5.21 SPIRODICLOFEN (237)

TOXICOLOGY

Spirodiclofen is the ISO approved name for 3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutyrate (IUPAC) or 3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutanoate (CAS), CAS No. 148477-71-8. Spirodiclofen is a selective, non-systemic foliar insecticide and acaricide belonging to the chemical class of ketoenols or tetronic acids, whose pesticidal mode of action is the inhibition of lipid synthesis.

Spirodiclofen is being reviewed for the first time by the present Meeting at the request of the CCPR.

All pivotal toxicological studies complied with GLP.

Biochemical aspects

The absorption, distribution, metabolism and excretion of spirodiclofen were investigated in rats. Orally administered ^{14}C-labelled spirodiclofen was rapidly absorbed and eliminated. Blood concentrations peaked at 3–4 h at low doses (1–2 mg/kg bw), and at $\geq$ 8 h at a higher dose (100 mg/kg bw). Decreased urinary excretion at the higher dose suggested saturation of absorption. Urine and faeces were the major routes of excretion. Retention in the carcass and organs was low (total body burden, < 1% of the administered dose within 48 h), and there was no evidence of bioaccumulation. Dietary pre-treatment with non-labelled compound did not have a significant impact on absorption or elimination.

After oral administration, ^{14}C-labelled spirodiclofen was extensively metabolized in rats. Spirodiclofen appears to be rapidly metabolized to the enol metabolite (BAJ 2510). No parent compound was detected in the urine or bile, and up to 11 metabolites were identified, representing 59–90% of the administered dose. Up to 16% of the parent compound was detected in the faeces. The profile of metabolites was generally similar qualitatively in males and females, but varied quantitatively. The major urinary metabolite in females was the enol metabolite, BAJ 2510, while the major urinary metabolite in males was the 3-hydroxy-enol metabolite. The metabolic profile in the bile was similar to that observed in the urine; however, a hydroxylated glucuronide metabolite was found to be unique to the bile.

Toxicological data

Spirodiclofen is of low acute toxicity when administered via the oral, dermal and inhalation routes. The oral and dermal LD_{50} values in rats were > 2500 and > 2000 mg/kg bw, respectively. The inhalation LC_{50} in rats was determined to be > 5.03 mg/L air. Spirodiclofen was not irritating to the eyes or skin of rabbits, but was found to be a dermal sensitizer under the conditions of the Magnussen & Kligman maximization test in guinea-pigs.

In short- and long-term studies of oral toxicity in mice, rats and dogs, the primary target organs of toxicity of spirodiclofen were the adrenal glands and testes. The predominant finding was vacuolation of the adrenal cortex, which was noted in the mouse, rat and dog, and was often accompanied by increased adrenal weight. With extended duration of dosing, adrenal vacuolation was associated with adrenal hypertrophy in rats, and adrenal enlargement and lymphocytic infiltration in mice. In rats, there were no adrenal findings after 28 days of dosing (NOAEL of 500 ppm, equal to 50 mg/kg bw per day, on the basis of changes in clinical chemistry parameters and induction of liver enzymes at 5000 ppm), and the overall NOAEL for adrenal effects from the 14-week and 2-year studies was 350 ppm, equal to 14.7 mg/kg bw per day from the 2-year study in rats. In mice, a NOAEL of 100 ppm, equal to 30 mg/kg bw per day, was identified in the short-term study on the basis of adrenal findings at 1000 ppm. After long-term dosing in mice, a NOAEL for adrenal findings

could not be identified as there was an increased incidence of adrenal pigmentation and vacuolation in females at the lowest dose tested (25 ppm, equal to 5.1 mg/kg bw per day). The incidence of pigmentation was only slightly above the reported range for historical controls, and the increase in vacuolation was not statistically significant. However, as the adrenal gland is clearly a target organ, these findings were considered to represent a marginal LOAEL for females at this dose. Compared with other species, the adrenal effects were observed at the lowest doses in dogs. Although a NOAEL could not be established for adrenal findings in the special 8-week study in dogs (LOAEL, 2.9 mg/kg bw per day) or for females in the 14-week study in dogs (LOAEL of 8.4 mg/kg bw per day), an overall NOAEL for adrenal histopathology in the dog was identified from the 1-year study in dogs (NOAEL of 1.4 mg/kg bw per day). Reversibility of the adrenal effects was observed in the short-term study in rats during a 28-day recovery period. The Meeting noted that these adrenal findings are a consequence of repeated dosing, which is supported by the lack of adrenal findings in the 28-day study in rats, and are potentially associated with prolonged perturbation of steroidogenesis.

Testicular effects in mice included Leydig-cell hypertrophy and vacuolation after short-term dosing, and increased weight, discoloration, degeneration, and interstitial-cell hyperplasia in the long-term study. In the long-term study, an increase in epididymal aspermia was also noted at the highets dose. In the dog, Leydig-cell vacuolation and hypertrophy, testicular immaturity, and degeneration of the germinal epithelium were noted in studies that ranged in duration from 28 days to 1 year. In the rat, Leydig-cell hyperplasia was observed in the 2-year study. The overall NOAEL for testicular effects was approximately 4 mg/kg bw per day from the 1-year study in dogs (150 ppm), 2-year study in rats (100 ppm), and 18-month study in mice (25 ppm), although it should be noted that increased testes weights were noted at this dose in the 1-year study in dogs. In dogs, the Meeting noted that when dosing began at a younger age, effects in reproductive tissues appeared to be more severe, and that the testicular effects were often accompanied by other effects, including immaturity of the prostate and oligo-/aspermia of the epididymides, which were noted in the 28-day (at 10 000 ppm) and 14-week studies (at ≥ 630 ppm). The Meeting also observed that there was evidence that effects in male reproductive tissues progressed, and that NOAELs decreased, with increasing duration of exposure, and that the nature of the findings indicated that they were potentially a result of prolonged perturbation of steroidogenesis.

Other effects observed following short- or long-term oral exposure to higher doses of spirodiclofen included effects on the liver, cholesterol levels, the thyroid, jejunum and thymus. Liver effects included hypertrophy, vacuolation and hepatocytomegaly in the mouse (at ≥ 1000 ppm, equal to 164 mg/kg bw per day); necrosis, cytoplasmic change, granulation and inflammatory infiltration in dogs (at ≥ 2000 ppm, equal to 84.7 mg/kg bw per day); and decreased concentrations of plasma proteins and tigroid basophilic focus in rats (at 2500 ppm, equal to 110.1 mg/kg bw per day). Increased liver weight and enzyme induction occurring in mice and dogs at lower doses were considered to be an adaptive response to the administration of spirodiclofen. Decreased cholesterol concentrations, which were consistent with the proposed pesticidal mode of action of this chemical, were observed in rats (at ≥ 110 mg/kg bw per day), dogs (at ≥ 4 mg/kg bw per day) and mice (at 1600 mg/kg bw per day), and were accompanied by decreased triglyceride concentrations in the rat. Vacuolization of the jejunum was observed in rats and dogs, and slight atrophy of the thymic cortex was also observed in dogs. Thyroid effects included decreased concentrations of thyroxin in dogs (at 2000 ppm in the 4-week study), and an increase in concentrations of thyroid-stimulating hormone (at ≥ 2500 ppm in the 14-week study) and colloidal alteration of the thyroid (at 2500 ppm in the 2-year study) in rats.

Spirodiclofen was tested for genotoxicity in vitro and in vivo in an adequate range of assays. It was not found to be genotoxic in mammalian or microbial systems.

The Meeting concluded that spirodiclofen was unlikely to be genotoxic.

In an 18-month study of carcinogenicity in mice, administration of spirodiclofen at dietary concentrations of 0, 25, 3500 or 7000 ppm resulted in the development of late-onset hepatocellular adenomas and carcinomas in males and females at doses of ≥ 3500 ppm. Systemic toxicity was noted

at the same doses, including changes in organ weights (liver, adrenal gland, testes, and kidney), and histopathological findings in the adrenal gland (vacuolation and pigmentation), liver (hepatocytomegaly), and testes (hypertrophy and hyperplasia). As discussed earlier, a NOAEL for systemic toxicity was not identified, on the basis of marginal effects on the adrenal gland in females at 25 ppm, equal to 5.1 mg/kg bw per day, the lowest dose tested. The NOAEL for carcinogenicity was 25 ppm, equal to 4.1 mg/kg bw per day, in this study. The Meeting noted that while pre-neoplastic lesions were not observed at lower doses than those at which the liver tumours were observed, this may have been due to the large dose-spacing. Additionally, the Meeting noted that these tumours were only observed at high doses (≥ 3500 ppm), which also produced hepatotoxicity, and that the dose–response relationship for these tumours was likely to exhibit a threshold.

The toxicity and carcinogenicity of spirodiclofen were investigated in a 2-year dietary study in rats. The incidence of late-onset Leydig-cell adenomas was increased in male rats at the highest dose tested (2500 ppm), preceded by an increased incidence of Leydig-cell hyperplasia at ≥ 350 ppm. An increased incidence of uterine adenocarcinomas and uterine nodules was also observed in female rats at the highest dose that had died or were sacrificed before study termination. These adenocarcinomas were noted to have metastasized into various organs of the abdominal cavity, as well as into the lung and bone marrow. Systemic toxicity was also noted at the highest dose, including increased mortality (females), decreased body weight (by 6–10%), increased levels of alkaline phosphatase, decreased concentrations of cholesterol and trigylerides, and histopathological findings in the adrenal gland (vacuolation and hypertrophy; males only), ovary (increased portion of stroma), vagina (possible increase in the number of animals in estrus based on morphology of vaginal epithelium), jejunum (vacuolation), thyroid (colloidal alteration), and olfactory epithelium (atrophy/degeneration; males only). The NOAEL for systemic toxicity was 100 ppm, equal to 4.1 mg/kg bw per day, on the basis of the increased incidence of Leydig-cell hyperplasia in males. The NOAEL for carcinogenicity was 350 ppm, equal to 14.7 mg/kg bw per day.

Several special studies were conducted with spirodiclofen and with three of the enol metabolites (BAJ 2510, 3-OH-enol and 4-OH-enol). Studies in vitro provided evidence that the enol metabolite (BAJ 2510) may contribute significantly to the effects observed with spirodiclofen via disruption of the metabolism of cholesterol, which is a precursor to a variety of hormones. Studies also confirmed that BAJ 2510 could inhibit the activity of malate dehydrogenase in tissue culture, resulting in a decrease in reducing equivalents required by various P450 monooxygenases involved in steroidogenesis, the downstream effect of which was ultimately predicted to reduce hormone production. Studies with BAJ 2510 in vitro, as well as special studies with spirodiclofen in vivo, provided some evidence of effects on steroid synthesis. The Meeting noted that the increased incidence of Leydig-cell and uterine tumours observed in rats was consistent with prolonged perturbations in steroidogensis, and the dose–response relationship for these effects would be anticipated to exhibit a threshold. However, a clear description of key events, with dose–response relationships and temporal associations, was not available, and the Meeting concluded that the data were not sufficient to develop a mode of action for formation of the observed tumours by spirodiclofen.

