5.13 FLUENSULFONE (265)

TOXICOLOGY

Fluensulfone was evaluated by JMPR in 2013, when an ADI of 0–0.01 mg/kg bw and an ARfD of 0.3 mg/kg bw were established. The 2013 Meeting also evaluated limited toxicological data on three metabolites found in plants and/or animals, characterized as thiazole sulfonic acid (M3625, TSA), methylsulfone metabolite (M3626, MeS) an

d butene sulfonic acid metabolite (M3627, BSA). The sulfonic acid metabolites have been found at low levels in rats (< 6% of the administered dose), whereas the methylsulfone metabolite is not present in rats. The 2013 Meeting did not reach any conclusions in respect of the dietary risk assessment of these metabolites based on the limited toxicological data and the fact that the residues assessment by JMPR was not scheduled until 2014.

Toxicological data on metabolites and/or degradates

Repeated-dose toxicity studies on M3625 and M3627 were submitted to the 2014 Meeting, were evaluated and are summarized below. Table 1 presents the toxicological data on the metabolites evaluated by the 2013 Meeting plus the additional information submitted to this Meeting; summary information on fluensulfone is presented for comparison purposes.

Table 1 Summary of the genotoxicity and toxicity studies on fluensulfone and metabolites

Metabolite	Description	Toxicological profile
M3625 (thiazole sulfonic acid)	Formed at low levels in rat (2–5%)	Oral LD_{50} > 2 000 mg/kg bw (rat)
		Unlikely to be genotoxic
		28-day study of toxicity: NOAEL = 113 mg/kg bw per day (rat)
		90-day study of toxicity: NOAEL = 975 mg/kg bw per day (rat)
M3626 (methylsulfone)	Not found in rat	Oral LD_{50} = 300–2 000 mg/kg bw (rat)
		Not genotoxic in vivo (micronucleus and liver unscheduled DNA synthesis)
M3627 (butene sulfonic acid)	Formed at low levels in rat (4–6%)	Oral LD_{50} > 2 000 mg/kg bw (rat)
		Unlikely to be genotoxic
		28-day study of toxicity: NOAEL = 8.6 mg/kg bw per day (rat)
Fluensulfone	Parent compound	Oral LD_{50} = 671 mg/kg bw (rat)
		Unlikely to be genotoxic
		28-day study of toxicity: NOAEL = 10 mg/kg bw per day (rat)
		90-day study of toxicity: NOAEL = 8 mg/kg bw per day (rat)

M3625 – Thiazole sulfonic acid metabolite (5-chloro-1,3-thiazole-2-sulfonic acid)

In a non-GLP-compliant, 28-day study of toxicity, groups of Wistar rats (three of each sex per dose) received M3625 at 0, 120, 500, 1200 or 12 000 ppm (equal to 0, 10, 41, 113 and 1194 mg/kg bw per day for males and 0, 12, 43, 123 and 1369 mg/kg bw per day for females, respectively). The range of in-life, haematology, clinical chemistry, gross pathology and organ weight examinations was satisfactory, but only liver, kidney, adrenal and lung were examined histopathologically. All three

top-dose males had kidney tubule basophilia (compared with one in control). The NOAEL for the study as performed was 1200 ppm (equal to 113 mg/kg bw per day).[1]

In a GLP-compliant 90-day study of toxicity, groups of Wistar rats (10 of each sex per dose) received M3625 at 0, 500, 2500 or 12 000 ppm (equal to 0, 38, 183 and 975 mg/kg bw per day for males and 0, 52, 290 and 1369 mg/kg bw per day for females, respectively). There were no adverse effects in any of the treated dose groups. Apparent alterations in white blood cell differential counts and plasma creatinine were due to individual animals with values that were outliers and are considered not to be adverse effects of treatment. The NOAEL was 12 000 ppm (equal to 975 mg/kg bw per day), the highest dose tested.[2]

