5.28 SEDAXANE (259)

TOXICOLOGY

Sedaxane is the common name that has been provisionally approved by the ISO for mixtures of two *cis* isomers, 2′-[(1*RS*,2*RS*)-1,1′-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide, and two *trans* isomers, 2′-[(1*RS*,2*SR*)-1,1′-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide (IUPAC), for which the CAS number is 874967-67-6. Sedaxane contains approximately 81–85% of the *trans* isomers and approximately 10–15% of the *cis* isomers.

Sedaxane is a broad-spectrum fungicide belonging to the chemical class of pyrazole-carboxamides. The pesticidal mode of action of this group of fungicides is inhibition of succinate dehydrogenase, which is a functional part of the mitochondrial electron transport chain and oxidative phosphorylation involved in the tricarboxylic acid cycle.

Sedaxane is being reviewed for the first time by JMPR at the request of CCPR. All critical studies complied with GLP.

Biochemical aspects

In rats given [^{14}C]sedaxane labelled in either the phenyl or pyrazole ring as a single oral dose of 1 or 80 mg/kg bw, the radiolabelled material was rapidly and extensively absorbed, based on recoveries in excreta from bile duct–cannulated rats. The times to reach C_{max} were approximately 1 hour and 5–6 hours following the low and high doses, respectively. The mean C_{max} and AUC values for the *trans* isomers were higher than those for the *cis* isomers and their mixture in rats. Approximately 90% of the administered dose was absorbed at both the low and high doses. Radiolabelled material was widely distributed throughout the body within 5 hours. The half-lives of elimination of total radioactivity from different tissues varied from 0.1–0.2 days in brain to 2.0–3.2 days in thyroid. Elimination half-lives from blood ranged from 30 to 40 hours and were generally similar in males and females at both dose levels. Less than 0.8% of the administered dose remained in the body at 96 hours after dosing.

The sedaxane administered to rats was rapidly excreted, predominantly in the faeces (75–88%) and in urine (12–20%). Sedaxane was extensively metabolized in rats by demethylation, hydroxylation, oxidation and conjugation, resulting in many hydroxylated metabolites and metabolites formed by cleavage of the terminal cyclopropyl moiety. The major metabolites have been identified as the *trans*-*para*-phenol sedaxane and the desmethyl *trans*-*para*-phenol sedaxane, which, together with the equivalent *cis*-*para*-phenol isomers of sedaxane, account for approximately half of the administered dose. There appear to be no major sex- or dose-related differences in the qualitative metabolite profile of sedaxane. There is little evidence of any cleavage between the phenyl and pyrazole moieties of the sedaxane molecule. A small amount (< 1%) of a pyrazole amide metabolite of sedaxane also found in plants can be found in bile samples. The phenolic and hydroxy metabolites of sedaxane and desmethyl sedaxane are subject to glucuronic acid, sulfate and glutathione conjugation.

Toxicological data

The oral LD_{50} was 5000 mg/kg bw in rats. Significant clinical signs of toxicity (ruffled fur, hunched posture, sedation, poor coordination, ventral recumbency, deep respiration, rales, salivation and bradypnoea) were observed at lower doses (1750 and 550 mg/kg bw) for a few hours following treatment. The dermal LD_{50} in rats was greater than 2000 mg/kg bw. The 4-hour acute inhalation LC_{50} in rats was greater than 5.2 mg/L. Sedaxane was not irritating to rabbit skin and minimally irritating to rabbit eyes. Sedaxane was not a skin sensitizer in the mouse local lymph node assay.

The short-term oral toxicity of sedaxane was evaluated in mice, rats and dogs, in which the main effects were on body weight gain and liver. In a 28-day study of toxicity in mice, no toxicity was observed at doses up to 7000 ppm (equal to 1268 mg/kg bw per day). In a 90-day dietary toxicity

study in mice, the NOAEL was 3500 ppm (equal to 566 mg/kg bw per day), based on a decrease in body weight gain throughout the study in males at 7000 ppm (equal to 1167 mg/kg bw per day).

Two 90-day toxicity studies were conducted in rats, each demonstrating the liver as the target for sedaxane. In the first study, the NOAEL was 1000 ppm (equal to 72.9 mg/kg bw per day), based on lower body weights, centrilobular hepatocyte hypertrophy and pigmentation, and blood chemistry indicating liver dysfunction in males and females at 4000 ppm (equal to 299.6 mg/kg bw per day). In the second study, the NOAEL was 300 ppm (equal to 28 mg/kg bw per day), based on reduced body weight and body weight gain and significant decreases in forelimb grip strength at 2000 ppm (equal to 186 mg/kg bw per day); liver toxicity was observed at 4000 ppm (equal to 325.1 mg/kg bw per day). The overall NOAEL from these studies was 1000 ppm (equal to 72.9 mg/kg bw per day).

The toxicity of sedaxane administered in capsules was tested in dogs in 90-day and 1-year toxicity studies. The overall NOAEL was 50 mg/kg bw per day, based on reduced body weight gain in females at 150 mg/kg bw per day.

The NOAEL in an 18-month dietary study in mice was 1250 ppm (equal to 157 mg/kg bw per day), based on a decrease in body weight and body weight gain in both sexes at 7000 ppm (equal to 900 mg/kg bw per day). A slightly increased incidence of hepatocellular adenomas and carcinomas combined was observed in male mice at the high dose in comparison with the control group incidence. The NOAEL for equivocal carcinogenicity in mice was 1250 ppm (equal to 157 mg/kg bw per day).

The NOAEL in a 104-week dietary study in rats was 200 ppm (equal to 11 mg/kg bw per day), based on increases in liver weight and histopathological changes (centrilobular hypertrophy) in the liver in males, histopathological changes in the thyroid in males and females, and reduced body weight gain in females at 1200 ppm (equal to 67 mg/kg bw per day). Hepatocellular eosinophilic foci were also increased at 200 ppm in females at 52 weeks, but did not persist at 2 years. Uterine adenocarcinomas were increased at 3600 ppm (equal to 218 mg/kg bw per day). The NOAEL for carcinogenicity was 1200 ppm (equal to 86 mg/kg bw per day), based on uterine tumours in female rats.

Sedaxane was tested for genotoxicity in vitro and in vivo in an adequate range of assays. In none of these assays was there any evidence of genotoxic potential.