The Meeting concluded that the relevance of the tumorigenic responses in rats and mice to humans could not be discounted. However, the Meeting noted that spirodiclofen was not genotoxic, and that the dose–response relationship for the tumours would be anticipated to exhibit a threshold.

The effect of spirodiclofen on reproduction in rats was investigated in a two-generation study. Parental effects in both generations (F_0 and F_1) included vacuolation of the adrenal cortex and epithelium of the small intestine. Decreases in body weight and in concentrations of cholesterol, triglycerides and unesterified fatty acids were also observed in the F_1 generation (clinical chemistry evaluations were not performed for the F_0 generation). The NOAEL for parental toxicity was 70 ppm, equal to 5.2 mg/kg bw per day. Offspring toxicity included body-weight loss and decreased body-weight gain in the F_1 and F_2 pups at 350 ppm; the NOAEL for these findings in offspring was 70 ppm, equal to 5.2 mg/kg bw per day. Reproductive toxicity was observed in the F_1 generation only, at the highest dose tested (1750 ppm). Delayed sexual maturation was observed in male

offspring, and increased severity of ovarian vacuolation/degeneration, decreased testes, spermatid and epididymes sperm counts, reduced testes and epididymes size, as well as atrophy of the testes, epididymes and prostate were observed in some F_1 adults at the highest dose . The NOAEL for these findings in F_1 rats was 350 ppm, equal to 26.2 mg/kg bw per day. Although it is possible that the toxic effects on reproduction were associated with exposure in utero (as they were observed in the F_1 generation only), this remains uncertain, considering that F_1 rats began consuming treated diet at an earlier age, experienced a longer duration of dosing and were thus exposed to a higher overall average dose of spirodiclofen than the F_0 generation. The Meeting noted that this reproductive toxicity was potentially caused by sustained alteration of steroidogenesis.

The effect of spirodiclofen on developmental toxicity was investigated in rats and rabbits. In rats, no maternal toxicity was noted (the NOAEL was 1000 mg/kg bw per day, the highest dose tested), although the Meeting noted that investigation of target organs was not conducted in maternal animals. In the fetus, marginal increases in the incidences of slight renal pelvis dilatation and asymmetrical fourth sternebrae were observed at the highest dose tested. However, since these findings occurred at the highest dose tested (1000 mg/kg bw per day) and the incidences were within the range for historical controls, the Meeting considered that these effects represented a marginal LOAEL. The Meeting also noted that these findings would not be expected to occur after a single exposure (Solecki *et al.*, 2003; Makris *et al*., 2009).[35] The NOAEL for developmental toxicity in rats was 300 mg/kg bw per day on the basis of marginal findings at the highest dose tested. In the study in rabbits, maternal toxicity consisted of increased body-weight loss and decreased food consumption at 300 mg/kg bw per day. The NOAEL for maternal toxicity in rabbits was 100 mg/kg bw per day, and the NOAEL for developmental toxicity was 1000 mg/kg bw per day, the highest dose tested.

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

Neurotoxicity was investigated in studies of acute neurotoxicity, short-term studies of toxicity and studies of developmental neurotoxicity in rats. There was no evidence of neurotoxicity in the study of acute neurotoxicity, and the only evidence of neurotoxicity in the short-term study was decreased motor and locomotor activity in females at 12 500 ppm, equal to 1310 mg/kg bw per day, (the limit dose) during 1 week of treatment. Two studies of developmental neurotoxicity were conducted. The second was a modified study, intended to clarify potential findings related to brain morphometry and learning and memory parameters in offspring in the first study. Effects in parental animals were limited to small changes in body weight and/or food consumption at the highest dose tested, and these effects were not considered to be biologically relevant. The NOAEL for parental toxicity in both studies was 1500 ppm, equal to 119 mg/kg bw per day, the highest dose tested. In offspring, observed morphometric changes were small (3–7%), did not attain statistical significance in many cases, were not consistent between studies, and thus were not considered to be related to treatment. In tests of learning and memory, the findings were also inconsistent, and the considerable variability in the data limited their interpretation. Overall, the Meeting considered that these studies did not indicate any treatment-related findings on neurotoxicity parameters in offspring. The NOAEL was 350 ppm, equal to 28.6 mg/kg bw per day, on the basis of decreases in body weight and body-weight gain in offspring at 1500 ppm.

Studies of acute toxicity, short-term studies of toxicity and studies of genotoxicity were conducted with some of the metabolites of spirodiclofen, including BAJ 2740 ketohydroxy (a soil metabolite) and BAJ 2740-MA-3OH-cyclohexylester (a plant metabolite) – neither of which were detected in the studies of metabolism in rats – as well as the enol metabolite (BAJ 2510). BAJ 2740 ketohydroxy and BAJ 2740-MA-3OH-cyclohexylester were both of low acute toxicity when

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[35] (Solecki *et al*. Harmonization of rat fetal external and visceral terminology and classification Report of the Fourth Workshop on the Terminology in Developmental Toxicology, Berlin, 18–20 April 2002 ┌ Reproductive Toxicology 17 (2003) 625–637, Makris *et al*., Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 2) Birth Defects Research (Part B) 86:227–& 2009 Wiley-Liss, Inc. 327 (2009)

administered orally. BAJ 2510 was moderately toxic via the oral route (LD_{50}, 300–500 mg/kg bw per day), and was not irritating to the eyes and skin. A 6-week dietary study comparing the relative toxicity of spirodiclofen and the enol metabolite was conducted. Effects noted with both test substances included decreased body weight and food consumption, increased adrenal weights and enlargement and vacuolation of the adrenal gland. Both were also associated with decreased progesterone concentrations in females. In this short-term study, spirodiclofen and the enol metabolite were found to exert similar effects in rats given repeated doses, under the conditions of the study, and there was no indication that BAJ 2510 produced a different spectrum of toxic effects, or caused marked effects at lower doses than did spirodiclofen. Studies of reverse mutation in vitro were conducted with three metabolites of spirodiclofen (BAJ 2510, BAJ 2740 ketohydroxy and BAJ 2740-MA-3OH-cyclohexylester) to assess potential for inducing gene mutation in vitro. None of these metabolites of spirodiclofen were found to demonstrate any mutagenic potential under the conditions tested.

The following metabolites were identified only in plants: M05 (2,4-dichloro-mandelic acid hydroxy-cyclohexyl ester), M04 (2,4-dichloro-mandelic acid cyclohexyl ester glycosylpentoside) and M08 (2,4-dichloro-mandelic acid glucoside). The latter two metabolites are sugar conjugates of minor metabolites found in the rat. Limited toxicology data were provided for M05, and no toxicology data were provided for the other two plant metabolites. The Meeting therefore concluded that the information available was not sufficient to conduct a risk assessment for these metabolites. The enol metabolite was detected in plants and livestock matrices. As the enol metabolite was found to be of similar toxicity to the parent compound, the Meeting considered this metabolite to be toxicologically relevant for the dietary risk assessment.

There were no reports of adverse health effects in manufacturing-plant personnel or in operators and workers exposed to spirodiclofen formulations.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.01 mg/kg bw per day based on the NOAEL of 1.4 mg/kg bw per day identified on the basis of adrenal effects in males and females, and increased relative testes weights in males at 4.3 mg/kg bw per day in the 1-year study in dogs and with a safety factor of 100. This ADI provides adequate protection for the marginal adrenal effects noted in females at the lowest dose in the 18-month study in mice. The ADI provides a margin of at least 410-fold relative to the NOAEL for liver tumours in mice, and 1470-fold relative to the NOAEL for Leydig-cell and uterine tumours in rats, and thus the Meeting considered that spirodiclofen was not likely to pose a carcinogenic risk to humans at dietary levels of exposure.

The Meeting noted that spirodiclofen was not acutely toxic after short-term dosing, that there were no adverse findings in a study of acute neurotoxicity, and that there were no developmental toxicity findings that were expected to occur after a single dose in studies in rats or rabbits. The Meeting also noted that findings in the male reproductive system (observed in dogs, rats and mice) would not be caused by a single dose. Consequently, the Meeting determined that an ARfD was unnecessary.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	—	25 ppm, equal to 5.1 mg/kg bw per day[f]

		Carcinogenicity	25 ppm, equal to 4.1 mg/kg bw per day	3500 ppm, equal to 610 mg/kg bw per day
Rat	Two-year studies[a]	Toxicity	100 ppm, equal to 4.1 mg/kg bw per day	350 ppm, equal to 14.7 mg/kg bw per day
		Carcinogenicity	350 ppm, equal to 14.7 mg/kg bw per day	2500 ppm, equal to 110.1 mg/kg bw per day
	Two-generation study of reproductive toxicity[a]	Parental toxicity	70 ppm, equal to 5.2 mg/kg bw per day	350 ppm, equal to 26.2 mg/kg bw per day
		Offspring toxicity	350 ppm, equal to 26.2 mg/kg bw per day	1750 ppm, equal to 134.5 mg/kg bw per day
		Reproductive toxicity	70 ppm, equal to 5.2 mg/kg bw per day	350 ppm, equal to 26.2 mg/kg bw per day
	Developmental toxicity[b]	Maternal toxicity	1000 mg/kg bw per day[c]	—
		Embryo/fetotoxicity	300 mg/kg bw per day	1000 mg/kg bw per day
		Parental toxicity	1500 ppm, equal to 119 mg/kg bw per day[c]	—
	Developmental neurotoxicity[a,d]	Offspring toxicity	350 ppm, equal to 28.6 mg/kg bw per day	1500 ppm, equal to 119 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
		Embryo/fetotoxicity	1000 mg/kg bw per day[c]	—
Dog	Eight-week study of toxicity[a, e]	Toxicity	—	100 ppm, equal to 2.9 mg/kg bw per day[f]
	Fourteen-week study of toxicity[a]	Toxicity in males	200 ppm, equal to 7.7 mg/kg bw per day	630 ppm, equal to 26.6 mg/kg bw per day
		Toxicity in females	—	200 ppm, equal to 8.4 mg/kg bw per day[f]
	One-year study of toxicity[a]	Toxicity	50 ppm, equal to 1.4 mg/kg bw per day	150 ppm, equal to 4.3 mg/kg bw per day

[a]Dietary administration.

[b]Gavage administration.

[c]Highest dose tested.

[d]Two studies combined.

[e]Study conducted with males only.

[f]Lowest dose tested.

