5.2 ACETAMIPRID (246)

TOXICOLOGY

Acetamiprid is the International Organization for Standardization (ISO)–approved name for (*E*)-N^1-[(6-chloro-3-pyridyl)methyl]-N^2-cyano-N^1-methyl acetamidine (International Union of Pure and Applied Chemistry). Its Chemical Abstracts Service number is 135410-20-7. Acetamiprid is a neonicotinoid insecticide that is used for the control of sucking-type insects on leafy vegetables, fruiting vegetables, cole crops, citrus fruits, pome fruits, grapes, cotton and ornamental plants and flowers. Acetamiprid is being reviewed 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 contained statements of compliance with good laboratory practice.

Biochemical aspects

Acetamiprid is rapidly absorbed, with a maximum concentration in blood being achieved in approximately 2–3 hours. The extent of absorption was more than 90% of the administered radioactivity. Acetamiprid is widely distributed in the tissues, with highest concentrations being found in the adrenal gland, liver and kidney following oral administration to the rat. The concentration of radioactivity in the brain was lower than the concentration in blood at all time points. No sex differences were observed. The major route of elimination was via urine (53–65%). The recovery of the radioactivity excreted in the bile was less than 20% of the administered dose, which suggests that the bile is not a major route of excretion. The disappearance of radioactivity from the body of the rat was rapid, and there was no indication of accumulation in any tissue. Less than 1% of the administered radioactivity remained in the tissues by day 4 following dosing. The major radioactive compounds in the excreta of rats were acetamiprid (~5–7%), the demethylated compound IM-2-1 (~15–20%), the nicotinic acid derivative IC-O (~8–11%) and the IC-O glycine conjugate IC-O-Gly (~10%). In addition, MeS-IC-O, IM-1-4, IM-2-4, IM-O, IM-1-3 and IM-2-3 were detected, each at less than 2% of the dose. There were several unknown compounds in the urine, with a maximum abundance of 1%. The main metabolic pathway of acetamiprid in rats is the transformation to IM-2-1 by demethylation. IM-2-1 is further metabolized to IC-O, with the release of IS-1-1 and IS-2-1 after cleavage from the side-chains of NI-25 (parent compound) and IM-2-1.

Toxicological data

In mice and rats, the oral median lethal dose (LD_{50}) was in the range of 140–417 mg/kg body weight (bw). Dose-related reversible toxic signs (crouching, tremor, convulsion and mydriasis) were observed. The dermal LD_{50} in rats was greater than 2000 mg/kg bw. When acetamiprid was administered by inhalation through nose-only exposure, the median lethal concentration (LC_{50}) was greater than 1.15 mg/L of air. Mydriasis in many rats and tremor and convulsion in a few rats were observed when acetamiprid was administered by the oral route, and these effects disappeared after 1 day. Acetamiprid was not an irritant in studies of ocular or dermal irritation in rabbits or a dermal sensitizer in the Magnusson and Kligman maximization test in guinea-pigs.

Short-term studies of oral toxicity in mice, rats and dogs were conducted using acetamiprid. These studies are characterized by similar toxic responses, such as decreased feed consumption and body weight.

In a 13-week study in mice, the no-observed-adverse-effect level (NOAEL) was 400 ppm (equal to 53.2 mg/kg bw per day), on the basis of a significant decrease in total cholesterol level in females at 800 ppm (equal to 106.1 mg/kg bw per day). Tremor, decreased body weight gain, decreased feed consumption, decreased haemoglobin concentration, decreased serum total cholesterol

and glucose levels, decreased urinary pH, increased liver to body weight ratio and centrilobular hypertrophy were observed at higher doses.

In a 90-day study of oral toxicity in rats, the NOAEL was 200 ppm (equal to 12.4 mg/kg bw per day), on the basis of decreased body weight gain, decreased feed consumption and increased serum total cholesterol levels at 800 ppm (equal to 50.8 mg/kg bw per day).

In three oral dog studies (4 weeks, 90 days and 1 year), initial body weight losses and decreased body weight gains were observed in males and females receiving the highest dietary concentrations of acetamiprid. In the 4-week study, the NOAEL was 22 mg/kg bw per day. However, an overall NOAEL for the other two oral dog studies was 800 ppm (equal to 32 mg/kg bw per day).

In an 18-month study of toxicity and carcinogenicity in mice, decreased feed consumption was observed in males and females at 1200 ppm. At 400 ppm in males, body weights were decreased, and the body weight gain was statistically significantly decreased compared with controls through 13 weeks of study. At the end of 18 months, mean relative liver weights were increased in males and females receiving 1200 ppm and also in females receiving 400 ppm. On microscopic examination, treatment-related hepatocellular hypertrophy was seen in male and female mice receiving 1200 ppm after 12 and 18 months of treatment. These microscopic findings are considered to be an adaptive response of the liver to exposure to acetamiprid. The NOAEL was 130 ppm (equal to 20.3 mg/kg bw per day), based on transient decreased body weight observed at 400 ppm (equal to 65.6 mg/kg bw per day) in males. There was no evidence of any carcinogenic effect in mice.

The 2-year study of toxicity and carcinogenicity in rats demonstrated an increased incidence of clinical signs, such as rales, hunched posture and laboured breathing, in the 400 and 1000 ppm dose groups. The body weights of the 1000 ppm males and females and the 400 ppm females (until week 100) were statistically significantly lower than those of controls during the study. Trace to mild centrilobular hepatocellular hypertrophy and vacuolation were seen at 400 ppm and above. Incidences of mammary gland adenocarcinomas and hyperplasias were increased in females at 1000 ppm (equal to 60 mg/kg bw per day); however, incidence levels were within normal limits for ageing Crl:CD rats, and therefore these lesions are considered to be unlikely to be due to an endocrine or carcinogen effect of acetamiprid. Because the observation of rales at 160 ppm was not correlated to the other clinical signs, such as laboured breathing, moribundity, hunched posture and decreased activity, the NOAEL in this study was 160 ppm (equal to 7.1 mg/kg bw per day), based on hepatocyte vacuolation at 400 ppm (equal to 17.5 mg/kg bw per day). Acetamiprid was not carcinogenic in rats.

Acetamiprid was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No significant result is obtained in these tests, except for chromosomal aberration induction in vitro. In vivo, there was no confirmation of chromosomal aberration in a number of tests, and there was no evidence of induction of deoxyribonucleic acid (DNA) damage.

The Meeting concluded that acetamiprid is unlikely to be genotoxic in vivo.

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

In a two-generation study in rats, the NOAEL for systemic parental toxicity was 100 ppm (equal to 6.67 mg/kg bw per day), on the basis of a decline in body weights and feed consumption and an increased incidence of hepatocellular hypertrophy and vacuolation at 280 ppm (equal to 18.9 mg/kg bw per day) and above. The NOAEL for offspring toxicity was 280 ppm (equal to 13.9 mg/kg bw per day), on the basis of decreases in body weight gain in both generations and reduced postnatal survival in the F_2 offspring at 800 ppm (equal to 38.7 mg/kg bw per day). However, there are no effects on reproduction with treatment up to 800 ppm (equal to 38.7 mg/kg bw per day), the highest dose tested.

In a study of developmental toxicity in rats, the NOAEL for maternal toxicity was 16 mg/kg bw per day, based on decreased feed consumption and body weight gain during the treatment period in maternal rats in the 50 mg/kg bw per day group at scheduled sacrifice. The developmental NOAEL

in rats was 16 mg/kg bw per day, based on the increased incidence of fetuses with shortening of the 13th rib at 50 mg/kg bw per day.

In a study of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 15 mg/kg bw per day, based on decreased feed consumption and body weight gain during the treatment period at 30 mg/kg bw per day. The developmental NOAEL was 30 mg/kg bw per day, the highest dose tested.

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

In an acute oral neurotoxicity study, increased urination frequency and reduced locomotor activity were observed at doses of 30 mg/kg bw and above. Other clinical signs of neurotoxicity (e.g., hunching, tremors) were observed at higher doses. No apparent effects on sensory systems or evidence of neuropathology was seen. The NOAEL was 10 mg/kg bw, based on evidence of increased urination frequency (males) and a statistically significant reduction of locomotor activity (males) at 30 mg/kg bw.

A 13-week dietary neurotoxicity study in rats did not result in any changes that were considered indicative of neurotoxicity. The NOAEL was 200 ppm (equal to 14.8 mg/kg bw per day), on the basis of lower body weights and feed consumption at 800 ppm (equal to 59.7 mg/kg bw per day).

