5.21 SAFLUFENACIL (251)

TOXICOLOGY

Saflufenacil is the International Organization for Standardization (ISO)–approved name for *N*′-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-*N*-isopropyl-*N*-methylsulfamide (International Union of Pure and Applied Chemistry), for which the Chemical Abstracts Service number is 372137-35-4. Saflufenacil is a new herbicide from the uracil family of herbicides, acting as a protoporphyrinogen IX oxidase (PPO) inhibitor. Saflufenacil has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues and was reviewed at the present Meeting at the request of the Codex Committee on Pesticide Residues.

All pivotal studies with saflufenacil were certified as complying with good laboratory practice unless otherwise stated.

Biochemical aspects

Absorption, distribution, excretion and metabolism of orally administered (gavage) saflufenacil were studied in male and female rats using [phenyl-U-^{14}C]- and [uracil-4-^{14}C]-labelled saflufenacil. The time to reach the maximum concentration of radioactive material in plasma was less than 1 hour. Thereafter, the plasma level of radioactivity declined rapidly, and only residual radioactivity was detected at 168 hours (0.2% of the administered dose). The area under the plasma concentration–time curve values indicated a sex difference, with up to 3-fold higher internal exposures for males than for females. Saflufenacil was rapidly and extensively (> 97%) absorbed from the gastrointestinal tract and rapidly excreted from the body in urine and faeces (> 97% of the administered dose) within 168 hours. The majority of excretion occurred in the first 24–48 hours, and excretion was complete by 96 hours. In 48 hours, bile duct–cannulated rats excreted approximately 76% and 60% of the administered dose in the bile in males and females, respectively. The urinary and biliary excretion data suggested that significant enterohepatic circulation of saflufenacil had occurred. Within 1 hour after oral administration of [^{14}C]saflufenacil, the highest radioactivity was found in the liver, gastrointestinal tract, liver, kidney, lung and thyroid.

The unchanged parent compound accounted for 10.9–48.2% and 48.7–88.9% of the administered dose for male and female rats, respectively. The predominant metabolic reactions of saflufenacil in the rat were demethylation of the uracil ring system, stepwise degradation of the *N*-methyl-*N*-isopropylsulfonamide to form an unsubstituted sulfonamide and cleavage of the uracil ring with loss of a three-carbon fragment to form an *N*-methylurea attached to the phenyl ring. The major metabolites identified in the urine of male and female rats were M800H01 (3.5–9.1% of the dose) and M800H07 (0.6–4.6% of the dose), respectively. In faeces, the parent compound accounted for 3–16% of the dose. The main metabolite in faeces was M800H01, which amounted to 18–44% and 1–3% of the dose in male and female rats, respectively.

Toxicological data

The median lethal dose (LD_{50}) in rats treated orally and dermally with saflufenacil was greater than 2000 mg/kg body weight (bw). The median lethal concentration (LC_{50}) in rats treated by inhalation (nose only) was greater than 5.3 mg/L. Saflufenacil was minimally irritating to the eyes and non-irritating to the skin of rabbits. Saflufenacil was not a skin sensitizer in guinea-pigs, as determined by the Magnusson and Kligman (maximization) test.

Short-term toxicity studies in mice, rats and dogs showed similar profiles of toxicity with respect to blood and liver. Males were more susceptible than females. The haematological effects were mostly related to the pesticidal mode of action of saflufenacil (i.e. inhibition of PPO). Effects indicative of this included increased total porphyrins in urine, faeces and liver, as well as increased

total bilirubin and urinary bilinogen. Decreased haematological parameters indicative of microcytic hypochromic anaemia (MHA) are consistent with this mode of action. Indicators of MHA included increased normoblasts, reticulocytes and polychromasia, increased microcytosis and anisoscytosis, increased spleen weight, extramedullary haematopoiesis in liver and spleen (iron storage) and erythroid hyperplasia in bone marrow. At higher doses, an indication of liver toxicity, which included increased serum liver enzymes, centrilobular fatty change and lymphoid cell infiltration, was observed.

In 28-day and 90-day toxicity studies in mice, MHA, altered clinical chemistry (increased alanine aminotransferase, aspartate aminotransferase, urea and total bilirubin) (28-day study) and liver pathology (increased weight and centrilobular fatty change) were observed. In addition, decreased body weight and body weight gain were observed in the 90-day toxicity study. The no-observed-adverse-effect level (NOAEL) in the 28-day and 90-day studies of toxicity in mice was 50 ppm (equal to 12.5 mg/kg bw per day). The lowest-observed-adverse-effect level (LOAEL) in the 28-day and 90-day toxicity studies in mice was 150 ppm (equal to 36.7 mg/kg bw per day).

In a 28-day toxicity study in rats, the NOAEL was 150 ppm (equal to 13.4 mg/kg bw per day), based on MHA at 1350 ppm (equal to 110 mg/kg bw per day). In addition to MHA, decreased total protein and decreased globulin were observed in a 90-day toxicity study in rats. The NOAEL in the 90-day toxicity study was 150 ppm (equal to 10.5 mg/kg bw per day), and the LOAEL was 450 ppm (equal to 32.3 mg/kg bw per day).

In a 28-day toxicity study in dogs, the NOAEL was 30 mg/kg bw per day, based on MHA at 100 mg/kg bw per day. The NOAEL in a 90-day toxicity study in dogs was 10 mg/kg bw per day, based on MHA in both sexes at 50 mg/kg bw per day. At the highest dose tested, more severe anaemia was seen, along with decreased body weight and body weight gain and dark brown/red brown discoloured faeces. In a 1-year toxicity study in dogs, the NOAEL was 20 mg/kg bw per day, based on discoloured faeces, lower body weight in males, decreased feed consumption, MHA, increased serum alkaline phosphatase activity and lowered total blood protein and albumin levels at 80 mg/kg bw per day. The overall NOAEL for the 90-day and 1-year toxicity studies in dogs was 20 mg/kg bw per day.

The carcinogenic potential of saflufenacil was studied in mice and rats. In mice, there was unusually high mortality in controls and all dose groups after approximately 16 months (485 days) of treatment. However, survival was adequate to assess the carcinogenic potential of saflufenacil. The early mortality was greatest in the control and low-dose male mice and was clearly unrelated to test substance treatment. There were no treatment-related effects on clinical signs of toxicity, mortality, body weight and body weight gain, feed consumption and feed efficiency, gross pathology or organ weights. The NOAEL was 25 ppm (equal to 4.6 mg/kg bw per day), based on MHA seen in the satellite group (killed at 10 months) at 75 and 150 ppm (equal to 13.8 and 38.1 mg/kg bw per day) in males and females, respectively. No treatment-related tumours were observed in mice.

In a 2-year study of toxicity and carcinogenicity in rats, the NOAEL was 100 ppm (equal to 6.2 mg/kg bw per day), on the basis of decreased body weight and body weight gains (males), anogenital region smeared with urine in females and MHA in males and females at 500 ppm (equal to 24.2 mg/kg bw per day). No treatment-related tumours were observed in rats.

The Meeting concluded that saflufenacil was not carcinogenic in mice or rats.

Saflufenacil gave a negative response in an adequate range of in vitro and in vivo genotoxicity tests, except for a positive finding that occurred with metabolic activation in an in vitro chromosomal aberration assay in mammalian cells. In contrast, no clastogenicity was observed in an in vivo mouse micronucleus assay.

The Meeting concluded that saflufenacil was unlikely to be genotoxic in vivo.

On the basis of the absence of genotoxicity in vivo and the absence of carcinogenicity in mice and rats, the Meeting concluded that saflufenacil is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, reproductive parameters were not affected at the highest dose tested (50 mg/kg bw per day). The NOAEL for parental systemic toxicity was 15 mg/kg bw per day, based on adverse effects on feed intake, body weight gain and MHA at 50 mg/kg bw per day. The NOAEL for offspring toxicity was 15 mg/kg bw per day, based on the increased number of stillborn pups and increased pup mortality during the early phase of lactation, reduced pup weight gains and indications of MHA at 50 mg/kg bw per day.

In a developmental toxicity study in rats, the NOAEL for maternal toxicity was 20 mg/kg bw per day, based on MHA at 60 mg/kg bw per day. The developmental toxicity NOAEL was 5 mg/kg bw per day, based on decreased fetal body weights in males and females, an increased incidence of skeletal anomalies and delayed ossification at 20 mg/kg bw per day. In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 200 mg/kg bw per day, based on increased mortality, clinical signs (lateral positioning, poor general state, abortion, blood in bedding, discoloured and no urination and reduced or no defecation) and increased necropsy findings (stomach ulcerations, lack of faeces, increase in pale livers and kidneys, empty stomachs, enlarged bladders and assorted findings on implantations in dams that aborted or were moribund) at 600 mg/kg bw per day. The developmental toxicity NOAEL was 200 mg/kg bw per day, based on a decrease in total litters and total live fetuses and live fetuses per dam at 600 mg/kg bw per day.

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

In an acute neurotoxicity study in rats via gavage, no effects on functional observational battery, motor activity or neuropathology were observed at doses up to 2000 mg/kg bw. For systemic toxicity, the NOAEL was 5000 mg/kg bw for male rats, based on the decreased motor activity, representing mild and transient systemic toxicity, likely due to general malaise, at 2000 mg/kg bw, the highest dose tested.

In a 90-day dietary study of neurotoxicity in rats, no effects on functional observational battery parameters, motor activity or neuropathology were observed in males and females at doses up to 1000 and 1350 ppm, respectively (equal to 66.2 and 101 mg/kg bw per day for male and female rats, respectively). The NOAEL for systemic toxicity was 250 ppm (equal to 16.6 mg/kg bw per day), based on MHA at 1000 ppm (equal to 66.2 mg/kg bw per day).

In an immunotoxicity study, no evidence of immunotoxicity was observed in male mice treated with saflufenacil in the diet for 4 weeks at doses up to 250 ppm (equal to 52 mg/kg bw per day).

Two dietary toxicity studies were conducted in rats to evaluate the effects of saflufenacil administration on porphyrin levels in plasma, urine, faeces and liver and also to evaluate the reversibility of porphyrin levels. Total porphyrin measurements showed significantly higher total porphyrin levels in the faeces of the males at 5 and 25 ppm (equivalent to 0.5 and 2.5 mg/kg bw per day, respectively) and of the females at 25 ppm (equivalent to 2.5 mg/kg bw per day). These findings are considered to be treatment related and are a consequence of increased accumulation and excretion of porphyrins due to inhibition of PPO by saflufenacil. In the recovery study, during a treatment-free recovery period of 2 weeks, the statistically significant increases in total porphyrins in the faeces of both sexes returned to normal. Most of the haematological parameters indicated their complete reversibility.