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

Unnecessary

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 spirodiclofen

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid (t_{max} of 3–4 h) and extensive (up to 76%; based on renal excretion data)
Distribution	Widely distributed; highest concentrations in liver and kidneys
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapidly excreted; 90% eliminated at 48 h
Metabolism in animals	Extensively metabolized; no parent compound detected in urine or bile. Quantitative differences in metabolic profile between sexes.
Toxicologically significant compounds (animals, plants, environment)	Parent compound and enol metabolite
Acute toxicity	
Rat, LD_{50} oral	> 2500 mg/kg bw
Rat, LD_{50} dermal	> 2000 mg/kg bw
Rat, LC_{50} inhalation	> 5.03 mg/L air
Guinea-pig, dermal sensitization (test method used)	Sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	Adrenal gland (cortical vacuolation and increased weight)
Lowest relevant oral NOAEL	50 ppm (equal to 1.4 mg/kg bw per day; 1-year study in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (28-day study in rats)
Genotoxicity	
	No genotoxic potential

Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Adrenal gland (cortical vacuolation and increased weight)
Lowest relevant NOAEL	50 ppm (equal to 1.4 mg/kg bw per day; 1-year study in dogs)
Carcinogenicity	Tumours in livers (mice), testes (rat) and uterus (rat) at doses that caused target organ and/or systemic toxicity. NOAELs identified; unlikely to pose a risk to humans at levels of dietary exposure.
Reproductive toxicity	
Reproduction target/critical effect	Delayed sexual maturation, decreased spermatid and sperm counts, atrophy of male sex organs, and ovarian vacuolation/degeneration in F_1 animals
Lowest relevant reproductive NOAEL	350 ppm (equal to 26.2 mg/kg bw per day)
Developmental target/critical effect	Renal pelvis dilatation and assymetric fourth sternebrae
Lowest relevant developmental NOAEL	300 mg/kg bw per day (rat)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	No evidence of neurotoxicity; NOAEL: 1000 mg/kg bw per day
Subchronic neurotoxicity	Decreased motor and locomotor activity (females only); NOAEL: 87 mg/kg bw per day
Developmental neurotoxicity	No evidence of developmental neurotoxicity
Other toxicological studies	
Mechanism studies	Possible effect on steroidogenesis by the enol metabolite via effects on malate dehydrogenase
Studies with metabolites	
Acute toxicity	BAJ 2510 was moderately acutely toxic via the oral route (LD_{50} 300–500 mg/kg bw); BAJ 2740 ketohydroxy and BAJ 2740-3-OH-cyclohexylester were of low acute oral toxicity (LD_{50} > 2500 mg/kg bw)
Short-term toxicity	Similar results following short-term dosing with BAJ 2510 and spirodiclofen: decreased body weight and adrenal effects
Genotoxicity	BAJ 2510, BAJ 2740 ketohydroxy and BAJ 2740-3-OH-cyclohexylester were not mutagenic in vitro
Medical data	
	No occupational or accidental poisoning reported

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.01	Dog, 1-year	100
ARfD	Unnecessary	—	—

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of spirodiclofen were considered for the first time by the present Meeting. The residue evaluation was scheduled for the 2009 JMPR by the Forty-first Session of the CCPR (ALINORM 09/32/24).

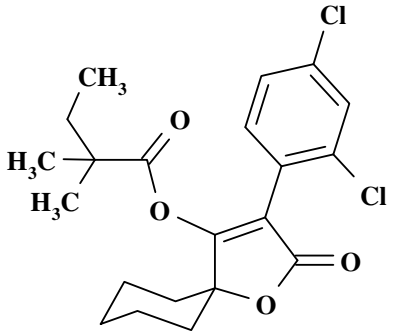
Spirodiclofen is an insecticide/acaricide belonging to the chemical class of ketoenols or tetronic acids and acts as inhibitor of lipid biosynthesis, mainly against mites. It has registered uses in many countries on fruits, fruiting vegetables, tree nuts, coffee and hops.

The Meeting received information from the manufacturer on identity, metabolism, storage stability, residues analyses, use patterns and residues resulting from supervised trials on grapefruit, lemons, mandarins, oranges, apples, pears, cherries, peaches, plums, blackberries, currants, grapes, raspberries, strawberries, papayas, cucumbers, gherkins, sweet peppers, tomatoes, almonds, coconuts, pecans, coffee, and hops, fates of residue during processing, processing, distribution in the edible portion and livestock feeding studies. In addition, the Meeting received information from the Netherlands, on use patterns.

Chemical name:

Spirodiclofen or 3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutyrate

Structural formula:



Metabolites referred to in the appraisal by codes:

M04: 2,4-dichloro-mandelic acid cyclohexyl ester glycosyl pentoside

M05: 2,4-dichloro-mandelic acid hydroxy-cyclohexyl ester

M08: 2,4-dichloro-mandelic acid glucoside

Animal metabolism

The Meeting received results of animal metabolism studies in a lactating goat. Experiments were carried out using spirodiclofen ^{14}C labelled in the 3-position of the dihydrofuranone ring.

Metabolism in laboratory animals was summarized and evaluated by the WHO panel of the JMPR in 2009.

A lactating goat, orally treated once daily for 3 consecutive days with [^{14}C]spirodiclofen at a calculated dose rate of 252 ppm in the dry weight feed (equivalent to 10.7 mg ai/kg bw/d), was sacrificed 6 hours after the last dose. Of the administered dose 72% was recovered of which 28% was found in faeces, 17% in urine, while 54% remained in the gastro-intestinal tract. Tissues contained 0.29%, while milk contained 0.05% of the recovered radioactivity. The radioactivity in the tissues ranged from 2.9 mg/kg in kidney and 0.78 mg/kg in liver to 0.14 mg/kg in fat and 0.068 mg/kg

spirodiclofen equivalents in muscle. Radioactivity in milk increased until sacrifice to a level of 0.20 mg/L spirodiclofen equivalents. A plateau was not reached after three days of dosing.

Radioactivity was characterized in tissues and milk. No spirodiclofen (parent) was found in any of the tissues or in milk. The major metabolite was spirodiclofen-enol (M01) at 95% of the total radioactivity in kidney, 81% in liver, 85% in fat, 84% in muscle, and 82–86% in milk. 4-OH-enol spirodiclofen (M03) was identified as minor metabolite at levels up to 9% of the total radioactivity. A minor part of the extractable residue in tissues and milk remained unidentified (3.2–20% of the total radioactivity). Radiochromatograms showed that these residues did not occur in relevant amounts. Only up to 7% of the total radioactivity remained unextracted.

The absorbed dose was extensively metabolised as evidenced by full disappearance of the parent compound in tissues and milk.

One basic metabolic pathway of spirodiclofen in goat is proposed. The metabolic pathway consists of cleavage of the alkyl ester group resulting in spirodiclofen-enol (major metabolite) followed by hydroxylation of spirodiclofen-enol in the 4-position of the cyclohexyl ring, forming 4-OH-enol spirodiclofen (minor metabolite).

The metabolic pathway proposed for ruminants is consistent with that for rats, except that spirodiclofen is metabolised further in rats.

Plant metabolism

The Meeting received plant metabolism studies for spirodiclofen spray treatments on fruit (lemons, oranges, apples and grapes) and topical treatments on grapefruit leaves and hop leaves. Experiments were carried out using spirodiclofen ^{14}C labelled in the 3-position of the dihydrofuranone ring.

Greenhouse grown lemon trees were sprayed with [^{14}C]spirodiclofen once at a dose rate of 0.45 kg ai/ha. Total radioactive residues (TRR) in the lemon fruit harvested 21 days following the last application were 0.263 mg/kg spirodiclofen equivalents. The radioactivity was almost exclusively located in/on the peel (99.8% of the total radioactivity). Washing with acetonitrile removed 62% of the total radioactivity. The main component in the lemon peel was the parent compound, accounting for 75% of the total radioactivity. A total of 27 metabolites could be found, together amounting to 22% of the total radioactivity. None of these metabolites exceeded 3% of the total radioactivity or 0.01 mg/kg spirodiclofen equivalents.

Greenhouse grown orange trees were sprayed with [^{14}C]spirodiclofen once at a dose rate equivalent to 0.6 kg ai/ha. Total radioactive residues in the orange fruit harvested 160 days after the application were 0.072 mg/kg spirodiclofen equivalents. The radioactivity was almost exclusively located in/on the peel (92% of the total radioactivity). Washing with acetonitrile removed 56% of the total radioactivity. The main component in the orange peel was the parent compound, accounting for 34% of the total radioactivity. A total of 22 metabolites could be found, together amounting to 52% of the total radioactivity. None of these metabolites exceeded 10% of the total radioactivity or 0.01 mg/kg spirodiclofen equivalents. Of the total radioactivity 6% remained unextracted from the peel.

Field grown apple trees were sprayed with [^{14}C]spirodiclofen once at a dose rate of 1.1 kg ai/ha. Total radioactive residues in the apple fruit harvested 23 and 84 days following application were 0.85 and 0.39 mg/kg spirodiclofen equivalents. The vast majority of the total radioactivity could be removed by surface washing with dichloromethane and acetone: 98% and 83% for 23 and 84 day samples, respectively. The main component in apple fruit was the parent compound, accounting for 89–99% of the total radioactivity. A total of 10–11 metabolites could be found, together amounting to 0.5–10% of the total radioactivity. Only one metabolite was found in quantifiable amounts and was identified as M08 (4.5% of the total radioactivity).

Field grown grape vines were sprayed with [^{14}C]spirodiclofen once at a dose rate of 0.224 kg ai/ha. Total radioactive residues in the grape berries harvested 21 and 64 days following the

application were 1.9 and 1.1 mg/kg spirodiclofen equivalents. The majority of the total radioactivity could be removed by surface washing with dichloromethane: 96% and 57% for 21 and 64 day harvest samples, respectively. The main component in the grape berries was the parent compound, accounting for 58%–96% of the total radioactivity. In the 23 day harvest day samples, a total of 11 metabolites could be found, together amounting to 3.5% of the total radioactivity. In the 64 day harvest samples, a total of 17 metabolites could be found, together amounting to 41% of the total radioactivity. Four metabolites were found as quantifiable amounts and these were identified as M08 (12.2 % of the total radioactivity), M04 (7.9% of the total radioactivity), M05 (7.2% of the total radioactivity), and 3-OH-enol spirodiclofen (2.6% of the total radioactivity).

Grapefruit leaves from greenhouse grown trees were treated topically with [^{14}C]spirodiclofen at 0.45 kg ai/ha and adjacent fruits were harvested 85 days later. Sampled fruit contained only 0.09% of the applied dose and total radioactive residues in the fruit were less than 0.01 mg/kg spirodiclofen equivalents. This translocation study indicates that spirodiclofen does not move systemically through the plant, which is consistent with the approximate log K_{ow} of 5.8.

In each commodity tested, spirodiclofen was found to be the major residue (34%–99% of the total radioactivity). The radioactive residue primarily resided on the surface of the fruits. A total of 11–27 metabolites could be found which accounted for the remainder of the residue. In lemons and oranges none of these metabolites was present in quantifiable amounts. In apples, only one metabolite was found in quantifiable amounts and was identified as M08 (4.5% of the total radioactivity). In grapes, four metabolites were found in quantifiable amounts and these were identified as M08 (12% of the total radioactivity), M04 (7.9% of the total radioactivity), M05 (7.2% of the total radioactivity), and 3-OH-enol spirodiclofen (2.6% of the total radioactivity). The formation of these metabolites is time-dependent. Quantifiable amounts of these metabolites were only found in the apple and grape samples with long pre-harvest intervals (64–84 days).