A developmental neurotoxicity study in rats revealed the NOAEL for maternal toxicity, developmental toxicity and developmental neurotoxicity to be 10 mg/kg bw per day, based on a reduction in body weight gain in dams during the first 3 days of dosing (gestation days 6–9), decreased feed consumption in F_0 animals, early postnatal mortality, reduced post-weaning body weights and deficits in auditory startle response without neuropathology or changes in brain morphometry in F_1 animals at 45 mg/kg bw per day.

Acetamiprid did not cause delayed neuropathy in hens.

Studies for immunotoxicity in mice (highest dose tested was 157 mg/kg bw per day) and rats (highest dose tested was 67.7 mg/kg bw per day) indicated no specific effect on immune function as assessed by the measurement of antigen-specific T cell–dependent antibody formation.

Toxicological data on impurities and metabolites

Acute toxicity studies and studies of genotoxicity have been undertaken for four compounds that are present as impurities in technical acetamiprid. None of them were genotoxic in a number of assays, and they had acute oral LD_{50} values in rats between 603 and greater than 5000 mg/kg bw. Nine compounds identified as plant metabolites are IM-1-3, IM-1-4, IM-2-1, IM-2-3, IM-2-4, IM-0, IC-0, IS-1-1 and IS-2-1. None were genotoxic in a number of assays, and they had acute oral LD_{50} values in rats between 900 and greater than 5000 mg/kg bw. The NOAEL following repeated exposure of rats to diets containing IM-1-4 for 13 weeks was 600 ppm (equal to 36.5 mg/kg bw per day), based on effects on spleen (increased pigments in splenic sinusoids) at 1800 ppm (112.2 mg/kg bw per day) in treated males. The NOAEL for IM-0 in a 13-week study in rats was 800 ppm (equal to 48.9 mg/kg bw per day), on the basis of eosinophilic intranuclear inclusions seen in proximal tubular epithelium of kidneys at 4000 ppm (250.1 mg/kg bw per day) in males. All the impurities and metabolites were of lesser toxicity than the parent (acetamiprid).

No adverse health effects or poisoning in manufacturing plant personnel or in operators and workers exposed to acetamiprid have been reported.

Three cases of intentional poisoning with acetamiprid formulation have been reported. In one case, the concentration of acetamiprid in blood was measured at the time of reporting for treatment. In all cases, some signs similar to those associated with acute organophosphate intoxication were reported. Supportive treatments for a variety of signs were sufficient for recovery, and all recovered within 24–48 hours of the initiation of treatment.

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.07 mg/kg bw on the basis of the NOAEL of 7.1 mg/kg bw per day from the 2-year study of toxicity and carcinogenicity in rats, based on clinical signs and hepatocyte vacuolation seen at 17.5 mg/kg bw per day. A safety factor of 100 was applied. This ADI was supported by the NOAEL of 6.67 mg/kg bw per day observed in a two-generation study of reproductive toxicity in rats on the basis of decreased parental body weight gain and feed consumption and hepatocyte vacuolation at 18.9 mg/kg bw per day.

The Meeting established an acute reference dose (ARfD) of 0.1 mg/kg bw on the basis of a NOAEL of 10 mg/kg bw in an acute neurotoxicity study in rats, based on evidence of neurotoxicity, decreased locomotor activity and increased urination frequency. This ARfD was supported by the NOAEL for maternal toxicity in the developmental neurotoxicity study of 10 mg/kg bw per day, based on reduced body weight gain in dams during the first 3 days of dosing (gestation days 6–9).

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity [a]	Toxicity	130 ppm, equal to 20.3 mg/kg bw per day	400 ppm, equal to 65.6 mg/kg bw per day
		Carcinogenicity	1200 ppm, equal to 214.6 mg/kg bw per day [b]	—
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	160 ppm, equal to 7.1 mg/kg bw per day	400 ppm, equal to 17.5 mg/kg bw per day
		Carcinogenicity	1000 ppm, equal to 60 mg/kg bw per day[b]	—
	Two-generation study of reproductive toxicity[a]	Offspring toxicity	280 ppm, equal to 13.9 mg/kg bw per day	800 ppm, equal to 38.7 mg/kg bw per day
		Reproductive toxicity	800 ppm, equal to 38.7 mg/kg bw per day[b]	—
		Parental toxicity	100 ppm, equal to 6.67 mg/kg bw per day	280 ppm, equal to 18.9 mg/kg bw per day
	Developmental toxicity study[c]	Maternal toxicity	16 mg/kg bw per day	50 mg/kg bw per day
		Embryo and fetal toxicity	16 mg/kg bw per day	50 mg/kg bw per day
	Acute neurotoxicity study[c]	Acute neurotoxicity	10 mg/kg bw	30 mg/kg bw
	Developmental neurotoxicity study[c]	Developmental neurotoxicity	10 mg/kg bw per day	45 mg/kg bw per day
Rabbit	Developmental toxicity	Maternal toxicity	15 mg/kg bw per day	30 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
	study[c]	Embryo and fetal toxicity	30 mg/kg bw per day[b]	—
Dog	Ninety-day and 1-year studies of toxicity[a,d]	Toxicity	800 ppm, equal to 32 mg/kg bw per day	1500 ppm, equal to 55 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two studies combined.

Estimate of acceptable daily intake for humans

0–0.07 mg/kg bw

Estimate of acute reference dose

0.1 mg/kg bw

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

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and almost completely absorbed (> 90%)
Distribution	Widely distributed; highest concentrations in adrenal, liver and kidney
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid, more than 90% within 96 h, mainly via urine
Metabolism in animals	Moderately metabolized; the major radioactive compounds in the excreta of rats were acetamiprid itself and IC-O glycine conjugate
Toxicologically significant compounds (animals, plants and the environment)	Acetamiprid (parent compound)
Acute toxicity	
Rat, LD_{50}, oral	140–417 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 0.30 mg/L (whole-body exposure) > 1.15 mg/L (nose-only exposure)
Rabbit, dermal irritation	Non-irritant
Rabbit, ocular irritation	Non-irritant
Guinea-pig, dermal sensitization (Magnusson and Kligman test)	Non-sensitizer

Short-term studies of toxicity	
Target/critical effect	Increased cholesterol, decreased body weight, decreased feed consumption
Lowest relevant oral NOAEL	53.2 mg/kg bw per day (13-week study in mice)
Genotoxicity	
	Not genotoxic in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Increased clinical signs; hepatic vacuolation
Lowest relevant NOAEL	7.1 mg/kg bw per day (rats)
Carcinogenicity	Not carcinogenic in rats or mice
Reproductive toxicity	
Reproduction target/critical effect	None
Lowest relevant reproductive NOAEL	38.7 mg/kg bw per day, highest dose tested
Developmental target/critical effect	Skeletal anomalies
Lowest relevant developmental NOAEL	16 mg/kg bw per day (rat)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity target/critical effect	Motor activity and increased frequency of urination
Lowest relevant acute neurotoxic NOAEL	10 mg/kg bw
Subchronic neurotoxicity target/critical effect	Not neurotoxic (rats)
Developmental neurotoxicity target/critical effect	Deficits in auditory startle response
Lowest relevant developmental neurotoxic NOAEL	10 mg/kg bw per day (rat)
Immunotoxicity	
28-day immunotoxicity	Not immunotoxic (mice and rats)
Medical data	
	No significant health effects were reported among manufacturing personnel; however, three cases of intentional poisoning have been reported with some signs similar to those of acute organophosphate poisoning

Summary

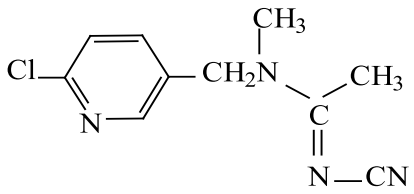
	Value	**Study**	**Safety factor**
ADI	0–0.07 mg/kg bw	Two-year rat study (supported by parental toxicity in the multigeneration rat reproduction study)	100
ARfD	0.1 mg/kg bw	Acute neurotoxicity, rat (supported by maternal toxicity in the developmental neurotoxicity rat study)	100

RESIDUE ND ANALYTICAL ASPECTS

Acetamiprid is a neonicotinoid insecticide with contact and stomach action against a range of *Hemiptera*, *Thysanoptera* and *Lepidoptera* plant pests, acting as an agonist of the nicotinic acetylcholine receptor in the insect central nervous system. It exhibits translaminar activity in plants and is authorised for use in North America, Europe and in a number of countries in Asia and the Pacific.

