

5.20 SPINETORAM (233)

TOXICOLOGY

Spinetoram, also known as XDE-175 or XR-175, is a fermentation product derived from the actinomycete bacterium *Saccharopolyspora spinosa*, which has been slightly modified by chemical reaction. Spinetoram is a macrocyclic lactone insecticide. It acts by causing persistent activation of insect nicotinic acetylcholine receptors.

Spinetoram is composed of numerous spinosyns, known as “factors”, which differ slightly from each other. Each spinosyn consists of a large complex hydrophobic ring, a basic amine group, and two sugar moieties. The insecticidal activity of spinetoram is attributed to two spinosyns, identified as XDE-175-J (“factor J”) and XDE-175-L (“factor L”), which comprise the overwhelming majority of the technical material. The ratio of factor J to factor L ranges from 70 : 30 to 90 : 10.

The remaining components of spinetoram comprise a number of additional spinosyns (that have minor substitutions at various locations in the spinosyn molecule) and other impurities consisting of inorganic salts, carbohydrates and proteinaceous material that would be expected to be produced during a fermentation process.

Spinetoram has not been evaluated previously by the JMPR and was reviewed by the present Meeting at the request of the CCPR.

All the pivotal studies met the basic requirements of the relevant OECD or national test guidelines and included certificates of compliance with GLP.

Biochemical aspects

The toxicokinetics and metabolism of the two insecticidally active factors in spinetoram, factor J and factor L, are quite similar. In rats, the factors were rapidly and extensively ($\geq 70\%$) absorbed. Peak plasma concentrations of radiolabel were achieved within 2–4 h. Systemic bioavailability was at least 26–29% for factor J and 39–57% for factor L. The factors were extensively distributed in the tissues, with highest concentrations in the gastrointestinal tract, fat, carcass and the liver. Excretion was primarily via the faeces (85%), mainly as metabolites, with only 3–4% of the administered dose excreted in the urine. Most of the administered dose was recovered within 24 h. The plasma half-lives for radiolabelled factor J and factor L were 4–11 h and 8–24 h, respectively. Very little radiolabel remained in the carcass after 7 days: 0.6–1.4% with factor J and 3–7% with factor L. Pre-treatment of rats with a low dose of either factor for 14 days did not affect the subsequent absorption and excretion of the respective factor.

Both factor J and factor L were extensively metabolized. The major metabolic pathway was glutathione conjugation, either of the parent, or of the products of *N*-demethylation, *O*-deethylation and deglycosylation of each factor, as well as hydroxylation of parent factor J. The aglycone of factor L was also subject to sulfate and glucuronide conjugation. The major metabolite was the cysteine conjugate of the parent factor.

Toxicological aspects⁴¹

Spinetoram was of low acute toxicity in rats: oral LD₅₀ > 5000 mg/kg bw; dermal LD₅₀ > 5000 mg/kg bw; and 4-h inhalational LC₅₀ > 4.44 mg/L. There was no mortality at limit doses of 5000 mg/kg bw and 4.4 mg/L, respectively. Spinetoram is not a skin or eye irritant.

In a local lymph node assay in BALB/c mice, spinetoram was shown to be a moderate skin sensitizer, while in a second assay in CBA/J mice (the recommended strain for this assay according to OECD TG 429 guidelines), spinetoram was not a skin sensitizer.

A range of effects was observed in short- and long-term studies with repeated dosing, and the effects were broadly similar in mice, rats and dogs. In short-term studies in mice, rats and dogs, cytoplasmic vacuolation of parenchymal cells, epithelial cells, macrophages and fibroblasts of a variety of tissues was observed, with some degeneration of muscle. There was also an increase in the incidence and/or severity of aggregates of macrophages/histiocytes in the lymphoid structures of numerous tissues. In mice, the NOAEL was 150 ppm, equal to 24.5 mg/kg bw per day, in a 28-day study. The NOAEL was 50 ppm, equal to 7.5 mg/kg bw per day, in a 90-day study in which there was also slight splenic extramedullary haematopoiesis in females at the LOAEL. In rats, the NOAEL was 500 ppm, equal to 48 mg/kg bw per day, in a 28-day study in which there was vacuolation of the thyroid follicular epithelium and the renal tubular epithelium at the LOAEL. In three 90-day studies in which rats were exposed to spinetoram at two different ratios of factor J to factor L (75 : 25 and 85 : 15), the overall NOAEL was 10 mg/kg bw per day, the factor ratio having little effect on sensitivity. There was also an increase in reticulocyte and leukocyte counts at the LOAEL in one of these studies. In beagle dogs, the NOAEL was 200 ppm, equal to 5.9 mg/kg bw per day, in a 28-day study. In addition to vacuolation of numerous tissues, there was extramedullary splenic haematopoiesis at the LOAEL. In a 90-day study, the NOAEL was 150 ppm, equal to 5.0 mg/kg bw per day. Arteritis or perivascular inflammation and extramedullary haematopoiesis were also observed at the LOAEL in this study. The NOAEL in a 1-year study was 100 ppm, equal to 2.5 mg/kg bw per day, on the basis of arteritis, accompanied by necrosis of the arterial walls at the LOAEL of 200 ppm. The incidence of arteritis in the group receiving spinetoram at 200 ppm was low (one out of four males and one out of four females), and may have reflected the normal background incidence of lesions often seen in beagle dogs; however, the fact that more severe effects that were considered to be treatment-related were noted in dogs given spinetoram at 300 or 900 ppm for 90 days suggested that these changes in the 1-year study may be treatment-related. The overall NOAEL was 5 mg/kg bw per day in dogs.

In long-term studies in rats and mice, tissue vacuolation was again commonly observed at doses at and above the LOAEL. In an 18-month study in mice, the NOAEL was 150 ppm, equal to 18.8 mg/kg bw per day, on the basis of histopathological changes in the stomach, lungs and epididymides at the LOAEL. In addition to cytoplasmic vacuolation of the epithelium of the ducts lining the head of the epididymides and aggregates of alveolar macrophages in the lungs, hyperplasia and inflammation of the glandular mucosa of the stomach, with dilatation of the mucosal glands were also observed. In a 2-year study in rats, the NOAEL was 250 ppm, equivalent to 10.8 mg/kg bw per day.

Selected tissues from short-term studies of toxicity with spinetoram and with the structurally related compound spinosad in rats (both compounds) and in mice (spinosad only) were examined by electron microscopy. Vacuolation was shown to be associated with cytoplasmic lamellar inclusion bodies, reflecting dysregulation of lysosomal storage (i.e., phospholipidosis). While such effects may arise through a variety of mechanisms that prevent degradation of cell constituents usually processed

⁴¹ Most of the studies of toxicity were conducted with factor J and factor L in a ratio equal to 75 : 25. Some studies were repeated with factor J and factor L in the ratio of 85 : 15; this was done to demonstrate that the 85 : 15 ratio produces a toxicity profile that is essentially the same as that seen with the 75 : 25 ratio.

in the lysosomes, it is most likely that spinetoram acts through a physicochemical mechanism associated with its cationic amphiphilic structure, in common with other such compounds.

In long-term studies of toxicity and carcinogenicity, there was no evidence of treatment-related tumourigenicity in rats or mice. The Meeting concluded that spinetoram was not carcinogenic.