The following metabolic pathway of spirodiclofen is proposed. The initial degradation reaction is cleavage of the ester bond forming the spirodiclofen-enol compound, followed by hydroxylation of spirodiclofen-enol in the 3- or 4- position of the cyclohexyl ring. Cleavage of the acid ring structure leads to a ring-open mandelic acid cyclohexyl ester intermediate which is further metabolised by derivatisation of this intermediate (hydroxylation, conjugation with carbohydrates) or by further degradation into the free 2,4-dichloro-mandelic acid, finally followed by glycosylation.

Plant metabolites identified were also found in rats, except for M05, M04 and M08. The latter two metabolites are sugar conjugates of minor metabolites found in rats. M05 is an intermediate in the degradation to 2,4-dichloro-mandelic acid, which is found in rats.

Environmental fate

The Meeting received information on the hydrolysis and photolysis of spirodiclofen in sterile water. Experiments were carried out using spirodiclofen ^{14}C labelled in the 3-position of the dihydrofuranone ring (hydrolysis, photolysis) or ^{14}C labelled at the cyclohexyl 1-position (photolysis).

Spirodiclofen is regarded as hydrolytically stable at pH 4 at ambient temperature, but is unstable at pH 7 and 9. The half-life for spirodiclofen at 20 °C was calculated as 119.6 days at pH 4, 52.1 days at pH 7 and 2.5 days at pH 9. Spirodiclofen is degraded by ester cleavage with the formation of spirodiclofen-enol.

A photolysis study was conducted with artificial sunlight, equivalent to 28.5 days of natural sunlight. Half life was 54 days for natural sunlight at summer. Since the pH during the experiment ranged from 4.4 to 5.6, part of the degradation might have been caused by hydrolysis. The half life must be considered an estimate. Spirodiclofen is degraded by ester cleavage with the formation of spirodiclofen-enol.

Methods of Analysis

The Meeting received description and validation data for analytical methods for enforcement-monitoring of spirodiclofen and some of its metabolites and residue analytical methods used in the various study reports for spirodiclofen and its metabolites.

Four analytical methods were proposed to the Meeting as post-registration monitoring and enforcement method for parent spirodiclofen in crops and animal commodities. Two of these methods also determined metabolite spirodiclofen-enol.

The Meeting considers the GC-ECD version of multi-residue method DFG S19 sufficiently validated for the determination of parent spirodiclofen in plant commodities with high water content, plant commodities with high acid content, plant commodities with high fat content, dry plant commodities, animal tissues, milk and eggs. The HPLC-MS-MS multi-residue method 109351 is considered sufficiently validated for the determination of parent spirodiclofen in plant commodities with high acid content, plant commodities with high water content and plant commodities with high fat content. The two HPLC-MS-MS single-residue methods 109720 and 00919 are considered sufficiently validated for the determination of parent and metabolite spirodiclofen-enol in animal tissues and milk. The use of deuterated standards in method 109720 makes the method very expensive and therefore less suitable as an enforcement-monitoring method for world-wide use.

The methods reported to the Meeting and used in the supervised residue trials, processing studies, storage stability studies and feeding studies determined parent spirodiclofen and in some cases also the metabolites spirodiclofen-enol, 3-OH-enol spirodiclofen and 4-OH-enol spirodiclofen. Macerated samples were extracted with acetone, acetonitrile/water (2:1), acetonitrile/water/20% cysteine HCl (200:100:1, v/v/v), acetonitrile/0.1% aqueous formic acid (4:1, v/v) or acetone/dichloromethane/petroleum ether (1:1:1, v/v/v). The extract was cleaned up by solvent partition and/or column chromatography and/or solid phase extraction, if necessary. The final residue could then be determined by GC-ECD or HPLC-MS-MS. LOQs were in the 0.004–1.0 mg/kg range for spirodiclofen and its metabolites.

Extraction efficiencies for acetone and acetonitrile/water (2:1) were verified using samples with incurred radioactive residues from metabolism studies on oranges (180 day harvest sample), apples (84 day harvest sample) and grapes (21 day harvest sample). Extraction efficiency for acetone for spirodiclofen was 94–99% in apples. Extraction efficiency for acetonitrile/water (2:1) for spirodiclofen was 124%, 92%–100% and 96%, respectively in orange peel, apples and grapes. The Meeting considered the extraction efficiencies for the extraction solvents as used in the analytical methods sufficient.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of spirodiclofen in samples stored frozen.

Parent spirodiclofen was stable when stored frozen for at least 13 months in crops with high water content (peaches), at least 24 months in crops with high acid content (citrus and grapes), 16 months in crops with oil content (almond nutmeat, and dry hop cones), at least 8 months in fruit juice (apple juice and grape juice), and at least 10 months in dried fruit (dried apples, raisins and dried plums).

No storage stability studies were provided for animal commodities. Since the samples from the animal feeding study were analysed within 30 days after slaughter, there is no need to have storage stability studies on animal commodities.

Definition of the residue

In goats, the absorbed dose was extensively metabolised as evidenced by full disappearance of the parent compound in tissues and milk. The major metabolite was spirodiclofen-enol at 95% of the total radioactivity in kidney, 81% in liver, 85% in fat, 84% in muscle, and 82–86% in milk.

However, the Meeting noted that in a feeding study on lactating cows, which is described later, at a dose rate of 13 ppm dry feed, residues of up to 0.011 and 0.012 mg/kg spirodiclofen were found in milk fat (cream) and beef fat, respectively.

The metabolism study in goats was conducted at an exaggerated dose rate of 252 ppm and a feeding study on dairy cows was conducted at moderate levels of 1.3–13 ppm dry feed. Since anticipated livestock dietary burdens are below 1 ppm dry feed, no residues are expected in animal commodities. The feeding studies show that the first compound to be detected at exaggerated dose rates will be the parent compound in fat and spirodiclofen-enol in kidney. Since kidney is not an important commodity for enforcement, and fat is, the Meeting concluded that parent spirodiclofen is a suitable analyte in animal commodities for enforcement purposes. For dietary risk assessment spirodiclofen and spirodiclofen-enol are considered suitable analytes.

Based on the available comparative plant metabolism studies, parent spirodiclofen is the major component (34–99% of the total radioactivity TRR) of the crops tested. Quantifiable amounts of metabolites identified in plant commodities but not found in rat and livestock (goat), were M05 (7.2% TRR), M04 (7.9% TRR) and M08 (4.5–12% TRR). The latter two metabolites are sugar conjugates of minor metabolites found in the rat. Limited toxicology data were provided for M05, and no toxicology data were provided for the other two plant metabolites. The Meeting therefore concluded that sufficient information was not available to conduct a hazard assessment for these metabolites. Spirodiclofen-enol was detected in plants (2.1% TRR), livestock matrices (82–95% TRR) and rats. As spirodiclofen-enol was found to be of similar toxicity to the parent compound, it is considered to be toxicologically relevant for the dietary risk assessment.

Given the predominant presence of spirodiclofen in the fruit residues, none of these plant metabolites should be included in the residue definition, as none of these metabolites are expected to be present at levels above 0.01 mg/kg at the GAPs considered for the present evaluation. The Meeting concluded that parent spirodiclofen is a suitable analyte in plant commodities for enforcement purposes and for dietary risk assessment.

Fat solubility of spirodiclofen (parent) is shown in a feeding study on cows, where spirodiclofen was only found in milk fat and beef fat and not in any of the other tissues. The log K_{ow} for spirodiclofen of approximately 5.8 also suggests fat solubility. The Meeting considered the residue in animal commodities (spirodiclofen) to be fat-soluble.

The Meeting recommended the following as residue definitions for spirodiclofen:

Definition of the residue for compliance with the MRL or for estimation of the dietary intake for plant commodities: *spirodiclofen*

Definition of the residue for compliance with the MRL for animal commodities: *spirodiclofen.*

Definition of the residue for estimation of the dietary intake for animal commodities: *the sum of spirodiclofen and spirodiclofen-enol, expressed as spirodiclofen.*

The Meeting considers the residue in animal commodities to be fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised residue trial data for spirodiclofen on grapefruit, lemons, mandarins, oranges, apples, pears, cherries, peaches, plums, blackberries, currants, grapes,

raspberries, strawberries, papayas, cucumbers, gherkins, sweet peppers, tomatoes, almonds (nutmeat and hulls), coconuts, pecans, coffee and hops.

As an ARfD was considered unnecessary, no HR values are reported as an IESTI calculation was not needed.

The NAFTA 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 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 NAFTA 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 supplied. Some common factors that may lead to rejection of the statistical estimate include when the number of data points in a data set is < 15 or when there are a large number of values < LOQ.

Citrus fruits

Field trials involving grapefruit were performed in the USA. GAP for citrus in the USA is for one spray application at 0.35 kg ai/ha (PHI 7 days). In trials from the USA matching this GAP (1 × 0.343–0.387 kg ai/ha, PHI 7 days), spirodiclofen residues in grapefruit whole fruit were 0.032, 0.087, 0.088, 0.099, 0.12 and 0.31 mg/kg (n=6) from low volume spraying and 0.085, 0.090, 0.093, 0.13, 0.14 and 0.18 mg/kg (n=6) from normal (high or dilute) volume spraying on/under the same locations/conditions. In those cases where residues at a longer PHI were higher, these residues were selected for use in the estimation.

The Meeting noted that the residues corresponding to low volume spray and normal spray were from similar populations (Mann-Whitney U test) and because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in the following dataset for grapefruit whole fruit: 0.087, 0.09, 0.093, 0.13, 0.18 and 0.31 mg/kg (n=6).

Field trials involving lemons were performed in the USA. GAP for citrus in the USA is for one spray application at 0.35 kg ai/ha (PHI 7 days). In trials from the USA matching this GAP (1 × 0.340–0.376 kg ai/ha, PHI 7 days), spirodiclofen residues in lemon whole fruit were 0.041, 0.046, 0.16, 0.19 and 0.32 mg/kg (n=5) from low volume spraying and 0.026, 0.048, 0.13, 0.16 and 0.24 mg/kg (n=5) from normal spraying on/under the same locations/conditions. In those cases where residues at a longer PHI were higher, these residues were selected for use in the estimation.

The Meeting noted that the residues corresponding to low volume and normal spraying were from similar populations (Mann-Whitney U test) and because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in the following dataset for lemon whole fruit: 0.046, 0.048, 0.16, 0.19 and 0.32 mg/kg (n=5).