Residue and analytical aspects of acetamiprid were considered for the first time by the present meeting. The manufacturer submitted studies on metabolism, analytical methods, authorised uses, supervised field trials, the effects of processing, freezer storage stability, environmental fate in soil and rotational crop residues.

Acetamiprid, (*(E)*-N^1-[(6-chloro-3-pyridyl)methyl]-N^2-cyano-N^1-methylacetamidine) is partially soluble in water (3-4 g/litre), stable to hydrolysis and photolysis, has a log P_{OW} of 0.8 and is soluble in acetone, methanol, ethanol, dichloromethane, and acetonitrile.



The following abbreviations are used for the metabolites discussed below:

IM-1-2	N^2-carbamoyl-N^1- [(6-chloro-3-pyridyl)methyl]-N^1-methylacetamidine
IM-1-3	*N*-[(6-chloro-3-pyridyl)methyl]-*N*-methylacetamide
IM-1-4	*N*-methyl(6-chloro-3-pyridyl)methylamine
IM-2-1	N^1-[(6-chloro-3-pyridyl)methyl]-N^2-cyanoacetamidine
IM-2-2	N^2-carbamoyl-N^1- [(6-chloro-3-pyridyl)methyl]-acetamidine
IM-2-3	*N*-[(6-chloro-3-pyridyl)methyl]acetamide
IM-2-4	(6-chloro-3-pyridyl)methylamine
IM-2-5	*N*1-(6-Chloropyridin-3-ylmethyl)-acetamidine
IM-0	(6-chloro-3-pyridyl)methanol
IM-0-Glc	(6-chloro-3-pyridyl)methyl-β-D-glucopyranoside
IC-0	6-chloronicotinic acid

Animal metabolism

The Meeting received acetamiprid metabolism studies on animals (rats, lactating goats and laying hens) using ^{14}C-acetamiprid (labelled in the 2 and 6 positions of the pyrimidine ring).

In rats, acetamiprid is rapidly and almost completely absorbed and is widely distributed into the tissues, being found at highest concentrations in GI tract, adrenal gland, liver and kidney, following oral administration to the rat. The major route of elimination was via the urine and bile (relevant but not a major route in excreta). The disappearance of radioactivity from the body of the rat was rapid and there was no indication of accumulation in any tissue. Less than 1% of the administered radioactivity was left in the tissues by day four following dosing. The major radioactive compounds in the excreta of rats were acetamiprid (approx. 5–7%); the demethylated compound IM-2-

1(approximately 15–20%), the nicotinic acid derivative IC-O (approximately 8–11%) and the IC-O glycine conjugate IC-O-Gly (approximately 10%). In addition, MeS-IC-O, IM-1-4, IM-2-4, IM-O, IM-1-3 and IM-2-3 were detected, but they were less than 2% of dose. There were several unknown compounds in urine with a maximum abundance of 1%.

The main metabolic pathway of acetamiprid in rats is the transformation to IM-2-1 by demethylation which is further metabolized to IC-O with the release of IS-1-1 and IS-2-1 after the cleavage from the side chains of IN-25 and IM-2-1.

Lactating goats were orally dosed twice daily for 7 days with encapsulated [pyridine-2, 6-^{14}C]-acetamiprid at dietary equivalent levels of 1.0 ppm or 8.6 ppm per day. At the end of the 7-day dosing period, the goats were sacrificed 22 hours after the last administration.

Most of the administered radioactivity (AR) was excreted via urine or faeces (about 95–99% AR) and less than 1% AR in milk (reaching a plateau after about 3 days). In tissues, radioactivity did not exceed 1.6% AR and in milk, about 94–96% TRR was found in the whey with about 3–5% TRR occuring in milk fat and precipitated milk proteins.

The predominant residue in milk, liver and kidney was the IM-2-1 metabolite (70–89% TRR) and in muscle, the major residue was IM-2-2 (about 50% TRR), with the IM-2-3 and IM-2-4 metabolites also being found at 6% and 13% TRR respectively. Acetamiprid (parent) was only found in milk, at less than 10% TRR and < 0.005 mg/kg.

Laying hens (five hens per dose group) were dosed each morning for 14 days with [pyridine-2, 6-^{14}C]-acetamiprid at dietary equivalent levels of 1.1 ppm or 12.5 ppm. At the end of the 14-day dosing period, the hens were sacrificed about 24 hours after the last administration.

Most of the applied radioactivity was excreted or found in the cage wash (93–97% AR). Small amounts of radioactivity were detected in edible organs/tissues (0.7–0.8% AR) with about 1.3% AR found in eggs (reaching a plateau after about 8–11 days). In liver and skin, residues were about 0.1% AR and 0.3% AR in muscle.

The IM-2-1 metabolite was the predominant residue, at 83–86% TRR in egg white, about 60% TRR in egg yolk, 65–69% TRR in liver and 53–62% TRR in muscle and skin. The other metabolite found at more than 10% TRR was the IM-2-3 in muscle (17– 21% TRR). Metabolite IM-2-5 was the predominant residue in egg yolks (27% TRR) and IC-0 was found in skin at about 13% TRR. Acetamiprid (parent) was not found in any tissues or in eggs.

In summary, acetamiprid metabolism in animals is similar, with more than 95% of the residues being eliminated in excreta and less than 2% remaining in tissues or present in eggs or milk. Residues of the parent acetamiprid were not found (except at low levels in milk), and the predominant residue in most animal products was the IM-2-1 (53–89% TRR) with IM-2-2 occurring in goat muscle at about 50% TRR). The IM-2-4 and IM-2-3 metabolites were also found in muscle at 13–21% TRR, with the IM-2-5 metabolite being found at about 27% TRR in egg yolks.

The proposed metabolic breakdown of acetamiprid in both goats and hens involves degradation to IC-0 or demethylation to IM-2-1 with the IM-1-2 metabolite converting to the amide (IM-2-2) or IM-2-3 and the subsequent formation of the IM-2-4 and IM-2-5 metabolites.

Plant metabolism

The meeting received plant metabolism studies in apples, eggplant, cabbage, cotton and carrot following foliar applications of [pyridine-2, 6-^{14}C]-acetamiprid and an additional study with cabbages treated with [CN-^{14}C]-acetamiprid (both as a foliar application and a soil treatment).

In apple fruit, more than 98% of the radioactivity was recovered from the surface wash and extracts of fruit. Residues in surface washes decreased from more than 99% to about 12% TRR after 14 days and to about 6% TRR for fruit sampled 28 and 62 days after treatment. Residues in flesh increased to 48% TRR after 14 days and to about 78% TRR at the end of the 62-day study period.

Acetamiprid (parent) was the predominant residue, making up more than 79% TRR. Minor metabolites (IM-2-1 and IM-0-Glc) were found at maximum 3.7%TRR and 1.8%TRR, respectively.

For apple leaves, more than 98% of the radioactivity was recovered from the surface wash and extracts from leaves. Initial residues in surface washes decreased from 99% to about 43% TRR at the end of the 90-day study period and the residues in the leaf extracts increased to about 51% TRR (11.8 mg/kg eq). Translocated radioactivity in untreated leaves was less 0.04 mg/kg.

The majority of the radioactivity was the unchanged acetamiprid, making up 90% or more of the TRR in the first 14 days after treatment, declining to 49% TRR after 90 days. The main metabolite found above 5% TRR was the IM-2-1 metabolite, present at about 10% TRR after 62 days and about 16% TRR after 90 days. The only other metabolite present at more than 5% TRR was IM-0-Glc (max 8.3% TRR at day-90).

For eggplant, most of the radioactivity was found in the surface washes (79–75% TRR for leaves and 84–70% TRR for fruit), with 20–30% TRR present in the extracts from washed fruit and leaves. Translocated radioactivity was negligible. Acetamiprid was the major residue, making up about 85–89% TRR in leaves and 94–95% TRR in fruit. Of the three identified metabolites, IM-2-1 was present in fruit at 0.4% TRR and 1.8% TRR in leaves and the IM-0 metabolite and its glycoside were identified in leaves at 0.6% TRR and 4.6% TRR respectively.