The Meeting concluded that sedaxane is unlikely to be genotoxic.

On the basis of the absence of genotoxicity and the fact that equivocal increased incidences of hepatocellular adenomas and carcinomas combined in male mice and uterine endometrial adenocarcinomas in rats occurred only at the highest doses tested, the Meeting concluded that sedaxane is unlikely to pose a carcinogenic risk to humans at dietary exposure levels.

In a multigeneration reproductive toxicity study in rats, the NOAEL for parental toxicity was 500 ppm (equal to 41 mg/kg bw per day), based on significantly reduced body weight gain at 1500 ppm (equal to 120 mg/kg bw per day) in parental generation males. Decreased ovarian follicle counts were observed at 1500 ppm (low and middle doses not examined). Slightly decreased ovary weights were observed at 1500 ppm. The NOAEL for reproductive toxicity was 1500 ppm (equal to 120 mg/kg bw per day). The NOAEL for offspring toxicity was 500 ppm (equal to 43 mg/kg bw per day), based on significantly lower body weights of F_1 generation males during pre-mating at 1500 ppm (equal to 134 mg/kg bw per day).

In a developmental toxicity study in rats, the NOAEL for maternal toxicity was 25 mg/kg bw per day, based on reductions in body weight gain and feed consumption at 100 mg/kg bw per day. The NOAEL for developmental toxicity was 200 mg/kg bw per day, the highest dose tested.

In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 100 mg/kg bw per day, based on reductions in body weight gain and feed consumption at 200 mg/kg bw per day. The NOAEL for developmental toxicity was 100 mg/kg bw per day, based on slight reductions in fetal body weights at 200 mg/kg bw per day.

The Meeting concluded that sedaxane is not teratogenic in rats or rabbits.

The NOAEL in a single-dose neurotoxicity study in rats was 30 mg/kg bw, based on severe loss of general condition, decreased body weight and decreased feed consumption at 250 mg/kg bw.

The NOAEL for systemic toxicity in a 13-week neurotoxicity study was 1000 ppm (equal to 66 mg/kg bw per day), based on decreased body weight, body weight gain, feed consumption and feed efficiency, as well as reduced locomotor activity, at 4000 ppm (equal to 260 mg/kg bw per day).

The Meeting concluded that sedaxane is not neurotoxic.

In an immunotoxicity study in mice, sedaxane was not immunotoxic at doses up to 5500 ppm (equal to 1080 mg/kg bw per day).

A 28-day comparative study of the toxicities of *trans* and *cis* isomers and their mixture in rats demonstrated that their toxicological profiles were qualitatively similar.

The toxicity of a sedaxane plant metabolite (3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid) has been investigated. The LD_{50} value in rats was greater than 2000 mg/kg bw, and the NOAEL in a 28-day oral (gavage) toxicity study in rats was 12 000 ppm (equal to 1018 mg/kg bw per day), the highest dose tested. There was no evidence for genotoxicity in in vitro assays.

No information on medical surveillance or poisoning incidents was available.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.1 mg/kg bw on the basis of a NOAEL of 200 ppm (equal to 11 mg/kg bw per day) in a 2-year study of toxicity and carcinogenicity in rats, based on reduced body weight gain in females and histopathological changes in the liver in males and in the thyroid in males and females at 1200 ppm (equal to 67 mg/kg bw per day). A safety factor of 100 was applied. The ADI provides a margin of exposure of at least 860 relative to the NOAEL for uterine tumours in rats and at least 1570 for equivocal liver tumour response in mice. Thus, the Meeting considered that sedaxane is not likely to pose a carcinogenic risk to humans at dietary levels of exposure.

An ARfD of 0.3 mg/kg bw was established on the basis of a NOAEL of 30 mg/kg bw in a single-dose neurotoxicity study in rats, based on severe loss of general condition, decreased body weight and decreased feed consumption. A safety factor of 100 was applied.

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	1250 ppm, equal to 157 mg/kg bw per day	7000 ppm, equal to 900 mg/kg bw per day
		Carcinogenicity (equivocal)	1250 ppm, equal to 157 mg/kg bw per day	7000 ppm, equal to 900 mg/kg bw per day
Rat	Single-dose test of neurotoxicity[b]	Toxicity	30 mg/kg bw	250 mg/kg bw
	Ninety-day studies of toxicity[a,c]	Toxicity	1000 ppm, equal to 73 mg/kg bw per day	2000 ppm, equal to 186 mg/kg bw per day
	Twenty-four-month study of toxicity and carcinogenicity[a]	Toxicity	200 ppm, equal to 11 mg/kg bw per day	1200 ppm, equal to 67 mg/kg bw per day
		Carcinogenicity	1200 ppm, equal to 86 mg/kg bw per day	3600 ppm, equal to 218 mg/kg bw per day
	Two-generation study of	Reproductive	1500 ppm, equal to	—

Species	Study	Effect	NOAEL	LOAEL
	reproductive toxicity[a]	toxicity	120 mg/kg bw per day[d]	
		Parental toxicity	500 ppm, equal to 41 mg/kg bw per day	1500 ppm, equal to 120 mg/kg bw per day
		Offspring toxicity	500 ppm, equal to 43 mg/kg bw per day	1500 ppm, equal to 134 mg/kg bw per day
	Developmental toxicity study[b]	Maternal toxicity	25 mg/kg bw per day	100 mg/kg bw per day
		Developmental toxicity	200 mg/kg bw per day[d]	—
Rabbit	Developmental toxicity study[b]	Maternal toxicity	100 mg/kg bw per day	200 mg/kg bw per day
		Developmental toxicity	100 mg/kg bw per day	200 mg/kg bw per day
Dog	Ninety-day and 12-month studies of toxicity[b,c]	Toxicity	50 mg/kg bw per day	150 mg/kg bw per day

[a] Dietary administration.

[b] Gavage administration.

[c] Two or more studies combined.

[d] Highest dose tested.

