tract contents and cage wash (92/92% ^{3}H/^{14}C TRR), while 2.5/2.6% ^{3}H/^{14}C TRR was found in tissues (liver, kidney, muscle and fat), 1.8/1.7% [^{3}H/^{14}C] TRR in ovaries and 1.4/1.5% [^{3}H/^{14}C] TRR in egg yolk. Egg white did not contain radioactivity. The radioactivity levels were on average for ^{3}H/^{14}C 3.1/3.1 mg/kg eq in liver, 0.70/0.65 mg/kg eq in kidney, 0.78/0.64 mg/kg eq in abdominal fat, 0.45/0.40 mg/kg eq in muscle fat with adhering skin, 0.15/0.13 mg/kg eq thigh muscle and 0.067/0.061 mg/kg eq in breast muscle. While residue levels in the egg white remained negligible (maximum 0.021/0.004 mg/kg eq, ^{3}H/^{14}C), residue levels in the egg yolk generally increased with treatment period from an average of 0.002/0.001 mg/kg eq [^{3}H/^{14}C] in specimens collected the day after the initial dose (day 2) to an average of 3.1/2.4 mg/kg eq [^{3}H/^{14}C] in specimens collected after application of the last dose (pre-euthanasia).

Radioactivity was characterized in liver, muscle, fat and eggs. At least 74% of the total radioactivity (TRR) could be identified in tissues and eggs. Residues identified in tissues and eggs were parent emamectin B1a benzoate, AB1a, 24-OH MAB1a, and fatty acid conjugates of both 24-OH MAB1a and 24-OH AB1a. The proportion of ^{3}H/^{14}C emamectin B1a benzoate was 37/39% TRR in liver, 60/59% TRR in muscle fat with adhering skin, 58/58% TRR in abdominal fat, 57/49% TRR in thigh muscle, 63/67% TRR in breast muscle and 13/13% to 41/40% in egg yolks. The major metabolites in tissues and eggs were a group of eight fatty acid conjugates of 24-OH MAB1a, ranging

from 32–57% TRR in egg yolks, 22–26% in liver and fat, 15/16% in thigh muscle and to 5.2/5.1% TRR in breast muscle. Finally, minor amounts of AB1a (0.9–3.3% TRR), 24-OH MAB1a (1.3–6.3% TRR) and a group of eight fatty acid conjugates of 24-OH AB1a (0.9–4.8% TRR) were found in all tissues and egg yolks, while 24-OH AB1a was not detected. Upon treatment with lipase, the fatty acid conjugate ester bonds could be cleaved and subsequently 24-OH MAB1a and 24-OH AB1a could be released. Part of the extractable residue in tissues and eggs remained unidentified (11–22% of the total radioactivity). Up to 13% of the total radioactivity remained unextracted.

Animal metabolism summary

Metabolism of emamectin B1a benzoate in livestock involves small changes to the emamectin molecular structure like N-demethylation and hydroxylation followed by conjugation. The emamectin structure itself stays intact. Emamectin B1a benzoate was not extensively metabolised in either rats or goats. In goats emamectin B1a benzoate was the major compound found at 54–82% of the total radioactivity in goat liver, kidney, muscle, fat and milk. The only reported metabolite was AB1a, ranging from 0.74–7.8% TRR in tissues and milk. In chickens, emamectin benzoate was metabolised more intensely with parent remaining as 13–60% TRR and the major metabolite being 24-OH MAB1a. In tissues and egg yolk, nearly all of the 24-OH MAB1a was present as fatty acid conjugates (1.3–6.3% TRR as unconjugated form, 5.1–57%TRR as conjugate), which could be released by lipase treatment. Minor amounts of AB1a (0.9–3.3% TRR), 24-OH MAB1a (1.3–6.3% TRR) and a group of eight fatty acid conjugates of 24-OH AB1a (0.9–4.8% TRR) were found in all tissues and egg yolks, while 24-OH AB1a was not detected. Fatty acid conjugates of 24-OH AB1a could be released by lipase treatment. The poultry specific metabolites 24-OH MAB1a and 24-OH AB1a were not found in rats.

Plant metabolism

The Meeting received information on the fate of emamectin B1a benzoate after foliar spray treatment of fruits (pear trees), leafy crops (lettuce, head cabbage) and cereals (maize). Radio-labelled studies were carried out with the emamectin B1a benzoate variant only, labelled as 23-^{14}C emamectin B1a benzoate in pear and 3, 7, 11, 13, 23-^{14}C-emamectin B1a benzoate for the other crops. Residues are expressed as emamectin B1a benzoate equivalents.

Outdoors grown pear trees were sprayed three times with an SG formulation of [23-^{14}C] emamectin B1a benzoate at a spray concentration 10 g ai/hL (1× rate) or 100 g ai/hL (10× rate) containing 0.125% non-ionic surfactant. Dose rates were equivalent to 3× 16.8 g ai/ha (1× rate) and 3× 168 g ai/ha (10× rate) with an interval of 7 days each. Total radioactive residues in mature fruit samples for the 1×/10× rate were 0.020/0.13 mg/kg eq harvested 48 hours after the first application, 0.15/1.7 mg/kg eq at 14 days after the last application (DAT) and 0.071/1.3 mg/kg eq at DAT = 28 days. The 14 and 28 day fruit samples were 81–89% extractable with methanol/water.

Extracts were fractionated in an 'avermectin-like' fraction and a 'polar fraction'. Parent emamectin B1a benzoate was the only identified component in the 'avermectin-like' fraction ranging from 20–27% TRR in the 48 hour samples to 4.2–8.8% TRR at DAT = 14 and 28. Many unidentified compounds were present in the 'avermectin-like' fraction, none exceeding 0.01 mg/kg eq (1× rate), 0.014 mg/kg eq (10× rate, 48 hours) or 10% TRR (10× rate, day 14 and 28). A significant portion in the polar fraction comprised simple sugars (fructose, glucose, sucrose, maltose, galactose and xylose) and combined sugars with incorporated radioactivity ranging from 9–38% TRR. Radioactivity in the post-extraction solids corresponded to 3.2–13.9% TRR. With more stringent extraction procedures more than half the total radioactivity in the remaining solids was released, with no single fraction accounting for more than 0.005 mg/kg eq (3.7% TRR) in the 1× rate samples and 0.06 mg/kg eq (4.3% TRR) in the 10× rate samples.

Outdoors grown head lettuce was sprayed eight times with an EC formulation of [3, 7, 11, 13, 23-^{14}C]-emamectin B1a benzoate at a spray concentration 6 g ai/hL (1× rate) or 30 g ai/hL (5× rate).

Dose rates were equivalent to 8× 16.8 g ai/ha (1× rate) and 8× 84.0 g ai/ha (5× rate) with an interval of 7 days each. The distribution of radioactive residue from 1× and 5× rate treated crops at all DATs was approximately 25–80% in the head plus wrapper leaves (RAC), 20–75% in the dead leaves, and less than 1% in the roots. Total radioactive residues in the head plus wrapper leaves (RAC) declined from 0.36 to 0.081 mg/kg eq at DAT 0 and 10 for the 1× rate and declined from 1.6 to 0.62 mg/kg at DAT 0 and 10 for the 5× rate. The residue in the RAC was 74–88% extractable with methanol/water. The majority of the radioactivity (> 85% TRR) was located in the wrapper leaves at all PHIs with little translocation to head leaves. The removal of a large proportion of residue by the MeOH rinsing procedure (> 46% TRR) indicated that much of the extractable residue was located on the crop surface.

The major identified component was parent emamectin B1a benzoate (maximum 29% TRR), which decreased with PHI (minimum 2.9% TRR). An unresolved polar fraction (26–58% TRR), which increased with PHI, consisted of a complex mixture of unidentified minor components. Further treatment of the polar fraction indicated the absence of acid-hydrolysable, glucose conjugates or glucuronide conjugates of parent or known metabolites. Most of the remaining radioactivity co-eluted with one of the 'avermectin like' primary metabolites of the parent (MSB1a, FAB1a, MFB1a, 8a-OXOMAB1a, 8a-OHMAB1a, 15-OHB1a, AB1a, and 8,9-ZMa), none of which exceeded 5% TRR (0.01 mg/kg eq) at or after 3 days PHI. The sum of the identified avermectin-like primary metabolites was 5.4–27% TRR and was in the same order of magnitude as the parent compound. Approximately 6.5–12% TRR of the extract remained uncharacterised. Radioactivity in the post-extraction solids corresponded to 12–26% TRR. More stringent extraction attempts released approximately 7% TRR, which was assumed to be associated with lignin and a further 5–10% TRR, which was assumed to be associated with glucose derived from cellulose.