Spinetoram gave negative results in an adequate range of studies of genotoxicity in vitro and in vivo. The Meeting concluded that spinetoram had no genotoxic potential.

On the basis of the absence of carcinogenicity and genotoxicity, the Meeting concluded that spinetoram is unlikely to pose a carcinogenic risk to humans

The reproductive effects of spinetoram have been investigated in a two-generation study in rats. Cytoplasmic vacuolation of thyroid follicular epithelial cells was observed in adults of both generations at the highest dose (75 mg/kg bw per day). Among females at this dose, three parental (F₀) and three F₁ females had complications of parturition (dystocia), in most cases evidenced by the protracted delivery of pups over several days. These females also exhibited clinical signs (e.g., postpartum vulvar discharge, pale skin/mucous membranes, perinasal/perineal soiling), had reduced body weights and feed consumption during lactation, and associated decreases in survival and body weight of their pups. The dystocia occurred in a few females (about 13%) at the highest dose of 75 mg/kg bw per day. A similar effect (in up to about 24% of litters) was seen with spinosad at a higher dose of 100 mg/kg bw per day. For both substances, the NOAEL for this effect was 10 mg/kg bw per day, which was also the NOAEL for maternal toxicity. For females at the highest dose without dystocia, gestational survival was slightly decreased, with an associated increase in postimplantation loss. No other measures of reproductive performance were affected in either males or females. The NOAELs for parental, reproductive and offspring toxicity were 10 mg/kg bw per day on the basis of slight thyroid vacuolation in adult males and females, dystocia in females and decreased gestation survival in pups at 75 mg/kg bw per day

The developmental toxicity of spinetoram had been investigated in rats and rabbits. In rats, maternal body weight and feed consumption were reduced at 300 mg/kg bw per day, with a NOAEL of 100 mg/kg bw per day. There was no treatment-related embryo/fetal toxicity or teratogenicity at doses up to and including 300 mg/kg bw per day. The NOAEL for developmental toxicity was 300 mg/kg bw per day, the highest dose tested.

In a preliminary study of developmental toxicity in rabbits, dams given doses of 150 or 100 mg/kg bw per day showed decreased feed consumption, decreased faecal output, and decreased body-weight gain from the beginning of the treatment period. No other clinical findings were present in these two groups.

The effect on body weight and faecal output, which were associated with a marked and consistent decrease in feed consumption, were most likely a consequence of local irritation of the gastrointestinal tract.

Owing to severe inanition and subsequent weight loss, all rabbits from these groups were killed by day 15 of gestation with no further data collection.

In the main study of developmental toxicity in rabbits, treatment with spinetoram resulted in decreases in feed consumption, faecal output, and body-weight gain, and increased mean absolute and relative liver weights at a dose of 60 mg/kg bw per day. In addition, one dam at 60 mg/kg bw per day was killed on day 21 of gestation owing to inanition and subsequent weight loss, considered to be treatment-related. There were no signs of developmental toxicity at any dose. The NOAEL for maternal toxicity was 10 mg/kg bw per day. The NOAEL for developmental toxicity was 60 mg/kg bw per day, the highest dose tested.

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

Neurotoxicity was investigated in rats given single doses of up to 2000 mg/kg bw, or repeated doses of up to 750 ppm (36.7 mg/kg bw per day) for 12 months. Comprehensive behavioural and histopathological investigations revealed no evidence of neurotoxicity.

The plant metabolites *N*-formyl-XDE-175-J and *N*-formyl-XDE-1175-L were evaluated in a test for acute oral toxicity and in an Ames test for genotoxicity. Both metabolites were of low acute oral toxicity ($LD_{50} > 5000$ mg/kg bw) and gave negative results in the Ames test.

The development of spinetoram as a commercial product had been too short for any information from medical surveillance of manufacturing-plant personnel to be available. There were no documented cases of intoxication or of any other clinical effects associated with its use.

Toxicological evaluation

The Meeting established an ADI 0–0.05 mg/kg bw based on an overall NOAEL of 5.0 mg/kg bw per day, identified on the basis of arteritis, accompanied by necrosis of the arterial walls in the affected organ(s), in studies of toxicity in dogs, and with a safety factor of 100. Although arteritis was observed only in some dogs, at an incidence that was within the range for historical controls, the incidence of arteritis at the LOAEL was greater in the concurrent controls and clear effects were found at higher doses in another study. Additionally, the structurally related compound spinosad had also been observed to cause arteritis in dogs given spinosad for 1 year, at doses not dissimilar to the LOAEL for the present study. Hence, the Meeting concluded that while there was some uncertainty as to the toxicological significance of the finding of arteritis at the LOAEL for spinetoram, use of the overall NOAEL from studies of toxicity in dogs as a basis for establishing the ADI was scientifically justified.

The Meeting concluded that it was not necessary to establish an acute reference dose for spinetoram on the basis of its low acute toxicity, the absence of neurotoxic potential and of developmental or any other effects of relevance for acute exposure in studies of longer duration. Effects on gestational survival of pups observed in the multigeneration study in rats were most likely to be secondary to maternal toxicity, which was not a consequence of acute exposure.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	18-month combined toxicity and carcinogenicity ^a	Toxicity	150 ppm, equal to 18.8 mg/kg bw per day	300 ppm, equal to 37.5 mg/kg bw per day ^c
		Carcinogenicity	300 ppm, equal to 37.5 mg/kg bw per day ^c	—
Rat	2-year combined study of toxicity and carcinogenicity ^a	Toxicity	250 ppm, 10.8 mg/kg bw per day	500 ppm, equal to 21.6 mg/kg bw per day
		Carcinogenicity	750 ppm, equal to 32.9 mg/kg bw per day ^c	—
	Two-generation study ^a	Parental	10 mg/kg bw per day	75 mg/kg bw per day ^c
		Offspring toxicity	10 mg/kg bw per day	75 mg/kg bw per day ^c
		Reproductive toxicity	10 mg/kg bw per day	75 mg/kg bw per day ^c
	Developmental toxicity ^b	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day ^c
Foetotoxicity		300 mg/kg bw per day ^c	—	

Rabbit	Developmental toxicity ^b	Maternal toxicity	10 mg/kg bw per day	60 mg/kg bw per day ^c
		Foetotoxicity	60 mg/kg bw per day ^c	—
Dog	Oral 90-day and 1-year studies	Toxicity	150 ppm, equal to 5.0 mg/kg bw per day	200 ppm, equal to 5.4 mg/kg bw per day ⁴²

^a Dietary administration.

^b Gavage administration.

^c Highest dose tested.

Estimate of acceptable daily intake for humans

0–0.05 mg/kg bw

Estimate of acute reference dose

Unnecessary

Information that would be useful for continued evaluation of the compound

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

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

Absorption, distribution, excretion, and metabolism in mammals

Rate and extent of oral absorption	Rapid (t_{\max} 2–4 h) and extensive (> 70%). Systemic bioavailability of factor J (26–29%) < factor L (39–57%)
Distribution	Rapidly and extensive. Highest concentrations of radioactivity in the gastrointestinal tract, followed by fat, carcass and liver
Potential for accumulation	Tissue and carcass concentrations low after 7 days (0.6–1.4% of administered dose).
Rate and extent of excretion	Rapidly excreted, plasma half-lives 4–24 h; 85% of dose in faeces, mainly as metabolites; 3–4% in urine, mostly in first 24 h
Metabolism in animals	Extensively metabolized, primarily by glutathione conjugation of parent and products of phase-one metabolism. Some sulfate and glucuronide conjugation of aglycone of factor L
Toxicologically significant compounds (animals, plants and environment)	Spinetoram, comprising factors J and L

⁴² Marginal differences out of concurrent controls but within the historical control range.