In studies in rats, bioavailability and toxicity were comparable between hydrated and anhydrate crystalline forms of saflufenacil.

An in vitro study was conducted to investigate the inhibitory effects of saflufenacil on PPO in the liver mitochondrial preparations from female rats, mice, rabbits and human donors. The results of this study indicated that rats are approximately 14 and 16 times more susceptible than humans and rabbits, respectively, to PPO inhibition. This difference in species susceptibility is consistent with the absence of haematological effects in rabbits at doses at least 14 times the NOAEL for these effects in rats.

No adverse effects due to occupational exposure to saflufenacil were reported in employees having contact with the active substance.

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.05 mg/kg bw on the basis of a NOAEL of 4.6 mg/kg bw per day in the carcinogenicity study in mice, based on MHA at 13.8 mg/kg bw per day, and using a safety factor of 100. This ADI was supported by the NOAEL of 6.2 mg/kg bw per day observed in the chronic toxicity and carcinogenicity study in rats, on the basis of MHA and anogenital region smeared with urine in female rats seen at 31.4 mg/kg bw per day. It is further supported by the NOAEL of 5 mg/kg bw per day observed in the developmental toxicity study in rats on the basis of increased skeletal anomalies at 20 mg/kg bw per day.

The Meeting concluded that it was not necessary to establish an acute reference dose (ARfD) for saflufenacil in view of its low acute toxicity and the absence of developmental toxicity or any other toxicological effects that would be likely to be elicited by a single dose. MHA is not considered to be an appropriate end-point to establish an ARfD because it is not expected to appear after single exposure due to the mechanism of toxicity by which it is produced.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mice	Sixteen-month study of toxicity and carcinogenicity[a]	Toxicity	25 ppm, equal to 4.6 mg/kg bw per day	75 ppm, equal to 13.8 mg/kg bw per day
		Carcinogenicity	75 ppm, equal to 13.8 mg/kg bw per day[b]	—
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	100 ppm, equal to 6.2 mg/kg bw per day	500 ppm, equal to 24.2 mg/kg bw per day
		Carcinogenicity	500 ppm, equal to 24.2 mg/kg bw per day[b]	—
	Two-generation study of reproductive toxicity[a]	Parental toxicity	15 mg/kg bw per day	50 mg/kg bw per day
		Reproductive toxicity	50 mg/kg bw per day[b]	—
		Offspring toxicity	15 mg/kg bw per day	50 mg/kg bw per day
	Developmental toxicity study[c]	Maternal toxicity	20 mg/kg bw per day	60 mg/kg bw per day
		Embryo and foetal toxicity	5 mg/kg bw per day	20 mg/kg bw per day
	Acute neurotoxicity study[c]	Systemic toxicity	500 mg/kg bw	2000 mg/kg bw
		Neurotoxicity	2000 mg/kg bw[b]	—
Rabbit	Developmental toxicity study[c]	Maternal toxicity	200 mg/kg bw per day	600 mg/kg bw per day
		Embryo and fetal toxicity	200 mg/kg bw per day	600 mg/kg bw per day
Dog	Ninety-day and 1-year studies of toxicity[a,d]	Toxicity	20 mg/kg bw per day	50 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.05 mg/kg bw

Estimate of acute reference dose

Not necessary

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 saflufenacil

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapidly absorbed, complete within 168 h
Dermal absorption	No data available
Distribution	Widely distributed in tissues; highest residues in liver, gastrointestinal tract, liver, kidney, lung and thyroid
Potential for accumulation	None
Rate and extent of excretion	Rapid and extensive
Metabolism in animals	Moderately metabolized
Toxicologically significant compounds (animals, plants and environment)	Saflufenacil
Acute toxicity	
Rat, LD_{50}, oral	> 2000 mg/kg bw (female rats)
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.3 mg/L (4 h exposure, nose only)
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Minimally irritating
Guinea-pig, dermal sensitization (Magnusson and Kligman test)	Not a sensitizer
Short-term studies of toxicity	
Target/critical effect	MHA (mice, rats and dogs)
Lowest relevant oral NOAEL	10.5 mg/kg bw per day (90-day study of toxicity in rats)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rats)
Lowest relevant inhalation NOAEC	Not available
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	MHA

Lowest relevant NOAEL	4.6 mg/kg bw per day (carcinogenicity study in mice)
Carcinogenicity	Not carcinogenic in mice and rats
Genotoxicity	
	Not genotoxic in vivo
Reproductive toxicity	
Reproduction target/critical effect	None
Lowest relevant reproductive NOAEL	50 mg/kg bw per day (rats; highest dose tested)
Developmental target/critical effect	Developmental toxicity, including skeletal anomalies in rats
Lowest relevant developmental NOAEL	5 mg/kg bw per day (rats)
Neurotoxicity/delayed neurotoxicity	
Neurotoxicity target/critical effect	Not neurotoxic (acute and 90-day studies in rats)
Lowest relevant neurotoxicity NOAEL	66.2 mg/kg bw per day, highest dose tested
Mechanistic data	
	Mechanistic studies indicating species differences in PPO inhibition and reversibility of porphyria
Medical data	
	No adverse effects reported

Summary

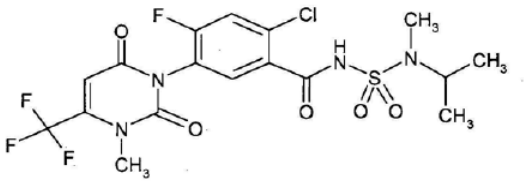
	Value	Study	Safety factor
ADI	0–0.05 mg/kg bw	Carcinogenicity study in mice supported by 2-year study of toxicity and carcinogenicity in rats and developmental toxicity study in rats	100
ARfD		Not necessary	

RESIDUE AND ANALYTICAL ASPECTS

Saflufenacil is a new herbicide applied for contact and residual control of broad leaf weeds and is used in many crops in pre- and post-emergence, or desiccation. It is evaluated by the JMPR for the first time.

The Meeting received information from the manufacturer on metabolism in animals, plants, soil and water, analytical methods, effect of storage and processing and animal transfer studies. Residue data derived from supervised trials on a variety of crops, including fruits, tree nuts, potatoes, legume vegetables, cereals, oil seeds, coffee, sugar cane and follow up crops were also submitted.

The IUPAC name of saflufenacil is N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide



Metabolism

The metabolism and distribution of saflufenacil in plants and animals were investigated using the active substance radio labelled in the phenyl ring and the uracil ring.

The following abbreviations are used for the metabolites discussed:

Metabolite Code	Chemical Name
M800H01	N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropylsulfamide
M800H02	N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydropyrimidin-1(2H)-yl)-4-fluorobenzoyl]-N-isopropyl-N-methylsulfamide
M800H03	N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-N-isopropyl-N-methylsulfamide
M800H04	(2E)-3-{4-chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino) carbonyl]phenyl)amino]carbonyl(methylamino)}-4,4,4-trifluorobut-2-enoic acid
M800H05	N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-sulfamide
M800H07	N-{4-chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino)carbonyl]phenyl}-N'-methylurea
M800H08	N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)tetrahydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide
M800H09	N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-sulfamide
M800H10	N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-N-methylsulfamide
M800H11	N'-[2-chloro-5-(2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)-4-fluorobenzoyl]-N-isopropylsulfamide
M800H15	N-{4-chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino)carbonyl]phenyl}-4-4-4-trifluoro-3,3-dihydroxybutanamide
M800H17	N-{4-chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino)carbonyl]phenyl}-N-(methylamino)carbonyl-4,4,4-trifluoro-3-oxo-butanamide
M800H18	N-{4-chloro-2-fluoro-5-[({[isopropylamino]sulfonyl}amino)carbonyl]phenyl}-N'-methylurea
M800H22	3-[({4-chloro-2-fluoro-5-[({[isopropyl(methyl)amino]sulfonyl}amino)carbonyl]anilino}carbonyl) (methyl)amino]-4,4,4-trifluorobutanoic acid
M800H26	N-Methyl-2,2,2-trifluoroacetamide
M800H29 (TFA)	Trifluoroacetic acid (or its Na salt)

Metabolite Code	Chemical Name
M800H31	3-[carboxy(methyl)amino]-4,4,4-trifluorobutanoic acid
M800H33	Trifluoroacetone
M800H34	N-{4-chloro-2-fluoro-5-[([aminosulfonyl]amino)carbonyl] phenyl}-N'-methylurea
M800H35	N-[4-chloro-2-fluoro-5-({[(isopropylamino)sulfonyl]amino} carbonyl)phenyl]urea
M800H36	Not IUPAC classified due to ambiguous hydroxyl position
M800H37	N-{4-chloro-2-fluoro-5-[({[ethyl(methyl)amino]sulfonyl}amino) carbonyl]phenyl}-N'-methylurea

Animal metabolism

Animal metabolism studies were conducted with saflufenacil on lactating goats and laying hens. The metabolism in rats performed as part of toxicological studies is reported under toxicology.

Lactating goats

Two-year old lactating goats dosed with [phenyl-U-^{14}C] saflufenacil were administered 18.4 mg/day, equivalent to 13.9 ppm in the feed. The animal dosed with [uracil-4-^{14}C] saflufenacil received a dose of 17.8 mg/day, equivalent to 13.4 ppm in the feed.

Production of urine and faeces was recorded once daily and production of milk twice daily (in the afternoon and in the morning before dosing). Animals were sacrificed within 24 h of the last dose. Liver, kidney, blood, adipose tissue, muscle, GI tract with contents and bile were collected. The total recovery of radioactivity was found to be 91.83% in the phenyl-label group and 89.89% in the uracil-label group.

Radioactivity in milk amounted to 0.001–0.005% and 0.002–0.009% of the radioactivity administered for the phenyl-labelled and the uracil-labelled [^{14}C]saflufenacil, respectively. Concentrations of radioactivity in milk stayed relatively constant after three application days ranging from 0.004–0.019 mg eq/kg and 0.006–0.024 mg eq/kg for the phenyl-labelled and the uracil-labelled [^{14}C]saflufenacil, respectively.