Field trials involving mandarins were performed in Spain, Portugal and Italy. GAP for citrus in Spain is for one spray application at 0.0048 kg ai/hL (PHI 14 days). In trials from Spain, Portugal and Italy matching this GAP (1 × 0.0048 kg ai/hL, PHI 14 days), spirodiclofen residues in mandarin whole fruit were: 0.021, 0.034, 0.042, 0.047, 0.050, 0.053, 0.059 and 0.076 mg/kg (n=8). In those cases where residues at a longer PHI were higher, these residues were selected for use in the estimation.

Field trials involving oranges were performed in Spain, Portugal, Italy, South Africa, Brazil and the USA. GAP for citrus in Spain is for one spray application at 0.0048 kg ai/hL (PHI 14 days). In trials from Spain, Portugal and Italy matching this GAP (1 × 0.0048 kg ai/hL, PHI 13–16 days), spirodiclofen residues in orange whole fruit were: < 0.02, 0.030, 0.034, 0.034, 0.047, 0.049, 0.053 and 0.055 mg/kg (n=8). In those cases where residues at a longer PHI were higher, these residues were selected for use in the estimation.

GAP for "citrus excluding lemon and kumquat" in South Africa is for one spray application at 0.0036 kg ai/hL (PHI 76 days). The Meeting considered trials with two applications (2 × 0.0036 kg ai/hL, interval 56–64 days, PHI 71–76 days) acceptable, since residue results from two applications at such long intervals are unlikely to differ from single applications. Spirodiclofen residues were: < 0.01 and 0.01 mg/kg (n=2).

GAP for citrus in Brazil is for one spray application at 0.0072 kg ai/hL (PHI 21 days). Field trials performed in Brazil did not match the GAP.

GAP for citrus in the USA is for one spray application at 0.35 kg ai/ha (PHI 7 days). In trials from the USA matching this GAP (1 × 0.340–0.395 kg ai/ha, PHI 7 days), spirodiclofen residues in orange whole fruit were 0.041, 0.051, 0.066, 0.11, 0.11, 0.12, 0.12, 0.13, 0.14, 0.14 and 0.15 mg/kg (n=11) from low volume spraying and 0.066, 0.081, 0.082, 0.098, 0.099, 0.12, 0.13, 0.13, 0.14, 0.14, 0.20 and 0.22 mg/kg from normal spraying (n=12) on/under the same locations/conditions. In those cases where residues at a longer PHI were higher, these residues were selected for use in the estimation.

The Meeting noted that the residues corresponding to low volume and normal spray applications were from similar populations (Mann-Whitney U test) and because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in the following dataset for orange whole fruit: 0.066, 0.082, 0.11, 0.11, 0.12, 0.13, 0.13, 0.14, 0.14, 0.14, 0.2 and 0.22 mg/kg (n=12).

The South African dataset was considered insufficient to support a recommendation. The Meeting noted that the residues based on the GAP for USA were higher than the residues based on the GAP for Spain (Mann-Whitney U test) and decided to use only the orange data corresponding to the USA GAP.

The Meeting noted that the Spanish dataset for mandarins had lower residues than the USA datasets for grapefruit, lemons or oranges (Kruskal-Wallis test) and agreed to use only the citrus data from the USA.

The Meeting noted that the USA datasets from grapefruit, lemon and orange were from similar populations (Kruskal-Wallis test). Since residue behaviour within the citrus group is expected to be similar, the Meeting agreed that the datasets could be combined. Spirodiclofen residues in citrus whole fruit were: 0.046, 0.048, 0.066, 0.082, 0.087, 0.09, 0.093, 0.11, 0.11, 0.12, 0.13, 0.13, 0.13, 0.14, 0.14, 0.14, 0.16, 0.18, 0.19, 0.2, 0.22, 0.31 and 0.32 mg/kg (n=23).

The Meeting agreed that the USA data on grapefruit, lemon and orange could be used to support a citrus fruit commodity group maximum residue level and estimated a maximum residue level of 0.4 mg/kg for spirodiclofen on citrus fruit and estimated an $STMR_{RAC}$ of 0.13 mg/kg for spirodiclofen in citrus whole fruit (for processing purposes).

The value derived from use of the NAFTA calculator (NAFTA 95/99 95th percentile) was 0.4 mg/kg, which was in agreement with the estimate of made by the Meeting.

Spirodiclofen residue data on the edible portion of citrus fruit at the relevant GAPs were not available. Residue trials on the distribution of peel and pulp in mandarins and orange at a longer PHI of 28 days showed that no residues are found in pulp (< 0.02 mg/kg). Metabolism studies in grapefruit and lemon confirm that spirodiclofen residues reside in the peel. The Meeting estimated an STMR of 0.02 mg/kg in the edible portion (pulp/flesh) of citrus fruit.

Pome fruits

Field trials involving apples were performed in Germany, Belgium, the United Kingdom, France, Spain, Italy, USA, Canada and Brazil.

GAP for pome fruit in Germany is for one spray application at 0.0096 kg ai/hL (PHI 14 days). In trials from Germany, Belgium, United Kingdom and France matching this GAP

(1 × 0.0096 kg ai/hL, PHI 14 days), spirodiclofen residues in apple, whole fruit, were 0.025, 0.035, 0.039, 0.043, 0.049, 0.049, 0.059 and 0.077 mg/kg (n=8). In those cases where residues at a longer PHI were higher, these residues were selected for use in the estimation.

GAP for apples in Italy is for one spray application at 0.14 kg ai/ha (PHI 14 days). In trials from Italy and Spain matching this GAP (1 × 0.120–0.144 kg ai/ha, PHI 14 days), spirodiclofen residues in apple whole fruit were < 0.02, 0.024, 0.046 and 0.055 mg/kg (n=4).

GAP for pome fruit in the USA is for one spray application at 0.32 kg ai/ha (PHI 7 days). In trials from the USA and Canada matching this GAP (1 × 0.297–0.356 kg ai/ha, PHI 7–8 days), spirodiclofen residues in apple whole fruit were < 0.01, 0.069, 0.070, 0.094, 0.099, 0.10, 0.11, 0.13, 0.13, 0.13, 0.18, 0.2, 0.22, 0.23, 0.24, 0.25, 0.34, 0.40 and 0.50 mg/kg (n=19) for low volume spray and 0.061, 0.080, 0.087, 0.091, 0.1, 0.11, 0.12, 0.13, 0.18, 0.18, 0.18, 0.21, 0.21, 0.22, 0.23, 0.26 and 0.28 mg/kg (n=17) for normal spray on/under the same locations/conditions. In addition on two of these locations comparisons were made between SC formulations (0.10, 0.13, 0.18 and 0.18 mg/kg) and WG formulations (0.1, 0.11, 0.11 and 0.13 mg/kg). In those cases where residues from a longer PHI were higher, these residues were selected for use in the estimation.

The Meeting noted that the residues corresponding to low volume spray and normal spray were from similar populations (Mann-Whitney U test) and that the residues corresponding to SC and WG formulations are from similar populations (Mann-Whitney U test). Because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in the following dataset for apple whole fruit: 0.07, 0.08, 0.087, 0.094, 0.099, 0.18, 0.18, 0.18, 0.20, 0.21, 0.22, 0.24, 0.25, 0.28, 0.34, 0.40 and 0.50 mg/kg (n=17).

GAP for apples in Brazil is for one spray application at 0.0048 kg ai/hL (PHI 7 days). In trials from Brazil matching this GAP (1 × 0.0048 kg ai/hL, PHI 7 days), spirodiclofen residues in apple whole fruit were 0.17, 0.18 and 0.18 mg/kg (n=3).

The Brazilian dataset was considered insufficient to support a maximum residue level recommendation. The Meeting noted that the dataset for apples from the USA gave higher residues than either the German or Italian datasets for apples (Kruskal-Wallis test) and agreed to use only the apple data from the USA.

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

GAP for pears in Italy is for one spray application at 0.14 kg ai/ha (PHI 14 days). In trials from Italy and France matching this GAP (1 × 0.120–0.144 kg ai/ha, PHI 14 days), spirodiclofen residues in the whole fruit of pears were: 0.027, 0.035, 0.039 and 0.043 mg/kg (n=4).

GAP for pome fruit in the USA is for one spray application at 0.32 kg ai/ha (PHI 7 days). In trials from the USA and Canada matching this GAP (1 × 0.312–0.326 kg ai/ha, PHI 6–7 days), spirodiclofen residues in pears (whole fruit) were: 0.10, 0.11, 0.12, 0.14, 0.15, 0.19, 0.24, 0.31, 0.31, 0.45 and 0.70 mg/kg (n=11) for low volume spray and 0.10, 0.14, 0.17, 0.18, 0.18, 0.20, 0.20, 0.28 , 0.41 and 0.42 mg/kg (n=10) for dilute spray on/under the same locations/conditions. In addition, at one of the trial locations comparisons were made between SC formulations (0.14 and 0.31 mg/kg) and WG formulations (0.15 and 0.15 mg/kg). In those cases where residues at a longer PHI were higher, these residues were selected.

The Meeting noted that the residue populations corresponding to low volume spray and normal spray are from similar populations (Mann-Whitney U test) and that the residue populations corresponding to SC and WG formulations are from similar populations. Because only one residue could be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in the following dataset for pears (whole fruit): 0.10, 0.17, 0.18, 0.20, 0.20, 0.24, 0.31, 0.31, 0.45 and 0.70 mg/kg (n=10).

The Meeting noted that the dataset from the USA for pears had higher residues than that of the Italian dataset (Mann-Whitney U test) and decided to use only the pear data corresponding to the GAP of the USA.

The Meeting noted that the US datasets for apples and pears were from similar populations (Mann-Whitney U test). Since residue behaviour within the pome fruit group is expected to be similar, the Meeting agreed that they could be combined. Spirodiclofen residues in pome fruit (whole fruit) were: 0.070, 0.080, 0.087, 0.094, 0.099, 0.10, 0.17, 0.18, 0.18, 0.18, 0.18, 0.20, 0.20, 0.20, 0.21, 0.22, 0.24, 0.24, 0.25, 0.28, 0.31, 0.31, 0.34, 0.40, 0.45, 0.50 and 0.70 mg/kg (n=27).

The Meeting agreed that the US data for apples and pears could be used to support a pome fruit commodity group maximum residue level recommendation and estimated a maximum residue level of 0.8 mg/kg for spirodiclofen on pome fruit and estimated and STMR of 0.20 mg/kg for spirodiclofen in pome fruit.

The value derived from use of the NAFTA calculator (NAFTA 95/99 95th percentile) was 0.76 mg/kg, which was comparable with the estimate made by the Meeting (after rounding up to one figure).

Stone fruit

Field trials involving cherries were performed in Germany, Spain, Italy, and the USA.

For trials performed in Germany, Spain and Italy no GAP was available.