Acute toxicity

Rat, LD ₅₀ , oral	> 5000 mg/kg bw
Rat, LD ₅₀ , dermal	> 5000 mg/kg bw
Rat, LC ₅₀ , inhalation	> 5.44 mg/L for 4 h (nose only)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Transient irritation
Mouse, dermal sensitization	Not sensitizing (local lymph node assay in CBA/J mice) ⁴³

Short-term studies of toxicity

Target/critical effect	Mice, rats, dogs: vacuolation of macrophages in a wide range of lymphoid tissues within numerous organs and aggregates of macrophages/histiocytes in a number of tissues, non-regenerative anaemia, arteritis (dogs)
Lowest relevant oral NOAEL	5.0 mg/kg bw per day (90-day and 1-year study in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (28-day study in rats, highest dose tested)
Lowest relevant inhalation NOAEL	No data

Genotoxicity

Negative in vitro and in vivo

Long-term studies of toxicity and carcinogenicity

Target/critical effect	Mice, rats: vacuolation of cells (thyroid in rats; epididymes in mice) and increases in aggregates of macrophages/histiocytes in lymphoid tissues in numerous organs, hyperplasia of the glandular mucosa of the stomach and inflammation of the glandular submucosa (mice)
Lowest relevant NOAEL	2-year study, rat: 10.8 mg/kg bw per day
Carcinogenicity	Not carcinogenic

Reproductive toxicity

Reproduction target/critical effect	Dystocia (difficulty in delivery), decrease in gestation survival of pups.
Lowest relevant reproductive NOAEL	10 mg/kg bw per day (rats)
Developmental target/critical effect	None
Lowest relevant developmental NOAEL	60 mg/kg bw per day (rabbit; highest dose tested)

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity and short-term studies of neurotoxicity	No indications of neurotoxicity in single- or repeat-dose studies
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Medical data

No data available on manufacturing-plant personnel (production-scale manufacturing has yet to start). No

⁴³ Recommended strain.

reports of adverse health effects in exposed subjects.

Summary

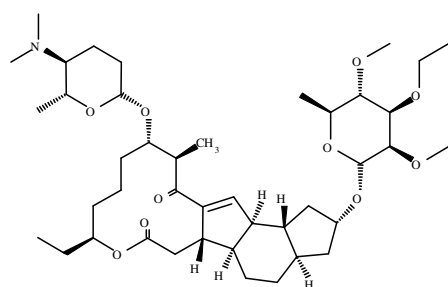
	<i>Value</i>	<i>Study</i>	<i>Safety factor</i>
ADI	0–0.05 kg bw	Dog, 90-day and 1-year study	100
ARfD	Unnecessary	—	—

Factor J, XDE-175-J

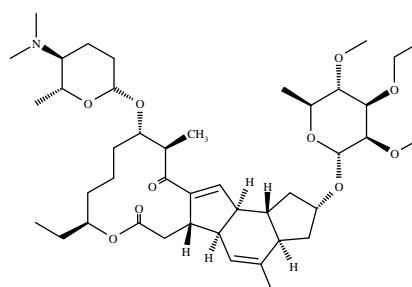
Factor L, XDE-175-L

RESIDUE AND ANALYTICAL ASPECTS

Spinetoram, a multi-component tetracyclic macrolide in the class of spinosyn insecticides, consists of two components shown below, present approximately in a three to one ratio. It was identified as a priority new compound at the 39th Session of the CCPR in 2007 (ALINORM 07/30/24—Rev.1) for evaluation by the 2008 JMPR. The Meeting received information on physical and chemical properties, animal and plant metabolism, environmental fate, analytical methods, storage stability, use patterns, supervised trials, processing and farm animal feeding.

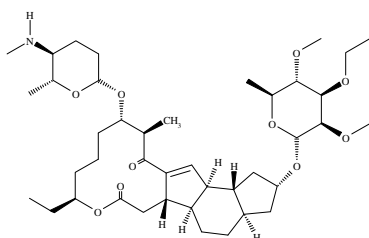


XDE-175-J (Major component)

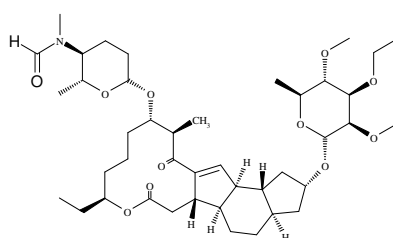


XDE-175-L (Minor component)

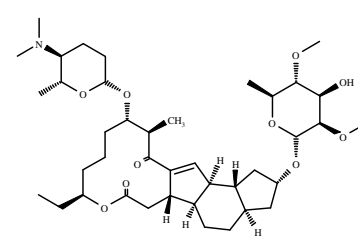
In this appraisal, the following abbreviated names were used for metabolites:



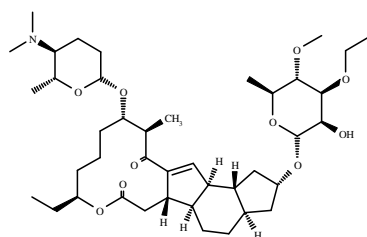
N-demethyl-175-J



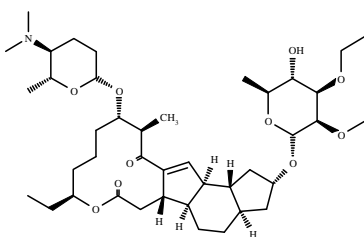
N-formyl-175-J



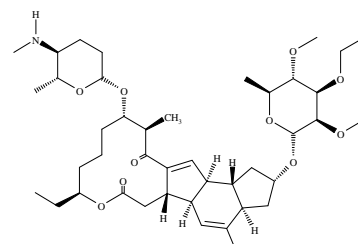
3'-O-deethyl-175-J



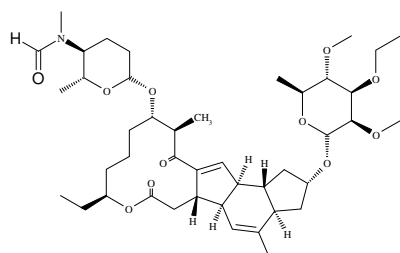
2'-O-demethyl-175-J



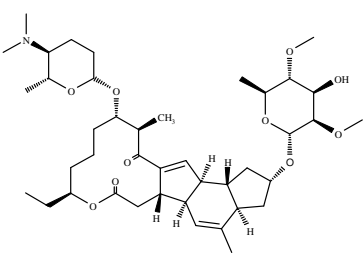
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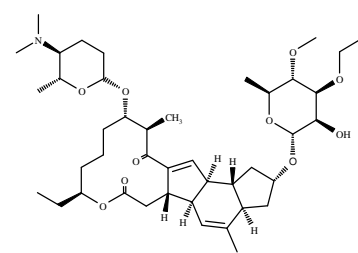
N-demethyl-175-L



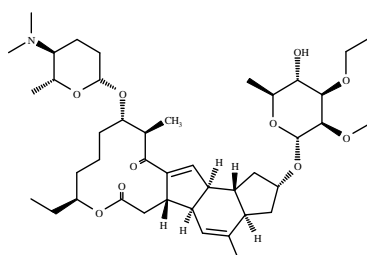
N-formyl-175-L



3'-O-deethyl-175-L



2'-O-demethyl-175-L



4'-O-demethyl-175-L

Animal metabolism

The Meeting received information on the fate of orally-dosed spinetoram in lactating goats and laying hens.