At sacrifice, highest concentrations of radioactivity were found in liver and bile. Residue concentrations of phenyl-labelled and uracil-labelled [^{14}C]saflufenacil in liver and bile samples were 0.962 and 3.832 mg eq/kg, and 0.634 and 1.461 mg eq/kg, respectively. In adipose tissue and muscle, 0.010 mg eq/kg and 0.017 mg eq/kg, as well as 0.008 mg eq/kg and 0.011 mg eq/kg were found for the phenyl-labelled and the uracil-labelled [^{14}C]saflufenacil, respectively.

Saflufenacil was transformed to a number of metabolites after administration to the goats. Following the application of phenyl and uracil labelled compound the TRR was 0.008 mg/kg and 0.011 mg/kg in muscle, 0.01 mg/kg and 0.017 mg/kg in fat, 0.13 mg/kg and 0.17 mg/kg in kidney, 0.962 mg/kg and 3.832 mg/kg in liver, 0.006 mg/kg and 0.012 mg/kg in milk, respectively. The unchanged parent compound was found as the predominant compound in muscle (44.2% and 56.7%), fat (44.1% and 65.1%), kidney (73.8% and 71.3%), liver (80.2% and 75.7%) whilst in milk its proportion was somewhat lower (47% and 25.4%) following the dosing with phenyl and uracil labelled compounds, respectively. In addition, metabolites M800H01, M800H03, M800H04 and M800H10 were present in few percentages, except M800H10 in milk (39–40%).

The metabolism of the active substance saflufenacil in lactating goats is characterized by several dealkylation steps (phase I reactions), which occurred at two sites of the molecule:

N-demethylation at the N-isopropyl-N-methylsulfamide side chain resulting in metabolite M800H01, and N-demethylation at the uracil ring producing M800H02. Both demethylation reactions formed metabolite M800H11. Elimination of the N-isopropyl group converted the parent compound to M800H03. This reaction furthermore transformed metabolite M800H01 to M800H05, and metabolite M800H02 to M800H10. The metabolites M800H05 and M800H10 could also be formed by the respective demethylation of metabolite M800H03. An additional transformation was hydrolytic opening of the uracil ring of saflufenacil to form metabolite M800H04. Degradation of the resulting side chain generated metabolite M800H07 with its N-methyl-amide group. This metabolite was only detected with the phenyl label. The metabolites are rapidly excreted, along with parent, and do not readily accumulate in tissues or milk. The residues in edible tissues and milk were low. All relevant metabolites were identified and a comprehensive metabolic pathway was elucidated.

Laying hens

Phenyl-U-[^{14}C] saflufenacil or uracil-[^{14}C] saflufenacil was administered orally by gavage once a day to two groups of eight laying hens for 10 consecutive days at a nominal rate of 12 mg/kg feed. The total recovery of radioactivity was found to be 88.76% in the phenyl-[^{14}C]-label group and 83.67% in the uracil-[^{14}C]-label group.

The eggs were collected in the afternoon after administration and in the morning before the administration. The radioactivity was determined in liver, adipose tissue, blood, muscles (leg and chest muscles), gastrointestinal tract (skin and contents). All samples were extracted and analysed within approximately four months after sampling. The extractability of radioactivity from all matrices was greater than 80%. The metabolic fate of approximately 75–80% of the total administered radioactivity considering both labels of saflufenacil could be elucidated.

Excreta contained 85.14% of the phenyl-labelled [^{14}C]saflufenacil administered (uracil-[^{14}C]label: 78.10%). Radioactivity recovered from excreta and cage wash amounted to 88.07% (phenyl-[^{14}C]-label) and 82.96% (uracil-[^{14}C]-label) of the total radioactivity administered.

In eggs, 0.029% (phenyl-[^{14}C]-label) and 0.046% (uracil-[^{14}C]-label) of the total radioactivity administered were found. With both labels, egg concentrations increased continuously up to day 6 and remained unchanged (0.01–0.012 mg/kg for phenyl and 0.016–0.018 mg/kg for uracil labels) until day 10, indicating that a steady state was reached.

At sacrifice, 23 h after the last administration, highest organ concentrations of radioactivity were found in liver (phenyl-[^{14}C]-label: 0.062 mg/kg; uracil-[^{14}C]-label: 0.060 mg/kg,). Residue concentrations of phenyl and uracil labelled [^{14}C]-material in muscles (0.011 mg/kg, 0.011 mg/kg), adipose tissue (0.011 mg/kg, 0.011 mg/kg), eggs (0.012 mg/kg, 0.018 mg/kg) in fat (0.011 mg/kg, 0.011 mg/kg) and in liver (0.062 mg/kg, 0.06 mg/kg) respectively.

The parent compound was the major residue (in muscle 54.7% of TRR, 0.006 mg/kg), fat (26.1%, 0.002 mg/kg) and liver (47.4%, 0.029 mg/kg). In eggs M800H10 amounted to 67.6% of TRR corresponding to 0.008 mg/kg (saflufenacil 20.8%, 0.002 mg/kg). Altogether, < 1% of the total radioactivity administered could be found in the tissues and organs analysed for both radiolabels.

The metabolic reactions are in good accordance with the metabolism of saflufenacil in rats and in lactating goats and hens.

Plant metabolism

Metabolism of saflufenacil was studied in maize, soya beans and tomatoes applying phenyl and uracil labelled compounds.

Maize

Maize plants were grown in soil treated once at a nominal application rate of 200 g ai/ha directly on the bare soil after sowing (pre-emergence treatment). Forage samples were taken 42 and 101/102 days after treatment (DAT) (at the growth stages BBCH 18 and 85). Maize husks, cob, grain and straw (stover) were harvested at 133 days after treatment (BBCH 89).

The highest level of total radioactive residues (TRR) for the phenyl label was detected in maize husks (0.215 mg/kg), followed by stover (0.096 mg/kg). Lower residue levels were found in maize forage 42 DAT (0.018 mg/kg), forage 101 DAT (0.029 mg/kg), cob (0.016 mg/kg) and grain (0.020 mg/kg). In the case of the uracil label, the highest amount of TRR was detected in corn straw (stover) (0.553 mg/kg). Maize husks contained 0.226 mg/kg, forage sampled 102 DAT contained 0.149 mg/kg and maize forage 42 DAT contained 0.039 mg/kg. In maize grain and cob, 0.049 mg/kg and 0.065 mg/kg were found, respectively. Extractability of radioactive residues with methanol and water ranged from 60 to 96% of the TRR), with the exception of cob and grain (phenyl label, ~ 19% TRR each).

In the experiments with the phenyl label, metabolites M800H09, M800H34 and M800H10 were the major components in the matrices sampled at harvest and in maize forage 101 DAT (up to 21.4% TRR). In maize forage sampled 42 DAT (phenyl label), the main components were M800H09, M800H10, M800H01, M800H03 and M800H05 (11% to 20% TRR). At harvest the parent saflufenacil was non-detectable in maize grain, cob and straw (< 0.0005) and present in husk in traces (0.0001 mg/kg), the metabolite M800H11 was found in portions of 1.6% to 4.6% TRR (< 0.0005–0.004 mg/kg).

In the case of the uracil label, the polar metabolite M800H29 (trifluoroacetic acid) was the predominant constituent of the methanol extracts of all plant matrices investigated (64% to 88% TRR, grain: 30.5% TRR, 0.004 mg/kg). Since the potentially corresponding [^{14}C]phenyl-labelled metabolites as counter parts of M800H29 were not detected at adequate quantities, the occurrence of TFA could be explained by the uptake of this metabolite or a respective precursor molecule from the soil. The parent saflufenacil was not detectable in maize grain and any of the other samples and metabolite M800H11 was present at ≤ 0.5% of TRR.

Saflufenacil is metabolized in maize plants by the following main transformation reactions: N-demethylation at the uracil ring; stepwise degradation (N-dealkylation) of the N-methyl-N-isopropyl group to NH_2 forming a sulfonamide group and hydrolytic cleavage of the uracil ring generating a urea side chain.

Soya beans

Pre-emergence treatment

Soya bean plants were grown in soil treated once at a nominal application rate of 150 g ai/ha directly on the bare soil after sowing (pre-emergence treatment). Soya bean forage samples were taken at 39/40 DAT (days after treatment). Soya bean beans, pods (hull), and straw were harvested at 95 DAT.

Following the application of phenyl and uracil labelled compounds the TRR expressed as mg/kg were in forage (0.086, 0.38), bean (0.038, 0.22), pod (0.18, 2.0) and straw (0.43, 1.2), respectively. The extractable radioactive residues ranged from 60% to 98% of TRR.

In soya bean forage sampled 39 DAT (phenyl label), the parent compound was present at 23.5% TRR (0.019 mg/kg). The parent compound and the metabolites M800H01, M800H03, M800H05 and M800H37 were found in portions of up to 6.5% TRR in the other matrices. M800H11 and M800H35 were found up to 13% of TRR in forage, bean and pod and 24.9% and 15.6% of TRR in straw. The corresponding concentrations expressed as mg/kg were in forage (0.005, 0.004), bean (0.001), pod (0.016, 0.023) and straw (0.11, 0.067), respectively. The parent saflufenacil was present in matured beans at 0.002 mg/kg.

In the case of the uracil label, the polar metabolite M800H29 was the predominant constituent of the extracts of all plant matrices investigated (85.2% in forage 65.4% in beans, 75.9% in pods and 69.2% in straw.

Pre-harvest (late season) use

Soya bean leaves, stems, pods and seeds were harvested at *7* days after the foliar application of [^{14}C]uracil labelled saflufenacil at a rate of 100 g ai/ha. The TRR were 0.419 mg/kg in stem, 1.86 mg/kg in pod, 0.043 mg/kg in seed and 17.9 mg/kg in leaves. The extractable radioactive residues ranged between 75.6% and 97.6% of TRR.

The unchanged parent compound was identified with 73% and 76% of the TRR in the extracts of stem and pod, with 64% TRR in leaves and with 26% of the TRR in seed (0.011 mg/kg). Four metabolites were identified in soya bean matrices. The most abundant metabolite identified in all soya bean matrices was M800H02 (5% to 26% of the TRR). The metabolites M800H01 and M800H03 were mainly detected in soya bean leaves (9% to 14% TRR) and in minor portions in soya bean pod (< 1% to 3% TRR). The metabolite M800H11 was detected in all matrices (3% to 10% TRR).