Outdoors grown head cabbage was sprayed eight times with an EC formulation of [3, 7, 11, 13, 23-^{14}C]-emamectin B1a benzoate at a spray concentration 6 g ai/hL (1× rate) or 30 g ai/hL (5× rate) or only once at 120 g ai/hL (20× rate). Dose rates were equivalent to 8× 16.8 g ai/ha (1× rate), 8× 84.0 g ai/ha (5× rate) with an interval of 7 days each or 1× 334 g ai/ha (20× rate). The distribution of radioactive residue from 1× and 5× rate treated crops at all DATs was approximately 70–90% in the head plus wrapper leaves (RAC), 16–33% in the dead leaves, and less than 1% in the roots. Total radioactive residues in the head plus wrapper leaves (RAC) declined from 0.45 to 0.20 mg/kg eq at DAT 0 and 10 for the 1× rate and declined from 2.9 to 1.3 mg/kg at DAT 0 and 10 for the 5× rate. The residue in the RAC was 78–91% extractable with methanol/water. The majority of the radioactivity (> 99% TRR) was located in the wrapper leaves with little translocation to the head. The removal of a large proportion of residue by the MeOH rinsing procedure (39–48% TRR) indicated that much of the extractable residue was located on the crop surface.

The major identified component was parent emamectin B1a benzoate (maximum 34% TRR), which decreased with PHI (minimum 3.2% TRR). A polar fraction (21–58% TRR) consisted of a complex mixture with numerous unidentified minor components (< 5% TRR). Further treatment of the polar fraction indicated the absence of acid-hydrolysable or glucose conjugates of parent or known metabolites. Most of the remaining radioactivity co-eluted with one of the 'avermectin like' primary metabolites of the parent (MSB1a, FAB1a, MFB1a, 8a-OXOMAB1a, 8a-OHMAB1a, AB1a, and 8,9-ZMa), none of which exceeded 10% TRR at or after 3 days PHI. In addition low amounts of 8,9-ZMFB1a, OXIB1a, ACROB1a (tentative), 8a-OHMFB1a (tentative) and 8a-OXOMFB1a (tentative) were identified in 5× rate plants. The sum of the identified avermectin-like primary metabolites was 9.0–32% TRR and was in the same order of magnitude as the parent compound. Approximately 8–13% TRR of the extract remained uncharacterized. Radioactivity in the post-extraction solids corresponded to 20% TRR. More stringent extraction attempts resulted in nearly quantitative release of radioactivity, and radioactivity appeared to be incorporated into glucose and protein.

Outdoors grown sweet corn was sprayed six times with an EC formulation of [3, 7, 11, 13, 23-^{14}C]-emamectin B1a benzoate at a spray concentration 4 g ai/hL (1× rate) or 20 g ai/hL (5× rate) or only once at 80 g ai/hL (20× rate). Dose rates were equivalent to 8× 16.8 g ai/ha (1× rate), 8×

84.0 g ai/ha (5× rate) with an interval of 3–5 days each or 1× 334 g ai/ha (20× rate). At harvest more than 98% of the intercepted radioactivity was located in parts of the crop directly exposed to the spray applications: leaf plus stalk and husk plus silk. Total radioactive residues in the leaf plus stalk (forage) ranged from 0.90–1.2 mg/kg eq at DAT 0–1–3–7 for the 1× rate, 3.5–5.9 mg/kg at DAT 0–1–3–7 for the 5× rate and 3.5–3.8 mg/kg eq at DAT 1–3 for the 20× rate. Total radioactive residues in the sweet corn kernels ranged from 0.018–0.023 mg/kg eq at DAT 0–1–3–7 for the 1× rate, 0.076–0.084 mg/kg at DAT 0–1–3–7 for the 5× rate and < 0.02 mg/kg eq at DAT 1–3 for the 20× rate. There was no significant decline in TRR with PHI in any plant part. The residue in the forage (leaf/stalk, husk) was 74–89% extractable with methanol/water, while extractability was lower (28–52% TRR) in protected parts of the crop (cob and kernels). The removal of a large proportion of residue by the MeOH rinsing procedure (49–57% TRR) from leaf/stalk and husk samples indicated that much of the extractable residue was located on the crop surface.

In sweet corn kernels and cobs from 1× and 5× rate samples, the extractable radioactivity was found almost entirely in the polar fraction (22–53% TRR), with parent emamectin B1a benzoate either absent or at very low concentrations (< 0.008 mg/kg). In forage (leaf plus stalk, husks) from 1× and 5× rate samples the major identified component was parent emamectin B1a benzoate (maximum 23% TRR), which decreased with PHI (minimum 3.1% TRR). The polar fraction (52–70% TRR for leaves/stalk and 22–53% TRR for husk, kernels and cobs) was characterized as a highly complex mixture of sugars (fructose, xylose and galactose in leaves/stalks (22% TRR) and fructose, glucose, sucrose and galactose in kernels and cobs (22–26%TRR)) and unidentified non-sugar metabolites. Acid hydrolysis indicated that conjugates of emamectin B1a benzoate and its avermectin-like metabolites were absent. Most of the remaining radioactivity in the leaf/stalk and husk extracts co-eluted with one of the 'avermectin like' primary metabolites of the parent (MSB1a, FAB1a, MFB1a, 8a-OXOMAB1a, 8a-OHMAB1a, AB1a, and 8,9-ZMa), none of which exceeded 5% TRR. In addition low amounts of 8,9-ZMFB1a and OXIB1a were identified. The sum of the identified avermectin-like primary metabolites was 4.7–16% TRR and was in the same order of magnitude as the parent compound. Furthermore, a large number of unidentified minor residue components were found, none individually exceeding 1.5% TRR. Radioactivity in the post-extraction solids corresponded to 12–17% TRR for leafs/stalks and 54–72% TRR in kernels. More stringent extraction attempts resulted in nearly quantitative release of radioactivity, and radioactivity appeared to be incorporated into plant natural products including phytoglycogen, starch, cellulose, protein and (for leaf/stalks and husks) possibly lignin.

Plant metabolism summary

In fruit, leafy vegetables and cereal forage, parent emamectin B1a benzoate was the only residue identified at significant quantities (2.6–34% TRR, depending on PHI). In cereal grains residues were low and residues could not be assigned to any avermectin-like compound. On the outer surface of leafy vegetables and cereal forage emamectin B1a benzoate metabolises to a large number of ‘avermectin-like’ compounds, none of which contribute more than 10% of the TRR. When summed, these avermectin-like compounds add up to amounts approximately equal to or slightly higher than the parent compound (ratio increasing to factor 2 with PHI). None of the avermectin-like metabolites (except AB1a) was found in rats or livestock. In fruit, leafy vegetables, cereal forage and cereal grains emamectin B1a benzoate undergoes extensive degradation resulting in low concentrations of many polar products (total 21–70% TRR), none of which corresponds to hydrolysable conjugates of either emamectin B1a benzoate or avermectin-like metabolites. A significant portion of these polar products (9.0–38% TRR) was shown to be sugars (xylose, glucose, galactose, sucrose, fructose and maltose). Plant metabolism of these polar residues then incorporates radioactivity into a range of natural plant components like phytoglycogen, starch, cellulose, protein and lignin. Since the majority of the radioactivity was located on the exposed plant parts (e.g., cabbage wrapper leaves) and did not translocate to more hidden plant parts (e.g., cabbage heads), emamectin B1a benzoate is considered non-systemic in plants.

Environmental fate in soil

The Meeting received information on soil photolysis and on rotational crops.

Soil photolysis

The degradation profile for [23-^{14}C]-emamectin B1a benzoate and [23-^{14}C]-emamectin B1b benzoate in a sandy loam soil during a 30 day exposure to artificial sunlight at 25 °C was similar to the dark control. The DT_{50} was 12–19 days in the irradiated samples and 30–34 days in the dark controls, indicating that the rate of degradation was faster in the irradiated samples. Emamectin benzoate degrades to some 'avermectin-like' compounds (FAB1a/b, MFB1a/b, AB1a/b) as well as a large number of unidentified compounds, none of which contribute more than 10% of the applied radioactivity.