GAP for stone fruit in the USA is for one spray application at 0.32 kg ai/ha (PHI 7 days). In trials from the USA matching this GAP (1 × 0.309–0.325 kg ai/ha, PHI 7 days), spirodiclofen residues in cherry whole fruit were: 0.14, 0.14, 0.15, 0.16, 0.17, 0.17, 0.24, 0.27, 0.28, 0.29, 0.31, 0.35, 0.49, 0.50 and 0.62, mg/kg (n=15) from low volume spraying and 0.12, 0.17, 0.18, 0.19, 0.20, 0.21, 0.23, 0.24, 0.26, 0.29, 0.34, 0.35, 0.53, 0.66 and 0.73 mg/kg (n=15) from dilute spraying at/under the same locations or conditions. In addition at three of these locations comparisons were made between SC formulations (0.14, 0.17, 0.17, 0.19, 0.53 and 0.62 mg/kg) and WG formulations (0.12, 0.14, 0.15, 0.21, 0.24 and 0.49 mg/kg). In those cases where residues at a longer PHI were higher, these residues were selected.

The Meeting noted that the residues corresponding to low volume and dilute spraying were from similar populations (Mann-Whitney U test) and that the residues corresponding to the SC and WG formulations were from similar populations (Mann-Whitney U test). Because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in a dataset for cherry, whole fruit of: 0.18, 0.19, 0.20, 0.21, 0.27, 0.29, 0.34, 0.35, 0.35, 0.62, 0.66 and 0.73 mg/kg (n=12).

Field trials involving peaches were performed in Germany, France, Spain, Italy, and the USA.

German GAP for peaches is for one spray application at 0.0096 kg ai/hL (PHI 14 days). In a trial from Germany matching this GAP (1 × 0.0096 kg ai/hL, PHI 14 days), spirodiclofen residues in peach whole fruit were 0.12 mg/kg.

Italian GAP for peaches is for one spray application at 0.14 kg ai/ha (PHI 14 days). In trials from Italy, France and Spain matching this GAP (1 × 0.109–0.144 kg ai/ha, PHI 14 days), spirodiclofen residues in peach whole fruit were: < 0.02, < 0.02, 0.020, 0.027, 0.037, 0.047 and 0.096 mg/kg (n=7). In those cases where residues at a longer PHI were higher, these residues were selected.

GAP for stone fruit in the USA is for one spray application at 0.32 kg ai/ha (PHI 7 days). In trials from the USA matching this GAP (1 × 0.311–0.339 kg ai/ha, PHI 6–7 days), spirodiclofen residues in peach whole fruit were: 0.15, 0.18, 0.24, 0.25, 0.26, 0.29, 0.29, 0.32, 0.36, 0.41, 0.49, 0.50, 0.51 and 0.52 mg/kg (n=14) from low volume spraying and 0.14, 0.16, 0.18, 0.25, 0.27, 0.28,

0.28, 0.29, 0.29, 0.39, 0.52, 0.61, 0.77, 0.86 and 0.89 mg/kg (n=15) from dilute spraying at/under the same locations or conditions. In addition, at three locations comparisons were made between SC formulations (0.16, 0.26, 0.39, 0.49, 0.51 and 0.52 mg/kg) and WG formulations (0.14, 0.18, 0.27, 0.41, 0.52 and 0.86 mg/kg). In those cases where residues at a longer PHI were higher, these residues were selected.

The Meeting noted that the residues corresponding to low volume and dilute spraying were from similar populations (Mann-Whitney U test) and that the residues corresponding to SC and WG formulations were from similar populations (Mann-Whitney U test). Because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in the following dataset for peach whole fruit: 0.24, 0.25, 0.26, 0.28, 0.29, 0.29, 0.36, 0.51, 0.61, 0.77, 0.86 and 0.89 mg/kg (n=12).

The German dataset was considered insufficient to support a recommendation. The Meeting noted that the dataset from the USA for peaches had higher residues than the Italian dataset for peaches (Mann-Whitney U test) and decided to use only the peach data corresponding to the GAP of the USA.

Field trials involving plums were performed in Germany, the Netherlands, Belgium, Spain, Italy, the USA and Canada.

GAP for plums in Germany is for one spray application at 0.0096 kg ai/hL (PHI 21 days). In trials from Germany, the Netherlands, Belgium, Spain and Italy matching this GAP (1 × 0.0084–0.0096 kg ai/ha, PHI 21–22 days), spirodiclofen residues in plum whole fruit were: 0.016, 0.02, 0.023, 0.03, 0.03, 0.035 and 0.05 mg/kg (n=7) for northern European trials and 0.02 and 0.02 mg/kg (n=2) for southern European trials. In those cases where residues at a longer PHI were higher, these residues were selected.

The Meeting noted that the residue populations corresponding to northern and southern European trials were from similar populations and could be combined. This resulted in the following dataset: 0.016, 0.02, 0.02, 0.02, 0.023, 0.03, 0.03, 0.035 and 0.05 mg/kg (n=9)

The GAP for stone fruit in the USA is for one spray application at 0.32 kg ai/ha (PHI 7 days). In trials from the USA and Canada matching this GAP (1 × 0.307–0.326 kg ai/ha, PHI 6–7 days), spirodiclofen residues in plums, whole fruit, were: 0.014, 0.014, 0.017, 0.028, 0.036, 0.037, 0.053, 0.073, 0.090, 0.15 and 0.19 mg/kg (n=11) for low volume spray and < 0.01, 0.013, 0.024, 0.031, 0.044, 0.047, 0.066, 0.089, 0.11, 0.11 and 0.16 mg/kg (n=11) for normal or dilute spraying, on/under the same locations/conditions. In addition, on one of these locations comparisons were made between SC formulations (0.089 and 0.15 mg/kg) and WG formulations (0.073 and 0.11 mg/kg). In those cases where residues at a longer PHI were higher, these residues were selected instead.

The Meeting noted that the residue populations corresponding to low volume spray and normal spray are from similar populations (Mann-Whitney U test) and that the residue populations corresponding to SC and WG formulations are from similar populations. Because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in the following dataset for plum whole fruit: 0.014, 0.017, 0.028, 0.031, 0.044, 0.047, 0.066, 0.11, 0.15 and 0.19 mg/kg (n=10).

The Meeting noted that the GAP for USA resulted in a similar dataset when compared to the GAP for Germany (Mann-Whitney U test). However, as the GAPs are different the data cannot be combined. Since the highest residues are found in the US dataset, the Meeting decided to use only the plum data corresponding to the GAP of the USA.

The Meeting noted that the USA dataset for plums had lower residues than the USA datasets for cherries and peaches (Kruskal-Wallis test). The Meeting noted that the USA datasets from cherries and peaches were from similar populations (Mann-Whitney U test) and agreed that they could be combined. Spirodiclofen residues in whole fruit were: 0.18, 0.19, 0.20, 0.21, 0.24, 0.25,

0.26, 0.27, 0.28, 0.29, 0.29, 0.29, 0.34, 0.35, 0.35, 0.36, 0.51, 0.61, 0.62, 0.66, 0.73, 0.77, 0.86 and 0.89 mg/kg (n=24).

The Meeting agreed that the USA data on cherries and peaches could be used to support a stone fruit commodity group recommendation and estimated a maximum residue level of 2 mg/kg for spirodiclofen on stone fruit and estimated and STMR of 0.315 mg/kg for spirodiclofen in stone fruit.

The value derived from use of the NAFTA calculator (NAFTA 95/99 95th percentile) was 1.2 mg/kg, which was comparable with the estimate made by the Meeting after rounding up to one significant figure.

Berries and other small fruits

Field trials involving blackberries were performed in Germany. However, for trials performed in Germany no GAP was available.

The Meeting agreed that data were insufficient to estimate a maximum residue level for blackberries.

Field trials involving currants were performed in Germany. GAP for currants in Germany is for one spray application at 0.096 kg ai/ha (PHI 14 days). In trials from Germany matching this GAP (1 × 0.096 kg ai/ha, PHI 14 days), spirodiclofen residues in currants were 0.026, 0.040 and 0.44 mg/kg (n=3). In those cases where residues at a longer PHI were higher, these residues were selected instead.

The Meeting estimated a maximum residue level of 1 mg/kg for spirodiclofen on currants and estimated and STMR of 0.040 mg/kg for spirodiclofen in currants.

The value derived from use of the NAFTA calculator (NAFTA UCL median 95) of 0.64 mg/kg differed from the estimate of 1.0 mg/kg made by the Meeting. The recommendation of the Meeting was higher in recognition of the low number of data points (n=3) and the high variability within the data.

Field trials involving grapes were performed in Germany, France, Spain, Italy, Portugal, Greece, USA and Canada.

GAP for grapes in Germany is for one spray application at 0.0096 kg ai/hL (PHI 14 days). In trials from Germany matching this GAP (1 × 0.0096 kg ai/hL, PHI 14 days), spirodiclofen residues in grape bunches were: 0.044, 0.058, 0.067, 0.089, 0.10 mg/kg (n=5). In those cases where residues at a longer PHI were higher, these residues were selected instead. Spirodiclofen residues in berries were: 0.036, 0.060, 0.069, 0.074 and 0.084 mg/kg (n=5).

GAP for grapes in Italy is for one spray application at 0.096 kg ai/ha (PHI 14 days). In trials from France, Spain, Italy, Portugal and Greece matching this GAP (1 × 0.096 kg ai/ha, PHI 14 days), spirodiclofen residues in grape bunches were: 0.025, 0.030, 0.034, 0.037, 0.045, 0.052, 0.063, 0.064, 0.066, 0.069, 0.071, 0.072 and 0.11 mg/kg (n=13). In those cases where residues at a longer PHI were higher, these residues were selected. Spirodiclofen residues in berries were: 0.021, 0.023, 0.026, 0.041, 0.044, 0.049, 0.059, 0.061, 0.062, 0.062, 0.072, 0.075 and 0.077 mg/kg (n=13).

Trials performed in the USA and Canada did not match the available GAPs for the USA or Canada.

The Meeting noted that the datasets from Germany and Italy are from similar populations (Mann-Whitney U test). Since the GAPs are different, the datasets cannot be combined. Since the Italian dataset is larger than the German dataset, the Meeting agreed to use only the dataset from Italy. The Meeting estimated a maximum residue level of 0.2 mg/kg for spirodiclofen on grapes and estimated an STMR of 0.059 mg/kg for spirodiclofen in the edible portion of the grape bunches (berries). For purposes of calculating residues in processed grape commodities an $STMR_{RAC}$ of 0.063 mg/kg was estimated based on grape bunches (with stems).

The value derived from use of the NAFTA calculator (NAFTA 95/99 95th percentile) was 0.14 mg/kg, which agreed with the estimate made by the Meeting (after rounding up to one figure).

Field trials involving raspberries were performed in Germany. For trials performed in Germany no GAP was available.

The Meeting agreed that data were insufficient to estimate a maximum residue level for raspberries.

Field trials involving strawberries were performed in Germany, the United Kingdom, the Netherlands and France. Indoor trials involving strawberries were performed in Germany, Belgium, the Netherlands, France, Spain and Italy.