For cabbages following foliar treatments with [pyridine-2, 6-^{14}C]-acetamiprid, surface residues decreased to 30-50% TRR in the 28 days after treatment and to about 12% at the end of the study period (day-63). Residues in the extracts from washed plants increased accordingly, from 15% TRR (day-0) to 83.5% TRR (day-63). Acetamiprid was the major residue component in leaves, found at about 67–91% TRR with residues of the IM-2-1 metabolite increasing over the study period to a maximum of about 7% TRR (day-63). No parent residues were measured in mature cabbage heads with the wrapper leaves removed, with the major residue being the IC-0 metabolite (about 46% TRR or 0.03 mg/kg).

In cabbages grown in soil treated with [pyridine-2, 6-^{14}C]-acetamiprid, radioactivity was readily translocated into leaves, reaching levels of about 2–3 × the root concentrations during the 28-day study period. Acetamiprid was also the only major residue in both leaves and roots, initially found at about 90% TRR (leaves) and 78% TRR (roots), decreasing to 60% TRR (leaves) and 50% TRR (roots) after 28 days. The IM-1-4 metabolite was the only other identified metabolite present at more than 5% TRR, being found in roots after 28 days.

An additional study on cabbages treated with a foliar application of [CN-^{14}C-acetamiprid] reported similar results. Surface residues decreased from an initial 86% TRR down to about 16% TRR after 63 days, with residues in the extracts from washed leaves increasing to about 78% TRR at the end of the study period. The major residue was the unchanged acetamiprid, making up more than 98% TRR (to day-7) and about 65% TRR by day-68.

For carrots treated twice with [pyridine-2, 6-^{14}C]-acetamiprid as foliar sprays, total radioactivity in carrots (including tops) at harvest was less than 0.1 mg/kg acetamiprid equivalents, mostly in the tops (0.44 mg/kg), with about 0.08 mg/kg in the roots. The main components found at harvest (2 weeks after the second treatment), in the carrot tops were IM-0-Glc (33% TRR), the parent acetamiprid (27% TRR) and IM-1-4 (15% TRR) with no other components exceeding 6% TRR. In the carrot roots the main components were acetamiprid (30-34% TRR and 0.03 mg/kg) and IC-0 (17–31% TRR and 0.02 mg/kg).

In cotton seed and gin trash from plants treated with four foliar applications of [pyridine-2, 6-^{14}C]-acetamiprid at 7 day intervals, the parent compound was the major residue identified in gin trash, found at 50% TRR (1.4 mg/kg) in the 14-day PHI samples and at 45% TRR (0.71 mg/kg) in the 28-day PHI samples.. The IC-0 metabolite was the predominant residue in cotton seed, found in the 14-day PHI samples at 46% TRR (0.69 mg/kg), decreasing to 24% TRR (0.27 mg/kg) in the 28-day samples.

In summary, the predominant residue in plant part exposed to foliar treatments is the parent compound, with low levels of the IM-2-1 metabolite being a common component in the plants studied, but generally at levels of 10% TRR or less. Acetamiprid is also the predominant residue in cabbage and carrot roots following soil treatments. The other significant metabolite found in plant parts not directly treated was the IC-0 cleavage product, found in cabbage heads (0.03 mg/kg), carrot roots (0.04 mg/kg) and cotton seed (up to 0.69 mg/kg).

The proposed metabolic breakdown of acetamiprid in plants following foliar application involves demethylation to IM-2-1 and further degradation to IC-0-Glc, or conversion of the parent compound to IM-0, with subsequent conjugation with glucose to form the IM-0-Glc. Degradation can also involve formation of the IM-1-2 metabolite which rapidly degrades to IM-1-3 and either IM-2-3 or IM-1-4, both of which degrade to IC-0.

Environmental fate

The Meeting received information the environmental metabolism and behaviour of acetamiprid in soil and rotational crops.

The estimated aerobic soil metabolism half-life for acetamiprid at 25 °C was about 8.2 days with a significant amount of $^{14}CO_2$ (up to about 19% of the applied dose) being measured during the study. The metabolite IM-1-4 was a major component of the radioactive residue, increasing to about 73% after 120 days and slowly decreasing thereafter. Two minor metabolites, IM-1-3 and IC-0 were also identified but at less than 5% of the applied dose during the study.

In three soils treated with the equivalent of 0.1 kg ai/ha [^{14}C-2, 6-pyridine]-acetamiprid and incubated in the dark for intervals up to 6 months, acetamiprid residues degraded rapidly, with estimated aerobic soil metabolism half-lives of about 1–8 days. The IM-1-4 metabolite was the major residue in soil, present at about 54–72% AR after 6 months.

Residues in succeeding crops

In rotational crop metabolism studies involving radish, lettuce, sorghum and wheat grown in a sandy loam soil treated (bare ground) with [pyridine-2, 6-^{14}C]-acetamiprid and aged for various intervals (up to 1 year), radioactive residues in samples from all plant-back intervals were less than 0.1 mg/kg parent equivalents except sorghum fodder from the 60-day plant-back interval (0.115 mg/kg). Acetamiprid was not found in any of the matrices and all metabolites were present at less than 0.05 mg/kg in any matrix at any rotation, the highest being IM-1-4 at 0.04 mg/kg in the first plant-back sorghum forage.

The Meeting agreed that residues of acetamiprid would not be expected in rotational crops.

Analytical methods

Several analytical methods have been reported for the analysis of acetamiprid and its IM-2-1 (desmethyl) metabolite in animal and plant matrices. The principle of most methods involves extraction steps using methanol or acetonitrile, liquid/liquid partition (commonly hexane) and further extraction into methylene chloride, column chromatographic clean-up (silica gel, Florisil and C18) and analysis by HPLC (animal and plant matrices) or by GC/ECD or LC-MS/MS (plant matrices).

The methods have been validated for plant and animal matrices with LOQs of 0.05 mg/kg for citrus commodities, liver and kidney and 0.01 mg/kg for other plant and animal commodities.

Based on the results of validation studies and the concurrent recovery rates achieved in the supervised field trials, the available analytical methods are considered suitable for determining residues of acetamiprid and its IM-2-1 metabolite.

Based on an investigation with orange as a test matrix, the US-FDA PAM 1 multi-residue method was shown to be unsuitable for measuring acetamiprid residues in plant commodities.

The multi-residue QuEChERS method using GCMS and/or liquid chromatography coupled with tandem mass spectrum detection (LC-MS/MS) was validated at the LOQ of 0.01 mg/kg for determining acetamiprid residues in dry, high water, acid, oily and high sugar content matrices and in animal matrices.

Stability of pesticide residues in stored analytical samples

Residue stability in stored analytical samples was investigated for a range of representative substrates covering those with a high water content (apple, cabbage, cucumber, grape, lettuce, tomato) a high starch content (potato), a high oil content (cotton seed) and a high acid content (orange) and their processed fractions, stored at ambient temperatures and at freezer temperatures.

In samples fortified with acetamiprid at levels of 0.5 mg/kg or 0.1 mg/kg and stored at either at room temperature for up to 7 days or frozen for up to 12 months (16 months for lettuce and 8 months for potatoes), residues were stable in all samples at the end of the storage periods, both at ambient temperature and under freezer conditions.

In the supervised field trials, frozen storage intervals between sampling and analysis were less than the storage periods in these stability studies, except for one citrus trial (15 months), two tomato trials (13–14 months) and three celery trials (17 months). The Meeting considered that any residue degradation during these extended storage intervals would be negligible.

Definition of the residue

In livestock metabolism studies (goats, hens), residues of the parent acetamiprid were not found (except at low levels in milk), and the predominant residue in most animal products was the IM-2-1 (53–89% TRR). The IM-2-2 metabolite was the predominant residue (about 50% TRR) in goat muscle, with the IM-2-4 metabolite also present at about 13% TRR. The IM-2-5 metabolite was the predominant residue in eggs (9% TRR). Residues in fat were too low to be characterised.

For MRL compliance, the IM-2-1 metabolite is the predominant residue in milk, liver, kidney poultry muscle and skin and eggs, and is a major residue component in goat muscle. Based on the significance of this metabolite in all animal matrices and because the parent compound was only found in milk (and then only at low levels), the Meeting considered the use of the IM-2-1 metabolite as a marker residue for MRL compliance.

For dietary intake risk assessment, in addition to the IM-2-1 metabolite, other significant residue components above 10% TRR are IM-2-2 (the amide of IM-2-1, found only in goat muscle at up to 0.03 mg/kg), the IM-2-5 metabolite (the imide of IM-2-1, found only in egg yolk at up to 0.24 mg/kg) and the cleavage product IM-2-4, found only in goat muscle at up to 0.008 mg/kg.