The degradation profile for [3, 7, 11, 13, 23-^{14}C]-emamectin B1a benzoate in a sandy loam soil during a 30 day exposure at 25 ºC to artificial sunlight was similar to the dark control. The DT_{50} was 5 days in the irradiated samples and 8 days in the dark controls, indicating that the rate of degradation was faster in the irradiated samples. Emamectin benzoate degrades to some 'avermectin-like' compounds (MSB1a, FAB1a, MFB1a, 8a-OXOMAB1a, 8a-OHMAB1a, AB1a and 8,9-ZMa) as well as a large number of unidentified compounds, none of which contribute more than 10% of the applied radioactivity.

To identify the compounds that are the result of photo-degradation alone, [3,7,11,13,23]-^{14}C-emamectin B1a benzoate was exposed to artificial sunlight on a glass plate during 96 hours. Emamectin benzoate degraded completely in this period: < 0.1% of the applied radioactivity (TAR) remained. Only AB1a (< 0.3% TAR) and benzoic acid (12% TAR) could be identified. The remaining part of the radioactivity (84–85% TAR) were polar photo-degradates, which are considered to be an extremely heterogeneous mixture of very minor and highly degraded residues without any resemblance to the macrocycle of the parent molecule.

These studies confirm that photolysis plays an important role in the degradation of emamectin B1a benzoate and emamectin B1b benzoate.

Rotational crops

In a confined rotational crop study, [3, 7, 11, 13, 23-^{14}C]-emamectin B1a benzoate was sprayed on a sandy loam soil in six weekly applications of 168 g ai/ha. The application was outdoors in Madera, CA, USA. Rotational crops were sown 30, 120/141 and 365 days after application, representing first, second and third rotations. No residues were detected in lettuce, carrot roots and barley forage after first-second-third rotations, while total radioactivity was < 0.009–0.009–< 0.009 mg/kg eq in carrot tops and barley grain, and 0.016–0.030–< 0.009 mg/kg eq in wheat straw after first-second-third rotations. No parent emamectin B1a benzoate and no avermectin-like metabolites could be detected. Residues were characterised as more polar than the parent.

From this study it can be concluded that residues are unlikely to be found in rotational or succeeding crops.

Analytical methods

The Meeting received description and validation data for analytical methods of emamectin B1a benzoate and emamectin B1b benzoate in plant and animal commodities as well as for four of the avermectin-like metabolites 8,9-ZMa, AB1a, MFB1a, and FAB1a in plant commodities.

Four single residue analytical methods were proposed to the Meeting as post-registration monitoring and enforcement methods for emamectin B1a benzoate and emamectin B1b benzoate in plant commodities (RAM 465/01, AVARD 244-92-3) and animal commodities (RAM 489/01 and AVARD 244-95-1). All methods are considered sufficiently validated for the determination

emamectin B1a benzoate and emamectin B1b benzoate. The LOQ ranged from 0.001–0.005 mg/kg. Two methods for plant commodities have been subjected to independent method validation. Compatibility of emamectin B1a benzoate and emamectin B1b benzoate in an existing multi-residue HPLC-MS method (e.g., DFG S19) was not tested, but is desirable.

Method RAM 465/01 and RAM 489/01 and modifications thereof are also sufficiently validated for the avermectin-like metabolites 8,9-ZMa, AB1a, MFB1a, and FAB1a. The LOQ for these methods was 0.001 mg/kg for each matrix and analyte.

HPLC-fluorescence method AVARD 244-92-3 and AVARD 244-95-1 and modifications thereof are considered less suitable for enforcement, since the method cannot discriminate between emamectin B1a benzoate and 8,9-ZMa and between emamectin B1b benzoate and 8,9-ZMb. Residues for parent compound may be overestimated. Although the method claims to quantify also the avermectin-like metabolites AB1a/b, MFB1a/b, and FAB1a/b, recoveries for these analytes are very often below the 70% limit, precision (RSD) was very often above the 20% limit and MFB1a/b and FAB1a/b cannot be separated from each other. Therefore the method is considered not valid for the avermectin-like metabolites.

Method AVARD 244-92-3 was radio-validated using samples from the cabbage metabolism study. Extraction efficiency for the sum of emamectin B1a benzoate and 8,9-ZMa using method AVARD 244-92-3 had similar efficiency compared to the extraction methods used in the metabolism study.

Method AVARD 244-95-3 was radio-validated using samples from the goat metabolism study. Extraction efficiency for the sum of emamectin B1a and 8,9-ZMa using method AVARD 244-95-3 had similar extraction efficiency for goat liver and goat milk as compared to the extraction methods used in the metabolism study.

In addition to the enforcement methods, one additional HPLC-fluorescence method was reported for cottonseeds (AVARD 244-96-01) with an LOQ of 0.002 mg/kg. As for the other HPLC-fluorescence methods the method cannot discriminate between emamectin B1a benzoate and 8,9-ZMa and residues for emamectin B1a benzoate may be overestimated.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of emamectin B1a benzoate and emamectin B1b benzoate and four avermectin-like metabolites 8,9-ZMa, AB1a, MFB1a, and FAB1a in plant commodities stored frozen. No storage stability studies were provided for animal commodities. Since the samples from the animal feeding study were stored longer than 30 days (73 days) after slaughter, it is desirable to have storage stability studies on animal commodities.

Emamectin B1a benzoate and emamectin B1b benzoate were stable when stored at –20 °C or lower for at least 27 months (804 days) in plant commodities with high water content (tomatoes and green beans with pods), at least 18 months (545 days) in plant commodities with high starch content (potatoes), and at least 9 months (273 days) in plant commodities with high oil content (cottonseed), and special plant commodities (cotton gin trash). Storage stability of commodities with high acid content (grapes) and processed commodities (apple pomace and apple juice) has not been reported, but is desirable.

Avermectin-like metabolites 8,9-ZMa, AB1a, MFB1a, and FAB1a were stable when stored at –20 °C or lower for at least 18 months in plant commodities with high water content (tomatoes and green beans with pods), at least 18 months commodities with high starch content (potatoes), while 8,9-ZMa was stable for at least 6 months in commodities with high oil content (cottonseed), and special commodities (cotton gin trash).

All crop commodities from supervised residue trials were analysed within the verified storage stability period, except almond nutmeat (7.2 months). For these commodities the Meeting decided to accept the trials. The storage temperatures in the supervised trials varied. Since parent is shown to be

stable for a long period of time, trials where temperatures during storage were raised to –1 °C, were not rejected.

Definition of the residue

The composition of the residue was investigated for emamectin B1a benzoate in ruminants (lactating goats), poultry (laying hens), fruits (pear), leafy crops (lettuce and head cabbage) and cereals (sweet corn).

Based on the available livestock studies, emamectin B1a benzoate was the major compound found at 54–82% of the total radioactivity in goat livers, kidneys, muscle, fat and milk. In chickens, emamectin B1a benzoate was metabolised more intensely with parent accounting for 13–60% TRR and the major metabolite being the poultry specific 24-OH MAB1a. In tissues and egg yolk, nearly all of the 24-OH MAB1a was present as fatty acid conjugates (1.3–6.3% TRR as unconjugated form, 5.1–57% TRR as conjugate), which could be released by lipase treatment. Other poultry specific metabolites, not found in rats, were fatty acid conjugates of 24-OH AB1a (0.9–4.8% TRR) which could be released by lipase treatment. Inclusion of these poultry specific metabolites 24-OH MAB1a and 24-OH AB1a and their fatty acid conjugates in the residue definition for dietary risk assessment for poultry commodities is considered below.

Since poultry is not exposed to emamectin benzoate from uses considered by the present Meeting, no residues are anticipated in poultry tissues and eggs not even if the dietary burden increases because of possible future changes in the intended use pattern for emamectin. As there is no reasonable expectation of emamectin and its poultry specific metabolites, the Meeting concluded that the residue definition for animal commodities for enforcement and for dietary risk assessment should only include the parent compound.

In the goat metabolism study the distribution of emamectin B1a benzoate in the goat tissues shows a slight preference for fat tissue: emamectin B1a benzoate was found at levels of 0.070–0.11 mg/kg in muscle and 0.22–0.28 mg/kg in fat. In the cow feeding study, emamectin B1a benzoate levels were < 0.002–0.0058 mg/kg in muscle and 0.0021–0.013 mg/kg in fat at the 0.03–0.30 ppm dose levels. In the metabolism study on lactating goats, total radioactive residues in cream were on average 6.3 fold higher than in whole milk. The distribution of the emamectin B1a benzoate itself was not investigated in this study. In the cow feeding study emamectin B1a benzoate levels in cream were 3–10 fold higher than in whole milk and also the log K_{ow} for emamectin benzoate of 5.0 at pH 7 does suggest fat solubility. However, in the cow feeding study emamectin B1a benzoate levels in skim milk (1.2–3.0 mg/kg, 0.30 ppm dose) were only slightly lower than in whole milk (1.7–5.3 mg/kg, 0.30 ppm dose). Since there is only a slight preference for fat in both tissues and milk, the Meeting considers the residue in animal commodities (i.e., emamectin B1a benzoate) not fat soluble.