When either ^{14}C -XDE-175-J or ^{14}C -XDE-175-L, uniformly labelled with ^{14}C in the macrolide ring, was administered orally at a dose equivalent to a dietary concentration of 10–11 ppm to a lactating goat once a day for five consecutive days, 51% or 78% of the administered dose of ^{14}C -XDE-175-J or ^{14}C -XDE-175-L, respectively, were recovered in faeces. Radioactivity recovered in urine was insignificant; less than 0.2% of the administered dose.

Radioactivity started to appear in milk within 24 hours after the first application but cumulative milk sample contained only about 0.3% of the total administered dose of ^{14}C -XDE-175-J or 0.2% of that of ^{14}C -XDE-175-L. The maximum total radioactive residues were 0.047 mg/kg in parent equivalents for ^{14}C -XDE-175-L and 0.039 mg/kg ^{14}C -XDE-175-L.

Total radioactive residues (TRR) in tissues after sacrifice (21 h after the last dose) showed the tendency to be higher in fatty tissues, with 0.235 mg/kg and 0.119 mg/kg in parent equivalents in fat (after the administration of ^{14}C -XDE-175-J and ^{14}C -XDE-175-L, respectively), and 0.116 mg/kg and 0.099 mg/kg in liver. TRR in kidney, muscle and milk were much lower.

The primary residue was XDE-175-J or XDE-175-L (42–84% of TRR) in all tissues and milk, except liver, indicating that minimal metabolism had occurred. In liver, XDE-175-J or XDE-175-L was the primary residue but at lower levels (30 or 26% of TRR) with N-demethyl-175-J or -L at very low levels (< 2% of the TRR), and an unidentified metabolite. No residue components other than the unchanged parent compounds were identified in milk, kidney or fat. Radioactive residues in muscle also consisted primarily of XDE-175-J or XDE-175-L and much lesser amounts of what seemed to be the same unidentified metabolite as found in liver. There were many minor metabolites detected but all were less than 10% of the TRR. Unextracted radioactivity was less than 15% of the TRR in all samples except liver in which it was around 25%.

When either ^{14}C -XDE-175-J or ^{14}C -XDE-175-L, (uniformly labelled with ^{14}C in the macrolide ring), was administered orally at a dose equivalent to a dietary concentration of 10 ppm to a group of laying hens once a day for seven consecutive days, 93% or 91% of the administered dose of ^{14}C -XDE-175-J or ^{14}C -XDE-175-L, respectively, were recovered in excreta.

Eggs and tissues contained a low proportion of the administered dose (< 3%) for both ^{14}C -XDE-175-J and ^{14}C -XDE-175-L. TRR in eggs increased over the experimental period and reached a maximum of 0.20 and 0.49 mg/kg for ^{14}C -XDE-175-J and ^{14}C -XDE-175-L, respectively, on day 7. TRR in the tissues were highest in abdominal fat (1.04 mg/kg for XDE-175-J, and 2.46 mg/kg for XDE-175-L), followed by skin with subcutaneous fat, liver, eggs and muscle. There is a tendency for radioactivity to be found at higher levels in tissues with higher fat content.

Unchanged XDE-175-J or XDE-175-L remained as the primary residue in the egg (58–49%) and tissues (45–70% of TRR) other than liver (13–12%). 3'-O-deethyl-175-J was detected in abdominal fat (1.8% of TRR) and in liver (18%) and O-demethyl-175-J was present in all tissues (3.2–6.5% of TRR) while 3'-O-deethyl-175-L and O-demethyl-175-L were found in all tissues and eggs (5.2–13% and 13–20% of TRR respectively). Unextracted radioactivity was less than 7% of the TRR in all samples except muscle and eggs in which it was 12–20%.

Limited metabolism of spinetoram was observed in ruminants and hens as the unchanged parent compound was the primary residue component in milk and all ruminant tissues as well as eggs and all avian tissues except liver for both XDE-175-J and XDE-175-L. Metabolism of spinetoram appears to be primarily through demethylation of the N-dimethyl moiety on the forosamine sugar to give the N-demethyl metabolite (goat) and dealkylation of the rhamnose sugar to give the O-deethyl and/or O-demethyl (two possible isomers) metabolites (hen).

Plant metabolism

The Meeting received information on the fate of spinetoram after foliar applications of ^{14}C -XDE-175-J or ^{14}C -XDE-175-L, uniformly labelled with ^{14}C in the macrolide ring, on apple, lettuce and turnip representing the fruits, leafy crops and root crops respectively.

In all three crops tested, applied parent compounds decreased over test period. Among the two spinetoram components, XDE-175-L tended to be metabolized faster than XDE-175-J.

Apple

When a branch of apple tree with immature fruits was treated with single foliar application of either ^{14}C -XDE-175-J or ^{14}C -XDE-175-L at the rate of 1.8 kg ai/ha (4.8x) or 1.1 kg ai/ha (8.9x), respectively, apple fruits harvested seven days (PHI in US GAP) after the application contained 1.2 mg/kg or 0.36 mg/kg of radioactive residues. Washing of fruits (0–30 DAT) with acetonitrile and then dichloromethane removed 63–97% of TRR.

In the case of XDE-175-J application, in apples taken seven DAT, the parent compound was the major residue at 43% of the TRR with N-demethyl-175-J at 9.5% and N-formyl-175-J at 5.1% of the TRR. After the treatment with XDE-175-L, the parent compound was extensively degraded and

metabolized and only 1.3% of the TRR remained as the parent compound with 1.0% of the TRR as N-demethyl-175-L and another 1.0% as N-formyl-175-L.

In the washed fruits obtained from the ¹⁴C-XDE-175-J treated branch, peels contained 2–11% of TRR while pulp contained less than 1% (≤ 0.007 mg/kg). In washed fruits from ¹⁴C-XDE-175-L treated branch, peel contained 6–33% of TRR while pulp contained less than 4%.

Unextractable radioactive residues were < 10% of TRR in or on all samples after extraction with a mixture of acetonitrile and water (80:20, v/v). Several minor metabolites were also detected in the treated apples and leaves, each at $\leq 7.5\%$ of TRR. A multi-component mixture of extensively degraded compounds represented up to 39–77% of TRR but each component was less than 1% of TRR.

Comparison of radioactivity in treated fruits and shielded fruits indicates that translocation was negligible.