Estimate of acceptable daily intake for humans

0–0.1 mg/kg bw

Estimate of acute reference dose

0.3 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 sedaxane

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid , > 87%
Dermal absorption	No data
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Rapid, > 99.5% within 2 days
Metabolism in animals	Main four metabolites by demethylation, hydroxylation, oxidation and conjugation
Toxicologically significant compounds in animals, plants and the environment	Parent compound and all of the individual isomers
Acute toxicity	
Rat, LD_{50}, oral	5000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw per day
Rat, LC_{50}, inhalation	> 5.244 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Mildly irritating
Dermal sensitization	Not sensitizing (local lymph node assay)
Short-term studies of toxicity	
Target/critical effect	Liver and reduced body weight gain
Lowest relevant oral NOAEL	50 mg/kg bw per day
Lowest relevant dermal NOAEL	1000 mg/kg bw per day

Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver, thyroid and reduced body weight gain
Lowest relevant NOAEL	11 mg/kg bw per day
Carcinogenicity	Equivocal hepatic tumours in mice and uterine tumours in rats; unlikely to pose a carcinogenic risk at dietary exposure levels
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Target/critical effect	No reproductive toxicity
Lowest relevant reproductive NOAEL	120 mg/kg bw per day (highest dose tested)
Lowest relevant parental NOAEL	41 mg/kg bw per day
Lowest relevant offspring NOAEL	43 mg/kg bw per day
Developmental toxicity	
Target/critical effect	No developmental toxicity
Lowest relevant maternal NOAEL	25 mg/kg bw per day
Lowest relevant developmental NOAEL	100 mg/kg bw per day
Neurotoxicity	
Acute neurotoxicity	Not neurotoxic; 250 mg/kg bw (highest dose tested) NOAEL for toxicity: 30 mg/kg bw
Subchronic neurotoxicity	Not neurotoxic; 260 mg/kg bw per day (highest dose tested)
Other toxicological studies	
Comparative toxicity	Toxicological profile similar for trans and cis isomers and their mixture in rats
Immunotoxicity	Not immunotoxic; 1080 mg/kg bw per day (highest dose tested)
Medical data	
	No reports of toxicity in workers exposed during manufacture or use

Summary

	Value	Study	Safety factor
ADI	0–0.1 mg/kg bw	Two-year study (rats)	100
ARfD	0.3 mg/kg bw	Single-dose study (rats)	100

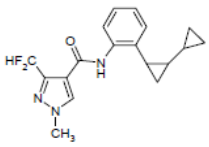
RESIDUE AND ANALYTICAL ASPECTS

Sedaxane is a novel seed treatment fungicide. It is a succinate dehydrogenase inhibitor and affords broad spectrum control of pathogens such as Ascomycete and Oomycete species in crops. It has been registered in France, Canada, and the USA. At the Forty-third Session of the CCPR, it was scheduled for evaluation as a new compound by the 2012 JMPR.

The Meeting received information from the manufacturer on identity, metabolism, storage stability, residue analysis, use pattern, fate of residues during processing, livestock feeding studies, and residues resulting from supervised trials on cereal grains (wheat, oats, and barley), soya bean, and rape.

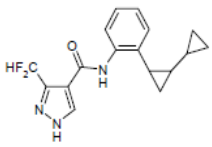
The IUPAC name for sedaxane recognizes a mixture of two *cis*-isomers 2'-[(RS,2RS)-1,1'-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide and two *trans*-isomers 2'-[(RS,2SR)-1,1'-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide. The CA name is *N*-[2-[1,1′-bicyclopropyl]-2-ylphenyl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide.

Sedaxane labelled in the pyrazole and phenyl rings was used in the metabolism and environmental fate studies. The chemical structures of sedaxane and its metabolites/degradates are shown below. Sedaxane is a mixture of *trans* and *cis* isomers, in an approximate 6:1 ratio.



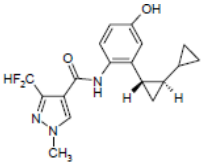
SYN524464

Sedaxane



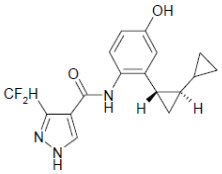
CSCD667584

N-desmethyl sedaxane



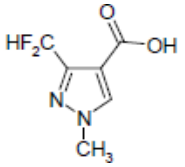
CSCD658906

Trans-para phenol sedaxane



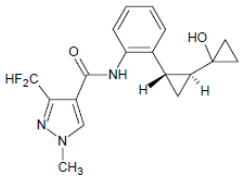
CSCD659087

N-desmethyl trans para phenol sedaxane



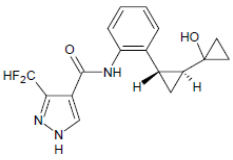
CSAA798670

Pyrazole acid



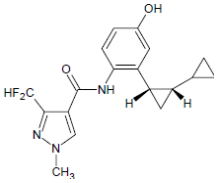
CSCD659089

Cyclopropyl alcohol sedaxane



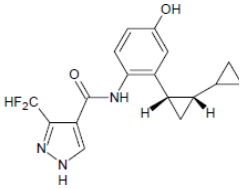
CSCD659088

Desmethyl cyclopropyl alcohol sedaxane



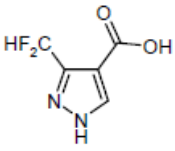
CSCD659090

Cis para phenol sedaxane



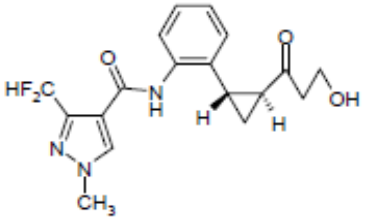
CSCD668404

Cis desmethyl para phenol sedaxane



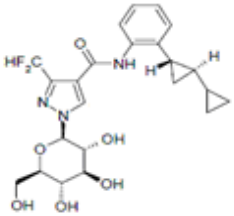
CSCD465008

N-desmethyl pyrazole acid



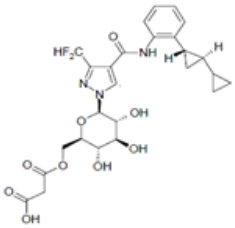
CSCD668403

β-hydroxy carbonyl sedaxane



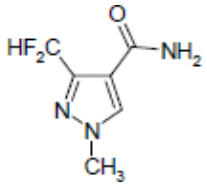
CSCD667555

N-glucoside (trans) sedaxane



CSCD667556

N-malonyl-glucoside of sedaxane



CSCC210616

pyrazole amide

Animal metabolism

Information was available on metabolism of sedaxane in laboratory animals, lactating goats and laying hens.