M3627 – Butene sulfonic acid metabolite (3,4,4-trifluorobut-3-ene-1-sulfonic acid)

In a non-GLP-compliant, 28-day study of toxicity, groups of Wistar rats (three of each sex per dose) received M3627 at 0, 100, 500, 1000 or 10 000 ppm (equal to 0, 6.4, 30, 82 and 732 mg/kg bw per day for males and 0, 8.6, 39, 120 and 1024 mg/kg bw per day for females, respectively). The range of in-life, haematology, clinical chemistry, gross pathology and organ weight examinations was satisfactory, but only liver, kidney, adrenal and lung were examined histopathologically. There was a trend for increased kidney weights in males (105%, 106%, 111% and 114% of controls, respectively). At macroscopic examination, bilateral, dilated renal pelvis was seen at 500 ppm (two females), 1000 ppm (one male) and 10 000 ppm (two males, two females), compared with zero in controls; this was confirmed at microscopic evaluation. Although there was no dose–response relationship for the kidney effects, the small group size and limited level of histopathological investigation in the study support the treatment of this finding as potentially adverse. The NOAEL for the study as performed was 100 ppm (equal to 8.6 mg/kg bw per day), based on dilated renal pelvis in females at 500 ppm (equal to 39 mg/kg bw per day). This study indicates that M3627 is of similar repeated-dose toxicity to fluensulfone.[3]

Toxicological evaluation

The current Meeting concluded that M3625 is significantly less toxic than fluensulfone over 90 days of dietary exposure in rats and that M3627 appears to be of similar toxicity to fluensulfone over 28 days of dietary exposure in rats.

On this basis, it was concluded that residues of M3625 in plants or animals were unlikely to be of any toxicological relevance.

For M3626, in the absence of any repeated-dose toxicity data, the lack of genotoxicity in vivo supports the comparison of chronic intake estimates with the TTC value of 1.5 µg/kg bw per day for a Cramer class III compound. The international estimated daily intake (IEDI) is below this threshold value. A single-exposure TTC for Cramer class III compounds of 5 µg/kg bw has been proposed by EFSA, and the Meeting concluded that the use of this value would be conservative. The international estimate of short-term dietary intake (IESTI) is below this value. On this basis, the Meeting concluded that M3626 is considered not to be a relevant plant or animal metabolite of fluensulfone.

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[1] Takewale P (2014a). 28 day dose range finding dietary toxicity study in Wistar rats with 5-chlorothiazole-2-sulfonic acid. BSL Bioservice. Planegg, Germany; Study No. 122929. Submitted to WHO by Makteshim Chemical Works, Beer-Sheva, Israel.

[2] Takewale P (2014b). 90 day dietary toxicity study in Wistar rats with 5-chlorothiazole-2-sulfonic acid. BSL Bioservice. Planegg, Germany; Study No. 122930. Submitted to WHO by Makteshim Chemical Works, Beer-Sheva, Israel.

[3] Takewale P (2014c). 28 day dose range finding dietary toxicity study in Wistar rats with 3,4,4-trifluro-but-3-ene-1-sulfonic [*sic*] acid. BSL Bioservice. Planegg, Germany; Study No. 136081. Submitted to WHO by Makteshim Chemical Works, Beer-Sheva, Israel.

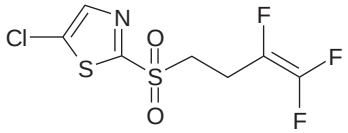
For M3627, which is of similar toxicity to fluensulfone, the ADI and ARfD for fluenesulfone could be used for an initial comparison with the IEDI and IESTI, respectively. The intake estimates showed that the margin of exposure between the IEDI for M3627 and the upper bound of the ADI for fluensulfone is 33, and the margin of exposure between the IESTI for M3627 and the ARfD for fluensulfone is 15. On this basis, the Meeting concluded that M3627 is not a relevant plant metabolite of fluensulfone.