Lettuce

Red leaf lettuce was treated with either single or multiple foliar spray applications of ¹⁴C-XDE-175-J or ¹⁴C-XDE-175-L. For ¹⁴C-XDE-175-J, single applications were made at rates equivalent to 0.90 kg ai/ha while the same amount of the test compound was sprayed in three separate applications with the equal rate at weekly intervals. For ¹⁴C-XDE-175-L, plants were treated in a similar fashion but at a rate equivalent to 0.30 kg ai/ha. For both compounds, the applied amounts approximately correspond to four times the maximum seasonal rate on the label and reflect the ratio between XDE-175-J and XDE-175-L in spinetoram formulations.

Washing leaves (0-7 DAT) with dichloromethane and then acetonitrile removed 76–96% of TRR.

The lettuce samples taken one day (PHI in US GAP) after the single application of XDE-175-J or XDE-175-L contained 34 mg/kg in parent equivalents or 7.6 mg/kg of radioactive residues, respectively. For treatment with XDE-175-J, the parent was 31%, N-demethyl-175-J was 20% and N-formyl-175-J was 11% of the TRR. For treatment with XDE-175-L, the parent was 12%, N-demethyl-175-L was 7.2% and N-formyl-175-L was 4.0% of the TRR. With the multiple applications, both TRR and percentage of these three compounds tended to be lower than with single applications of the same total rate for both parent compounds. Only 0.2–5.2% of TRR remained unextractable in all treated lettuce samples after extraction with acetonitrile/water (75:25, v/v).

Several minor metabolites were observed in the ¹⁴C-XDE-175-J and ¹⁴C-XDE-175-L treated lettuce at $\leq 6\%$ of TRR. A multi-component mixture of extensively degraded compounds represented up to 13–78% of TRR, each component at less than 3% of TRR.

Turnip

Turnips were treated with either a single or multiple foliar applications of ¹⁴C-XDE-175-J or ¹⁴C-XDE-175-L in the same manner as in the lettuce study. In turnip roots harvested three days after the application, TRR was quite low at 0.12 mg/kg for XDE-175-J treatment and 0.031 mg/kg for XDE-175-L treatment.

In ¹⁴C-XDE-175-J treated turnip tops, 59–91% of TRR were surface residues found in the dichloromethane and acetonitrile washings. In ¹⁴C-XDE-175-L treated turnip tops, surface residues were 39–80% of TRR.

Major components identified at three DAT were the parent compounds (XDE-175-J and -L), N-dimethyl-175-J and N-formyl-175-J in roots and tops but all less than 25% of the TRR.

Several minor metabolites assumed to be structurally similar to the parent compound were also observed in treated turnip roots and tops, each less than 4% of TRR. A multi-component mixture

of extensively degraded compounds represented 10–74% of TRR; each compound at less than 1% TRR.

Metabolism of spinetoram was observed to be similar in the three crops studied—apple, lettuce and turnip—indicating that a common metabolism is expected for not only fruits, leafy vegetables and root vegetables but also other plants. It appears that three metabolic pathways are responsible for the breakdown of spinetoram in plants. The first one involves changes to the N-demethyl moiety on the forosamine sugar to give the N-demethyl and N-formyl metabolites. N-formyl metabolites were found only in plants. The second involves cleavage of the macrolide ring system at one or more positions, ultimately resulting in a complex residue mixture consisting of numerous components. The third, (applicable only to XDE-175-J), involves changes to the rhamnose sugar producing the 3-O-deethyl and C9-pseudoaglycone-175-J metabolites. All the metabolites occurring as a result of changes in forosamine and rhamnose are further degraded via the second pathway.

Environmental fate in soil

The Meeting reviewed information on aerobic soil metabolism, aqueous photolysis and hydrolysis, and rotational crop study, as spinetoram was intended for protection of root vegetables.

Aerobic soil metabolism

Aerobic soil metabolism studies were conducted using ^{14}C -XDE-175-J or ^{14}C -XDE-175-L, uniformly labelled with ^{14}C in the macrolide ring applied to various soils and incubated under aerobic conditions at 25, 20 or 10 °C. Under aerobic conditions, spinetoram applied to soil was degraded relatively rapidly. In all soils tested, XDE-175-L was degraded faster than XDE-175-J. After one year of incubation at 25 °C, 1.2–2.8% and 0.3–2.9% of applied XDE-175-J and XDE-175-L respectively, remained as the parent in US soils tested. In European soils (except the loamy sand), after 127 days of incubation at 20 °C, 2.0–4.9% and 1.4–5.0% of applied XDE-175-J and XDE-175-L respectively remained as the parent. Carbon dioxide was evolved slowly from all soils and accounted for 5.0–35% and 9.5–32% of the applied XDE-175-J and XDE-175-L respectively after one year at 25 °C, and 0.8–1.1% and 1.2–3.2% of the applied XDE-175-J and XDE-175-L respectively after 127 days at 20 °C.

Major degradation products, N-demethyl-175-J and N-demethyl-175-L were formed and then degraded during the study periods. As minor products (at or less than 10% of the applied dose), N-demethyl-N-nitroso-175-J, N-demethyl-N-nitroso-175-L, N-succinyl-175-J and N-succinyl-175-L were also formed and degraded. Many other degradates were formed but at very low concentrations.

While extractable radioactivity decreased, non-extractable radioactivity steadily increased to reach 22–29% and 32–37% of the applied XDE-175-J and XDE-175-L respectively after one year at 25 °C; and 5–15% and 11–24% of the applied XDE-175-J and XDE-175-L respectively after 127 days at 20 and 10 °C.

Aqueous photolysis

Under xenon light (simulating 40°N latitude summer sunlight) in aqueous buffer solution at pH 7 at 25 °C, XDE-175-J and XDE-175-L degraded rapidly with DT_{50} of 0.5 days and 0.3 days respectively. Numerous (more than 70) minor degradates were observed after irradiation of XDE-175-J and -L. N-demethyl-175-L was observed as a major photodegradation product of XDE-175-L.

At test termination, greater than 90% of the applied amount remained as parent in the dark controls indicating that negligible transformation of the parent compounds occurred in the dark. No degradates were observed in the dark controls.

Aqueous hydrolysis

In sterile aqueous buffer solutions at pH 5 and 7, no degradation was observed for both XDE-J and XDE-175-L for 30 days at 20 °C. At pH 9, a degradate of XDE-175-J was observed but the concentration of XDE-175-J did not decrease below 89% and therefore, XDE-175-J can be regarded to be relatively stable, also at pH 9. After 30 days at pH 9, XDE-175-L decreased from 92% to 82% with N-demethyl-175-L as the major degrade at 12% at the end of the testing period. No minor degradates were detected. DT₅₀ of XDE-175-L at pH 9 was calculated to be 154 days.

Residues in succeeding crops

In an outdoor confined rotation study, radish, lettuce and wheat were planted at 30, 120 and 365 days after the application of ¹⁴C-XDE-175-J or ¹⁴C-XDE-175-L at rate of 405 or 135 g ai/ha respectively to soil corresponding to the maximum seasonal rate and reflecting the ratio of these two active ingredients in spinetoram formulations.

TRRs were very low for all samples at all plant back intervals with the maximum at 0.085 mg/kg in parent equivalents. Unextractable residues in crops were less than 0.019 mg/kg.