GAP for strawberries in the Netherlands is for two spray applications at 0.0096 kg ai/hL (PHI 3 days) in the field. In field trials from Germany, the United Kingdom, the Netherlands and France matching this GAP (2 × 0.0096 kg ai/hL, PHI 3 days), spirodiclofen residues in strawberry fruit were: 0.022, 0.041, 0.047, 0.06, 0.063, 0.12, 0.88 and 1.1, mg/kg (n=8). In those cases where residues at a longer PHI were higher, these residues were selected instead.

The GAP for strawberries in the Netherlands is for two spray applications at 0.0096 kg ai/hL (PHI 3 days) in a greenhouse. In indoor trials from Germany, Belgium, the Netherlands, the United Kingdom, France, Spain, Italy and Portugal matching this GAP (2 × 0.0096 kg ai/hL, PHI 3 days), spirodiclofen residues in strawberry fruit were: < 0.02, 0.041, 0.044, 0.056, 0.13, 0.16, 0.17 and 0.28 mg/kg (n=8). In those cases where residues at a longer PHI were higher, these residues were selected instead.

The Meeting noted that the Dutch datasets from field and indoor strawberries were from similar populations (Mann-Whitney U test) and agreed that they could be combined. Spirodiclofen residues in whole fruit were: < 0.02, 0.022, 0.041, 0.041, 0.044, 0.047, 0.056, 0.06, 0.063, 0.12, 0.13, 0.16, 0.17, 0.28, 0.88 and 1.1 mg/kg (n=16).

The Meeting estimated a maximum residue level of 2 mg/kg for spirodiclofen on strawberries and estimated and STMR of 0.0615 mg/kg for spirodiclofen in strawberries.

The value derived from use of the NAFTA calculator was 1.4 mg/kg (NAFTA 95/99 99th percentile), which was comparable with the estimate made by the Meeting (after rounding up to one figure).

Assorted tropical and sub-tropical fruits—inedible peel

Field trials involving papaya were performed in Brazil. GAP for papaya in Brazil is for one spray applications at 0.0072 kg ai/hL (PHI 7 days). Field trials performed in Brazil did not match this GAP. In field trials from Brazil with three applications at equal or higher application rates to GAP (3 × 0.0072 kg ai/hL, PHI 7 days or 3 × 0.014 kg ai/hL, PHI 7 days), spirodiclofen residues in papaya whole fruit could not be found: < 0.03 mg/kg (n=8).

The Meeting estimated a maximum residue level of 0.03(*) mg/kg for spirodiclofen in papaya whole fruit and estimated an STMR of 0.03 mg/kg for spirodiclofen in papaya (edible portion).

Statistical calculations were not possible, as all residues were below the LOQ.

Fruiting vegetables, Cucurbits

Indoor trials involving cucumbers were performed in Germany. GAP for cucumbers and gherkins in Germany is for two spray applications at 0.12 kg ai/ha (PHI 3 days) in a greenhouse. In indoor trials from Germany matching this GAP (2 × 0.115 kg ai/ha, PHI 3 days), spirodiclofen residues in cucumbers were: 0.02, 0.02, 0.03, 0.03, 0.03 mg/kg (n=5).

Indoor trials involving gherkins were performed in Germany. GAP for cucumbers and gherkins in Germany is for two spray applications at 0.12 kg ai/ha (PHI 3 days) in a greenhouse. In indoor trials from Germany matching this GAP (2 × 0.115 kg ai/ha, PHI 3 days), spirodiclofen residues in gherkins were 0.04, 0.04 mg/kg (n=2).

The dataset for gherkins was considered insufficient to support a recommendation, but the Meeting agreed that the dataset from gherkins could be combined with the dataset from cucumbers to mutually support a maximum residue level for each commodity. Spirodiclofen residues in whole fruit were: 0.02, 0.02, 0.03, 0.03, 0.03, 0.04 and 0.04, mg/kg (n=7).

The Meeting estimated a maximum residue level of 0.07 mg/kg for spirodiclofen on cucumbers and on gherkins and estimated and STMR of 0.03 mg/kg for spirodiclofen on cucumbers and on gherkins.

The value derived from use of the NAFTA calculator (NAFTA 95/99 99th percentile) of 0.056 mg/kg differed from the estimate of 0.07 mg/kg made by the Meeting. The level recommended by the Meeting was higher in recognition of the low number of data points (n=7).

Fruiting vegetables, other than Cucurbits

Indoor trials involving sweet peppers were performed in Germany. GAP for sweet peppers in Germany is for two spray applications at 0.0096 kg ai/hL (PHI 3 days) in a greenhouse. In indoor trials from Germany matching this GAP (2 × 0.0096 kg ai/hL, PHI 3 days), spirodiclofen residues in sweet peppers were: 0.03, 0.08, 0.08, 0.09 and 0.09 mg/kg (n=5).

The Meeting estimated a maximum residue level of 0.2 mg/kg for spirodiclofen in sweet pepper whole fruit and estimated an STMRRAC of 0.08 mg/kg for spirodiclofen in sweet pepper.

The value derived from use of the NAFTA calculator (NAFTA mean + 3SD) was 0.15 mg/kg, which was in agreement with the estimate made by the Meeting (after rounding up to one figure).

Field trials involving tomatoes were performed in Brazil. Indoor trials involving tomatoes were performed in Germany.

GAP for tomatoes in Brazil is for one spray application at 0.072 kg ai/ha (PHI 7 days). Field trials performed in Brazil did not match this GAP. In field trials from Brazil where three applications were made at equal or higher than GAP rates (3 × 0.072 kg ai/ha, PHI 7 days or 3 × 0.144 kg ai/ha, PHI 7 days), spirodiclofen residues in tomato fruit could not be found: < 0.03 mg/kg (n=8). The Meeting was not confident of the results, as no residues were detected 0 day samples and such an outcome was not consistent with results from other trials. Consequently, the Meeting agreed to disregard the residue values from the Brazilian trials.

GAP for tomatoes in Germany is for two spray applications at 0.12 kg ai/ha (PHI 3 days) in a greenhouse. In indoor trials from Germany on large tomato varieties matching this GAP (2 × 0.115 kg ai/ha, PHI 3 days), spirodiclofen residues in tomato fruit were: 0.03, 0.06, 0.07, 0.08, 0.08, 0.10, 0.10 and 0.24 mg/kg (n=8).

Based on the German dataset, The Meeting estimated a maximum residue level of 0.5 mg/kg for spirodiclofen on tomatoes and estimated and STMR of 0.08 mg/kg for spirodiclofen in tomatoes.

The value derived from use of the NAFTA calculator (NAFTA 95/99 99th percentile) of 0.31 mg/kg differed from the estimate of 0.5 mg/kg made by the Meeting. The level recommended by the Meeting was higher to accommodate smaller tomato varieties and in recognition of the small number of data points (n=8).

Tree nuts

Field trials involving almonds were performed in the USA. GAP for tree nuts in the USA is for one spray application at 0.60 kg ai/ha (PHI 7 days). In field trials from USA matching this GAP (1 × 0.593–0.617 kg ai/ha, PHI 6–7 days), spirodiclofen residues in almond nutmeat were < 0.01, < 0.01, 0.010, 0.014, 0.015 and 0.024 mg/kg (n=6) for low volume spraying and < 0.01, 0.013, 0.017, 0.023 and 0.023 mg/kg (n=5) for normal or dilute high volume spraying on/under the same locations/conditions. In addition, at two of the locations comparisons were made between SC formulations (0.013, 0.014, 0.015 and 0.017 mg/kg) and WG formulations (0.019, 0.023, 0.024 and 0.024 mg/kg). In those cases where residues at a longer PHI were higher, these residues were selected.

The Meeting noted that the residue populations corresponding to low volume spray and normal spray are from similar populations (Mann-Whitney U test) and that the residue populations corresponding to SC and WG formulations are from similar populations (Mann-Whitney U test). Because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprising of the highest residue from each location. This resulted in the following dataset for almond nutmeat: < 0.01, < 0.01, 0.017, 0.023 and 0.024 mg/kg (n=5).

At a PHI of 7 days the almond hulls are already split, the possibility exists for the spray to reach the almond shells. The potential also exists for further contamination of the shells during harvest when the trees are shaken casusing the nuts to fall and come into contact with any spray residue on the soil. There is also potential for contamination of the almond nutmeat during de-shelling, i.e., transferred from the shell to the kernel, suggesting a possible cause for the residues detected in the trials, given spiridoclofen is not considered systemic.

Field trials involving coconuts were performed in Brazil.

GAP for coconut in Brazil is for one spray application at 0.0072 kg ai/hL (PHI 21 days). Field trials performed in Brazil did not match this GAP. In field trials from Brazil where three applications were made at rate equal to or higher than GAP rates (3 × 0.0072 kg ai/hL, PHI 21 days or 3 × 0.014 kg ai/hL, PHI 21 days), spirodiclofen residues in coconut (flesh and liquid) were not detected: < 0.05 mg/kg (n=6).

Field trials involving pecans were performed in the USA.

GAP for tree nuts in the USA is for one spray application at 0.60 kg ai/ha (PHI 7 days). In field trials from USA matching this GAP (1 × 0.587–0.603 kg ai/ha, PHI 7 days), spirodiclofen residues in pecan nutmeat were: < 0.01, < 0.01, < 0.01, < 0.01, 0.013 and 0.042, mg/kg (n=6) for low volume spraying and < 0.01, 0.011, 0.011, 0.015, 0.016 and 0.036 mg/kg (n=6) for normal highvolume or dilute spraying on/under the same locations/conditions. In addition, at one of the sites comparisons were made between SC formulations (< 0.01 and 0.011 mg/kg) and WG formulations (< 0.01 and < 0.01 mg/kg). In those cases where residues at a longer PHI were higher, these residues were used in the estimation.

The Meeting noted that the residue populations corresponding to low volume spraying and normal spraying were from similar populations (Mann-Whitney U test) and that the residue populations corresponding to SC and WG formulations were from similar populations. Because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprising of the highest residue from each location. This resulted in the following dataset for pecan nutmeat: 0.011, 0.011, 0.015, 0.016 and 0.042 mg/kg (n=5).

As with almonds, the Meeting considered that a consequence of the 7 day PHI could be pesticide contact with the shell and transferral of residues to the nutmeat during de-shelling, suggesting a possible cause for the residues detected in the trials.

The Meeting noted that the USA datasets from almonds and pecans were from similar populations (Mann-Whitney U test) and agreed that they could be combined. Spirodiclofen residues

in nutmeat were: < 0.01, < 0.01, 0.011, 0.011, 0.015, 0.016, 0.017, 0.023, 0.024 and 0.042 mg/kg (n=10).

The Meeting noted that the quantification limit in the Brazilian trials was higher than in the other trials. Therefore, it was not possible to verify the actual levels in coconut flesh and liquid. However, as the results of the Brazilian trials do not disagree with those of the US trials on tree nuts, the Meeting agreed that the USA data on almonds and pecans could be used to support a tree nut commodity group maximum residue level recommendation. The Meeting estimated a maximum residue level of 0.05 mg/kg for spirodiclofen on tree nuts and estimated a STMR of 0.0155 mg/kg for spirodiclofen in tree nuts (nutmeat).