Based on the available comparative plant metabolism studies, parent emamectin B1a benzoate is the major component (2.6–34% TRR, depending on PHI) in fruits, leafy vegetables and cereal forage. In cereal grains residues were low and residues could not be assigned to any avermectin-like compound. In leafy vegetables and cereal forage emamectin B1a benzoate metabolises to a large number of 'avermectin-like' compounds, none of which contribute more than 10% of the TRR (MSB1a, FAB1a, MFB1a, 8a-OXOMAB1a, 8a-OHMAB1a, 15-OHB1a, AB1a, 8,9-ZMa, 8,9-ZMFB1a, OXIB1a, ACROB1a (tentative), 8a-OHMFB1a (tentative) and 8a-OXOMFB1a (tentative)). None of the avermectin-like metabolites (except AB1a) was found in rats or livestock. Inclusion of these 13 plant specific avermectin-like metabolites in the residue definition for risk assessment of plant commodities is considered below.

In the metabolism studies, eight of the 13 identified avermectin-like metabolites have been quantified (MSB1a, FAB1a, MFB1a, 15-OHB1a, 8a-OXOMAB1a, 8a-OHMAB1a, AB1a and 8,9-ZMa). Each of the eight avermectin-like metabolites at PHI 3–10 days in the leafy crop parts is present at levels below 10% TRR and at levels below parent emamectin B1a benzoate (ratio avermectin-like/parent of 0.2–0.7). When summed, this results in ratios of avermectin-like/parent of

0.9–1.9 (PHI 3d), 1.3–2.5 (PHI 7 d), 2.1–2.8 (PHI 10d) in lettuce, head cabbage and sweet corn forage.

Four of the 13 avermectin-like metabolites (8,9-ZMa, AB1a, MFB1a and FAB1a) have been quantified in the supervised residue trials. Parent emamectin B1a benzoate was generally found at low levels (< 0.001–0.079 mg/kg) in fruits, brassica (PHI > 1d), fruiting vegetables, green beans with pods, tree nuts and cottonseed. Individual avermectin-like metabolites ranged from < 0.001–0.009 mg/kg in these commodities. Only in brassica (PHI 0–1d), lettuce, mustard greens, immature cauliflower plants, bean vines and almond hulls higher levels of emamectin B1a benzoate were found (< 0.001–1.2 mg/kg) and consequently also higher levels of avermectin-like metabolites were found (< 0.001–0.160 mg/kg). Taking all commodities together, the ratios of the four avermectin-like metabolites to parent ranged from 0.00–0.78 (median 0.05 and n = 353), where the emamectin B1a benzoate concentration was at least 0.01 mg/kg. When looking at individual commodities, the median ratios of the four avermectin-like metabolites to parent ranged from 0.00–0.08 for most commodities. Higher median ratios were found for peaches (0.11), head lettuce (0.12), leaf lettuce (0.12), almond hulls (0.27), whole cauliflower plants (0.15), nectarine flesh (0.14), and peach flesh (0.13). When the same four metabolites were summed in the metabolism studies, ratios of the avermectin-like metabolites were only slightly lower than when all eight quantified avermectin like metabolites were included, indicating that the most prominent avermectin-like residues have been quantified in the supervised residue trials.

Supervised residue trials are considered to be more representative for residue levels in commodities than metabolism studies and because levels of avermectin-like metabolites in the supervised residue trials do not contribute substantially to the residue level in commodities (sum of emamectin B1a benzoate and 13 avermectin-like metabolites only a factor 1.00–1.27 higher than emamectin B1a benzoate, depending on commodity), the Meeting agreed that the avermectin-like metabolites need not be included in the residue definition for risk assessment for plant commodities.

The Meeting recommended the following residue definitions for emamectin benzoate:

Definition of the residue for compliance with the MRL or for estimation of the dietary intake for plant and animal commodities: emamectin B1a benzoate.

The Meeting considers the residue not fat soluble.

Results of supervised trials on crops

The Meeting received supervised trials data for emamectin benzoate on apples, pears, nectarines, peaches, grapes, (sprouting) broccoli, cauliflower, head cabbages, cucumber, melons, tomatoes, sweet peppers, Cos lettuce, head lettuce, leaf lettuce, mustard greens, fresh beans with pods, almonds, pecans and cottonseed.

In some trials (apple, pear and grapes) the number of applications was higher than according to GAP. For trials where a sample was taken just before the last application it could be shown that the residues had declined to 4–33% of the emamectin B1a benzoate residues just after the last treatment. This shows that the number of applications does not have a significant effect on the final residue levels. For this reason, the Meeting decided to include trials with an exaggerated number of applications.

In those trials where residues levels were higher at higher PHI than required for critical GAP, these residues were selected instead of the residues at the critical GAP PHI. In trials on the same location where the only difference was the addition of an adjuvant, the maximum value is selected for each of the trial locations. In trials on the same location with the same dose rate in kg ai/ha, where the only difference is the spray volume (i.e., spray concentration), the maximum value is selected for each of the trial locations.

Since in all USA trials (except tree nuts) residues were measured as the sum of emamectin B1a benzoate and the 8,9-ZMa isomer, the residues do not comply with the residue definition. Since

the ratio between the 8,9-ZMa isomer and emamectin B1a benzoate ranged from 0.001–0.18 in various supervised residue trials, where emamectin B1a benzoate was > 0.01 mg/kg, the Meeting decided to use these trials.

The recommendations proposed by the Meeting were compared using the OECD MRL calculator. For those trials where the outcome of the OECD MRL calculator was different from the recommendation made by the Meeting, a rationale is provided for this deviation.

Pome fruits

Field trials involving apples were performed in Italy, Spain, France, Switzerland and the USA.

Critical GAP for apples in Italy is for two foliar spray applications (interval 7 days) at 38.0 g ai/ha and PHI 7 days. In trials from Italy and Spain (3× 29–40 g ai/ha, interval 6–7 days and PHI 7 days) matching this GAP emamectin B1a benzoate residues in apple whole fruit were < 0.001, < 0.001, 0.002, 0.003, 0.004, 0.004, 0.005 and 0.005 mg/kg (n = 8).

Critical GAP for apples in Hungary is for three foliar spray applications (interval 7 days) at 4.75 g ai/hL and PHI 3 days. In trials from Northern France and Switzerland (3 × 3.7–4.2 g ai/hL, interval 6–8 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in apple whole fruit were 0.004, 0.006, 0.006 and 0.009 mg/kg (n = 4).

Critical GAP for pome fruit in the USA is for an unspecified number of foliar spray applications at 16.8 g ai/ha (max 50.4 g ai/ha per season and interval 7 days) and PHI 14 days. In trials from the USA (3× 17 g ai/ha; interval 7 days and PHI 14–15 days) matching this GAP emamectin B1a benzoate residues in apple whole fruit were < 0.005 (13) mg/kg (n = 13).

The Meeting noted that the GAPs for Italy, Hungary and the USA for apples are different and that data cannot be combined. Although the highest residue is found in the dataset matching Hungarian GAP, this dataset had an insufficient number of data to support a recommendation for apples or pome fruit. The Italian dataset resulted in the next highest residues and the Meeting decided to use only the apple dataset matching Italian GAP.

Field trials involving pears were performed in Spain, France and the USA.

Critical GAP for pears in Italy is for two foliar spray applications (interval 7 days) at 38.0 g ai/ha and PHI 7 days. In trials from Spain (3× 33–38 g ai/ha, interval 7 days and PHI 7 days) matching this GAP emamectin B1a benzoate residues in pear whole fruit were: 0.008 and 0.011 mg/kg (n = 2).

Critical GAP for pears in Hungary is for three foliar spray applications (interval 7 days) at 4.75 g ai/hL and PHI 3 days. In trials from Northern France (3 × 3.7–3.8 g ai/hL, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in pear whole fruit: 0.001 and 0.001 mg/kg (n = 2).