An addendum to the toxicological monograph was not prepared.

RESIDUE AND ANALYTICAL ASPECTS

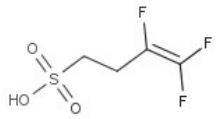
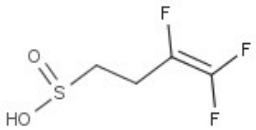
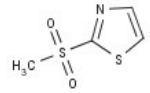
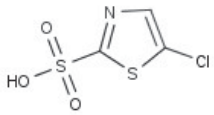
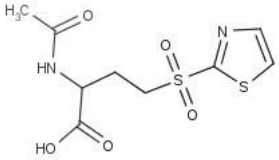
Fluensulfone is a non-fumigant nematicide in the fluoroalkenyl class of pesticides. Fluensulfone shows activity in multiple nematicide physiological systems. It was considered for the first time by the 2013 JMPR for toxicology and by the 2014 JMPR for residues. The 2013 JMPR established an ADI of 0–0.01 mg/kg bw and an ARfD of 0.3 mg/kg bw.

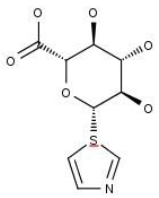
The IUPAC name for fluensulfone is 5-chloro-1,3-thiazol-2-yl 3,4,4-trifluorobut-3-en-1-yl sulfone.



Fluensulfone with ^{14}C radiolabelling in the thiazole ring or in the ethane bridge between the sulfone and trifluorobutene moieties was used in the metabolism and environmental fate studies. In this appraisal, these positions are referred to as the Th and Bu labels, respectively.

The following abbreviations, along with IUPAC names and structures, are used for the metabolites discussed in this appraisal:

BSA	3,4,4-trifluorobut-3-ene-1-sulfonic acid	
Butene sulfinic acid	3,4,4-trifluorobut-3-ene-1-sulfinic acid	
MeS	2-methylsulfonyl-1,3-thiazole	
TSA	5-chloro-1,3-thiazole-2-sulfonic acid	
Thiazole mercapturate	2-acetamido-4-(1,3-thiazole-2-sulfonyl)butanoic acid	

Thiazole glucuronides (α and ß isomers)	Name not specified	

Animal metabolism

The Meeting received studies elucidating the metabolism of fluensulfone in laboratory animals (evaluated by the 2013 Meeting), lactating goats, and laying hens.

In rats, absorption of fluensulfone administered by gavage at 5 mg/kg bw is rapid, with maximal plasma concentrations achieved within 4 hours. At 5 and 500 mg/kg bw, the extent of oral absorption is high (> 80%). Fluensulfone is widely distributed in the body. High concentrations of both butene- and thiazole-labelled material were found in the liver and kidney. The labelled material was rapidly excreted via urine (> 70%), with faecal excretion accounting for no more than 5–13%. Absorbed fluensulfone was extensively metabolized, with almost no unmetabolized parent compound detected. Other than low amounts of thiazole sulfonic acid, no other faecal metabolites were present at levels above 5% of the administered dose. The parent compound probably reacts with glutathione and cleaves, giving rise to thiazole mercapturate, thiazole glucuronide, and butene sulfinic acid, the major urinary metabolites.

In goats dosed for five consecutive days at approximately 28.8 mg/animal/day (10.5 ppm in the diet), most of the recovered radioactivity was in urine and GI tract/faeces, with only 10.7% (Th-^{14}C) or 3.5% (Bu-^{14}C) of the applied dose (AD) accounted for in tissues and body fluids. In excreta, the major identified residues were trifluorobutene sulfinic acid and the MeS metabolite. In other matrices, the highest levels of radioactivity were associated with liver (max. 2.6 mg eq./kg, 1.7% AD), kidney (maximum 1.4 mg eq./kg, 0.2% AD), and milk fat (2.0 mg eq./kg, 0.31% AD). Seventy-five to ninety percent of the radioactivity in the goat matrices was extracted with a combination of solvent extraction and alkaline digestion. No BSA, TSA, or fluensulfone was detected in any goat matrix. Radioactivity in milk and tissues was primarily associated with glucose (0.039–0.24 mg/kg; 4–17% TRR), lactose (0.036–0.21 mg/kg; 4–63% TRR), proteins/amino acids (0.015–1.2 mg/kg; 5–37% TRR), and triglycerides/fatty acids (0.009–1.1 mg/kg; 7.6–52% TRR), and the radioactivity appears to be due to incorporation of the radiolabelled carbon.