Tomatoes

The metabolism study was conducted with phenyl- and uracil- labelled saflufenacil applied on bare soil before planting of tomato plants at a nominal application rate of 100 g ai/ha. Tomato plants were sampled 68 and 113 days after application. Mature tomato fruits were harvested 113 days after treatment.

The total radioactive residues in tomato plants sampled 68 days after treatment accounted for 0.089 mg/kg (phenyl label) and 0.131 mg/kg (uracil label). In tomato plants at harvest (113 DAT), the radioactive residues were 0.113 mg/kg for the phenyl label and 0.138 mg/kg for the uracil label. In tomato fruits (113 DAT), the residue levels were significantly lower, accounting for 0.015 mg/kg (phenyl label) and 0.037 mg/kg (uracil label). Extractability of radioactive residues with methanol and water was good and generally amounted to 80–100% of the TRR.

In the methanol extract of tomato plants sampled at day 68 (phenyl label), the unchanged parent compound was the most abundant component, accounting for 29% TRR. Major metabolites were M800H07 (14% TRR) and M800H11 (13% TRR). Other metabolites were detected at minor quantities below 7% TRR: M800H01, M800H02, M800H09, M800H10 and M800H35. The methanol extract of tomato plants at harvest (phenyl label) contained the parent compound at a significantly lower concentration (11% TRR). The following metabolites were identified as minor metabolites at 6% TRR or below: M800H01, M800H02, M800H07, M800H09, M800H10, M800H11 and M800H35. The harvested tomato fruits contained the parent compound in traces < 0.0005 mg/kg, all metabolites were non-detectable.

Following the treatment with uracil labelled saflufenacil, the tomato plants contained the parent compound, M800H10 and M800H11 metabolites in ≤ 8.5% of TRR and M800H29 was the major residue component (82.2% and 51.7% of TRR at days 68 and 113, respectively). The fruit contained only M800H29 in detectable amounts (0.004 mg/kg). The parent saflufenacil amounted to 0.7% of TRR (< 0.0005 mg/kg). The formation of natural sugar compounds after complete breakdown of the test substance was proven for tomato fruit.

In summary, the metabolite pathway of saflufenacil in animals and plant materials is qualitatively similar. The metabolism of the active substance saflufenacil is characterized by several dealkylation steps (phase I reactions), which occurred at two sites of the molecule: N-demethylation at the N-isopropyl-N-methylsulfamide side chain resulting in metabolite M800H01, and N-demethylation at the uracil ring producing M800H02. Both demethylation reactions formed metabolite M800H11. Elimination of the N-isopropyl group converted the parent compound to M800H03. This reaction furthermore transformed metabolite M800H01 to M800H05, and metabolite

M800H02 to M800H10. The metabolites M800H05 and M800H10 could also be formed by the respective demethylation of metabolite M800H03. An additional transformation was hydrolytic opening of the uracil ring of saflufenacil to form metabolite M800H04.

In the case of the uracil label, the polar metabolite M800H29 (trifluoroacetic acid) was the predominant constituent of the methanol extracts of plant matrices investigated. The occurrence of TFA was explained by the uptake of this metabolite or a respective precursor molecule from the soil.

Environmental fate

The fate and behaviour of saflufenacil and its metabolites in the environment was investigated under various conditions using the uracil ring- and phenyl ring labelled saflufenacil.

Aerobic degradation

The aerobic degradation of [^{14}C]uracil and phenyl-labelled saflufenacil was studied on sandy loam, silty clay loam, silt loam, and loamy sand soils treated approximately at the proposed maximum use rate of 400 g ai/ha. Following the application of uracil labelled saflufenacil M800H01, M800H02, M800H08, M800H22, M800H26 and M800H31 were identified. Their proportion ranged during the study. M800H02 occurred in largest proportion amounting to 26.4% of total administered radioactivity (TAR) by the end of the study (334 days).

In case of phenyl label, M800H01, M800H02, M800H07, M800H08 and M800H22 were identified. The M800H08 was present in largest proportion in the four soils (14.5–55% of TAR).

The average aerobic degradation DT_{50} values for saflufenacil approximately ranged from 4 days to 22 days in the four soils.

Field trials conducted at various location of USA revealed that the major route of dissipation of saflufenacil in bare soil was degradation by aerobic processes. The DT_{50} and DT_{90} values ranged between 1.36–32.2 days and 4.52–118 days, respectively.

Different metabolites were present at very low concentrations or were not detectable at all. The rate of mineralisation is low and up to 15% of the applied test material is converted to carbon dioxide and other organic volatiles within 365 days. Soil bound residues increased with time during test period.

Photolysis on soil surface

Photolysis of U-[^{14}C]phenyl label] saflufenacil in a light/dark experiment and [^{14}C] uracil and U-[^{14}C] phenyl label] saflufenacil in a continuous irradiation experiment was studied using a loamy sand soil.

In the light/dark experiment saflufenacil in the dark control samples accounted for approximately 97.7% at 0 DAT and decreased to 65.2% TAR at 30 DAT. From the irradiated samples, saflufenacil accounted for approximately 97.7% at 0 DAT and decreased to 43.1% TAR after 30 days of light/dark irradiation. Under the conditions of the study which were similar to the real field situation, there were no major degradation products from the irradiated samples, for either label, which were greater than 10% TAR at any time during the experiment. There were 10 minor products (< 10% TAR) observed.

In the continuous irradiation experiment saflufenacil accounted for approximately 96.43–97.80% at 0 DAT and decreased to 70.21–73.25% TAR at 15 DAT (in the dark control samples of both labels). For the irradiated samples of both labels, saflufenacil accounted for approximately 96.43–97.80% at 0 DAT and decreased to 50.64–58.03% TAR after 15 days of continuous irradiation. The only one major transformation product was an unidentified and unstable product that degraded quickly to M800H01. Minor amounts of M800H01, M800H07, M800H08 and M800H17 were also tentatively identified by HPLC.

Under the dark conditions, saflufenacil undergoes microbial reactions similar to those in aerobic soil metabolism. Saflufenacil was mainly converted to M800H08 and M800H07, as seen in the aerobic soil metabolism study. In addition, the loss of the methyl group on the sulfonylurea side chain of parent to form M800H01 was also observed. There was one major degradation product from the dark samples, and seven other minor products, none of which exceeded 5% TAR at any time during the experimental period. The major dark control product was identified as M800H08.

The DT_{50} for true phototransformation could be calculated as 66 days for the phenyl labelled saflufenacil in the light/dark cycle and 43 and 41 days for the phenyl and uracil labels, respectively, for continuous irradiation.

Saflufenacil undergoes photolysis on soil mainly via demethylation at the sulfonylurea side chain of parent to form M800H01, followed by the demethylation of the uracil ring and the cleavage of the sulfamide side chain. Photolysis also resulted in the opening and fragmentation of the uracil ring to form M800H07. Ultimately all the products could be further degraded to CO_2, but CO_2 production was less than 3% for any of the experiments.

Degradation in aquatic system

The hydrolysis of U-[^{14}C phenyl label] saflufenacil and [^{14}C uracil label] saflufenacil was investigated in dark at 25 °C in 0.01 N sterile buffer solutions at pH 5 (acetate), pH 7 (TRIS) and pH 9 (TRIS).

Saflufenacil was stable to hydrolysis in buffer at pH 5, and no half-life was determined. It degraded slowly in buffer at pH 7 reaching an average of 89% TAR and 94% TAR at 30 DAT for the phenyl and uracil label treatments, respectively. At pH 8 the degradation was rapid.

The photolysis of [^{14}C]saflufenacil (phenyl and uracil label) was conducted in aqueous buffer (pH 5, 0.01 M) and natural water (pH 7.1) at 22 ± 1 °C. The treated solutions (10 mg/kg saflufenacil) were continuously exposed to artificial sunlight (filtered Xenon lamp) for about 20 days for the photolysis conducted in aqueous buffer and 21 days for the natural water.

Saflufenacil degraded rapidly under photolytic conditions with half-lives of 26.8–35.2 and 9.7–9.8 days from the pH5 buffer and the natural water, respectively. Saflufenacil is fairly stable in both pH5 buffer and the natural water in the dark, although trifluoroacetone (M800H33) and M800H07 were found in the latter.

From the pH 5 buffer there are several minor photoproducts formed from both the phenyl and uracil labels; however, only one of them exceeds 10% TAR, but only after 20 days of constant irradiation. This unknown was < 10% TAR in the natural water. In the natural water, there are two major photoproducts formed from the uracil label and identified as trifluoroacetic acid (M800H29) and M800H33 and several other minor photoproducts (none of them exceeds 10% TAR) from both labels.

Saflufenacil degrades in water under photolytic conditions by the opening of the uracil ring followed by the fragmentation of the uracil ring to form M800H04, M800H15, M800H07, M800H33, and M800H29. Hydroxylation of the trifluoromethyl group and the cleavage of the sulfonylurea side chain result in other minor degradation products.

Crop rotation studies

Studies with labelled saflufenacil

The metabolism of saflufenacil was investigated in rotational crops after one single application of the test substance in the EC formulation at a nominal application rate of 150 g ai/ha. Treatment was performed with either [phenyl-U-^{14}C]- or [^{14}C]-[uracil-4-^{14}C]-saflufenacil by spraying onto bare loamy sand soil. After soil aging periods of 30, 58, 120 and 365 days and ploughing saflufenacil,

lettuce, white radish and spring wheat were planted/sowed and cultivated under natural climatic conditions.

Plant samples were harvested at maturity, and additional wheat forage samples were taken 48 to 68 day after planting (DAP). Soil samples were taken after ploughing and after harvest of the mature crops for each plant-back interval.

The total radioactive residues (calculated as the sum of extractable and non-extractable residues, ERR + RRR) in lettuce head (phenyl label) were below or equal to 0.010 mg/kg for all plant-back intervals. In the case of the uracil label, the TRR in lettuce head reached values between 0.078 mg/kg and 0.092 mg/kg after plant-back intervals of 30, 58 and 120 days, and only 0.002 mg/kg after 365 days of soil aging.

The TRR levels in white radish root did not exceed 0.005 mg/kg for all plant-back intervals in the case of the phenyl label. For the uracil label, the TRR in white radish root accounted for 0.034 to 0.038 mg/kg after soil aging periods of 30 and 58 days and for 0.008 to 0.010 mg/kg after the longer plant-back intervals.