Sedaxane metabolism in rats was reviewed by the WHO panel of the JMPR in 2012. The sedaxane administered to rats was rapidly excreted, predominantly in the faeces (75–88%) and in urine (12–20%). Sedaxane was extensively metabolized in rats by demethylation, hydroxylation, oxidation and conjugation, resulting in many hydroxylated metabolites and metabolites formed by cleavage of the terminal cyclopropyl moiety. The major metabolites have been identified as the trans para phenol sedaxane and the desmethyl trans para phenol sedaxane, which together with the equivalent cis para phenol isomers of sedaxane account for approximately half of the administered dose. There appear to be no major sex or dose related differences in the qualitative metabolite profile

of sedaxane and the position of radiolabelling. There is little evidence of any cleavage between the phenyl and pyrazole moieties of the sedaxane molecule. A small amount (< 1%) of a pyrazole amide metabolite of sedaxane also found in plants can be found in bile samples. The phenolic and hydroxy metabolites of sedaxane and desmethyl sedaxane are subject to glucuronic acid, sulphate and glutathione conjugation.

Two studies were conducted to investigate the nature of residues in milk and tissues from lactating goats, involving dosing of [phenyl-U-^{14}C]sedaxane and [pyrazole-5-^{14}C]sedaxane. Two goats were treated (one per radiolabel) at a dose rate equivalent to a dietary concentration of 20 ppm (in dry matter) daily for 7 consecutive days. Of the total administered radioactivity (TAR), 49–62% and 18–26% was eliminated in the faeces and urine, respectively. Total recovered radioactivity was 85% of the TAR.

The highest total radioactive residues (TRRs) were found in liver (0.47–0.61 mg eq./kg) and kidney (0.080–0.19 mg eq./kg) and the lowest in fat (0.011–0.015 mg eq./kg) and muscle (0.004–0.006 mg eq./kg). Results for milk indicated that a plateau was reached after approximately 2 days, at 0.033 and 0.045 mg eq./kg in the pyrazole and phenyl experiments, respectively.

In the milk, kidney, and muscle samples, sedaxane was not detected. Low TRR levels in muscle (0.004–0.006 mg eq./kg) precluded metabolite identification. In the liver, sedaxane was found at low levels: 0.009 mg/kg [2.0 % TRR] and 0.034 mg/kg [5.5% TRR] in the pyrazole and phenyl experiments, respectively. In the fat, sedaxane was the predominant residue at 28–44% TRR, but at low concentrations of 0.004–0.005 mg/kg.

Metabolites were present mainly as conjugates except in fat and milk. The principle metabolites identified were the *trans* para phenols CSCD658906 and CSCD659087 and the *cis* para phenol isomer CSCD668404. CSCD658906 was the major component in liver (13–19% TRR, 0.063–0.12 mg eq./kg) and kidney (14–22% TRR, 0.011–0.042 mg eq./kg). CSCD659087 and CSCD668404 were found in milk (9–10% TRR, 0.003–0.004 mg eq./kg), and kidney (11–13% TRR, 0.008–0.024 mg eq./kg).

Two studies were conducted to investigate the nature of residues in eggs and tissues from laying hens, involving dosing of [phenyl-U-^{14}C]sedaxane and [pyrazole-5-^{14}C]sedaxane. The test substances were administered at a dose rate equivalent to a dietary concentration of 20 ppm (in dry matter) daily for 14 consecutive days. Of the total administered radioactivity (TAR), 89–94% was eliminated in the excreta. Total recovered radioactivity was 94–98% of the TAR.

Total radioactivity results for egg indicated that a plateau was reached after approximately 9 days. TRRs in the egg white and yolk samples were 0.007–0.009 and 0.070–0.078 mg eq./kg, respectively, in the phenyl and pyrazole studies.

The TRR in tissues after sacrifice (12 hours after the last dose) were 0.19–0.26 mg eq./kg, 0.005 mg eq./kg, 0.12–0.24 mg eq./kg, and 0.008–0.016 mg eq./kg in liver, muscle, skin and attached fat, and abdominal fat, respectively.

Sedaxane was found at low levels (< 0.01 mg/kg) in all hen matrices except liver, where no sedaxane residues were detected. Sedaxane was the predominant residue in hen abdominal fat (46–53% TRR, 0.004–0.007 mg/kg).

Metabolites were present mainly as conjugates in liver and egg yolk. CSCD658906 was the principle metabolite identified in liver (14–16% TRR, 0.031–0.036 mg eq./kg) and egg yolk (13–16% TRR, 0.009 –0.013 mg eq./kg).

Animal metabolism summary

Metabolism studies in the laying hen and lactating goat demonstrated similar metabolic pathways. Specifically, oxidation reactions at the phenyl and cyclopropyl rings were noted, as well as demethylation, either prior to or after oxidation. No major differences were noted in the metabolic profiles resulting from the two radiolabelled experiments. There was no indication of significant cleavage between the phenyl and pyrazole moieties. The primary mechanisms for the proposed

biotransformation pathway of sedaxane in animals were: N-demethylation to form CSCD667584; hydroxylation of sedaxane to give the para phenols CSCD658906 and CSCD659090, and the cyclopropyl alcohol CSCD659089; hydroxylation of desmethyl sedaxane to give the para phenols CSCD659087 and CSCD668404, and the desmethyl cyclopropyl alcohol CSCD659088. Metabolites were present mainly as conjugates.

The distribution of sedaxane residues in tissues was consistent, with lowest residues in muscle, and highest in liver. Parent sedaxane was the predominant residue in fat tissues at up to 53% TRR in hen fat, although the absolute level was low (0.004 mg/kg). No sedaxane was found in goat muscle samples; trace levels were reported in hen muscle samples (0.001 mg/kg). Overall, the metabolism found in livestock was qualitatively similar to that observed in the rat.

Plant metabolism

Information was available on the metabolism of sedaxane from seed treatment uses in wheat, Swiss chard, and soya bean. Separate studies were reported using phenyl and pyrazole labelled sedaxane for all three crops. In addition, an uptake study in oilseed rape was conducted.

The oilseed rape uptake study demonstrated no residue uptake into oilseed rape seed when a sedaxane seed treatment application rate of 7.5 g ai/100 kg seed is used to grow oilseed rape plants to maturity.