Noting that these three metabolites were not found in any other edible animal products; that current analytical methods did not exist to measure these compounds and that at the low levels expected, they are not likely to contribute significantly to the dietary exposure, the Meeting agreed that these metabolites need not be included in the residue definition for dietary risk assessment.

The Meeting recommended that for animal commodities, the residue definition for both dietary intake assessment and MRL compliance should be the sum of acetamiprid and its IM-2-1 metabolite, expressed as acetamiprid.

Based on the results of the cattle feeding study, where residues in muscle and fat were of the same order, and considering the ratio of radioactive residues in milk whey and milk fat/proteins (95:4) in the lactating goat metabolism study, the Meeting agreed that acetamiprid is not fat soluble. The log K_{ow} of acetamiprid (log K_{ow} 0.8) supports this conclusion.

In plants, the metabolism of acetamiprid has been studied in vegetables (cabbage, eggplant, carrots), in fruit (apples) and cotton. In all crops studied, the parent compound is the major residue component following foliar applications, initially as a surface residue and subsequently being taken up into the treated leaf or fruit, with little further translocation. The only significant metabolite identified in the studies was the desmethyl metabolite (IM-2-1), found at less than 10% TRR in edible crop parts.

The other metabolite found in edible plant parts not directly treated (e.g., carrot roots, cabbage heads, cotton seed) was the IC-0 cleavage product, present in carrot roots at 26% TRR and being the predominant residue in cabbage heads and cotton seed (24-46% TRR). This metabolite (6-chloronicotinic acid) was found in significant quantities (24–28 % TRR) in rat metabolism and with an oral LD_{50} > 5000, of is of lower acute toxicity than the parent compound and does not exhibit any genotoxic potential. The Meeting noted that IC-0 is also a metabolite of other neonicotinoids and agreed it should be excluded from the residue definition.

The Meeting recommended that for MRL-compliance and dietary intake risk assessment, the residue definition for plant commodities should be acetamiprid.

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

Definition of the residue for animal commodities (for compliance with the MRL and estimation of dietary intake): *acetamiprid and N-desmethyl-acetamiprid, expressed as acetamiprid*

The residue is not fat soluble

Results of supervised trials on crops

The Meeting received supervised trial data for foliar applications of acetamiprid (SP and WP formulations) on a range of fruit, nut, vegetable and cotton crops, conducted mainly in Europe and North America.

The OECD MRL calculator was used as a tool to assist in the estimation of maximum residue levels from the selected residue data set obtained from the supervised residue trials. As a first step, the Meeting reviewed all relevant factors related to each data set in arriving at a best estimate of the maximum residue level using expert judgement. Then the OECD calculator was employed. If the statistical calculation spreadsheet suggested a different value from that recommended by the Meeting, a brief explanation of the deviation was supplied.

Citrus fruits

Residue data were provided to the Meeting from trials in Italy and Spain on lemons, mandarins and oranges involving 2–3 applications of 0.01 kg ai/hL.

GAP for citrus fruits in Spain is for foliar applications of up to 0.01 kg ai/hL and a PHI of 14 days, with a maximum of two applications/season.

In citrus trials from Italy and Spain matching this Spanish GAP, acetamiprid residues in lemons were : 0.09, 0.15 and 0.45 mg/kg.

In mandarins, residues were: 0.14, 0.17, 0.19, 0.25, 0.25, 0.26 and 0.44 mg/kg. The Meeting noted that in 2 of the Spanish trials (in bold), the 1st of 3 applications was applied more than 100 days before harvest and agreed to include these results because the contribution from these initial sprays would be negligible.

In oranges, residues were: 0.09, 0.1, 0.12, 0.22, 0.28, 0.28, 0.39 and 0.4 mg/kg.

The Meeting noted that these data sets were similar and agreed to combine them to estimate a group maximum residue level, STMR and HR for citrus fruit.

The combined data set from trials on lemons, oranges and mandarins (whole fruit) matching the GAP in Spain for citrus fruits is: 0.09, 0.09, 0.1, 0.12, 0.14, 0.15, 0.17, 0.19, 0.22, 0.25, 0.25, 0.26, 0.28, 0.28, 0.39, 0.4, 0.44 and 0.45 mg/kg (n = 18)

The Meeting estimated an STMR of 0.25 mg/kg, an HR of 0.45 mg/kg and recommended a maximum residue level of 0.8 mg/kg for acetamiprid in citrus fruit.

Pome fruits

Residue data were provided to the Meeting from trials in the USA on apples and pears. GAP for pome fruit in USA is for a maximum of four foliar applications of up to 0.168 kg ai/ha and a PHI of 7 days.

In trials on apples from the USA matching this GAP, acetamiprid residues were: 0.12, 0.12, 0.14, 0.14, 0.16, 0.18, 0.19, 0.22, 0.23, 0.25, 0.25, 0.26, 0.27, 0.28, 0.31, 0.55 and 0.59 mg/kg.

In trials on pears from USA matching this GAP, acetamiprid residues were: 0.09, 0.09, 0.15, 0.17, 0.2, 0.25, 0.31, 0.32 and 0.32 mg/kg.

The Meeting noted that these data sets were from similar populations and agreed combine them to estimate a group maximum residue level, STMR and HR for pip fruit. The combined data set for apples and pears is: 0.09, 0.09, 0.12, 0.12, 0.14, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.2, 0.22, 0.23, 0.25, 0.25, 0.25, 0.26, 0.27, 0.28, 0.31, 0.31, 0.32, 0.32, 0.55 and 0.59 mg/kg (n = 26).

The Meeting estimated an STMR of 0.225 mg/kg, an HR of 0.59 mg/kg and recommended a maximum residue level of 0.8 mg/kg for acetamiprid in pome fruits.

Stone fruits

Residue data were provided to the Meeting from trials in USA on cherries, peaches and plums. GAP in USA for stone fruits is for a maximum of four foliar applications of up to 0.168 kg ai/ha and a PHI of 7 days.

In trials on cherries from the USA matching this GAP, acetamiprid residues (in fruit without stones) were: 0.1, 0.29, 0.36, 0.42, 0.48, 0.54, 0.68 and 0.88 mg/kg (n = 8).

The Meeting estimated an STMR of 0.45 mg/kg, an HR of 0.88 mg/kg and recommended a maximum residue level of 1.5 mg/kg for acetamiprid in cherries.

In trials on peaches from the USA matching this GAP, acetamiprid residues (in fruit without stones) were: 0.11, 0.16, 0.18, 0.19, 0.2, 0.2, 0.22, 0.23, 0.34 and 0.44 mg/kg (n = 10).

The Meeting estimated an STMR of 0.2 mg/kg, an HR of 0.44 mg/kg and recommended a maximum residue level of 0.7 mg/kg for acetamiprid for peaches and agreed to extrapolate these recommendations to nectarines.

In trials on plums from the USA matching this GAP, acetamiprid residues (in fruit without stones) were: 0.01, 0.02, 0.04, 0.04, 0.06 and 0.11 mg/kg (n = 6).

The Meeting estimated an STMR of 0.04 mg/kg, an HR of 0.11 mg/kg and recommended a maximum residue level of 0.2 mg/kg for acetamiprid in plums (including prunes).

Berries and other small fruits

Residue data were provided to the Meeting from trials in USA and Canada on grapes, strawberries, blackberries, boysenberries and raspberries.

GAP in USA for grapes and small vine fruits is for a maximum of two foliar applications of up to 0.112 kg ai/ha and a PHI of 3 days.

In trials on grapes from USA matching this GAP, acetamiprid residues in grape bunches were: 0.01, 0.03, 0.04, 0.04, 0.05, 0.06, 0.07, 0.08, 0.08, 0.09, 0.11, 0.13, 0.15, 0.16, 0.20, 0.22, 0.23 and 0.25 mg/kg (n = 18).

The Meeting estimated an STMR of 0.085 mg/kg, an HR of 0.25 mg/kg and recommended a maximum residue level of 0.5 mg/kg for acetamiprid in grapes.

GAP in USA for bush and caneberries (including strawberries and low-bush blueberries) is for a maximum of two foliar applications of up to 0.146 kg ai/ha and a PHI of 1 day.

In trials on strawberries from Canada and the USA matching this GAP, acetamiprid residues in fruit (without sepals) were: 0.03, 0.04, 0.05, 0.06, 0.09, 0.11, 0.12, 0.24, 0.24 and 0.24 mg/kg (n = 10).