Extraction of residues indicated that no greater than 0.065, 0.004 and 0.007 mg/kg were found in the neutral organic phases, acidic organic phases, and in the extracted aqueous phase, respectively. In any immature or mature sample, no single component exceeded 0.025 mg/kg or 0.007 mg/kg, respectively. At 120 DAT and 365 DAT, no radioactive residues were associated with any of XDE-175-L, N-demethyl-175-L or N-formyl-175-L. Of the XDE-175-J treated 120 DAT and 365 DAT crop samples, radish (immature tops and mature tops), lettuce (immature), and wheat forage, hay, and straw contained TRR greater than 0.010 mg/kg, but the concentrations were too low for identification. The lower residues in 30 DAT samples were characterized, but could not be identified.

The levels of radioactivity taken up from soil treated with [¹⁴C]spinetoram into the three succeeding crops (radish, lettuce, and wheat) planted 30, 120, or 365 days after treatment, were below 0.085 mg/kg spinetoram equivalents. Since such low radioactive residues were found in analysed fractions of these rotational crop samples, spinetoram is unlikely to be taken up readily by succeeding crops.

Methods of analysis

Analytical methods for determination of residues of spinetoram and its metabolites were developed for a wide range of matrices of plant and animal origin. In general, these methods employ extraction of spinetoram and its metabolites with a mixture of acetonitrile and water (80:20, v/v), addition of a stable isotope internal standard solution containing XDE-175 and metabolites, and then, without any clean-up or with solid phase clean-up using a C18 cartridge, analysis with HPLC with positive-ion electrospray tandem mass spectrometry (LC-MS/MS). Three methods, two for plant matrices and one for animal matrices, are capable of determining XDE-175-J, XDE-175-L, N-demethyl-175-J and -L, and N-formyl-175-J and -L. One method for animal matrices, however, determines XDE-175-J, XDE-175-L, N-demethyl-175-J and -L, and 3'-O-deethyl-175-J and -L.

The methods for plant matrices were validated for each analyte at 0.01–1.0 mg/kg, and in the case of lettuce at 0.01–10 mg/kg. Mean recovery was in a range of 82–111%. The validated limit of quantification was 0.01 mg/kg for all matrices.

The methods for animal matrices were validated for each analyte at 0.01–15 mg/kg in bovine muscle and kidney; 0.01–0.10 mg/kg in poultry muscle; 0.01–50 mg/kg in liver, milk and cream, and eggs; and 0.01–150 mg/kg in fat. Mean recovery ranged between 83 and 119%. The validated limit of quantification was 0.01 mg/kg for all matrices.

The existing multi-residue enforcement methods, FDA PAM I screen methods, were found to be unsuitable for the determination of spinetoram and its metabolites in plant and animal matrices. The DFG S19 multi-residue method was validated successfully only for the determination of spinetoram and its N-demethyl and N-formyl metabolites in apples, grapes and oranges.

Stability of pesticide residues in stored analytical samples

Stability of spinetoram and its N-demethyl and N-formyl metabolites (each at a fortification level of 0.10 ppm) in homogenized orange, lettuce, sugar beet, soya bean and wheat grain stored in deep freezer at -20°C was investigated over 12 months. No significant decrease of spinetoram was observed in all samples, except lettuce, during the test period. In lettuce, remaining XDE-175-L and N-dimethyl-175-L were 60 and 65% respectively (unadjusted for procedural recovery) at 372 days after initiation of the study.

The Meeting concluded that at -20°C , spinetoram and its N-demethyl and N-formyl metabolites were stable for 12 months in orange, sugar beet, soya bean and wheat. In lettuce, XDE-175-J, the major component, and its N-demethyl and N-formyl metabolites were also stable for 12 months but XDE-175-L and N-dimethyl-175-L were stable only up to eight months.

As samples of animal tissues, milk and eggs from the metabolism and feeding studies were analysed within 20 days of sample collection in supervised trials, no information was provided to the Meeting on storage stability of spinetoram in animal commodities.

Residue definition

Spinetoram consists of two closely related active ingredients, XDE-175-J and XDE-175-L, present approximately in a three to one ratio.

In apple, lettuce and turnip receiving 4 \times to 9 \times the rate of either of the two active ingredients, major metabolites were the parent compounds (XDE-175-J and XDE-175-L), N-demethyl-175-J and N-formyl-175-J. In most cases, PHI XDE-175-J was the primary component of residues. N-demethyl-175-L and N-formyl-175-L were also detected but no more than 7.2% and 4.0% respectively of TRR on one DAT or thereafter.

In goats and hens, metabolism of spinetoram was limited. The parent compounds remained as major components in milk and all ruminant tissues as well as eggs, and all avian tissues except liver, in which 3'-O-deethyl metabolites were detected at similar levels as the parent, but less than 20%.

Sufficiently validated LC-MS/MS methods were available for determining the parent compounds and their N-demethyl and N-formyl metabolites in a wide range of plant commodities and animal tissues, milk and eggs.

Based on the above findings, the Meeting considered that the two parent compounds, XDE-175-J and XDE-175-L, were suitable residues for enforcement. However, as N-demethyl-175-J is a major metabolite in both plants and animals and covered by the ADI, and N-formyl-175-J, a major metabolite in plants, is also found in crops after application of spinetoram, the Meeting decided to include these two metabolites as well as the two spinetoram components in the residue definition for estimation of dietary intake.

XDE-175-J and XDE-175-L have logPow of 4.09 and 4.49 respectively at pH 7 at 20°C , implying that spinetoram may be fat-soluble. In animal metabolism studies, residue concentrations were found to be higher in tissues with higher fat content. In addition, an animal feeding study with lactating cows indicates that spinetoram residue concentrations in milk fat were 4.4–9.5 times higher than those in whole milk and those in composite fat were 14–24 times higher than in muscle. The Meeting agreed that spinetoram residue is fat-soluble.

The Meeting recommended the following residue definition for plant and animal commodities:

- Definition of the residue (for compliance with the MRL): *Spinetoram*.
- Definition of the residue (for estimation of dietary intake): *Spinetoram and N-demethyl and N-formyl metabolites of the major spinetoram component*.
- The residue is fat-soluble.
- Note: Spinetoram consists of two related components.

Results of supervised residue trials on crops

The Meeting received supervised trial data for spinetoram on orange, pome fruits, stone fruits, leaf lettuce, tomato, sugar beet and tree nuts.

For all analytes and matrices, the LOQ was 0.01 mg/kg. The LOD was reported to be 0.003 mg/kg for trials conducted in the USA and 0.005 mg/kg for trials conducted in Australia.

Citrus fruits

Twelve supervised trials were conducted on oranges in the USA.

Six trials conducted using low spray volume applications (approximately 700 L/ha) were in accordance with US GAP for citrus fruits (maximum rate of 103 g ai/ha, three applications, maximum seasonal rate of 210 g ai/ha, PHI one day). Spinetoram residues from these trials in rank order were: < 0.01 (2), 0.012, 0.022, 0.028 and 0.03 mg/kg.

Corresponding total residues of spinetoram and the two metabolites in rank order were: < 0.02, 0.022, 0.03, 0.052, 0.052 and 0.066 mg/kg.

Six other trials conducted using high spray volume applications (approximately 3300 L/ha) were in accordance with US GAP. Residues from these trials in rank order were: < 0.01, 0.012, 0.015, 0.018, 0.021 and 0.02 mg/kg.