Formulated [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane was applied directly to spring wheat seeds at a concentration of 40 g ai/100 kg seeds. Seeds were sown into containers filled with sandy loam soil on the same day as treatment. The wheat was grown under greenhouse conditions and harvested at the following intervals: forage, 27 days after planting (DAP), BBCH 22; hay, 56 DAP, BBCH 41–57; and grain and straw, 111 DAP, BBCH 89.

The total radioactive residues in wheat grain RAC samples from both radiolabels were < 0.01 mg eq./kg and were not further analysed. The TRR of the remaining wheat commodities ranged from 0.45 mg eq./kg for wheat forage (phenyl label) to 1.1 mg eq./kg for wheat straw (phenyl label). The residue profiles for wheat forage, hay, and straw were all similar.

The highest residue level of sedaxane was in wheat forage (16% TRR, 0.16 mg/kg). Parent sedaxane was found in all commodities at 11 to 18% TRR (0.066 to 0.16 mg/kg). The N-demethylated compound, CSCD667584, was also found in all commodities at 2.9–5.1% TRR (0.019–0.036 mg eq./kg). The *trans* para phenol metabolite CSCD658906, in both free and conjugated forms, was a major residue in all commodities with residues between 9.5–17% (0.069–0.18 mg eq./kg). Other significant metabolites in forage, hay and straw were the cyclopropyl alcohol CSCD659089 (4.3–12% TRR, 0.042–0.068 mg eq./kg), the β-hydroxyl carbonyl compound CSCD668403 (4.9–11% TRR, 0.036–0.083 mg eq./kg), and the N-desmethyl *trans* para phenol metabolite CSCD659087 (5.0–7.2% TRR, 0.032–0.062 mg eq./kg). Trace levels [< 1% TRR & < 0.01 mg/kg] of the N-desmethyl pyrazole acid CSCD465008, the pyrazole acid CSAA798670 and the pyrazole amide CSCC210616 were also observed.

Formulated [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane was applied directly to soya bean seeds at a nominal concentration of 110 g ai/100 kg seeds. Seeds were sown into containers filled with sandy loam soil on the same day as treatment. The soya bean plants were grown under greenhouse conditions and harvested at the following intervals: forage, 28 DAP, BBCH 16; hay, 35–42 DAP, BBCH 61; and seed, 96–103 DAP, BBCH 89.

The highest residue levels of sedaxane were in soya bean hay (23% TRR, 0.082 mg/kg) and soya bean forage (17% TRR, 0.020 mg/kg). The parent compound was not detected in the soya bean seeds; the only metabolite identified in this matrix was CSCD465008, free and conjugated, at a level of 0.017 mg eq./kg. The N-glucoside metabolite (CSCD667555) and N-malonyl glucoside metabolite (CSCD667556) were major metabolites in forage and hay (13–28% TRR, 0.018–0.098 mg eq./kg), resulting from N-demethylation of sedaxane and subsequent conjugation with glucose and then malonic acid. CSCC210616 and CSCD465008, resulting from the cleavage of the amide bridge, were

also observed in pyrazole label forage and hay samples, at levels ranging from 1.0–4.2% TRR (0.004–0.014 mg eq./kg).

The metabolism of [phenyl-U-^{14}C]sedaxane and [pyrazole-5-^{14}C]sedaxane was investigated in Swiss chard after treatment of seeds with a suspension concentrate containing either [phenyl-U-^{14}C]sedaxane or [pyrazole-5-^{14}C]sedaxane. Swiss chard seeds were treated at a nominal application rate of 40 g ai/100 kg seeds and sown into containers of soil on the same day as treatment. Swiss chard plants were grown under greenhouse conditions and harvested 49 days after the seeds were planted at the growth stage BBCH 14–15 (4 to 5 fully open leaves).

The predominant residue identified in Swiss chard was sedaxane: 29% TRR and 0.016 mg/kg in the pyrazole-label experiment, and 52% TRR and 0.024 mg/kg in the phenyl-label experiment.

In the phenyl-label study, N-desmethyl sedaxane, CSCD667584, was present at 4.5% TRR (0.002 mg eq./kg) and two components were tentatively identified as glycoside conjugates: CSCD658906/CSCD659089 at 1.1% TRR (< 0.001 mg eq./kg) and CSCD668403 at 1.5% TRR (< 0.001 mg eq./kg).

In the pyrazole label study, CSCC210616 (pyrazole amide; free and conjugated) was present at 12.9% TRR (0.0072 mg eq./kg), CSCD465008 (N-desmethyl pyrazole acid; free and conjugated) was present at 12% TRR (0.0064 mg eq./kg), the N-desmethyl parent CSCD667584 was present at 2.3% TRR (0.0013 mg eq./kg) and CSAA798670 (pyrazole acid; free and conjugated) was present at 0.8% TRR (< 0.001 mg eq./kg). Two glycoside conjugated components tentatively identified as CSCD658906/CSCD659089, and CSCD668403 were present at 0.9% TRR and < 0.001 mg eq./kg each.

Plant metabolism summary

Metabolism of sedaxane was similar in wheat, Swiss chard, and soya bean, although different major metabolites were found among the plants studied. Residues in wheat grain were too low for analysis. In soya bean seed, the only identified compound was CSCD465008, free and conjugated. In Swiss chard, parent sedaxane was the predominant residue.

The two most abundant compounds in wheat feedstuffs were parent sedaxane and CSCD658906; in soya feedstuffs were sedaxane and conjugates of CSCD667584; and in Swiss chard were sedaxane and the pyrazole metabolites. Although cleavage of the amide bond was relatively more important in Swiss chard in comparison to wheat or soya, the absolute levels were low (≤ 0.01 mg eq./kg).

Metabolism of sedaxane in plants occurs via the following reactions: oxidative metabolism of the phenyl and cyclopropane rings, N-demethylation of the pyrazole ring, and cleavage between the pyrazole and phenyl rings. There was variation in the significance of the different pathways and the nature of the observed conjugations between crops.

Environmental fate in soil

The Meeting reviewed aerobic soil degradation, soil photolysis, and succeeding crop studies.