The Meeting estimated an STMR of 0.1 mg/kg, an HR of 0.24 mg/kg and recommended a maximum residue level of 0.5 mg/kg for acetamiprid in strawberries.

GAP in USA for bush berries (including low-bush and high-bush blueberries) and cane berries (including blackberries, raspberries and cultivars/hybrids) is for a maximum of five foliar applications of up to 0.112 kg ai/ha and a PHI of 1 day.

In trials on blueberries from USA matching this GAP for bush berries, residues in fruit were: 0.09, 0.2, 0.25, 0.48, 0.49 and 0.62 mg/kg (n = 6).

In trials on blackberries, raspberries and boysenberries from USA matching this GAP for cane berries, residues in fruit were: 0.53, 0.56, 0.64, 0.78 and 1.0 mg/kg (n = 5).

The Meeting agreed to use the data for blackberries, raspberries and boysenberries to propose a group maximum residue level for berries and other small fruit (except grapes and strawberries)

The Meeting estimated an STMR of 0.64 mg/kg, an HR of 1.0 mg/kg and recommended a maximum residue level of 2 mg/kg for acetamiprid in berries and other small fruit except grapes and strawberries

Bulb vegetables

Residue data were provided to the Meeting from trials in USA and Canada on bulb onions and spring onions.

GAP in USA for bulb vegetables (including onions and spring onions) is for a maximum of four foliar applications of up to 0.168 kg ai/ha and a PHI of 7 days.

In trials on onions from USA matching this GAP, acetamiprid residues in onion bulbs were: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 and 0.01 mg/kg (n = 6).

The Meeting estimated an STMR of 0.01 mg/kg, an HR of 0.01 mg/kg and recommended a maximum residue level of 0.02 mg/kg for acetamiprid for bulb onions and agreed to extrapolate these recommendations to garlic.

The OECD Calculator proposed a maximum residue level of 0.015 mg/kg but as one of the replicate analytical samples contained 0.018 mg/kg, the Meeting recommended a higher level of 0.02 mg/kg.

In trials on spring onions from USA matching this GAP, residues were: 0.05, 0.38 and 2 mg/kg.

The Meeting estimated an STMR of 0.38 mg/kg, an HR of 2 mg/kg and recommended a maximum residue level of 5 mg/kg for acetamiprid in spring onions.

Brassica vegetables

Residue data were provided to the Meeting from trials in USA on broccoli and head cabbage.

GAP in USA for cole crops (including broccoli and head cabbage) is for a maximum of five foliar applications of up to 0.084 kg ai/ha and a PHI of 7 days.

In trials on broccoli from USA matching this GAP, acetamiprid residues in broccoli were: 0.01, 0.01, 0.02, 0.02, 0.02, 0.03, 0.05, 0.09 and 0.22 mg/kg (n = 9).

The Meeting agreed to extrapolate these results to other flower-head brassicas and estimated an STMR of 0.02 mg/kg, an HR of 0.22 mg/kg and recommended a group maximum residue level of 0.4 mg/kg for acetamiprid in flower-head brassicas.

In trials on head cabbage from USA matching this GAP, acetamiprid residues in cabbage heads (with wrapper leaves) were: 0.03, 0.03, 0.06, 0.07, 0.07, 0.11, 0.11, 0.11, 0.13 and 0.5 mg/kg (n = 10).

The Meeting recommended a maximum residue level of 0.7 mg/kg for acetamiprid in head cabbages and for use in calculating the animal dietary burden, estimated a median residue of 0.09 mg/kg, and a highest residue of 0.5 mg/kg.

In the same trials on head cabbage from the USA matching the USA GAP, acetamiprid residues in cabbage heads without wrapper leaves were: < 0.01, < 0.01, < 0.01, 0.01, 0.02, 0.02, 0.02, 0.03, 0.03 and 0.05 mg/kg (n = 10)

The Meeting estimated an STMR of 0.02 mg/kg and an HR of 0.05 mg/kg for acetamiprid in head cabbages (for dietary intake risk assessment).

Fruiting vegetables, Cucurbits

Residue data were provided to the Meeting from trials in USA on cucumber, summer squash and melons.

GAP in USA for cucurbits is for a maximum of five foliar applications of up to 0.112 kg ai/ha and a PHI of 0 days.

In trials on cucumbers from USA matching this GAP, acetamiprid residues were: 0.02, 0.02, 0.03, 0.03, 0.04 and 0.09 mg/kg.

In trials on summer squash from USA matching this GAP, acetamiprid residues were: 0.05, 0.06, 0.06, 0.09 and 0.11 mg/kg.

In trials on melons from USA matching this GAP, acetamiprid residues were: 0.02, 0.02, 0.04, 0.06, 0.08 and 0.1 mg/kg.

The Meeting noted that these data sets for cucumbers and summer squash (representing cucurbits with edible peel) and melons (representing cucurbits with inedible peel) were similar and agreed to combine them to recommend a group maximum residue level, STMR and HR for cucurbits.

The combined data set for cucumbers, summer squash and melons is: 0.02, 0.02, 0.02, 0.02, 0.03, 0.03, 0.04, 0.04, 0.05, 0.06, 0.06, 0.06, 0.08, 0.09, 0.09, 0.1 and 0.11 mg/kg (n = 17).

The Meeting estimated an STMR of 0.05 mg/kg, an HR of 0.11 mg/kg and recommended a maximum residue level of 0.2 mg/kg for acetamiprid in fruiting vegetables, cucurbits.

Fruiting vegetables, other than Cucurbits

Residue data were provided to the Meeting from trials in USA on tomatoes, sweet peppers and chili peppers.

GAP in USA for fruiting vegetables (including tomatoes and peppers) is for a maximum of four foliar applications of up to 0.084 kg ai/ha and a PHI of 7 days. A GAP also exists in USA for indoor tomatoes, applying acetamiprid as a single soil application through drip irrigation systems, using up to 0.084 kg ai/ha (3.4 g ai/1000 plants) and with a PHI of 1 day.

In trials on field tomatoes from USA matching this foliar application GAP, acetamiprid residues in tomatoes were: < 0.01, < 0.01, < 0.01, 0.01, 0.01, 0.02, 0.03, 0.03, 0.03, 0.03, 0.04, 0.04, 0.04, 0.06, 0.06, 0.08, 0.09 and 0.1 mg/kg.

In trials on indoor tomatoes from USA matching the US drip irrigation GAP, acetamiprid residues in tomatoes were: < 0.01, 0.04 and 0.05 mg/kg.

In trials on sweet peppers from USA matching this foliar application GAP, acetamiprid residues were: 0.01, 0.02, 0.03, 0.03, 0.04, 0.06, 0.07 and 0.09 mg/kg.

In trials on chili peppers from USA matching this foliar application GAP, acetamiprid residues were: 0.06, 0.08 and 0.14 mg/kg.

The Meeting noted that the data sets from foliar applications to field tomatoes, sweet peppers and chili peppers were similar and agreed combine them to estimate a group maximum residue level, STMR and HR for fruiting vegetables other than Cucurbits.

The combined data set for tomatoes, sweet peppers and chili peppers is: < 0.01, < 0.01, < 0.01, 0.01, 0.01, 0.01, 0.02, 0.02, 0.03, 0.03, 0.03, 0.03, 0.03, 0.03, 0.04, 0.04, 0.04, 0.04, 0.06, 0.06, 0.06, 0.06, 0.07, 0.08, 0.08, 0.09, 0.09, 0.1 and 0.14 mg/kg (n = 29).

The Meeting estimated an STMR of 0.04 mg/kg, an HR of 0.14 mg/kg and recommended a maximum residue level of 0.2 mg/kg for acetamiprid in fruiting vegetables, other than cucurbits (except sweet corn and mushrooms).

For dried chili peppers, using the combined data set for the fruiting vegetables (except cucurbits) and a dehydration factor of 10, the Meeting estimated an STMR of 0.4 mg/kg, an HR of 1.4 mg/kg and recommended a maximum residue level of 2 mg/kg for acetamiprid in dried chili peppers.

Leafy vegetables

Residue data were provided to the Meeting from trials in USA on head and leaf lettuce, spinach and mustard greens and from trials in Europe on field lettuce and protected lettuce.

GAP in Italy, France and Spain for leafy vegetables (or lettuce and other similar salad vegetables) is for a maximum of two foliar applications of up to 0.05 kg ai/ha and a PHI of 7 days (or 3 days for indoor crops in Italy).

In trials on field lettuce from France, Spain and Italy matching this GAP, acetamiprid residues in lettuce were: 0.04, 0.06, 0.06, 0.1, 0.11, 0.14 and 0.17 mg/kg.