Corresponding total residues of spinetoram and the two metabolites in rank order were: < 0.02, 0.039, 0.041, 0.046, 0.047 and 0.069 mg/kg.

The Meeting considered that these two sets of trials conducted in the same locations could not be regarded as independent from each other and decided to use one data set for the estimation of maximum residue level. Taking into consideration the results of the two data sets being mutually supportive, the Meeting estimated a maximum residue level based on spinetoram residues and an STMR based on the total residues of spinetoram and the two metabolites for oranges at 0.07 and 0.0435 mg/kg.

Pome fruits

Numerous supervised trials were conducted on apple in Australia (20), Canada (8), New Zealand (20) and the USA (12).

Six trials conducted in the USA using low spray volume applications (approximately 700 L/ha) were in accordance with US GAP for pome fruits (maximum rate of 123 g ai/ha, five applications, maximum seasonal rate of 500 g ai/ha, PHI seven days). Spinetoram residues from these trials in rank order were: < 0.01 (3), 0.01, 0.013 and 0.028 mg/kg.

Corresponding total residues of spinetoram and the two metabolites in rank order were < 0.02 (3), 0.023, 0.036 and 0.038 mg/kg.

Six other trials conducted in the USA using high spray volume applications (approximately 3300 L/ha) were in accordance with US GAP. Spinetoram residues from these trials in rank order were < 0.01 (4), 0.012 and 0.02 mg/kg.

Corresponding total residues of spinetoram and the two metabolites in rank order were < 0.02 (2), 0.022, 0.022, 0.026 and 0.037 mg/kg.

Supervised trials were conducted in four locations in Canada and in the USA in accordance with Canadian GAP for pome fruits (maximum rate of 103 g ai/ha, three applications, maximum seasonal rate of 315 g ai/ha, PHI seven days). Since two plots were in each location, only higher residues were selected for each location. Spinetoram residues from these trials in rank order were < 0.01, 0.015, 0.017 and 0.028 mg/kg. These trials were also in compliance with US GAP. Corresponding total residues of spinetoram and the two metabolites in rank order were < 0.02, 0.025, 0.038 and 0.038 mg/kg.

Two trials conducted in Australia and five trials in New Zealand were according to GAP in New Zealand for pome fruits (maximum 2.5 g ai/hL, minimum 50 g ai/ha, four applications and PHI seven days). Spinetoram residues from these trials in rank order were < 0.01 (7) mg/kg. Corresponding total residues of spinetoram and the two metabolites in rank order were < 0.02 (7) mg/kg.

Although application rates were different (PHI in all related GAPs is seven days), results of trials matching three different GAPs were mutually supportive. In ten trials conducted in the USA and Canada following US GAP, which would lead to the highest residues, spinetoram residues were in rank order: < 0.01 (4), 0.01 0.013 0.015 0.017 and 0.028 (2) mg/kg. Corresponding total residues of spinetoram and the two metabolites in rank order were: <0.02 (3), 0.023, 0.025, 0.036, 0.038 (3) mg/kg.

Eight trials were conducted on pear in Australia and eight other in New Zealand. No trials in Australia matched GAP of New Zealand for pome fruits. Spinetoram residues from two trials conducted in New Zealand in accordance with GAP of New Zealand in rank order were < 0.01 and 0.02 mg/kg. Corresponding total residues of spinetoram and the two metabolites in rank order were < 0.02 and 0.03 mg/kg.

Since the results from trials on apple and pear were similar, the Meeting estimated a maximum residue level based on spinetoram residues and an STMR based on the total residues of spinetoram and the two metabolites, for pome fruits on a basis of apple trials, at 0.05 and 0.025 mg/kg respectively.

Stone fruits

A large number of supervised trials were conducted on cherry, peach and apricot in Australia and New Zealand. A few trials on nectarines were also conducted in Australia.

However, since proposed GAP in Australia for stone fruits has not been approved, no maximum residue level could be estimated.

Tomato

Six supervised trials conducted in the USA were according to US GAP for fruiting vegetables (maximum rate of 88 g ai/ha, six applications, maximum seasonal rate of 298 g ai/ha and PHI one day). Residues from these trials in rank order were < 0.01 (2), 0.01, 0.0156, 0.024 and 0.025 mg/kg.

Corresponding total residues of spinetoram and the two metabolites in rank order were < 0.02 (3), 0.02, 0.025, 0.034 and 0.035 mg/kg.

The Meeting estimated a maximum residue level based on spinetoram residues and an STMR based on the total residue of spinetoram and the two metabolites in tomato at 0.06 and 0.02 mg/kg respectively.

Lettuce

Six supervised trials were conducted on leaf lettuce in the USA in accordance with US GAP for leafy vegetables (maximum rate of 88 g ai/ha, six applications, maximum seasonal rate of 298 g ai/ha and PHI one day). Residues in rank order were 0.15, 0.31, 0.32, 0.34, 0.55 and 7.80 mg/kg.

Corresponding total residues of spinetoram and the two metabolites in rank order were 0.28, 0.56, 0.64, 1.16, 1.35 and 9.55 mg/kg.

The residue values of 7.80 and 9.55 mg/kg were very high compared to the rest of results. The study report indicates that the trial was conducted in the same manner as the other trials and there was no indication for this trial being invalid. Using all the residue values, the Meeting estimated a maximum residue level based on spinetoram residues and an STMR for spinetoram in lettuce at 10 and 0.895 mg/kg.

As foliar applications on leaf lettuce were expected to result in higher residues than those on head lettuce, the Meeting agreed that these maximum residue level and STMR are applicable also to head lettuce.

Sugar beet

Six supervised trials were conducted in the USA. In one trial according to US GAP (maximum rate of 70 g ai/ha, four applications, maximum seasonal rate of 281 g ai/ha and PHI seven days) for tuberous vegetables, e.g., potato and sugar beet, the residue was < 0.01 mg/kg. In the other five trials, root samples were taken three days after the last application, earlier than the required PHI of seven days in GAP. Residues in these five trials were < 0.01 mg/kg (5).

Corresponding total residues of spinetoram and the two metabolites in rank order were < 0.02 (6) mg/kg.

The Meeting estimated a maximum residue level based on spinetoram residues and an STMR for spinetoram in sugar beet at 0.01 (*) and 0.02 mg/kg respectively.

Tree nuts

Six supervised trials were conducted on almonds in the USA. One trial was in accordance with US GAP for tree nuts (maximum rate of 123 g ai/ha, four applications, maximum seasonal rate of 490 g ai/ha and PHI 14 days), and residues were < 0.01 mg/kg. In the other five trials, nut samples were taken seven days after the last application rather than the required PHI of 14 days in GAP. Residues in these five trials were < 0.01 mg/kg (5).

Corresponding total residues of spinetoram and the two metabolites in rank order were < 0.02 (6) mg/kg.

Six supervised trials were also conducted on pecan in the USA. In one trial according to US GAP for tree nuts, residues were < 0.01 mg/kg. In the other five trials, nut samples were taken seven days after the last application rather than the required PHI of 14 days in GAP. Residues in these five trials were < 0.01 mg/kg (2) and 0.01 (3) mg/kg. A decline study indicates that it is likely that residues would be less than 0.01 mg/kg if samples were taken on the required PHI of 14 days and in general residues were not expected to occur in edible portions of tree nuts due to negligible translocation of spinetoram.