Aerobic Soil Degradation

The rate of degradation of radiolabelled sedaxane was investigated under aerobic conditions at in three soils in the dark for up to 367 days. The levels of sedaxane declined steadily, reaching ≤ 50% of total applied radioactivity (TAR) in all soils by 1 year in soil treated directly and generally by 100 days in soils where sedaxane-treated seeds had been sown. Two major metabolites, identified as CSAA798670 and CSCD465008, were observed in all soils. CSCD465008 reached a maximum value of 32% of TAR in North Dakota sandy clay loam after 237 days following seed treatment application of sedaxane. CSAA798670 reached a maximum value of 14% of TAR in California sand after 365 days following direct soil application of sedaxane.

Soil Photolysis

The photolysis of [^{14}C]-sedaxane (both labels) on moist and dry soils was investigated under aerobic conditions, with continuous irradiation by artificial sunlight. No photodegradation products were detected at more than4.3% of the applied radioactivity at any analysis time in moist or dry soils. These studies suggest that photolysis is not a significant pathway for degradation of sedaxane.

Rotational crops

Confined rotational crop studies demonstrated that sedaxane pyrazole metabolites may be taken up by plant roots of succeeding crops. Therefore, a field rotational crop study was conducted to assess the potential for accumulation in successive crops at typical plant back intervals. This study was conducted at application rates matching GAP, and showed that no residues of sedaxane or its metabolites are likely in succeeding crops resulting from the use of sedaxane as a seed treatment.

Methods of analysis

Acceptable analytical methods were developed and validated for determination of sedaxane and its metabolites in plant and animal matrices.

The methods for enforcement and data generation involve homogenization and extraction with a mixture of acetonitrile and water (80:20, v/v), clean-up with solid phase extraction, centrifugation and dilution; then determination of analytes using LC-MS/MS. Additional clean up procedures, often including hydrolysis reactions, were made as necessary to improve analytical results for the metabolites. The reported LOQ for the sedaxane isomers was 0.005 mg/kg, while the LOQ for all metabolites was 0.01 mg/kg in all matrices (plant and animal).

The FDA Multi-Residue Method Test guidelines in the Pesticide Analytical Manual (PAM) (Third Edition, January 1994) is not applicable for the analysis of sedaxane, due to low recoveries.

Stability of residues in stored analytical samples

The stability of sedaxane residues during frozen storage (approximately -18 ºC) was investigated in plant matrices and processed commodities. The plant matrices tested were: wheat grain and straw, spinach, potato, orange, lentils, and soya beans. The processed commodities were derived from wheat (flour, germ, and bran), soya bean (meal, hulls, and oil), and orange (dried pulp, juice, and oil).

Compounds tested on plants were: both isomers of sedaxane, CSAA798670, CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCC210616, and CSCD465008. For the processed commodities, the testing was limited to both isomers of sedaxane and CSCD456008. Each compound was added to matrices at 0.2 mg/kg.

No stability problems were found in any of the studies. Sedaxane and all isomers are stable for at least 24 months in frozen plant matrices, except for CSAA798670, which was only studied for 12 months. Similarly, stability for 12 months was demonstrated for sedaxane and CSCD456008 in processed commodities.

The periods of demonstrated stability cover the frozen storage intervals in the residue studies.

No separate storage stability studies were submitted for animal commodities. However, all samples were analysed within 30 days of collection in the bovine feeding study, and no significant changes were noted in the radio-profiles of the principle extracts from milk, liver, kidney, muscle and fat samples at the end of the analytical phase of the animal metabolism studies.

Definition of the residue

Results of the goat and hen metabolism studies were similar, indicating that residue levels are highest in liver and kidney, lower in milk, egg, and fat, and nearly undetectable in muscle. Parent sedaxane was found in fat, liver, egg, and hen muscle at levels ≤ 0.034 mg/kg. Sedaxane was the predominant residue in fat tissues at up to 53% TRR in hen fat, although the absolute level was low (0.004 mg/kg).

No sedaxane was found in goat muscle samples; trace levels were reported in hen muscle samples (0.001 mg/kg).

The predominant metabolites in kidney and liver are CSCD658906 and CSCD659087. Hence the bovine feeding study analysed for these compounds and for parent sedaxane. Although metabolite CSCD658906 was the only residue detected in the bovine feeding study, it was only found in liver and kidney samples from animals dosed at the most exaggerated rate (~24× the maximum dietary burden), and was present at ≤ 0.027 mg eq./kg. Because CSCD658906 is found in liver and kidney as glucose conjugates, inclusion in the residue definition would require an analytical method using hydrolysis procedures. Based on practical considerations regarding the analytical enforcement method together with the expectation of residue levels below the LOQ, it is not appropriate to include metabolite CSCD658906 in the residue definition for enforcement. Noting the low levels of sedaxane residues expected in animal tissues following sedaxane seed treatment uses, the Meeting concluded that the residue definition for animal commodities for purposes of enforcement and dietary intake is sedaxane.

The plant metabolism studies demonstrated that no sedaxane residues are found in grains or seeds. Low level residues may occur in the forage, hay and straw of plants grown from treated seeds. Predominant residues consist of parent sedaxane and CSCD658906 in wheat feedstuffs; sedaxane and conjugates of CSCD667584 in soya feedstuffs; and sedaxane and the pyrazole metabolites in Swiss chard.

The Meeting agreed that parent sedaxane is the best marker compound for plants as it was the only compound found at significant levels (> 10% TRR and 0.01 mg/kg) in all three plant metabolism studies, and is appropriate for both MRL enforcement and dietary intake assessments.

Sedaxane has a log K_{ow} of 3.3. In the goat and hen metabolism studies, sedaxane was the predominant residue found in fat, and was present only in trace amounts in muscle. The Meeting considered sedaxane to be a fat-soluble compound.

The Meeting recommended the following residue definition for sedaxane, when used as a seed-treatment.

For plants and animals: Definition of the residue (for compliance with the MRL and for estimation of dietary intake): *sedaxane*.

The residue is fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised field trials data for sedaxane uses on rape, cereal grains (barley, oats, and wheat), and soya bean.

The OECD MRL calculator was used as a tool in the estimation of the maximum residue level from the selected residue data set obtained from trials conducted according to proposed GAP. 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 JMPR, a brief explanation of the deviation was provided.

Soya bean (immature seeds)

The GAP for soya bean is from Canada and the USA, and specifies seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed. Trials from the USA were conducted at a rate of 40 g ai/100 kg seed. As no residues were detected, the Meeting agreed to make use of these exaggerated rate trials.