The value derived from use of the NAFTA calculator (NAFTA 95/99 99th percentile) was 0.048 mg/kg, which was in agreement with the estimate made by the Meeting (after rounding up to one significant figure.

Seed for beverages and sweets (024)

Field trials involving coffee were performed in Brazil. GAP for coffee in Brazil is for one spray application at 0.012 kg ai/hL (PHI 21 days). Field trials performed in Brazil did not match this GAP. In field trials from Brazil where two applications were made (2 × 0.014 kg ai/hL, PHI 21 days), spirodiclofen residues in green coffee beans were not detected: < 0.03 mg/kg (n=3).

Since coffee beans (seeds) are not directly exposed to spirodiclofen and no residues are expected in green coffee beans, the Meeting considered three trials sufficient for a recommendation. The Meeting estimated a maximum residue level of 0.03(*) mg/kg for spirodiclofen in coffee beans and estimated a STMR of 0.03 mg/kg for spirodiclofen in coffee beans.

Statistical calculations were not possible, as all residues were below the LOQ.

Miscellaneous fodder and forage crops (052)

Field trials involving almond hulls were performed in the USA.

GAP for tree nuts in the USA is for one spray application at 0.60 kg ai/ha (PHI 7 days). In field trials from USA matching this GAP (1 × 0.593–0.617 kg ai/ha, PHI 6–7 days), spirodiclofen residues in almond hulls were: 1.2, 1.6, 2.1, 2.4, 3.8 and 5.5 mg/kg (n=6) for low volume sprays and 2.0, 3.5, 4.2, 5.9 and 6.8 mg/kg (n=5) for normal high volume sprays on/under the same locations/conditions. In addition, at two of the sites comparisons were made between SC formulations (1.2, 2.0, 3.8 and 5.9 mg/kg) and WG formulations (1.2, 1.5, 2.4 and 4.2 mg/kg). In those cases where residues at a longer PHI were higher, these residues were selected for use in the estimation.

The Meeting noted that the residue populations corresponding to low volume sprays and normal sprays were from similar populations (Mann-Whitney U test) and that the residue populations corresponding to SC and WG formulations were from similar populations (Mann-Whitney U test). Because only one residue should be selected per location, the Meeting agreed to use only one dataset, comprised of the highest residue from each location. This resulted in the following dataset for almond hulls: 2.0, 2.1, 3.5, 5.9 and 6.8 mg/kg (n=5).

The Meeting estimated a maximum residue level of 15 mg/kg for spirodiclofen in almond hulls and estimated an STMR value of 3.5 mg/kg for spirodiclofen in almond hulls.

The value derived from use of the NAFTA calculator (NAFTA 95/99 99th percentile) was 13.389 mg/kg, which was in agreement with the estimate made by the Meeting (after rounding up).

Dried herbs

Field trials involving hops were performed in Germany and the USA.

GAP for hops in Germany is for one spray application at 0.43 kg ai/ha (PHI 14 days). In eight field trials from Germany matching this GAP (1 × 0.336–0.433 kg ai/ha, PHI 14 days), spirodiclofen residues in kiln-dried hop cones were 3.9, 6.6, 8.8, 11, 11, 14, 17, 24 mg/kg (n=8). In those cases where residues at alonger PHI were higher, these residues were selected for use in the estimation.

GAP for hops in the USA is for one spray application at 0.43 kg ai/ha (PHI 14 days). In a field trial from the USA matching this GAP (1 × 0.434–0.462 kg ai/ha, PHI 14 days), spirodiclofen residues in kiln-dried hop cones were 5.4 mg/kg (n=1).

The USA dataset was considered insufficient to support a recommendation and the Meeting agreed to use only the dataset from Germany. The Meeting estimated a maximum residue level of 40 mg/kg for spirodiclofen on hops, dry and estimated and STMR of 11 mg/kg for spirodiclofen in kiln dried hop cones.

The value derived from use of the NAFTA calculator (NAFTA 95/99 99th percentile) was 39 mg/kg, which was in agreement with the estimate made by the Meeting (after rounding up).

Fate of residues in storage

Not applicable.

Fate of residues during processing

The Meeting received information on the fate of spirodiclofen under simulated processing conditions and on the fate of incurred residues of spirodiclofen during the processing of oranges, apples, peaches, plums, grapes, strawberries and hops.

An aqueous solution of [dihydrofuranone-3-^{14}C]spirodiclofen was treated for 20 min at 90 °C at pH 4 (pasteurization), 60 min at 100 °C at pH 5 (brewing/baking/boiling), or for 20 min at 120 °C at pH 6 (sterilization). Spirodiclofen was stable at pH 4, but degraded at pH 5 and higher. After processing 99.1%, 35.4% and 37.3% of the applied radioactivity remained as unchanged spirodiclofen. Spirodiclofen is degraded by ester cleavage with the formation of spirodiclofen-enol.

For the preparation of orange marmalade, apple sauce, peach preserve, and wine juice processing procedures for the conditions were similar to pasteurisation and it is expected that the residues in processed commodities is primarily spirodiclofen (parent). However, in processing studies on grapes, where both parent and spirodiclofen-enol were quantified, the spirodiclofen-enol metabolite was found at quantifiable amounts in grape jelly, grape juice, and grape juice concentrate. The sum of spirodiclofen and spirodiclofen-enol residues in grape jelly, grape juice and grape juice concentrate was lower than in the RAC (9.5%, 17%, and 73% of the RAC residue, respectively). Since grape juice concentrate will be diluted before drinking, residues in these commodities would be unlikely to make a substantial contribution to the total residue intake. Also for the brewing process for hops the formation of spirodiclofen-enol is expected, but because of the large dilution, low residue levels are also anticipated. Since residue levels of spirodiclofen-enol in processed commodities were low, The Meeting concluded that the residue definition for plant commodities was also adequate for processed plant commodities.

Processing studies were undertaken for oranges, apples, peaches, plums, grapes, strawberries and hops. In the table below, relevant processing factors for these commodities are summarized. Using the STMR, the Meeting estimated STMR-Ps for these commodities as listed below. The Meeting considered the appropriate STMR-P to be used in the livestock dietary burden calculation or dietary intake calculation. The Meeting agreed to extrapolate the orange juice STMR-P to citrus juice.

Commodity	Processing factors	Processing factor (median or	STMR-P mg/kg

		best estimate)	
orange juice (single strength)	0.05	0.05	0.13 × 0.05 = 0.0065
orange pulp (dry, 93% DM)	1.4	1.4	0.13 × 1.4 = 0.18
apple juice (single strength)	< 0.02 (2), < 0.71 (3)	< 0.02	0.20 × 0.02 = 0.004
apple pomace (dry, 92–95% DM)	16, 17, 21	17	0.20 × 17 = 3.4
dried apples	< 0.02, 0.16	0.09	0.20 × 0.09 = 0.018
prunes (=dried plums, 70–71% DM)	2.5	2.5	0.315 × 2.5 = 0.79
raisins (76–83% DM)	0.95, 1.8, 2.1, 2.1, 2.7, 4.0	2.1	0.063 × 2.1 = 0.13
grape juice (single strength)	< 0.006, 0.0081, < 0.54 (3)	0.0081	0.063 × 0.0081 = 0.00051
white wine	< 0.28 (2)	< 0.28	0.063 × 0.28 = 0.018
beer (from hops)	< 0.001 (2), < 0.004, < 0.005	< 0.001	11 × 0.001 = 0.011

Based on an STMR of 0.20 mg/kg for apple, a processing factor of 1.4 and a correction for 92% dry matter, the Meeting estimated a maximum residue level of 4 mg/kg for apple pomace dry on a dry weight basis.

Based on an HR of 0.11 mg/kg for grape bunches and a processing factor of 2.1, The Meeting estimated a maximum residue level of 0.3 mg/kg for raisins.

Farm animal dietary burden

The Meeting estimated the dietary burden of spirodiclofen residues in farm animals from the livestock diets from US-Canada, EU and Australia in the table of OECD Feedstuffs (Annex 6 of the 2006 JMPR report). Almond hulls, apple pomace and citrus pulp were the only feedstuffs relevant for cattle. Poultry dietary burden was not considered as no exposure to spirodiclofen through pesticide treated feed was evaluated by the Meeting. A mean and maximum dietary burden of 0.74 ppm on a dry matter basis was estimated for beef cattle in Europe and Australia and a mean and maximum dietary burden of 0.39 ppm on a dry matter basis was estimated for dairy cattle in US and Australia as is shown in the table below.

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

	US	EU	AU
	mean/max	mean/max	mean/max
beef cattle	0.02	0.74 a	0.74 a
dairy cattle	0.39 b	0.37	0.39 b

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

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

Farm animal feeding studies

The Meeting received a lactating cow feeding study. Three groups of three lactating Holstein cows were dosed once daily, via capsules, at levels of 1.29, 3.93 and 13.1 ppm dry weight feed for 29 consecutive days. Milk was collected throughout the study on days 0, 4, 8, 12, 16, 20, 24, 26 and 28 and tissues were collected on day 29 within 8 hours after the last dose.

No residues of spirodiclofen or spirodiclofen-enol were found, except in one cream sample (0.011 mg/kg spirodiclofen), one fat sample (0.021 mg/kg spirodiclofen) and one kidney sample (0.094 mg/kg spirodiclofen-enol) on day 28 (cream) or day 29 (tissues) from the highest dose level (13.1 ppm).

Animal commodity maximum residue levels

In a feeding study where lactating cows were dosed at 1.29 ppm dry feed, no residues (sum of spirodiclofen and spirodiclofen-enol) were found in tissues and milk. As a consequence, no residues are anticipated in tissues and milk at the mean and maximum calculated dietary burden of 0.74 ppm.

The Meeting estimated a maximum residue level for spirodiclofen of 0.004(*) mg/kg for milks and 0.01(*) mg/kg for meat from mammals other than marine mammals and 0.05(*) mg/kg for mammalian edible offal. The Meeting estimated STMRs 0 mg/kg in milk, muscle/fat, and edible offal of mammals. The residue in animal commodities is considered fat-soluble.

DIETARY RISK ASSESSMENT

Long-term intake

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

The International Estimated Daily Intakes (IEDI) of spirodiclofen in the 13 GEMS/Food Consumption Cluster Diets, based on the estimated STMRs were in the range 0–9% of the maximum ADI of 0.01 mg/kg bw. The Meeting concluded that the long-term intake of residues of spirodiclofen from uses considered by the Meeting is unlikely to present a public health concern.

Short-term intake

No ARfD was considered necessary. The Meeting concluded that the short-term intake of residues of spirodiclofen from uses considered by the Meeting is unlikely to present a public health concern.