In white radish top, higher TRR levels of 0.025 mg/kg (30 DAP), 0.014 mg/kg (58 and 120 DAP) and 0.007 mg/kg (365 DAP) were found for the phenyl label. In the case of the uracil label, the TRR in white radish top were also higher compared to root, accounting for 0.167 and 0.205 mg/kg after 30 and 58 days, and reaching lower levels of 0.046 and 0.087 mg/kg after 120 days and 365 days of soil aging, respectively.

The highest residue levels were detected in spring wheat chaff after a plant-back interval of 30 days (0.383 mg/kg for the phenyl label, 1.604 mg/kg for the uracil label). After longer periods of soil aging (120 and 365 days), the residues in wheat chaff were lower (0.068 and 0.114 mg/kg for the phenyl label, 0.629 mg/kg and 0.439 mg/kg for the uracil label, respectively).

The residue levels in wheat straw (0.089 to 0.125 mg/kg for the phenyl label, 0.196 to 0.356 mg/kg for the uracil label) and forage (decreasing with time from 0.048 to 0.011 mg/kg for the phenyl label and from 0.183 to 0.017 mg/kg for the uracil label) were generally lower compared to chaff.

In spring wheat grain, TRR levels of 0.017 mg/kg (30 DAP), 0.006 mg/kg (120 DAP) and 0.044 mg/kg (365 DAP) were found for the phenyl label. In the case of the uracil label, the residues in grain accounted for 0.370 mg/kg (30 DAP), 0.094 mg/kg (120 DAP) and 0.116 mg/kg (365 DAP).

In summary, the predominant metabolites in the case of the phenyl label were M800H35, M800H05, M800H01, M800H11 and M800H10 (and/or an unknown medium polar component), representing stepwise degradation of the molecule by N-dealkylation reactions and by hydrolytic cleavage of the uracil ring generating an urea side chain. For the [^{14}C]uracil label, M800H29 as trifluoroacetic acid was the predominant metabolite. Since [^{14}C]phenyl-labelled metabolites as counter parts have not been detected at corresponding quantities, the occurrence of TFA could be explained by uptake of this metabolite or a respective precursor molecule from the soil. Most of the metabolites were found at low levels (< 0.1 mg/kg), except for metabolite M800H35 in spring wheat chaff (0.162 mg/kg at 30 DAP, phenyl label) and metabolite M800H29 in spring wheat chaff (0.32 mg/kg at 30 DAP, uracil label; 0.12 mg/kg at 120 DAP, uracil label). The unchanged parent compound was not detectable in wheat grain (< 0.000 mg/kg) and detected at very low quantities (≤ 5% TRR) in other matrices, except for lettuce head (13.7%, 0.001 mg/kg at30 DAP) and white radish top (13.8%, 0.004 mg/kg at 30 DAP) and 8.4% (0.001 mg/kg at 120 DAP) when phenyl labelled saflufenacil was applied.

Field studies

In 2006–2007 six trials (two for each representative crop) were conducted in representative rotational crops (radish, lettuce, and wheat) in the USA.

Saflufenacil (70% WG) was applied as a single pre-emergence application to the soil (at the time of sowing wheat as primary crop) at 0.148–0.154 kg ai/ha. At 4, 6 and 9 months after treatment, the primary crop was destroyed (removed) and the representative rotational crops were planted at a number of time intervals post-treatment.

The residues of saflufenacil, M800H11 and M800H35 were below 0.01 mg/kg (LOQ) in all samples of wheat (forage, hay, grain and straw), radish (tops and root), and lettuce (leaves) harvested from plant-back intervals of 119–125, 180–183, and 270–274 days.

The results of the studies indicate that no detectable residue deriving from the use of saflufenacil can be expected in follow-up crops.

Analytical methods

Information was available on efficiency of extraction, analytical methods for saflufenacil and its metabolites (M800H11 and M800H35) in plants and parent saflufenacil in animal commodities.

Efficiency of extraction

A study was designed to investigate the influence of different solvent mixtures on the extractability and accountability of plant matrices.

The solvent systems were used sequentially: acetonitrile/water 70:30 (v/v), methanol/water 70:30 (v:v), methanol and water. The plant samples used were soya bean forage, pod and straw after pre-emergence treatment with [^{14}C]saflufenacil (phenyl ring labelled) obtained from a soya bean metabolism study.

The extractability behaviour was comparable when using mixtures of acetonitrile/water or methanol/water or methanol and water sequentially on different soya bean matrices like forage, pod and straw. The extraction efficiency was highest for forage and straw using methanol and water sequentially.

The relative quantities of the specified analytes (saflufenacil, M800H11 and M800H35) determined by the residue analytical method were very similar after HPLC analysis of the different extracts obtained after extraction with acetonitrile/water or methanol/water mixtures or with methanol and water applied sequentially.

The results indicate that methanol/water, or acetonitrile/water, were the most suitable solvent systems for extraction and characterization. These systems released most of the total radioactive residues, and residues of concern, and the quantitative results were comparable with those obtained in the original metabolism study.

The use of acetonitrile was shown in the livestock metabolism studies to be suitable for extraction of saflufenacil residues of in animal matrices. Multiple extractions did not contribute significantly to the extraction of the parent saflufenacil.

Analytical methods used in supervised trials

BASF Method D0603/02 was developed for the analysis of residues of saflufenacil and its metabolites M800H11 and M800H35 in plant matrices.

Residues of saflufenacil and its metabolites are extracted from crop matrices (except oil) with methanol-water (70:30, v/v). The oil matrices are extracted with acetonitrile. The residues are determined using LC/MS/MS.

For quantitation ion, the mean recoveries of saflufenacil, and its metabolites, M800H11 and M800H35 in different plant matrices were generally between 70 and 120% within each fortification level. Standard deviations of the recovery were generally less than 15% for quantitation ion.

Good linearity was observed in the range of 0.05 to 0.5 ng/mL for all three analytes. The LOQ for saflufenacil residues is 0.01 mg/kg for each analyte in/on food matrices and 0.025 mg/kg each in/on feed matrices. The mean recoveries obtained at 0.01 mg/kg (LOQ) and 0.1 mg/kg level ranged from 74.3% to 93.6%. The relative standard deviation (RSD) ranged between 1.9% and 9.1%.

Method No L0073/01 was developed and validated for the determination of saflufenacil in liver, kidney, muscle, fat, milk, cream, skimmed milk and eggs. The sample materials are extracted with acetonitrile, partitioned into dichloromethane, evaporated and dissolved in methanol/water mixture.

The final determination is performed by HPLC-MS/MS. The recovery of saflufenacil tested at 0.01 and 0.1 mg/kg level ranged between 74–95% for both transition ions. The reproducibility of the procedure was good (RSD < 10%). The LOQ was 0.01 mg/kg for all matrices.

A study was conducted to evaluate the capability of the FDA multi-residue methods to analyse for residues of saflufenacil, M800H11 and M800H35, but the tests indicated that the method is not suitable for the determination of the targeted residues.

In conclusion, suitable analytical methods are available for the determination of parent saflufenacil and its metabolites (M800H11 and M800H35) in plant matrices and for the parent saflufenacil in animal tissues and milk.

Stability of pesticide residues in stored analytical samples

The stability of residues in samples stored at ≤ –18 ºC was tested as part of the metabolism studies on maize, soya beans and tomatoes by comparing the HPLC chromatographic patterns during the studies. No significant change of the metabolic patterns was observed during co-chromatographic investigations. The composition of the residues in the plant materials remained stable for a period of approximately 16 to 21 months. The extracts were stored for a period of approximately 10 to 13 months.

The stability of residues in stored samples was tested by conducting storage stability studies using spiked samples of plant and animal origin.

Samples of maize (grain, forage and stover), soya beans (seed, forage and hay), oranges (fruit, pulp, juice and oil), radish roots, raisins and garbanzo beans (seeds), spiked separately with saflufenacil, M800H11 or M800H35 at a level of 1.0 mg/kg for each analyte, were stored at < -5 °C for a duration of 548–553 days. Under these conditions, residues of parent and the metabolites appeared to be stable in each crop matrix tested. The data indicate that residues of saflufenacil and its metabolites at < -5 °C are stable for at least 18 months in maize (grain, forage and stover), soya beans (seeds, forage and hay), oranges (fruit, pulp, juice and oil), radish roots, raisins and chick peas .

Storage stability of saflufenacil at -18 °C in milk and bovine tissues such as muscle, liver, kidney and fat was tested at 0.01 and 0.1 mg/kg level. In addition, the stability in the dosing solution was tested. The study, covering the period between sampling and extraction, showed that saflufenacil was stable in milk, muscle, liver, kidney and fat. No decline in concentration of saflufenacil in the extracts and dosing solutions was observed.

Definition of the residue

Residues in animal matrices

Animal metabolism studies were conducted with saflufenacil on lactating goats and laying hens. In these studies, it was found that saflufenacil was transformed to a number of metabolites. All relevant metabolites were identified. The unchanged parent compound was the predominant residue component in the cases of administration of phenyl-labelled saflufenacil in muscle and fat (0.004 mg/kg; 44% of TRR), milk (0.003 mg/kg; 47% of TRR), kidney (0.096 mg/kg; 74 % of TRR)

and liver (0.77 mg/kg; 80% of TRR). Following the administration of uracil-labelled saflufenacil the parent saflufenacil was also present in largest proportion in muscle, fat, kidney and liver (57–76% of TRR). In milk the M800H10 was present at highest concentration (0.005 mg/kg) and the parent saflufenacil was second at 0.003 mg/kg level.

Metabolites M800H04 and M800H10 detected at quantities above 10% TRR within the animal metabolism studies conducted at highly exaggerated dose levels, are not considered relevant, because they would not be detectable in food items of animal origin when considering realistic feeding levels resulting from good agricultural practice.

The definition of residues in animal commodities for both enforcement and risk assessment purposes is: saflufenacil

The log P_{ow} of the parent compound is 2.6. The residues were present in fat and muscle at about the same concentration indicating that the residue is not fat soluble.

Residues in plant matrices

Metabolism studies in maize, soya beans and tomatoes were conducted to determine the metabolic fate of saflufenacil in plants after pre-emergence and pre-plant application as well as pre-harvest use for crop desiccation use.