A total of 20 trials were available from the USA. Sedaxane residue concentrations in soya bean seed from the USA were: < 0.01 (20) mg/kg.

Based on the results of the soya bean metabolism study, which showed that parent sedaxane residues are not found in soya bean seed, together with the results of the 20 field trials from the USA, the Meeting agreed that no sedaxane residues are expected in soya bean seed.

The Meeting estimated a maximum residue level of 0.01* mg/kg for sedaxane on soya bean (immature seeds), and an STMR of 0 mg/kg.

Cereal grains

Supervised trials data were available for barley, oats, and wheat.

Barley

The critical GAP for barley is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed.

A total of 28 trials on barley grain were available from Australia (4), Canada (12), and USA (12). However, only the four trials from Australia match the GAP of France.

Sedaxane residue concentrations in barley grain from Australia were: < 0.010 (4) mg/kg.

Based on the results of the wheat metabolism study, which showed no transfer of radioactivity to the grain, together with the four field trials from Australia, the Meeting agreed that no sedaxane residues are expected in barley grain.

The Meeting estimated a maximum residue level for sedaxane in barley grain of 0.01* mg/kg, and an STMR of 0 mg/kg.

Oats

The critical GAP for oats is from France and specifies seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed.

A total of four trials on oat grain were available from Australia matching the GAP of France.

Sedaxane residue concentrations in oat grain from Australia were: < 0.010 (4) mg/kg.

Based on the results of the wheat metabolism study, which showed no transfer of radioactivity to the grain, together with the results of the field trials from Australia, the Meeting agreed that no sedaxane residues are expected in oat grain.

The Meeting estimated a maximum residue level for sedaxane in oat grain of 0.01* mg/kg, an STMR of 0 mg/kg, and an HR of 0 mg/kg.

Wheat

The critical GAP for wheat is from France and specifies seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed. GAP rates in Canada and the USA were 5 g ai/100 kg seed. Single and double rate trials were conducted in Australia.

A total of 31 trials on wheat grain matching GAP were available from Australia (8), North Europe (13), and South Europe (10).

Sedaxane residue concentrations in wheat grain from Australia were: < 0.010 (8) mg/kg.

Sedaxane residue concentrations in wheat grain from North Europe were: < 0.010 (13) mg/kg.

Sedaxane residue concentrations in wheat grain from South Europe were: < 0.010 (10) mg/kg.

Based on the results of the wheat metabolism study, which showed no transfer of radioactivity to the grain, together with the results of the field trials from Australia and Europe, the Meeting agreed that no sedaxane residues are expected in wheat grain.

The Meeting estimated a maximum residue level for sedaxane in wheat grain of 0.01* mg/kg, and an STMR of 0 mg/kg.

The Meeting decided to extrapolate the maximum residue level, median residue and highest residue for wheat to rye and triticale, noting that these crops have an identical GAP.

Rape seed

The GAP for rape seed from Canada and the USA lists seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed.

A total of 16 trials on rape seed matching Canadian GAP were available from Canada.

Sedaxane residue concentrations in rape seed from Canada were: < 0.01 (16) mg/kg.

Based on the results of the rape seed metabolism study, which showed no transfer of radioactivity to the seed, together with the results of the rape field trials, the Meeting agreed that no sedaxane residues are expected in rape seed.

The Meeting estimated a maximum residue level for sedaxane in rape seed of 0.01* mg/kg, and an STMR of 0 mg/kg.

Animal feedstuffs

Soya bean forage and hay (fodder)

The GAP for soya bean is from Canada and the USA specifies seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed. Trials from the USA were conducted at a rate of 40 g ai/100 kg seed (8 × USA GAP rate). As residues were detected in soya bean forage and hay samples, the Meeting determined that no maximum residue estimates could be made for these commodities on the basis of the exaggerated rate trials.

Forages (Barley, Oats, and Wheat)

The critical GAP for forages is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed. Because there is no label feeding/grazing restriction for forages in France, the Meeting selected the highest residue concentration from each trial conducted that matched GAP.

Australian trials for barely and oat forage were submitted but not used for residue estimates since an Australian GAP for sedaxane is not available.

Barley straw and fodder

The critical GAP for barley is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed.

Barley straw

A total of four trials on barley straw matching France GAP were available from Australia. Sedaxane residue concentrations in barley straw from Australia were: < 0.010 (4) mg/kg.

Barley hay

No barley hay trials matching the GAP of France were available. The Canadian and USA GAP lists seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed.

A total of 24 trials on barley hay matching the GAP of the USA were available from Canada (12) and USA (12).

Sedaxane residue concentrations in barley hay from Canada and the USA were (n=24): < 0.010 (19), 0.011 (2), 0.025 (3) mg/kg.

Oat straw

The critical GAP for oat is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed. A total of 4 trials on oat straw matching France GAP were available from Australia.

Sedaxane residue concentrations in oat straw from Australia were: < 0.010 (4) mg/kg.

Wheat straw, fodder, and forage

The critical GAP for wheat is from France and lists seed treatment use of sedaxane at a rate of 10 g ai/100 kg seed. Supervised trials data were available for wheat straw, hay, and forage.

Wheat forage

A total of 23 trials on wheat forage matching France GAP were available from North Europe (13), and South Europe (10).

Sedaxane residue concentrations in wheat forage from North Europe were: < 0.010 (9), 0.013 (2), 0.016, and 0.017 mg/kg.

Sedaxane residue concentrations in wheat forage from South Europe were: < 0.010 (6), 0.011, 0.013, and 0.023 (2) mg/kg.

As the results from North and South Europe are similar, the Meeting decided to combine these datasets (n=23): < 0.010 (15), 0.011, 0.013 (3), 0.016, 0.017, and 0.023 (2) mg/kg.

Based on the trials conducted in Europe, the Meeting estimated an STMR of 0.01 mg/kg and a HR of 0.023 mg/kg for wheat forage. The Meeting agreed to extrapolate the residue estimates from wheat forage to the other forages (barley, oats, rye, and triticale).

Wheat straw

A total of 23 trials on wheat straw matching GAP from France were available from North Europe (13) and South Europe (10).

Sedaxane residue concentrations in wheat grain from Europe were: < 0.010 (21), 0.011, and 0.012 mg/kg.