In trials on field lettuce from France, Germany and UK matching this GAP, acetamiprid residues in lettuce were: 0.08, 0.14, 0.15, 0.16, 0.24, 0.25, 0.28 and 0.31 mg/kg.

In trials on protected lettuce from France, Germany, Italy and UK matching the Italian GAP (2 × 0.05 kg ai/ha, PHI 3 days), residues in lettuce were: 0.33, 0.33, 0.41, 0.5, 0.78, 0.88, 0.88 and 1.9 mg/kg (n = 8).

GAP in USA for leafy vegetables is for a maximum of five foliar applications of up to 0.084 kg ai/ha and a PHI of 7 days.

In trials on field grown head lettuce from USA matching this GAP, acetamiprid residues in head lettuce (with wrapper leaves) were: 0.06, 0.14, 0.26, 0.28, 0.38, 0.42, 0.65 and 0.68 mg/kg.

In trials on field grown leaf lettuce from USA matching this GAP, acetamiprid residues in leaf lettuce were: 0.11, 0.12, 0.3, 0.41, 0.46, 0.61, 0.87 and 0.96 mg/kg.

In trials on spinach from USA matching this GAP, acetamiprid residues were: 0.03, 0.04, 0.21, 0.46, 0.55, 1.1, 2.1 and 2.5 mg/kg (n = 8).

In trials on mustard greens from USA matching this GAP, acetamiprid residues were: 0.11, 0.18, 0.19, 0.3, 0.43, 0.49, 0.68, 0.74 and 1.1 mg/kg.

The Meeting noted that the data sets for head lettuce, leaf lettuce, spinach and mustard greens matching the USA GAP were similar and considered estimating a group maximum residue level, STMR and HR for leafy vegetables based on the spinach data.

However, noting that for spinach the proposed maximum residue level would result in an IESTI that exceeded the ARfD by 180%, the Meeting agreed to estimate a group maximum residue level for leafy vegetables except spinach, based on the data for indoor lettuce matching the Italian GAP.

The Meeting estimated an STMR of 0.64 mg/kg, an HR of 1.9 mg/kg and recommended a maximum residue level of 3 mg/kg for acetamiprid in leafy vegetables except spinach.

For spinach, the Meeting proposed a maximum residue level of 5 mg/kg and estimated an STMR of 0.51 mg/kg and an HR of 2.5 mg/kg, noting that this would result in an exceedance of the ARfD and that an alternative GAP for spinach could not be identified.

Legume vegetables

Residue data were provided to the Meeting from trials in USA on beans and peas (with and without pods).

GAP in USA for legume vegetables is for a maximum of three foliar applications of up to 0.112 kg ai/ha and a PHI of 7 days.

In trials on beans from USA matching this GAP, acetamiprid residues in beans (without pods) were: 0.02, 0.03, 0.04, 0.08, 0.11 and 0.18 mg/kg.

In trials on peas from USA matching this GAP, acetamiprid residues in peas (without pods) were: < 0.01, 0.01, 0.02, 0.02, 0.03, 0.03 mg/kg.

The Meeting estimated an STMR of 0.03 mg/kg, an HR of 0.18 mg/kg and recommended a maximum residue level of 0.3 mg/kg for acetamiprid in peas, shelled and for beans, shelled.

In trials on beans from USA matching the USA GAP for legume vegetables (3× 0.112 kg ai/ha, PHI 7 days), acetamiprid residues in beans (with pods) were: < 0.01, < 0.01, < 0.01, < 0.01, 0.02 and 0.18 mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg, an HR of 0.18 mg/kg and recommended a maximum residue level of 0.4 mg/kg for acetamiprid in beans, except broad bean and soya bean.

In trials on peas in USA matching this GAP, acetamiprid residues in peas (with pods) were: 0.08, 0.13 and 0.27 mg/kg.

The Meeting agreed the data were not sufficient to recommend a maximum residue level for acetamiprid in peas (with pods).

Stalk and stem vegetables

Residue data were provided to the Meeting from trials in USA on celery.

GAP in USA for leafy vegetables (including celery) is for a maximum of five foliar applications of up to 0.084 kg ai/ha and a PHI of 7 days.

In trials on celery from USA matching this GAP, acetamiprid residues in celery stalks and leaves were: 0.08, 0.17, 0.27, 0.27, 0.32, 0.41, 0.51 and 0.78 mg/kg (n = 8).

The Meeting estimated an STMR of 0.3 mg/kg, an HR of 0.78 mg/kg and recommended a maximum residue level of 1.5 mg/kg for acetamiprid in celery.

Tree nuts

Residue data were provided to the Meeting from trials in USA on almonds and pecans.

GAP in USA for tree nuts (including almonds and pecans) is for a maximum of four foliar applications of up to 0.2 kg ai/ha and a PHI of 14 days.

In trials on almonds in USA matching this GAP, acetamiprid residues in nut meat were: < 0.01, < 0.01, < 0.01, 0.01, 0.01 and 0.02 mg/kg.

In trials on pecans in USA matching this GAP, acetamiprid residues in nut meat were: < 0.01, < 0.01, < 0.01, < 0.01, 0.01 and 0.05 mg/kg.

The Meeting noted that these data sets for almonds and pecans were similar and agreed to combine them to support a group maximum residue level. The combined data set is: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, 0.01, 0.01, 0.01, 0.02 and 0.05 (n = 12).

The Meeting estimated an STMR of 0.01 mg/kg, an HR of 0.05 mg/kg and recommended a maximum residue level of 0.06 mg/kg for acetamiprid in tree nuts.

Oil seeds

Residue data were provided to the Meeting from trials in USA on cotton.

GAP in USA for cotton is for a maximum of four foliar applications of up to 0.112 kg ai/ha and a PHI of 28 days.

In trials on cotton in USA matching this GAP, acetamiprid residues in cotton seed were: < 0.01, 0.02, 0.02, 0.03, 0.05, 0.06, 0.09, 0.09, 0.1, 0.1, 0.12, 0.14, 0.36 and 0.5 mg/kg (n = 14).

The Meeting estimated an STMR of 0.09 mg/kg and recommended a maximum residue level of 0.7 mg/kg for acetamiprid in cotton seed.

Animal feeds

Almond hulls

In trials on almonds in USA matching the USA GAP, acetamiprid residues in almond hulls (as received) were: 0.22, 0.78, 0.78, 1.9, 2.0 and 3.8 mg/kg.

The Meeting estimated a median residue of 1.34 mg/kg for almond hulls.

Cotton gin trash

In trials on cotton in USA matching this GAP, acetamiprid residues in cotton gin trash were: 0.39, 1.5, 1.9, 1.9, 2.7, 3.0, 3.6, 3.9, 3.9, 4.0, 5.8, 6.5, 7.3 and 18 mg/kg (n = 14).

The Meeting estimated a median residue of 3.6 mg/kg and a highest residue of 18 mg/kg for acetamiprid for cotton gin trash.

Fate of residues during processing

The effect of processing on the nature of residues was investigated in buffer solutions under a range of hydrolysis conditions. Acetamiprid was shown to be stable for at least 35 days in buffer solutions at pH 4, 5, 7 and 9, incubated at up to 45 °C.

The fate of acetamiprid residues has been examined in a number of studies with oranges, tomatoes, apples, cotton seed and plums, reflecting household and simulated commercial processing.

A summary of processing factors (PF) derived from the data on the above commodities is shown below. Based on the estimations made on the raw agricultural commodities, STMR-Ps and HR-Ps were estimated by multiplying the STMR of the raw commodity by the PF. Maximum residue levels were only estimated for commodities with a Codex code and of importance in international trade.

Summary of selected processing factors for acetamiprid

Raw agricultural commodity (RAC)	STMR (mg/kg)	HR (mg/kg)	Processed commodity	Processing factor	STMR-P	HR-P
Oranges	0.25		Juice [a]	< 0.13	0.03	
			Pulp	0.24	0.05	
			Pulp, dry	2.8	0.7	
			Peel	2.83	0.71	
			Oil [a]	< 0.16	0.04	
Apple	0.23		Juice	0.88	0.2	
			Wet pomace	1.34	0.31	
Plums	0.04	0.11	Dried prunes	2.96	0.12	0.32
Grape	0.085		Juice	1.5	0.13	
			Raisins	0.93	0.08	0.23
Tomatoes	0.4		Purée	1.4	0.56	
			Paste	3.1	1.24	
Cotton	0.09		Meal	0.38	0.03	
			Hulls	0.79	0.07	
			Refined Oil [a]	< 0.04	0.004	

[a] Residues below LOQ

The Meeting recommended a maximum residue level of 0.6 mg/kg for dried prunes, based on the recommended maximum residue level for plums (0.2 mg/kg) and an average processing factor of 2.9.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of acetamiprid in farm animals on the basis of the diets listed in Annex 6 of the 2009 JMPR Report (OECD Feedstuffs Derived from Field Crops) and the STMR or highest residue levels estimated at the present Meeting. Dietary burden calculations are provided in Annex 6 and are summarized below.