Critical GAP for pome fruit in the USA is for an unspecified number of foliar spray applications at 16.8 g ai/ha (max 50.4 g ai/ha per season and interval 7 days) and PHI 14 days. In trials from the USA (3 × 17 g ai/ha; interval 7 days and PHI 14 days) matching this GAP emamectin B1a benzoate residues in pear whole fruit were < 0.005 (3) and 0.006 (3) mg/kg (n = 5).

The Meeting noted that the GAPs for Italy, Hungary and the USA for pears are different and that data cannot be combined. Each of the datasets has an insufficient number of data to support a recommendation for pears or pome fruit. Since the dataset matching Italian GAP has the highest residue, the Meeting decided to use only the pear dataset matching Italian GAP.

The Meeting noted that Italian GAPs for apples and pears are identical and that the datasets for apples and pears matching Italian GAP were from similar populations (Mann-Whitney U test). Since residue behaviour within the pome fruit group is expected to be similar, the Meeting agreed that the datasets for apples and pears matching Italian GAP could be combined. Emamectin B1a benzoate

residues in apples and pears were: < 0.001, < 0.001, 0.002, 0.003, 0.004, 0.004, 0.005, 0.005, 0.008 and 0.011 mg/kg (n = 10).

The Meeting agreed that the Italian data for apples and pears could be used to support a pome fruit commodity maximum residue level recommendation and estimated a maximum residue level of 0.02 mg/kg on pome fruit and estimated an STMR of 0.004 mg/kg and an HR of 0.011 mg/kg.

Stone fruits

Field trials involving nectarines were performed in Spain.

Critical GAP for peaches & nectarines in Italy is for three foliar spray applications (interval 7 days) at 38.0 g ai/ha and PHI 7 days. In trials from Spain (3× 34–40 g ai/ha, interval 7 days and PHI 7 days) matching this GAP emamectin B1a benzoate residues in nectarine whole fruit were 0.009 and 0.014 mg/kg (n = 2). Corresponding residues in the edible portion (flesh, i.e., fruit without stone and stem but with peel) resulted in: 0.011 and 0.015 mg/kg (n = 2).

Field trials involving peaches were performed in France and Italy.

Critical GAP for peaches & nectarines in Italy is for three foliar spray applications (interval 7 days) at 38.0 g ai/ha and PHI 7 days. In trials from Southern France and Spain (3× 29–38 g ai/ha, interval 7 days and PHI 7 days) matching this GAP emamectin B1a benzoate residues in peach whole fruit were 0.002, 0.003, 0.005, 0.008, 0.009 and 0.010 mg/kg (n = 6). Corresponding residues in the edible portion (flesh, i.e., fruit without stone and stem but with peel) resulted in: 0.002, 0.004, 0.006, 0.009, 0.010 and 0.011 mg/kg (n = 6).

Since residue behaviour for nectarines and peaches is expected to be similar and Italian GAPs for nectarine and peach are identical, the Meeting agreed that the datasets for nectarines and peaches matching Italian GAP could be combined. Emamectin B1a benzoate residues in nectarines and peaches (whole fruit) were: 0.002, 0.003, 0.005, 0.008, 0.009, 0.009, 0.010 and 0.014 mg/kg (n = 8). Corresponding residues in the edible portion (flesh, i.e., fruit without stone and stem but with peel) resulted in: 0.002, 0.004, 0.006, 0.009, 0.010, 0.011 (2) and 0.015 mg/kg (n = 8).

The Meeting agreed that the datasets for nectarines and peaches matching Italian GAP could be used to support a nectarine and peach commodity maximum residue level recommendation. The Meeting estimated a maximum residue level of 0.03 mg/kg on nectarines and peaches and estimated an STMR of 0.0095 mg/kg and an HR of 0.015 mg/kg.

Grapes

Field trials involving grapes were performed in Italy, Spain, France and Switzerland.

Critical GAP for grapes in Italy is for three foliar spray applications (interval 14 days) at 14.2 g ai/ha and PHI 7 days. In trials from Italy, Spain and Southern France (4 × 12–16 g ai/ha, interval 10–15 days and PHI 7 days) matching this GAP emamectin B1a benzoate residues in grape bunches were < 0.001 (3), 0.002, 0.003, 0.009, 0.014 and 0.022 mg/kg (n = 8).

Critical GAP for grapes in Hungary is for three foliar spray applications (interval 10 days) at 14.2 g ai/ha and PHI 7 days. In trials from Northern France and Switzerland (4 × 12–15 g ai/ha, interval 10-14 days and PHI 6–7 days) matching this GAP emamectin B1a benzoate residues in grape bunches were < 0.001 (2), 0.001, 0.003, 0.004 and 0.005 mg/kg (n = 6).

The Meeting noted that the GAP for the Italian and Hungarian datasets was the same. Since the datasets were from similar populations (Mann-Whitney U test), the Meeting agreed that they could be combined. Emamectin B1a benzoate residues in grape bunches were < 0.001 (5), 0.001, 0.002, 0.003, 0.003, 0.004, 0.005, 0.009, 0.014 and 0.022 mg/kg (n = 14).

The Meeting agreed that the combined datasets for grapes matching Italian and Hungarian GAP could be used to support a grape maximum residue level recommendation and estimated a

maximum residue level of 0.03 mg/kg on grapes and estimated an STMR of 0.0025 mg/kg and an HR of 0.022 mg/kg.

Brassica vegetables

Field trials involving broccoli and sprouting broccoli were performed in Spain, France, Germany, United Kingdom, Switzerland and the USA.

Critical GAP for broccoli in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In field trials performed in Spain and Southern France (3 × 15 g ai/ha, interval 7 days and PHI 3 days, without adjuvant) matching this GAP emamectin B1a benzoate residues in broccoli and sprouting broccoli (inflorescence) were 0.001 and 0.002 mg/kg (n = 2).

Trials performed in Germany, United Kingdom and Switzerland did not match with any GAP.

Critical GAP for brassica head and stem vegetables in the USA is for an unspecified number of foliar spray applications at 16.8 g ai/ha (max 101 g ai/ha per season, interval 7 days) and PHI 7 days. In broccoli trials from the USA (6–7 × 17–18 g ai/ha; interval 7 days and PHI 6–8 days) matching this GAP emamectin B1a benzoate residues in broccoli (inflorescence) were < 0.005 (3) mg/kg (n = 3).

Field trials involving cauliflower were performed in France, Germany, the United Kingdom and the USA.

Critical GAP for cauliflower in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In field trials performed in Southern France (3 × 14–15 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in cauliflower (inflorescence) were < 0.001 (3) and 0.001 mg/kg (n = 4).

Trials performed in Northern France, Germany and the United Kingdom did not match with any GAP.

Critical GAP for brassica head and stem vegetables in the USA is for an unspecified number of foliar spray applications at 16.8 g ai/ha (max 101 g ai/ha per season, interval 7 days) and PHI 7 days. In cauliflower trials from the USA (9 × 17 g ai/ha; interval 7 days and PHI 6–8 days) matching this GAP emamectin B1a benzoate residues in cauliflower (inflorescence) were < 0.005 mg/kg (n = 1).

Field trials involving head cabbage were performed in Italy, France and the USA.

Critical GAP for head cabbage in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In field trials performed in Italy and Southern France (3 × 15–16 g ai/ha, interval 7–8 days and PHI 3 days, without adjuvant) matching this GAP emamectin B1a benzoate residues in head cabbage (whole plant) were < 0.001 (3) and 0.002 mg/kg (n = 4).

Critical GAP for brassica head and stem vegetables in the USA is for an unspecified number of foliar spray applications at 16.8 g ai/ha (max 101 g ai/ha per season and interval 7 days) and PHI 7 days. In head cabbage trials from the USA (6–7 × 17 g ai/ha; interval 6–8 days and PHI 7 days) matching this GAP emamectin B1a benzoate residues in head cabbage (heads only) were < 0.005, < 0.005 and 0.020 mg/kg (n = 3).

The Meeting noted that the GAPs for Italy and the USA were different and therefore trials from the same commodities could not be combined. Data from each of the individual commodities were insufficient to propose a recommendation and combination of USA data for broccoli, cauliflower and head cabbage was not possible because residue distribution differed. The Meeting agreed that the data were insufficient to make a recommendation for brassica vegetables or each of the individual commodities (broccoli, cauliflower and head cabbage).

Fruiting vegetables, Cucurbits

Indoor trials involving cucumbers were performed in Spain, France and Switzerland.

Critical GAP for cucumbers & summer squash in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In indoor trials performed in Spain, Northern France and Switzerland (3× 14–21 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in cucumber were < 0.001 (2), 0.001 (3) and 0.002 (2) mg/kg (n = 7).