Wheat hay

No wheat hay trials matching the French GAP were available. The Canadian and USA GAP lists seed treatment use of sedaxane at a rate of 5 g ai/100 kg seed.

A total of 36 trials on wheat hay matching Canadian and US GAP were available from Canada (16) and USA (20).

Rank-order sedaxane residues in wheat hay from Canada and USA were (n=36): < 0.01 (27), 0.013, 0.014 (2), 0.025 (3), 0.035, 0.045, 0.075 mg/kg.

Summary of straw and fodder from barley, oats, rye, triticale, and wheat

Straw and fodder from barley, oats, rye, triticale, and wheat, may not always be readily distinguishable from each other in trade. Thus, it is preferable for these commodities to have the same MRLs. For sedaxane, residues in wheat hay were found to have the highest residue levels among the straw and fodder feedstuffs from small grains. The Meeting agreed to use the wheat hay data from Canada and the USA as a basis for estimating the maximum residue levels of these livestock feedstuffs.

On a dry-weight basis (DM = 88%), sedaxane residues in wheat hay were (n=36): < 0.011 (27), 0.015, 0.016 (2), 0.028 (3), 0.040, 0.051 and 0.085 mg/kg.

The Meeting estimated a maximum residue level of 0.10 mg/kg for sedaxane on barley, oats, rye, triticale, and wheat straw and fodder, dry. The Meeting estimated median and highest residue values of 0.01 and 0.075 mg/kg (as received), respectively, for sedaxane residues in straw and fodder of barley, oats, rye, triticale, and wheat, for the purposes of calculating livestock dietary burdens.

Fate of residues during food processing

High temperature hydrolysis

A high-temperature aqueous hydrolysis study was conducted to determine the nature of any sedaxane-derived residues in processed crop commodities or by-products under conditions typical of industrial or household processing.

In experiments conducted at 90, 100, and 120 ºC over a range of pHs, no significant degradation of sedaxane was found. Thus, sedaxane is hydrolytically stable under conditions representative of pasteurization, baking/brewing/boiling, and sterilization.

Processing

The Meeting received information on the processing of barley, oilseed rape, soya bean, and wheat. Neither sedaxane nor any metabolites were detected above the LOQ in any RAC or processed commodity sample. Thus, no processing factors for sedaxane could be determined.

Residues in animal commodities

The Meeting received a lactating dairy cow feeding study, which provided information on potential residues resulting in ruminant tissues and milk from sedaxane residues in the animal diet.

Lactating Holstein dairy cows were dosed for 28–30 days once daily via gelatin capsule with sedaxane. The sedaxane dosing rates were 0.11, 0.54, and 2.2 ppm in the dry-weight diet.

No sedaxane transferred into any tissue or milk at any dose level.

Due to low dietary burdens to poultry and low residue transfer noted in the poultry metabolism study, no poultry feeding study was conducted.

Livestock dietary burden

The Meeting estimated the dietary burden of sedaxane in livestock on the basis of the diets listed in OECD Feed Table 2009 (available from the FAO website: http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmpr/jmpr-docs/en/). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating maximum residue levels, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities.

Estimated maximum and mean dietary burdens of livestock

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

		Livestock dietary burden, sedaxane, ppm of dry matter diet			
		US-Canada	EU	Australia	Japan
Max	beef cattle	0.013	0.028	**0.092** [a]	0.002
	dairy cattle	0.028	0.028	**0.081** [c]	0.001
	poultry - broiler	0.002	0.002	0.002	0.000
	poultry - layer	0.002	**0.011** [e]	0.002	0.000
Mean	beef cattle	0.002	0.011	**0.040** [b]	0.000
	dairy cattle	0.011	0.011	**0.034** [d]	0.000

	Livestock dietary burden, sedaxane, ppm of dry matter diet			
	US-Canada	EU	Australia	Japan
poultry - broiler	0.000	0.000	0.000	0.000
poultry - layer	0.000	**0.004** [f]	0.000	0.000

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian tissues.

[b] Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.

[c] Highest maximum dairy cattle dietary burden suitable for MRL estimates for milk.

[d] Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

[e] Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.

[f] Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs.

Animal commodities, maximum residue level estimation

Cattle

The sedaxane maximum dietary burden for beef and dairy cattle is 0.09 and 0.08 ppm, respectively. Sedaxane residues in all tissues in the bovine feeding study were below the LOQ of 0.01 mg/kg at all three dosing levels (highest of 2.2 ppm). No detectable residues of sedaxane are expected in any ruminant tissue from seed-treatment uses of sedaxane.

The Meeting estimated a maximum residue level of 0.01* mg/kg for sedaxane in/on: edible offal (mammalian); mammalian fats (except milk fats); meat (from mammals other than marine mammals); milks; and milk fats.

Based on no detectable levels of sedaxane being found in any tissue in the bovine feeding study, and the results of the goat metabolism studies demonstrating sedaxane levels are < 0.01 mg/kg in all tissues at exaggerated dose rates, the Meeting estimated STMR and HR values of 0 for mammalian commodities.

Poultry

The sedaxane maximum dietary burden for layer and broiler poultry is 0.01 and 0 ppm, respectively. No detectable residues of sedaxane are expected in any poultry tissue from seed-treatment uses of sedaxane.

The Meeting estimated a maximum residue level of 0.01* mg/kg for sedaxane in/on: poultry fats; poultry meat; poultry, edible offal of; and eggs.

Based on the results of the hen metabolism studies demonstrating sedaxane levels are < 0.01 mg/kg in all tissues at exaggerated dose rates, the Meeting estimated STMR and HR values of 0 for poultry commodities.

DIETARY RISK ASSESSMENT

Long-term intake

The ADI for sedaxane is 0–0.11 mg/kg bw. No long-term intake dietary risk assessment is needed for sedaxane because no uses result in residues in human foods. The Meeting concluded that the long-term intake of residues of sedaxane, from uses that have been considered by the JMPR, is unlikely to present a public health concern.

Short-term intake

The ARfD for sedaxane is 0.3 mg/kg bw. No short-term intake dietary risk assessment is needed for sedaxane because no sedaxane uses result in residues in human foods. The Meeting concluded that the short-term intake of residues of sedaxane, from uses that have been considered by the JMPR, is unlikely to present a public health concern.