Pre-plant, pre-emergence directed application to bare soil or to weeds in plantations of orchards and vineyards:

Following the application of labelled saflufenacil at exaggerated rates (2–4×) directly on the bare soil after sowing/planting the residues of saflufenacil were generally low. The parent saflufenacil was not detectable (< 0.0005 mg/kg) in maize cob, grain and stover, and it was present at 0.001 mg/kg level in husk and forage at day 133. M800H11 was present in maize forage at 0.002 mg/kg at days 42 and 102, and in husk and stover at 0.003–0.004 mg/kg level. M800H35 could not be identified during the study.

In tomato fruits at harvest the parent saflufenacil, M800H11 and M800H35 were not present in detectable amounts (< 0.0005 mg/kg). The parent saflufenacil was the predominant residue in tomato plants 8.5–11% of TRR, while M800H11 and M800H35 residues were present in 5.8–5.9% of TRR.

In soya beans, the parent saflufenacil was the predominant residue in forage at day 39, but M800H11 and M800H35 were present in larger proportion in pod (9–13% of TRR) and straw (25–16% of TRR) at 95-day samples. The seed did not contain any detectable residues.

The results of supervised trials provide additional information on the levels of residues in food commodities. Samples of oranges, apples, cherries, peaches, plums, grapes, bananas, mangoes and sweet corn, cereal grains, potato sugar cane, tree nuts and coffee beans, maize forage and stover and almond hull derived from treatments according to GAP no residues were detectable at any pre-harvest intervals.

Pre-harvest (desiccant harvesting aid) applications:

In a soya beans metabolism study, with application at seven days before harvest, the parent saflufenacil was the predominant residue in soya bean leaves, stem and pod (64–76% of TRR) and in seed (26% of TRR, 0.011 mg/kg). M800H11 was present in much lower proportion (2.7–10% of TRR, 0.004 mg/kg)

In supervised trials the metabolites M800H11 and M800H35 were not found above LOQ, in any of the succulent or dried bean, dried pea, soya bean, cotton seed, and cotton gin by-product samples regardless of the PHI. In canola seed the M800H35 residues were below the LOQ of 0.01 mg/kg in all samples. M800H11 residues were < 0.01 in 12 samples. Where M800H11 was

detectable in 0.01–0.055 mg/kg concentration range, it amounted to 4.3% and 53% of the parent saflufenacil (ranging between 0.021–0.48mg/kg).

In sunflower seeds M800H35 was not detected in any of the samples taken between 3 and 20 days after last application. At day 7 only one sample contained detectable M800H11 residue (0.066 mg/kg) amounting to 13% of the parent saflufenacil (0.50 mg/kg) being in the same sample. In other two samples taken at 14 day the M800H11 were present in concentrations amounting to 19% and 22% of the parent compound except one trial where it was present five times higher concentration than the parent compound (0.065 mg/kg).

The Meeting noted that the majority of the commodities treated directly or grown in treated soil did not contain detectable residues at all. The metabolite M800H11 occurred at or below 53% of the parent compound. M800H35 was present in detectable amount only in desiccated pea vine samples.

Taking into account that the residues of parent saflufenacil provide sufficient information on the compliance with GAP, and the M800H11 and M800H35 metabolites are non-detected or present at very low concentration, the Meeting decided, that

The definition of residue in plant commodities for both enforcement and risk assessment purposes is: saflufenacil.

Results of supervised trials on crops

Residue data were submitted by the manufacturer from supervised trials conducted on citrus fruits, pome fruits, stone fruits, berries and small fruits, assorted tropical and sub-tropical fruits—inedible peel, fruiting vegetables, legume vegetables, pulses, root and tuber vegetables, cereals, grasses for sugar or syrup production, tree nuts, oilseeds, seeds for beverages and sweets. The trials were generally conducted at maximum GAP and well documented.

In case of applications on bare soil at early growing season (pre-emergence, pre-planting) The Meeting concluded that the commercial harvesting time of the crop is the relevant primary factor affecting the residues and not the PHI n case of applications on bare soil at early growing season (pre-emergence, pre-planting).

Samples were analysed within the period tested for storage stability of residues. The residues of parent saflufenacil, M800H11 and M800H35 were determined in all samples with method D0603/02 or equivalent. The LOQ for each compound was 0.01 mg/kg, unless otherwise stated. The performance of the methods was verified with concurrent recovery studies.

Where trial plots were at the same location (side-by-side trials), the higher residues were considered from the replicate results. The average of residues measured in replicate samples taken from one field is reported hereunder, and they were used for estimation of the residue levels.

The OECD MRL calculator was used for calculation of maximum residue levels. The reasons for deviation are indicated under corresponding recommendations.

Citrus fruits

Trials were conducted on sweet oranges (12), lemons (5) and grapefruit (6) in five states of the USA. Saflufenacil was applied in WG formulation three times as spray directed to weeds at a rate of 0.05 kg ai/ha with a re-treatment interval of 20–22 days in compliance with US GAP (1–3 broadcast, banded or spot spraying application at 0.05 kg ai/ha (max. annual dose 0.15) and 0 day PHI).

Saflufenacil residues were present below the LOQ of 0.01 mg/kg in all samples.

Three trials were performed in Brazil in oranges applying saflufenacil three times as spray directed to weeds at a rate of 49 g ai/ha in a spray volume of 200 L/ha. Citrus fruit were taken 7 days

after the last application. (No GAP.) Saflufenacil residues were present below the calculated limit of detection (< 0.002 mg/kg) in all samples.

Based on the US trial data the Meeting estimated a maximum residue level of 0.01* mg/kg and STMR of 0 mg/kg for citrus fruits.

Pome fruits

Fifteen trials in apples and 10 trials in pears were conducted in the USA according to GAP (1–3 broadcast applications directed to weeds at 0.025–0.05 kg ai/ha (max annual dose 0.15) and 0 day PHI. In addition three trials were performed in Brazil (no GAP).

No residues were detectable in any of the samples taken at day 0 up to 14 days.

Based on the US trial data the Meeting estimated a maximum residue level of 0.01* mg/kg and STMR of 0 mg/kg for pome fruits.

Stone fruits

In the USA six trials in cherries (3 tart, 3 sweet), 13 in peaches and 10 in plums were conducted according to US GAP for stone fruits (1–3 Broadcast banded or spot spraying applications directed to weeds at 0.05 kg ai/ha (max annual dose 0.15) and 0 day PHI). None of the samples taken between day 0 and 21 contained detectable residues (< 0.01 mg/kg).

For stone fruits, the Meeting estimated a maximum residue level of 0.01* mg/kg and STMR values of 0 mg/kg.

Berries and other small fruits

Twelve trials were conducted in the USA in grapes according to US GAP (1–3 Broadcast banded or spot spraying applications directed to weeds at 0.025 kg ai/ha (max annual dose 0.075 kg ai/ha) and 0 day PHI). Two trials were conducted in Brazil in grapes (no GAP).

None of the samples taken 0–17 days after last application contained detectable residues (< 0.01 mg/kg).

Based on the US trial data, the Meeting estimated a maximum residue level of 0.01* mg/kg and STMR of 0 mg/kg for grapes.

Assorted tropical and sub-tropical fruits—inedible peel

Bananas

Four trials were conducted in bananas in Brazil where plantations were sprayed with saflufenacil as a directed application to weeds at a rate of 0.049 kg ai/ha. Fruits were taken directly after last application and a day later (No GAP). None of the samples contained detectable residues < 0.01 mg/kg for parent and < 0.003 mg/kg for metabolites.

Ten supervised trials in bananas were conducted in Costa Rica (two trials), Columbia (one trial), Ecuador (three trials), Guatemala (one trial), Honduras (two trials), and Panama (one trial). Applications of saflufenacil directed to weeds were performed five times at rates between 0.072 and 0.08 kg ai/ha in a spray volume of 191–213 L/ha and re-treatment intervals of 20 ± 5 days. Banana fruit were sampled directly after the application and one day later. Saflufenacil is registered in Columbia with one application directed to weeds at 0.028–0.039 kg ai/ha, the PHI is not specified. Five applications were made at 0.08 kg ai/ha instead of the maximum 3 at 0.05 kg ai/ha, but the residues in all samples were below LOQ/LOD.

The Meeting noted that in the Central American trials five applications were made instead of one, and at 0.08 kg ai/ha instead of 0.05 kg ai/ha, but the residues in all samples were below LOQ/LOD.

As the samples did not contain any detectable residues, the Meeting estimated a maximum residue level of 0.01* mg/kg and STMR of 0 mg/kg for bananas.

Mangoes

Four supervised trials were conducted in Brazil applying saflufenacil three times as a directed spray to weeds. None of the samples contained detectable residues: < 0.01 mg/kg for parent, < 0.01–0.003 mg/kg for metabolites. As the product is not registered in Brazil, the residue data could not be evaluated.

Sweet corn

Five residue trials in sweet corn were conducted in the USA with a single application of saflufenacil either incorporated into the soil before planting or applied post-planting pre-emergence at 0.15 kg ai/ha. (GAP: ≥ 1 ground or aerial spraying applications at 0.065–0.1 kg ai/ha, max annual dose 0.15 kg ai/ha, and 80 day PHI)

The residues were below the LOQ of 0.01 mg/kg in all samples taken 91–106 days after treatment.

The Meeting estimated a maximum residue level of 0.01* mg/kg and STMR of 0 mg/kg for sweet corn.

Legume Vegetables, Pulses

Beans, dry

Five trials were conducted in Brazil in beans. The first application was done at a rate of 0.098 kg ai/ha on the day of sowing; the second (0.098 kg ai/ha) took place before harvest as a desiccant. Bean seed samples were taken at PHI of 7 days after the last application, and in three trials also after 0, 3, 10 and 14 days. None of the 17 dried bean samples contained any detectable residues (< 0.01 mg/kg) regardless of the PHI of 0–14 days. (No GAP).

Ten trials in beans were conducted in the USA and Canada applying saflufenacil at 0.05 kg ai/ha as a single late season treatment. Samples of mature dried bean seed were harvested at a 2-day pre-harvest interval (PHI). (GAP: 1× 50 g, as pre-harvest desiccant, PHI 2 days.)

The average residues of parent saflufenacil in dried bean seed sampled in US trials at the 2 day PHI were: < 0.01 (5), 0.01, 0.046, 0.096, 0.136, and 0.157 mg/kg. The maximum residue detected in one of the replicate samples from a single pot was 0.23 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg and STMR value of 0.01 mg/kg for dried bean seeds.