Field trials involving melons were performed in Italy and Spain, but these trials did not match with any GAP.

Indoor trials involving melons were performed in Spain and France.

Critical GAP for melons, watermelons, pumpkins and summer squash in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In indoor trials performed in Spain, Southern France and Northern France (3 × 15–20 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in melons (whole fruit) were: < 0.001, 0.001 (2), 0.002 (2), 0.003 and 0.004 mg/kg (n = 7). Corresponding residues in the edible portion (pulp) were: < 0.001, < 0.001, < 0.001, ≤ 0.001, < 0.001, < 0.001 and 0.002 mg/kg (n = 7).

The Meeting noted that the Hungarian GAPs for cucumbers, summer squash, melons, watermelons, pumpkins and summer squash cover the whole Codex group of cucurbits and that the trials matching the Hungarian GAPs for cucumbers and melons resulted in similar residues for each of the commodities. The Meeting agreed to propose a group maximum residue level for cucurbits, based on the residue data for melons. Emamectin B1a benzoate residues in melons (whole fruit) were: < 0.001, 0.001, 0.001, 0.002, 0.002, 0.003 and 0.004 mg/kg (n = 7). Corresponding residues in the edible portion (pulp) were: < 0.001, < 0.001, < 0.001, ≤ 0.001, < 0.001, < 0.001 and 0.002 mg/kg (n = 7).

The Meeting agreed that the dataset for melons matching Hungarian GAP could be used to support a maximum residue level recommendation for cucurbits and estimated a maximum residue level of 0.007 mg/kg in/on cucurbits. For cucurbits with edible peel, the Meeting estimated an STMR of 0.001 mg/kg and an HR of 0.002 mg/kg based on the cucumber data. For cucurbits with inedible peel, the Meeting estimated an STMR of 0.001 mg/kg and an HR of 0.002 mg/kg, based on the edible portion data of melons.

The value using the OECD calculator (0.01 mg/kg) was higher than the estimate of 0.007 mg/kg made by the Meeting. The Meeting considers the 0.007 mg/kg value a better estimate, given the values found in the various trials and given that the unrounded MRL estimate of the OECD calculator is 0.0066 mg/kg. It appears that the OECD calculator is not able to propose MRLs below 0.01 mg/kg.

Fruiting vegetables, other than Cucurbits

Field trials involving tomatoes were performed in Spain and France.

Critical GAP for tomatoes in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In field trials performed in Spain and Southern France (3 × 14–15 g ai/ha, interval 6–8 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in tomatoes (whole fruit) were: < 0.001 (2), 0.001 and 0.002 mg/kg (n = 4).

Critical GAP for tomatoes in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In field trials performed in Northern France (3 × 20–21 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in tomatoes (whole fruit) were: < 0.001 (3) and 0.002 mg/kg (n = 4).

The Meeting noted that the GAPs for Italy and Hungary for tomatoes are different and therefore data cannot be combined. Since the GAP for Hungary can be considered worst case, the Meeting agreed to use only the field-grown tomato dataset matching Hungarian GAP.

Indoor trials involving tomatoes were performed in Italy, Spain, France and the United Kingdom.

Critical GAP for tomatoes in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In indoor trials performed in Italy, Spain, France and the UK (3 × 14–21 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in tomatoes (whole fruit) were: < 0.001, 0.001 (2), 0.002, 0.003 and 0.004 mg/kg (n = 6) for standard sized tomatoes and 0.003, 0.004 (2), 0.006, 0.007 and 0.008 (2) mg/kg (n = 7) for cherry tomatoes. Since the datasets for standard size tomatoes and cherry tomatoes were from different populations (Mann-Whitney U test), the data cannot be combined. Since the cherry tomato dataset had higher residues, the Meeting decided to use only the cherry tomato data. This resulted in the following dataset for indoor-grown tomatoes: 0.003, 0.004 (2), 0.006, 0.007 and 0.008 (2) mg/kg (n = 7).

The Meeting noted that the residues for field and indoor grown tomatoes resulted from the same Hungarian GAP. Since the datasets were from different populations (Mann-Whitney U test) datasets cannot be combined. The Meeting agreed to use the indoor cherry tomato data to represent field and indoor grown tomatoes. This resulted in the following dataset for field and indoor grown tomatoes: 0.003, 0.004 (2), 0.007, 0.006 and 0.008 (2) mg/kg (n = 7).

Field trials involving sweet peppers were performed in Italy, Spain and France, but trials did not match with any GAP.

Indoor trials involving sweet peppers were performed in Spain, France and the United Kingdom.

Critical GAP for peppers in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In indoor trials performed in Spain, France and the UK (3 × 15–20 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in sweet peppers (whole fruit) were: < 0.001 (2), 0.002, 0.003 (2), 0.004, 0.007 and 0.013 mg/kg (n = 8).

The Meeting noted that trials matching the Hungarian GAPs for tomatoes and sweet peppers resulted in similar residues for each of the commodities. The Meeting agreed to propose a group maximum residue level for fruiting vegetables other than cucurbits except sweet corn and mushrooms, based on the residue data for sweet peppers. Emamectin B1a benzoate residues in sweet peppers were: < 0.001, < 0.001, 0.002, 0.003, 0.003, 0.004, 0.007 and 0.013 mg/kg (n = 8).

The Meeting estimated a maximum residue level of 0.02 mg/kg in/on fruiting vegetables other than cucurbits except sweet corn and mushrooms and estimated an STMR of 0.003 mg/kg and an HR of 0.013 mg/kg.

The JMPR manual (section 6.9.2) explains that a generic factor may be used for conversion of residues from fresh peppers to dried chilli peppers. The factor is 10 for the estimation of residue levels of pesticides in dried chilli peppers from the HR values estimated for residues in or on sweet peppers.

The Meeting agreed to apply the default factor of 10 for dried chilli peppers to the STMR (0.003 mg/kg) and HR (0.013 mg/kg) values for fruiting vegetables other than cucurbits except sweet corn and mushrooms (based on sweet pepper data) and estimated a maximum residue level, an STMR and an HR in dried chilli peppers of 0.2, 0.03 and 0.13 mg/kg respectively.

Leafy vegetables

Field trials involving Cos lettuce were performed in Italy, Spain and France.

Critical GAP for lettuce and other salad plants in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In field trials performed in Italy, Spain and Southern

France (3 × 14–15 g ai/ha, interval 6–9 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in Cos lettuce were: 0.030, 0.033, 0.042, 0.10 and 0.11 mg/kg (n = 5).

Indoor trials involving Cos lettuce were performed in Italy and France.

Critical GAP for lettuce and other salad plants in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In indoor trials performed in Italy and Northern France (3 × 14–15 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in Cos lettuce were: 0.052, 0.30 and 0.33 mg/kg (n = 3).

The Meeting noted that the residues for field and indoor grown Cos lettuce resulted from the same Italian GAP. Since the datasets were from similar populations (Mann-Whitney U test) the Meeting agreed to combine the datasets. This resulted in the following dataset for field and indoor grown Cos lettuce: 0.030, 0.033, 0.042, 0.052, 0.10, 0.11, 0.30 and 0.33 mg/kg (n = 8)

Field trials involving head lettuce were performed in France, Switzerland and the USA.

Critical GAP for lettuce and other salad plants in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In field trials performed in Southern France (3 × 14–15 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in field-grown head lettuce were: 0.004 mg/kg (n = 1).

Critical GAP for lettuce in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In field trials performed in Northern France and Switzerland (3 × 14–16 g ai/ha, interval 6–7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in field-grown head lettuce were: 0.005, 0.007 and 0.016 mg/kg (n = 3).

Critical GAP for leafy vegetables except brassica in the USA is for an unspecified number of foliar spray applications (interval 7 days, total 101 g ai/ha per season) at 16.8 g ai/ha and PHI 7 days. In field trials performed in the USA (6 × 17 g ai/ha, interval 3–8 days and PHI 7 days) matching this GAP emamectin B1a benzoate residues in field-grown head lettuce were: 0.0052, 0.015 and 0.016 mg/kg (n = 3).

The Meeting noted that the GAPs for Italy, Hungary and the USA were different and therefore datasets cannot be combined. Since the Hungarian GAP can be considered worst case, the Meeting agreed to use the dataset matching Hungarian GAP. This resulted in the following dataset for field grown head lettuce: 0.005, 0.007 and 0.016 mg/kg (n = 3).