Animal dietary burden for acetamiprid, ppm of dry matter diet

	Maximum Dietary Burden	Mean Dietary Burden
Beef cattle	1.085	0.435
Dairy cattle	0.836	0.413
Poultry broiler	0.007	0.007
Poultry layer	0.168	0.032

Farm animal feeding studies

Dairy cows

The Meeting received information on the residue levels arising in animal tissues and milk when dairy cows were dosed with acetamiprid for 28 days at 5.77, 17.4 and 58.6 ppm in the diet.

In milk, average residues (3 animals) of acetamiprid in whole milk from treated animals were < 0.02 in the low dose group (5.77 ppm) and were found at up to 0.21 mg/kg in the higher dose groups. Residues of IM-2-1 (the predominant residue) were 0.03–0.06 mg/kg in the low dose group and up to 0.95 mg/kg in the higher dose groups. Residue concentrations of acetamiprid in whole milk increased rapidly, reaching a plateau within 1 day with concentrations of IM-2-1 reaching a plateau at about 7–8 days.

In liver and kidney, acetamiprid residues were < 0.05 mg/kg in the low dose group and up to 0.25 mg/kg in the higher dose groups. Residues of acetamiprid in muscle and fat were < 0.01 mg/kg in the low dose group and did not exceed about 0.1 mg/kg and 0.06 mg/kg respectively in the higher dose groups.

The predominant residue in all tissues was the IM-2-1 metabolite, with highest residues in liver and kidney (0.1–0.2 mg/kg – low dose) and up to about 2.4 mg/kg in higher dose groups. Levels of about 0.05 mg/kg were present in muscle and fat (low dose group); these increasing to 1.0 mg/kg in muscle and 0.65 mg/kg in fat in the higher dose groups.

Residues of total acetamiprid (parent+IM-2-1) in the low dose group averaged 0.24 mg/kg (kidney), < 0.15 mg/kg (liver), 0.048 mg/kg (muscle), 0.037 mg/kg (fat) and 0.063 mg/kg (milk) and generally increased proportionally in the higher dose groups. Maximum residues in individual (low dose) animals were < 0.25 mg/kg mg/kg (kidney), < 0.15 mg/kg (liver), < 0.05 mg/kg (muscle) and < 0.072 mg/kg (fat).

Laying hens

A feeding study was also conducted with laying hens, fed 1.16 ppm, 3.55 ppm or 12 ppm acetamiprid daily for 28 days.

In eggs, residues of acetamiprid were not detectable or < 0.01 mg/kg in all dose groups, with the IM-2-1 metabolite being found at up to 0.33 mg/kg in the 12 ppm dose group, reaching a plateau at about day 8.

In tissues, acetamiprid was also not detected in any dose group, with IM-2-1 metabolite being found only in liver (< 0.1 mg/kg) in the low dose group and in the high dose group at levels of up to 0.5 mg/kg in liver, up to 0.075 mg/kg in muscle and up to 0.012 mg/kg in fat.

Animal commodity maximum residue levels

Cattle

For maximum residue level estimation, the high residues of acetamiprid plus IM-2-1 in tissues were calculated by extrapolating the maximum dietary burden (1.085 ppm) from the lowest feeding level (5.77 ppm) in the dairy cow feeding study and using the highest tissue concentrations of total acetamiprid from individual animals within those feeding groups.

The STMR values for the tissues were calculated by extrapolating the STMR dietary burden (0.435 ppm) from the lowest feeding level in the dairy cow feeding study and using the mean tissue concentrations of total acetamiprid from those feeding groups.

For milk maximum residue level estimation, the high residues in the milk were calculated by extrapolating the maximum dietary burden for dairy cattle (0.836 ppm) from the lowest feeding level (5.77 ppm) in the dairy cow feeding study and using the mean milk concentrations of total acetamiprid from this feeding group.

The STMR value for milk was calculated by extrapolating the mean dietary burden for dairy cows (0.413 ppm) from the lowest feeding level (5.77 ppm) in the dairy cow feeding study and using the mean milk concentrations of total acetamiprid from this feeding group.

	Acetamiprid feed level (ppm) for milk residues	Total acetamiprid residues (mg/kg) in milk	Acetamiprid feed level (ppm) for tissue residues	Total acetamiprid residues (mg/kg) in:			
				Muscle	Liver	Kidney	Fat
Maximum residue level for beef or dairy cattle							
Feeding study [a]	5.77	0.063	5.77	0.05	0.15	0.25	0.07
Dietary burden and residue estimate	0.836	0.009	1.085	0.009	0.028	0.047	0.013
STMR beef or dairy cattle							
Feeding study [b]	5.77	0.063	5.77	0.048	0.15	0.24	0.037
Dietary burden and residue estimate	0.413	0.004	0.435	0.004	0.011	0.018	0.003

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

[b] Mean residues for tissues and for milk

The Meeting estimated maximum residue levels of 0.02 mg/kg for acetamiprid in meat (from mammals other than marine mammals), 0.02 mg/kg for mammalian fat, 0.05 mg/kg for edible offal (mammalian) and 0.02 mg/kg for milks.

Estimated STMRs are 0.004 mg/kg for mammalian muscle, 0.003 mg/kg for mammalian fat, 0.011 mg/kg for mammalian liver, 0.018 mg/kg for mammalian kidney and 0.004 mg/kg for milks.

Estimated HRs are 0.01 mg/kg for mammalian fat, 0.007 mg/kg for mammalian muscle, 0.022 mg/kg for mammalian liver, 0.036 mg/kg for mammalian kidney and 0.009 mg/kg for milks.

Poultry

In lowest dose feeding study (1.16 ppm), residues of acetamiprid were not detectable in eggs or any poultry tissues and the combined residues of acetamiprid and IM-2-1 averaged 0.027 mg/kg in eggs, were < 0.01 mg/kg in muscle and fat and was up to 0.09 mg/kg in liver.

Noting that the maximum dietary burden for poultry layers (0.168 ppm) is about 7 times lower than the lowest dose in the feeding study, the Meeting concluded that residues of acetamiprid and its IM-2-1 metabolite would not be expected in eggs.

For poultry liver, muscle and fat, based on a maximum dietary burden of 0.032 ppm (more than 36 times lower than the lowest dose feeding study, the Meeting concluded that residues of acetamiprid and its IM-2-1 metabolite would not be expected in poultry edible tissues above the LOQs of 0.05 mg/kg (liver) and 0.01 mg/kg (muscle and fat).

The Meeting estimated maximum residue levels of 0.01 (*) mg/kg for acetamiprid in poultry meat, poultry fat, and eggs and 0.05 mg/kg for poultry edible offal.

Estimated HRs and STMRs for dietary intake estimation for acetamiprid are 0.0 mg/kg for poultry eggs, meat and fat and for poultry edible offal, the Meeting estimated an HR of 0.01 mg/kg and an STMR of 0.0 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intake (IEDI) for acetamiprid was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available. The results are shown in Annex 3.

The International Estimated Daily Intakes of acetamiprid for the 13 GEMS/Food regional diets, based on estimated STMRs were 0–3% of the maximum ADI of 0.07 mg/kg bw (Annex 3). The

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

Short-term intake

The International Estimated Short-term Intake (IESTI) for acetamiprid was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available (Annex 4).

For spinach, the IESTI represented 180% of the ARfD of 0.1 mg/kg bw. On the basis of the information provided to the JMPR it was not possible to conclude that the estimate of short-term intake of acetamiprid, from the consumption of spinach, was less than the ARfD. The Meeting noted that an alternative GAP for spinach was not available.

For the other commodities considered by the JMPR, the IESTI represented 0–80% of the ARfD and the Meeting concluded that the short-term intake of residues of acetamiprid, when used in ways that have been considered by the JMPR (other than spinach), is unlikely to present a public health concern.