Peas and soya bean immature seed with or without pods

Thirteen trials on peas and 11 trials on chick peas were conducted in the USA and Canada as pre-plant or pre-emergence application of saflufenacil directed to soil at 0.1 kg ai/ha rate according to the maximum annual label rate for peas in the USA (USA GAP: ≥ 1 ground or aerial spraying applications at 0.025–0.05 kg ai/ha, maximum annual dose 0.05–0.1, and a 65 day PHI). Succulent seed samples with and without pod were taken 63–81 days after the application.

None of the 28 succulent pea (with or without pods) samples contained detectable residues (< 0.01 mg/kg), regardless of the PHI.

Fifteen trials were conducted in the USA on soya beans with a single broadcast, pre-plant incorporated or pre-emergence application of saflufenacil (70% WG) at 0.10 kg ai/ha. (US GAP: > 1 Pre-plant or pre-emergence application at 14 days intervals at 0.025 kg ai/ha and seasonal maximum rate of 0.1 kg/ha with PHI of 65 days).

The immature soya bean (succulent seed with pod and succulent seed without pod) samples were harvested at 62–119 days after treatment

Succulent soya beans seed samples (42) with or without pods at 62–126 days did not contain detectable residues.

The Meeting estimated a maximum residue level and STMR of 0.01 mg/kg for immature seeds of peas (with or without pods) and immature soya beans seeds.

Peas, dry

Thirteen trials on peas and 11 trials on chick peas were conducted in the USA and Canada as pre-plant or pre-emergence application of saflufenacil at 0.1 kg ai/ha rate according to maximum annual label rate for peas in the USA (USA GAP: ≥ 1 ground or aerial spraying applications at 0.025–0.05 kg ai/ha, max annual dose 0.05–0.1, and 65 day PHI). Dried seed samples were taken at harvest 82–117 DAT.

None of the 22 dried pea samples, and 11 dried chick pea samples contained detectable residues (< 0.01 mg/kg), regardless of the PHI.

Further, nine pea trials were conducted in the USA and Canada with a single late season application of saflufenacil as a desiccant at 0.05 kg ai/ha. (US GAP ≥ 1 ground or aerial spraying applications at 0.025–0.05 kg ai/ha, max annual dose 0.05 kg ai/ha, and 3 day PHI). Samples of mature pea dried seed and vines were harvested at a 2–4 day pre-harvest interval (PHI).

Three days after one late season application of saflufenacil at 0.05 kg ai/ha, the average residues of parent saflufenacil in two replicate dried pea seed samples were: < 0.01 (3), 0.01, 0.0.02, and 0.03 mg/kg.

The maximum of saflufenacil residue measured in one of the replicate samples from a single trial was 0.05 mg/kg at day 2 and 0.03 mg/kg at day 3.

For dried pea and chickpea seeds, the Meeting estimated a maximum residue level of 0.05 mg/kg and STMR of 0.01 mg/kg.

Soya beans

Twenty trials were conducted in the USA and Canada with a single late-season broadcast application of the 70% water-dispersible granule (WG) formulation of saflufenacil as a harvest aid/ desiccant at 0.05 kg ai/ha. (US GAP: ≥ 1 application at 0.025–0.05 kg ai/ha, max annual rate 0.05 kg ai/ha, 3-day PHI.)

The average parent saflufenacil residues in dry soya bean seed samples at a 3-day PHI were: < 0.01 (14), 0.01 (2), 0.015 (2), 0.02 and 0.05 mg/kg.

Five trials were performed with saflufenacil in Brazil. The first application took place on the day of the planting at a rate of 0.049 kg ai/ha. The second application at a rate of 0.098 g ai/ha was applied to the crop as a pre-harvest desiccant. Soya bean seed was sampled 7 days after the last application. In three trials samples were also collected at 0, 3, 10 and 14 DAT. Soya bean seed samples contained 0.01, 0.02 and 0.03 mg/kg parent saflufenacil residues at day 0. Soya bean samples taken at days 3–14 did not contain any detectable saflufenacil residues, i.e., < 0.01 mg/kg (No GAP).

Based on the US trials, the Meeting estimated a maximum residue level of 0.07 mg/kg and STMR of 0.01 mg/kg for dried soya bean seeds

(OECD calculator gave 0.05 mg/kg which is equal to the highest residues in two samples.)

Potatoes

In Brazil four trials were conducted on potatoes applying saflufenacil as a WG formulation once at a rate of 98 g ai/ha as a pre-harvest desiccant. Potato tubers were sampled 7 days after treatment, and in two trials at 0, 3, 10 and 14 DAT. In potato tubers, saflufenacil residues were not detected above their calculated limit of detection, i.e., 0.009 mg/kg, throughout the study.

As the compound is not registered in Brazil, a maximum residue level could not be estimated.

Cereals

In the USA and Canada a total of 61 trials were conducted in wheat (25), barley (6), sorghum (9), rice (6) and field corn (15) with saflufenacil applied as a single broadcast pre-plant incorporated or pre-emergence application to the soil surface at 0.142–0.158 kg ai/ha. The cereal RAC samples were collected at commercial maturity. The US GAP permits 1 applications at 0.05–0.13 kg ai/ha (maximum annual rate 0.15 kg ai/ha) with PHI of 80 days for maize; 1 applications at 0.05–0.1 kg ai/ha (maximum annual rate 0.15 kg ai/ha) with a PHI of 30 days for barley, sorghum, rice and wheat.

In all trials no samples of wheat (64) taken 76–280 DAT, barley (12) taken 81–100 DAT, sorghum (18) taken 68–150 DAT, maize (32) taken 118–158 DAT and rice grains (12) taken 121–146 DAT contained detectable residues, i.e., < 0.01 mg/kg.

In Brazil two trials in wheat and four trials in rice were conducted applying saflufenacil once at a rate of 0.049 kg ai/ha at planting. No samples contained detectable residues in wheat or rice grain taken at normal harvest maturity (No GAP).

Based on the US data, the Meeting estimated a maximum residue level 0.01* mg/kg and STMR of 0 mg/kg for cereal grains.

Sugarcane

In Brazil five trials were conducted in sugar cane applying saflufenacil once at a rate of 98 g ai/ha as pre-harvest desiccant. Sugar cane stalk samples were taken after 7 and 10 days, and in two trials also after 0, 14 and 21 days.

In sugar cane stalk between 0 and 14 DAT residues of parent saflufenacil were below its calculated limit of detection (0.006 mg/kg) or below LOQ (0.01 mg/kg). After 21 days, no residues of saflufenacil were detected above LOD.

As the compound is not registered in Brazil, the maximum residue levels could not be estimated.

Tree nuts

In the USA five trials were conducted in almonds and five in pecans applying saflufenacil three times as broadcast applications to the orchard floor at a rate of 0.05 kg ai/ha. The last application made on the day of harvest. The US GAP permits up to 3 treatments at 0.05 kg ai/ha rate (annual maximum of 0.15 kg ai/ha) with a 7-day PHI.

No residues were detected in any of the samples taken between 0 and 28 days after last application.

For tree nuts, the Meeting estimated a maximum residue level, of 0.01* mg/kg and an STMR of 0 mg/kg.

Oilseeds

Cotton

In the USA 12 trials were conducted in cotton applying saflufenacil once as at-planting pre-emergence broadcast spray to the soil. The application rate was between 0.024–0.036 kg ai/ha and 0.049–0.072 kg ai/ha. The US GAP permits ≥ 1 application at 0.013–0.05 kg ai/ha with maximum annual rate of 0.05 kg/ha and a PHI of 5 days.

Undelinted cotton seed samples (24 for low rate and 22 for high rate) harvested at normal maturity did not contain any residues above the limit of quantitation (0.01 mg/kg).

In 2009, a study was conducted in the US with 12 trials in cotton in which saflufenacil was applied as a single late-season, broadcast application as a harvest aid/ desiccant at a rate of 0.05 kg ai/ha. Cotton seed samples were taken 5 days after the application, in one trial samples were also collected 1, 4, 5, 10 and 15 days after treatment.

In the US trials matching GAP, the residues in undelinted cotton seed were: < 0.01, 0.02, 0.025 (3), 0.075, 0.095, and 0.125 mg/kg.

In Brazil four trials were conducted in cotton applying saflufenacil three times: the first application took place on the day of planting, the second as a post-emergent directed spray, both applications were made at a rate of 0.049 kg ai/ha. The third application was done pre-harvest as desiccant at a rate of 0.098 kg ai/ha. Cotton seed samples were taken at the PHI of 7 days, in two trials and 0, 3, 10 and 14 DAT (there is no GAP).

The residues in delineated cotton seed samples at 7-day PHI were: < 0.01, 0.02, 0.02 and 0.09 mg/kg

Based on the US late season trial data the Meeting estimated a maximum residue level of 0.2 mg/kg and a STMR of 0.025 mg/kg for cotton seed.

Rape seed

In Canada and the USA 16 trials were conducted with a single late-season, broadcast application of the 70% water-dispersible granule (WG) formulation of saflufenacil as a harvest aid/ desiccant at 0.049–0.051 kg ai/ha. The US GAP permits one application at 0.053–0.178 kg ai/ha maximum seasonal rate 0.05 kg ai/ha, PHI 3 days (allowing up to 7 days for optimum desiccation effect depending on environmental conditions).

In addition, at three trial sites, a bridging comparison plot was treated in the same manner with a single late-season, broadcast application of a 342 g/L suspension concentrate (SC) formulation of saflufenacil applied as a harvest aid /desiccant at 0.046–0.052 kg ai/ha. The bridging trials comparing the two formulations (WG vs. SC) demonstrated that there was no observable difference in residues in canola treated with the two formulations.

The residues of parent saflufenacil in dried seeds at 3 days PHI were in rank order: 0.017, 0.0215, 0.044, 0.044, 0.0445, 0.0555, 0.0595, 0.066, 0.068, 0.0695, 0.096, 0.098, 0.0995, and 0.429 mg/kg. The highest residue observed in one of the replicate samples was 0.48 mg/kg.

For rape seed the Meeting estimated a maximum residue level of 0.6 mg/kg and a STMR of 0.054 mg/kg (the OECD calculator's estimate of 0.5 mg/kg does not cover adequately the maximum residue observed).

Sunflowers

In the USA eight trials were conducted in sunflowers applying saflufenacil in two late-season, over-the-top broadcast applications at a rate of 0.05 kg ai/ha and a re-treatment interval of 7 days. The US GAP permits ≥ 1 treatments with 0.025–0.05 kg ai/ha (maximum annual rate 0.1 kg ai/ha and a 7 day PHI).