Indoor trials involving head lettuce were performed in Italy, France, Switzerland and the UK.

Critical GAP for lettuce and other salad plants in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In indoor trials performed in Italy, Northern France, Switzerland and the UK (3 × 15–16 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in indoor-grown head lettuce were: 0.060, 0.15, 0.16, 0.20, 0.26, 0.40 and 0.62 mg/kg (n = 7).

The Meeting noted that the residues for field and indoor grown head lettuce resulted from different GAPs and therefore datasets cannot be combined. Since the dataset for indoor grown head lettuce matching Italian GAP resulted in higher residues, the Meeting agreed to use the dataset for indoor grown head lettuce to represent residues in field and indoor grown head lettuce. This resulted in the following dataset for field and indoor grown head lettuce: 0.060, 0.15, 0.16, 0.20, 0.26, 0.40 and 0.62 mg/kg (n = 7).

Field trials involving leaf lettuce were performed in France.

Critical GAP for lettuce and other salad plants in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In field trials performed in Southern France (3× 15 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in field-grown leaf lettuce were: 0.007 mg/kg (n = 1).

Critical GAP for lettuce in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In field trials performed in Northern France (3 × 14–16 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in field-grown leaf lettuce were: 0.004 mg/kg (n = 1).

The Meeting noted that the GAPs for Italy and Hungary for lettuce are different and therefore data sets cannot be combined. Since the Italian dataset resulted in highest residues, the Meeting agreed that the dataset matching Italian GAP represented field grown leaf lettuce: 0.007 mg/kg (n = 1).

Indoor trials involving leaf lettuce were performed in Italy.

Critical GAP for lettuce and other salad plants in Italy is for three foliar spray applications (interval 7 days) at 14.2 g ai/ha and PHI 3 days. In indoor trials performed in Italy (3 × 15 g ai/ha, interval 7 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in indoor-grown leaf lettuce were: 0.18 mg/kg (n = 1).

The Meeting noted that the residues for field and indoor grown leaf lettuce resulted from the same Italian GAP and agreed to combine the datasets to represent residues in field grown and indoor grown leaf lettuce. This resulted in the following dataset for leaf lettuce: 0.007 and 0.18 mg/kg (n = 2).

The Meeting agreed that the dataset for head lettuce matching Italian GAP could be used to support a maximum residue level recommendation for all lettuce varieties and estimated a maximum residue level of 1 mg/kg in/on Cos lettuce, leaf lettuce and head lettuce and estimated an STMR of 0.20 mg/kg and an HR of 0.62 mg/kg.

Field trials involving mustard greens were performed in the USA.

Critical GAP for brassica leafy vegetables in the USA is for an unspecified number of foliar spray applications at 16.8 g ai/ha (max 101 g ai/ha per season and interval 7 days) and PHI 14 days. In mustard green trials from the USA (6 × 17 g ai/ha; interval 6–8 days and PHI 14 days) matching this GAP emamectin B1a benzoate residues in mustard greens were < 0.005 (2), 0.0085, 0.011, 0.014 and 0.11 mg/kg (n = 6).

The Meeting agreed that the dataset for mustard greens matching USA GAP could be used to support a maximum residue level recommendation for mustard greens and estimated a maximum residue level of 0.2 mg/kg in/on mustard greens and estimated an STMR of 0.010 mg/kg and an HR of 0.11 mg/kg.

Legume vegetables

Field trials involving beans with pods were performed in Spain, France and the UK.

Trials performed in Spain and France did not match with any GAP.

Critical GAP for common beans in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In field trials performed in Northern France and the United Kingdom (3 × 19–21 g ai/ha, interval 7–8 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in common beans were: < 0.001, < 0.001, < 0.001, ≤ 0.001, 0.001, 0.001, 0.001 and 0.009 mg/kg (n = 8).

The Meeting agreed that the dataset for common beans matching Hungarian GAP could be used to support a maximum residue level recommendation for beans, except broad bean and soya beans, green pods and immature seeds, and estimated a maximum residue level of 0.015 mg/kg in/on beans, and estimated an STMR of 0.001 mg/kg and an HR of 0.009 mg/kg.

Tree nuts

Field trials involving almonds were performed in the USA.

Critical GAP for tree nuts in the USA is for three foliar spray applications at 16.8 g ai/ha (max 50.4 g ai/ha per season, interval 7 days) and PHI 14 days. In almond trials from the USA (3 × 17 g ai/ha; interval 7 days and PHI 14 days, with adjuvant) matching this GAP emamectin B1a benzoate residues in almonds (nutmeat) were < 0.001 mg/kg (n = 1).

Field trials involving pecans were performed in the USA.

Critical GAP for tree nuts in the USA is for three foliar spray applications at 16.8 g ai/ha (max 50.4 g ai/ha per season, interval 7 days) and PHI 14 days. In pecan trials from the USA (3 × 17 g ai/ha; interval 7 days and PHI 14 days, with adjuvant) matching this GAP emamectin B1a benzoate residues in pecans (nutmeat) were < 0.001 mg/kg (n = 1).

The dataset for almonds and pecans is considered insufficient to support a recommendation. The Meeting could not estimate an STMR or HR for almonds, pecans or tree nuts.

Oilseed

Field trials involving cotton undelinted seed were performed in the USA.

Critical GAP for cotton in the USA is for an unspecified number of foliar spray applications at 16.8 g ai/ha (max 67.4 g ai/ha per season, interval 5 days) and PHI 21 days. In cotton trials from the USA (4 × 17 g ai/ha; interval 4–6 days and PHI 20–24 days) matching this GAP emamectin B1a benzoate residues in cotton undelinted seed were: < 0.002 (8) mg/kg (n = 8).

The Meeting agreed that the dataset for cotton matching USA GAP could be used to support a maximum residue level recommendation for cotton seed and estimated a maximum residue level of 0.002* mg/kg in/on cotton seed and estimated an STMR of 0.002 mg/kg and an HR of 0.002 mg/kg.

The value using the OECD calculator (0.01 mg/kg) was higher than the estimate of 0.002 mg/kg made by the Meeting. The Meeting considers the 0.002 mg/kg value a better estimate, given the values found in the various trials and given that the unrounded MRL estimate of the OECD calculator is 0.0020 mg/kg. It seems that the OECD calculator is not able to propose MRLs below 0.01 mg/kg.

Legume animal feeds

Field trials involving bean forage (green) were performed in Spain, France and the UK. Trials on bean fodder were not submitted.

Trials performed in Spain and France did not match with any GAP.

Critical GAP for common beans in Hungary is for three foliar spray applications (interval 7 days) at 19.0 g ai/ha and PHI 3 days. In field trials performed in Northern France and the United Kingdom (3 × 19–21 g ai/ha, interval 7–8 days and PHI 3 days) matching this GAP emamectin B1a benzoate residues in bean forage (green) were: 0.002, 0.005, 0.006, 0.007, 0.009, 0.039, 0.058 and 0.093 mg/kg, as received (n = 8).

The Meeting agreed that the dataset for bean vines matching Hungarian GAP could be used and estimated a median residue of 0.008 mg/kg and a high residue of 0.093 mg/kg in/on bean forage (green). Since green bean forage is not traded, a maximum residue level estimation is not required.

Miscellaneous fodder and forage crops

Field trials involving almond hulls were performed in the USA.

Critical GAP for tree nuts in the USA is for three foliar spray applications at 16.8 g ai/ha (max 50.4 g ai/ha per season and interval 7 days) and PHI 14 days. In almond trials from the USA (3 × 17 g ai/ha; interval 7 days and PHI 14 days, with adjuvant) matching this GAP emamectin B1a benzoate residues in almonds (nutmeat) were 0.043 mg/kg, as received (n = 1).

The dataset for almond hulls is considered insufficient to support a recommendation. The Meeting could not estimate a median residue for almond hulls.

Field trials involving cotton gin by-products were performed in the USA.

Critical GAP for cotton in the USA is for an unspecified number of foliar spray applications at 16.8 g ai/ha (max 67.4 g ai/ha per season, interval 5 days) and PHI 21 days. In cotton trials from the USA (4 × 17 g ai/ha; interval 4–6 days, PHI 20–24 days) matching this GAP emamectin B1a benzoate residues in cotton gin by-products were: 0.0022, 0.0025 and 0.0038 mg/kg (n = 3).

The dataset for cotton gin by-products is considered insufficient to support a recommendation. The Meeting could not estimate a median or highest residue for cotton gin by-products.