From the results of trials on almonds and pecan, the Meeting estimated a maximum residue level based on spinetoram residues and an STMR based on the total residue of spinetoram and the two metabolites in tree nuts at 0.01 and 0.02 mg/kg.

Sugar beet leaves or tops

Among six supervised trials conducted in the USA, only one was in compliance with US GAP and residues were 0.024 mg/kg. In other trials, samples were collected only three days after the last application instead of the required PHI of seven days and they contained finite level of residues. However, these trials were in compliance with US GAP for leaf of root and tuberous vegetables for forage (maximum rate of 80 g ai/ha, four applications, maximum seasonal rate of 281 g ai/ha and PHI of three days). Residues from these trials were 0.086, 0.099, 0.11, 0.16 and 0.20 (2) mg/kg.

The Meeting estimated an STMR and a highest residue in sugar beet leaves or tops based on spinetoram residues for calculation of animal burden at 0.135 and 0.20 mg/kg.

Almond hulls

Among six supervised trials conducted in the USA, only one trial was in accordance with US GAP and residues are 0.75 mg/kg. In other trials, samples were collected seven days after the last application instead of the required PHI of 14 days and they contained finite level of residues. The Meeting concluded that it was not possible to estimate a maximum residue level for spinetoram in almond hulls from the results of these trials.

Fate of residues during processing

The Meeting received information on processing of oranges to juice and oil, and apples to juice and puree (sauce).

Processing factors were calculated for oranges (juice, peel and pulp after juicing, dried pulp and oil) and for apples (juice, dry pomace and puree (sauce)).

Processed Orange Product	Processing factor		STMR/STMR-P (mg/kg)
	Spinetoram residues	Spinetoram+2 metabolites	
Orange	-	-	0.045
Juice	< 0.05	< 0.07	0.003
Dried pulp	2.4	2.3	0.105
Apple	-	-	0.025
Juice	< 0.37	< 0.44	0.011
Dry pomace	8.1	6.0	0.15
Puree (sauce)	0.45	0.47	0.012

For the purpose of calculating animal dietary burden for estimating maximum residue levels for commodities of animal origin, STMR-P for citrus pulp, dry and apple pomace, dry were calculated based on spinetoram residues to be 0.048 and 0.081 mg/kg.

Farm animal dietary burden

Dry apple pomace, dry citrus pulp and sugar leaves or tops may be fed to dairy cattle and beef cattle but not as a major ingredient. The dietary burdens were calculated from the highest residue and STMR of sugar beet leaves or tops, and the STMRs of apple pomace, dry, using the OECD feedstuffs tables (Annex 6 of the 2006 Report of the JMPR).

Summary of livestock dietary burdens (ppm of dry matter diet)

	US-Canada		EU		Australia	
	max	mean	max	mean	max	mean
Beef cattle	0.018	0.018	0.192 ^a	0.135 ^b	0.018	0.018
Dairy cattle	0.0089	0.0089	0.270 ^c	0.185 ^d	0.0089	0.0089

^a Suitable for estimating maximum residue levels for meat and edible offal.

^b Suitable for estimating STMRs for meat and edible offal.

^c Suitable for estimating a maximum residue level for milk and fat.

^d Suitable for estimating an STMR for milk and fat.

Residues in milk and cattle tissues

Lactating dairy cows were dosed daily for 29 consecutive days via gelatin capsules containing a mixture of spinetoram and N-demethyl and N-formyl metabolites of XDE-175-J (1.2–38.6 ppm in diet) or spinetoram only (37.6 ppm).

Residues in the milk in 1.2 ppm (equivalent to 0.4 mg XDE-175-J and -L) dose group were generally between the LOD (0.003 mg/kg) and LOQ (0.01 mg/kg) throughout the dosing period.

No or low concentration residues were detected in skim milk; even in 11.5 and 38.6 ppm (total) doses groups, mean total residues of the four compounds in skim milk ranged from just below the LOQ to 0.075 mg/kg. In all of the dose groups on day 14 and 28, total residues in cream were much higher than the residues in skim milk at 0.187 and 0.237 mg/kg in the 1.2 ppm doses groups. The mean total residues in cream from the 11.5 and 38.6 ppm doses groups ranged from 0.64 to 5.84 mg/kg. The average ratio of residues in cream to those in whole milk is 6:6.

All tissues from treated cows contained residues and they increased from the lowest to highest dose groups. Residue concentrations were lowest in the muscle followed by kidney, liver, and fat. Residues in fat were significantly higher than residues in the other tissues. These results indicate that residues of spinetoram tend to accumulate in fatty tissue.

With one exception, residues were not detectable in milk by the fourth day after the last dose was administered. Concentrations just above the LOD were detected in one cow through day nine after the final dose. No further residue was detected beyond that point.

Residues in tissues continuously declined through 28-day depletion period after the last dose. No residue was detected in kidney, liver or muscle from any cow by 28 days after the final dose or in fat 56 days following the final dose.

The dietary burdens for beef and dairy cattle are both lower than the lowest feeding level (1.2 ppm, equivalent to 0.4 ppm of spinetoram only) in the feeding study. Therefore the MRL and STMR were estimated using the residue concentrations in milk and tissues at the lowest feeding level and the dietary burden. The calculated residues in cattle tissues and milk are summarized below.

Dietary burden mg/kg Feeding level [mg/kg]	Spinetoram residues, mg/kg				
	Milk	Muscle	Liver	Kidney	Fat
MRL	highest	highest	highest	highest	highest
0.270/0.192	< 0.00675	< 0.00480	< 0.00480	< 0.00480	0.0743
[0.4]	[< 0.01]	[< 0.01]	[< 0.01]	[< 0.01]	[0.11]
	Spinetoram, N-demethyl-175-J and N-formyl-175-J, mg/kg				
STMR	mean	mean	mean	mean	mean
0.185/0.135	< 0.00925	< 0.00625	< 0.00625	< 0.00625	0.0463
[0.4]	[< 0.02]	[< 0.02]	[< 0.02]	[< 0.02]	[0.10]

The Meeting estimated a maximum residue level for spinetoram in edible offal (mammalian) and whole milk at 0.01(*) mg/kg and in mammalian fats at 0.2 mg/kg. STMRs were estimated to be 0.00925 mg/kg for whole milk, 0.00625 mg/kg for meat (muscle) and edible offal (mammalian), and 0.046 mg/kg for mammalian fats.

The Meeting estimated a maximum residue level for spinetoram and an STMR for spinetoram and the two metabolites in milk fat, using the median ratio between residues in cream and whole milk of 6:6 and assuming that cream contains 50% fat, at 0.1 mg/kg and 0.12 mg/kg respectively.

Poultry

No data were provided on poultry feeding study. Since there was no treated commodities that can be fed to hens, the Meeting considered that it was unnecessary to estimate maximum residue levels for poultry tissues or eggs.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) of spinetoram were calculated for the 13 GEMS/Food cluster diets using STMRs estimated by the current Meeting (Annex 3). The ADI is 0–0.05 mg/kg bw and the calculated IEDIs were 0–1% of the maximum ADI. The Meeting concluded that the long-term intake of residues of spinetoram resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term intake

The 2008 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of residues of spinetoram is unlikely to present a public health concern.