The average residues of parent saflufenacil in replicate samples taken between 6 and 8 DAT were: 0.056, 0.0586, 0.0644, 0.089, 0.152, 0.163, 0.19, and 0.437 mg/kg

In Brazil four trials were conducted applying saflufenacil once at a rate of 0.098 kg ai/ha as pre-harvest desiccant. Sunflower seeds were taken 7 (the PHI) and 10 days after the last application, in two trials also after 0, 3 and 14 DAT. The residues of saflufenacil in sunflower seed samples taken 7 days after treatment were: < 0.01, < 0.01, 0.04 and 0.07 mg/kg (There is no GAP).

Based on the residue data obtained in the US trials, the Meeting estimated a maximum residue level of 0.7 mg/kg, and a STMR of 0.12 mg/kg for sunflower seed.

Coffee

In Brazil three trials were conducted in coffee applying saflufenacil three times directed to weeds at a rate of 0.049 kg ai/ha. Coffee grains were taken 7 days after the last application. (No GAP.)

Further trials were conducted in Costa Rica (2), Columbia (2) and Mexico (1) with four direct to base applications at rates between 0.098 and 0.104 kg ai/ha. Samples of commercially mature coffee beans (red coffee cherries) were harvested at a 0-day or 1-day pre-harvest interval (PHI) and processed according to typical commercial practices to produce the coffee raw agricultural commodity (RAC), green bean. (Columbian GAP permits one treatment at 0.028–0.03 kg ai/ha PHI is not specified.)

In all trials the residues of saflufenacil in coffee bean samples were below the limit of detection (0.003 mg/kg) or below quantitation (0.01 mg/kg).

Taking into account that no residue was detectable in any samples, the Meeting estimated a maximum residue level, of 0.01 mg/kg and a STMR of 0 mg/kg for green coffee beans.

Animal feeds

The details of the trials are provided under the respective commodities.

Soya bean forage and hay

In soya beans 15 trials were conducted in the USA with a pre-plant incorporated or pre-emergence application at 0.10 kg ai/ha. In soya bean forage and hay residues were all below the LOQ of < 0.025 mg/kg.

Based on the residue data in soya bean forage, the Meeting estimated a highest residue of 0.025 mg/kg and median of 0.025 mg/kg.

Straw, fodder and forage of cereals

The residues in forage, hay and straw samples derived from of all trials (25 in wheat, 9 in sorghum) were below the LOQ of 0.025 mg/kg at all PHI-s.

The Meeting considered that the results are applicable to barley as well.

For wheat, barley and sorghum forage, fodder and straw, the Meeting estimated a highest reside and median of 0.025 mg/kg.

For wheat, barley and sorghum straw and fodder, the Meeting estimated a maximum residue level of 0.05 mg/kg.

The results of 15 field trials on field corn indicated that the residues were below the LOQ of 0.025 mg/kg in maize forage sampled 86–114 days and maize stover sampled 120–158 days after the single pre-plant treatment at max GAP.

For maize forage and stover, the Meeting estimated a highest reside and median of 0.025 mg/kg.

For maize fodder, the Meeting estimated a maximum residue level of 0.05 mg/kg.

Almond hulls

The results of five field trials on almonds indicated that the residues were below the LOQ of 0.025 mg/kg in almond hulls sampled 7–28 days after the last of three treatments at maximum GAP.

For almond hulls, the Meeting estimated highest residue and median residue of 0.025 mg/kg.

Cotton gin by-product

The average residues of saflufenacil in cotton gin by-product samples, taken 5 days after last treatment, were in rank order: 0.09, 0.18, 0.19, 0.215, 1.84 and 2.08 mg/kg.

The highest residue observed in one of the replicate samples was 2.25 mg/kg

For cotton gin by-product, the Meeting estimated a median residue of 0.2025 mg/kg.

Fate of residues during processing

Studies were conducted for determination of the residues of saflufenacil in processed products of soya beans.

The processing factors, Pf, estimated by the meeting and the corresponding STMR-P values are summarized hereunder.

RAC	Processed product	Pf	STMR for RAC mg/kg	STMR-P, mg/kg
Soya beans	refined soya bean oil	0.25	0.01	0.0025
	soya bean meal	0.65	0.01	0.0065
	soya bean hulls	7.9	0.01	0.079
Sunflower	refined sunflower oil	0.03	0.12	0.0036
	sunflower meal	0.8	0.12	0.096

Field trials were conducted on oranges, apples, plums, wheat, maize, rice and cotton at exaggerated and maximum GAP rates. The saflufenacil residues were not detectable in the RAC samples, indicating that no processing studies were necessary.

Nevertheless, residues in citrus oil were determined because of the 1000× theoretical concentration factor for this commodity. Residues were < 0.01 mg/kg in the two oil samples derived from the orange fruit samples.

Residues in animal commodities

Farm animal dietary burden

Maximum residue level recommendations are not made for some processed and forage commodities as no maximum residue level is needed) but they are used in estimating livestock dietary burdens. Those commodities are listed here.

Commodity	High residue (mg/kg)	Median (mg/kg)
Almond hull		0.025
Cotton gin by-products	2.25	0.215
Maize forage and stover	0.025	0.025
Soya bean forage	0.025	0.025
Soya bean hulls		0.079
Soya bean meal		0.0065
Straw and fodder, forage of cereals	0.025	0.025
Sunflower meal		0.096

Applying the OECD feed table for maximum proportion of agricultural commodities in animal feed (FAO Manual 2nd ed 2009, appendix IX) the maximum and mean saflufenacil intake was calculated from the estimated high and STMR residues. Residue data from field pea vines were not taken into consideration because following the desiccation treatment it is practically dry and not used for feed. **(**The vines used for feed contains about 25% dry matter.)

	Livestock dietary burden, saflufenacil, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle	0.157[a]	0.043	0.078	0.080	0.101	0.101[b]	0.019	0.011
Dairy cattle	0.080	0.080	0.059	0.061	0.096	0.096[c]	0.041	0.011
Poultry, broilers	0.035	0.035	0.021	0.021	0.026	0.025	0.013	0.010
Poultry, layers	0.035	0.035	0.037[d]	0.037[e]	0.026	0.025	0.009	0.009

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

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

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

[d] Highest maximum broiler or layer poultry dietary burden suitable for Maximum residue level estimates for poultry meat and edible offal and eggs

[e] Highest mean broiler or layer poultry dietary burden suitable for STMR estimates for poultry meat and edible offal and eggs

Lactating dairy cows

The saflufenacil was administered orally to 14 lactating cows over a period of 28 days. Based on the proposed usage of the test substance as pre-emergence treatment and a maximal anticipated dietary intake from feed, the target dose level of 0.1 ppm in feed (1×) was determined. The actual dose levels of 0.15 ppm (1×), 0.48 ppm (3×) and 1.7 ppm (10×) were calculated based on actual feed intake.

No residues were detected in any milk specimens at any of the dosing levels.

No residues were detected in muscle or fat specimens at any of the dosing levels.

In the liver samples from the 1× dose group, the residue levels ranged from 0.17 mg/kg to 0.26 mg/kg (mean 0.21 mg/kg). In the 3× dose group, the residue levels ranged from 0.67 mg/kg to 0.88 mg/kg (mean 0.77 mg/kg). In the 10× dose group, the residue levels ranged from 2.09 mg/kg to 3.49 mg/kg (mean 2.61 mg/kg). A good correlation between feeding level and residue level was obtained for liver. Residues in the 10× dose group were 1.66 mg/kg and 0.34 mg/kg after 2 and 7 days of withdrawal, respectively.

No residues were detected in the kidney samples at the 1× dose level. Residues at the 3× dose level were 0.02 mg/kg; those at the 10× dose level ranged from 0.03 to 0.04 mg/kg (mean 0.04 mg/kg). The residues in the 10× group declined to 0.03 mg/kg after 2 days of withdrawal and were below the LOQ after 7 days of withdrawal.

The residues expected in animal commodities based on the calculated animal burden are shown in the table below.

	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Residues (mg/kg) in			
				Muscle	Liver	Kidney	Fat
Maximum residue level beef or dairy cattle							
Feeding study [a]	0.15	< 0.01	0.15	< 0.01	0.26	< 0.01	< 0.01
Dietary burden and residue estimate	0.096	< 0.01	0.157	< 0.01	0.26	< 0.01	< 0.01
STMR beef or dairy cattle							
Feeding study [b]	0.15	< 0.01	0.15	< 0.01	0.21	< 0.01	< 0.01
Dietary burden and residue estimate	0.096	< 0.01	0.101	< 0.01	0.14	< 0.01	< 0.01

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

[b] Mean residues for tissues and milk

The Meeting estimated maximum residue levels of 0.01 mg/kg for milk and milk cream, muscle and fat, 0.01 mg/kg kidney, and 0.3 mg/kg for edible offal of mammals based on residues in liver. The estimated STMR and HR values are 0.01 mg/kg for milk and milk cream and muscle, and HR of 0.26 mg/kg and STMR of 0.14 mg/kg for edible offal of mammals.

Laying hens

The calculated feed burden for poultry based on feed items with highest residues resulted in 0.035 ppm total dry matter feed. Thus, the trigger value of 0.1 mg/kg dry matter feed for conducting a farm animal feeding study was not reached.

In addition, it can be concluded from the data of the hen metabolism study that there are no residues to expect in any of the edible hen matrices assuming a hen feeding level of 0.035 ppm dry matter feed. This feeding level would be lower by a factor of more than 300 compared to the feeding level of 12.6–12.7 mg/kg in the hen metabolism study.

Therefore, by extrapolation from the residue levels in the metabolism study the residues in a hen feeding study would be far below the LOQ of 0.01 mg/kg of the residue analytical method for any of the edible hen matrices even at a 10× feeding level. Thus a hen feeding study has not been conducted.

Establishment of maximum residue limit for poultry product is not necessary.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of saflufenacil resulted in recommendations for maximum residue levels and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the thirteen Cluster Diets, based on estimated STMRs were 0% of the maximum ADI of 0.05 mg/kg bw. The Meeting concluded that the long-term intake of residues of saflufenacil from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The Meeting concluded that establishment of acute reference dose is not necessary. The estimation of short-term intake of residues of saflufenacil was not necessary.