Fate of residues during processing

Information on the fate of residues during processing by radioactivity studies showed that 23-^{14}C emamectin B1a benzoate undergoes limited hydrolysis under standard conditions used to simulate food processing operations. Break down products formed were the monosaccharide MSB1a (pH 5, 100 °C and pH 6, 120 °C), the aglycone milbemectin B (pH 5, 100 °C)) and the des-N-methyl derivative AB1a (pH 6, 120 °C). The extent of hydrolysis of emamectin B1a benzoate increases with pH and temperature, but all breakdown products are < 10% applied radioactivity under the standard processing conditions used. The Meeting agreed that the residue definition does not need adaption for processed commodities.

Processing studies with emamectin benzoate were undertaken for apples and cottonseed. In the table below, relevant processing factors for these commodities are summarized.

Using the $STMR_{RAC}$ obtained from emamectin benzoate use, the Meeting estimated STMR-Ps for processed commodities as listed below. The Meeting considered the appropriate STMR-P to be used in the livestock dietary burden calculation or dietary intake calculation. An HR-P is not required for processed commodities.

Commodity	Processing factors (PF)	STMR-P = $STMR_{RAC}$× PF mg/kg
Apple pomace (wet)	5.1 (n = 1)	0.004 × 5.1 = 0.0051 (pome fruits)
Apple juice	< 0.7 (n = 1)	0.004 × 0.7 = 0.0028 (pome fruits)
Cottonseed meal	< 0.1 (n = 1)	0.002 × 0.1 = 0.0002 (cottonseed)
Cottonseed hulls	0.28 (n = 1)	0.002 × 0.28 = 0.00056 (cottonseed)
Cottonseed, refined oil	0.38 (n = 1)	0.002 × 0.38 = 0.00076 (cottonseed)

Livestock dietary burden

The Meeting estimated the dietary burden of emamectin benzoate residues on the basis of the livestock diets listed in the FAO manual appendix IX (OECD feedstuff table). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating maximum residue levels, while calculation from STMR and STMR-P values from feed is suitable for estimating STMR values for animal commodities.

All plant commodities used in the dietary burden calculation are listed below. Dietary burden for livestock might be underestimated, since residue data are not available for several feedstuff derived from crops treated with emamectin benzoate.

Codex Group	CROP	FEED STUFF	Highest residue	STMR or STMR-P	DM (%)

AL	Bean	vines	0.093	0.008	35
AB	Apple	pomace, wet	–	0.0051	40
SO	Cotton	undelinted seed	0.002	0.002	88
SM	Cotton	hulls	–	0.00056	90
SM	Cotton	meal	–	0.0002	89

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. A mean and maximum dietary burden for livestock, based on emamectin benzoate use, is shown in the table below.

Animal dietary burden for emamectin benzoate, expressed as ppm of dry matter diet

	US	EU	AU	JPN	overall	
	max	max	max	max	max	
beef cattle	0.000062	0.0026	0.16	–	0.16 (AU)	
dairy cattle	0.0015	0.055	0.19	–	0.19 (AU)	[a,b]
poultry broiler	–	–	–	–	–	
poultry layer	–	–	–	–	–	–
	mean	mean	mean	mean	mean	
beef cattle	0.000062	0.0026	0.017	–	0.017 (AU)	
dairy cattle	0.0015	0.0061	0.018	–	0.018 (AU)	[a,b]
poultry broiler	–	–	–	–	–	
poultry layer	–	–	–	–	–	–

[a] Highest mean and maximum beef or dairy cattle dietary burden suitable for maximum residue level and STMR estimates for mammalian meat.

[b] Highest mean and maximum dairy cattle dietary burden suitable for maximum residue level and STMR estimates for milk.

Livestock feeding studies

The Meeting received a feeding study on lactating cows.

Four groups of three lactating Holstein-Friesian cows were dosed once daily via capsules at levels of 0.00, 0.03, 0.09 and 0.30 ppm dry weight feed for 28 consecutive days. Milk was collected throughout the study and tissues were collected on day 28 within 24 hours after the last dose. Residues in milk achieved a plateau level after approximately 5 consecutive days of dosing. Since the analytical method cannot discriminate between emamectin B1a benzoate and 8,9-ZMa, residues are the sum of both. Since metabolism studies have shown that 8,9-ZMa is not formed in livestock, values in the table represent mean and highest residues of emamectin B1a benzoate only.

Animal commodity	Dose level (ppm feed)	Mean Residue (mg/kg)	Highest Residue (mg/kg)
Liver	0.03	0.0086	0.010
	0.09	0.029	0.029
	0.3	0.097	0.12
Kidney	0.03	0.0037	0.0040
	0.09	0.012	0.013
	0.3	0.037	0.042
Fat	0.03	0.0021	0.0022
	0.09	0.0047	0.0066
	0.3	0.013	0.015
Muscle	0.03	< 0.002	< 0.002
	0.09	< 0.002	0.0020
	0.3	0.0058	0.0061
Milk	0.03	< 0.5 ng/g	–
	0.09	0.8 ng/g	–
	0.3	3.2 ng/g	–

Residues in animal commodities

Cattle

For maximum residue level estimation, the high residues in the tissues and milk were calculated by interpolating the maximum dietary burden (0.19 ppm) between the relevant feeding levels (0.09 and 0.30 ppm) from the dairy cow feeding study and using the highest tissue concentrations from individual animals within those feeding groups and using the mean milk concentration from those feeding groups (see table below).

The STMR values for the tissues and milk were calculated by interpolating the mean dietary burden (0.018 ppm) between the relevant feeding levels (0 and 0.03 ppm) from the dairy cow feeding study and using the mean tissue and milk concentrations from those feeding groups (see table below).

				Residues (mg/kg) in			
	Feed level (ppm) for milk residues	Residues (ng/g) in milk	Feed level (ppm) for tissue residues	Muscle	Liver	Kidney	Fat
Maximum residue level - beef or dairy cattle							
Feeding study a	0.09 0.30	0.8 3.2	0.09 0.30	0.0020 0.0061	0.029 0.12	0.013 0.042	0.0066 0.015
Dietary burden and residue estimate b	0.19	1.9	0.19	0.0040	0.072	0.027	0.011
STMR beef or dairy cattle							
Feeding study b	0 0.03	0 < 0.5	0 0.03	0 < 0.002	0 0.0086	0 0.0037	0 0.0021
Dietary burden and residue estimate	0.018	< 0.5	0.018	< 0.002	0.0052	0.0022	< 0.002

[a] highest residues for tissues and mean residues for milk

[b] mean residues for tissues and mean residues for milk

The Meeting estimated a maximum residue level for emamectin B1a benzoate of 0.004 mg/kg in meat from mammals other than marine mammals, 0.08 mg/kg in mammalian offal, 0.02 mg/kg in mammalian fat and 0.002 mg/kg in milks. The residue in animal commodities is considered not fat-soluble.

The Meeting estimated an STMR of 0.002 mg/kg in meat from mammals other than marine mammals, 0.006 mg/kg in mammalian offal, 0.002 mg/kg in mammalian fat and 0.0005 mg/kg in milks. The Meeting estimated an HR of 0.004 mg/kg in meat from mammals other than marine mammals, 0.072 mg/kg in mammalian offal, 0.011 mg/kg in mammalian fat.

Poultry

Since poultry is not exposed to emamectin benzoate from uses considered by the Meeting, a maximum residue level, STMR or HR is not considered necessary for poultry.

FURTHER WORK OR INFORMATION

Desirable

- Verification that emamectin B1a benzoate can or cannot be included in an existing multi-residue method for enforcement.
- Storage stability studies on animal commodities for at least 3 months at -20 °C.
- Storage stability studies on commodities with high acid content (grapes), and processed commodities (apple pomace, apple juice).

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDI) for emamectin benzoate was calculated from recommendations for STMRs for raw and processed commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 3.

The IEDI of in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 0–20% of the maximum ADI of 0.0005 mg/kg bw per day, expressed as emamectin benzoate. The Meeting concluded that the long-term intake of residues of emamectin benzoate from uses considered by the Meeting is unlikely to present a public health concern.

Short-term intake

The International Estimated Short Term Intake (IESTI) for emamectin benzoate was calculated from recommendations for STMRs and hours for raw and processed commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 4.

The IESTI for the diets submitted for 2011 JMPR represented 0–50% of the ARfD (0.03 mg/kg bw, expressed as emamectin benzoate). The Meeting concluded that the short-term intake of residues of emamectin benzoate from uses considered by the Meeting is unlikely to present a public health concern.