In hens dosed for seven consecutive days at 1.25 mg/animal/day (9.8 ppm in the diet), total radioactive residues (TRR) in excreta accounted for approximately 80% of the dosed material for both label positions. Total radioactivity in eggs did not plateau within the eight dosing days of the hen study. Radioactive residues in eggs were not identified. Most residues in eggs were associated with aqueous phases in the extraction schemes; however, 0.18 mg eq./kg from the butane label (27% TRR) was extracted with hexane:acetone. Fluensulfone was a major residue (0.009–0.041 mg/kg; 21–55% TRR) in poultry fat; otherwise, parent fluensulfone was not observed in any matrix. Comparison of extraction of radioactivity from liver samples treated with and without protease enzyme indicates that ca. 0.16 mg/kg (24%) of the radioactivity was associated with proteins and/or amino acids and approximately 3% (0.016 mg/kg) was identified as TSA. Incorporation of the radioactivity into triglycerides was noted in both fat matrices and in eggs. In eggs, triglyceride accounted for 7% and 27% of the TRR for the thiazole and butene labels, respectively. In fat matrices, triglycerides accounted for 7–12% and 79–87% of the TRR for the thiazole and butene labels, respectively.

Overall, the animal metabolism studies show that fluensulfone is well absorbed and that the majority (75–90%) of the dosed radioactivity is excreted. Results from rat, goat, and hen studies indicate that fluensulfone is cleaved at the sulfonyl bridge in all three animals; however, the identification of different residues in the studies suggests that there may be different metabolic pathways. In both poultry and goats, fluensulfone can be expected to break down and be incorporated

almost entirely into natural products. Based on the residue profile in poultry and the observed incorporation of radioactivity into natural components, the Meeting is of the opinion that the lack of a residue plateau in egg is not of concern.

Plant metabolism

The Meeting received studies depicting the metabolism of fluensulfone in tomato, lettuce, and potato. All of the studies were conducted with fluensulfone which was radiolabelled, separately, in the thiazole ring and the ethane bridge between the sulfonyl and trifluorobutene moieties.

To investigate the metabolism of fluensulfone on tomato, fluensulfone was applied at a rate of 4.07 kg ai/ha to soil. Later that same day, tomato seedlings were planted. Mature fruits were harvested 87 days after treatment. Total radioactive residues in tomato were higher in samples treated with Bu-^{14}C-labelled material (0.52 mg eq./kg) than those from Th-^{14}C treatment (0.27 mg eq./kg). The majority (88.7% Th-^{14}C; 91.3% Bu-^{14}C) of the radioactivity was extracted with acetonitrile:water (ACN:H_2O). TSA made up 0.12 mg/kg (45.4% TRR), with an additional 0.06 mg eq./kg (21.2% TRR) as salts/related compounds. BSA occurred at 0.22 mg/kg (41.6% TRR) with salts/related compounds making up 0.13 mg eq./kg (26.5% TRR). No other compounds, including parent fluensulfone, were identified in tomato.

Lettuce seeds were planted into soil and then fluensulfone was applied at a rate of 4.07 kg ai/ha. Samples were collected 49 days and 64 days after application to obtain immature and mature lettuce, respectively. Contrary to the results with tomato, TRR were higher from treatment with Th-^{14}C-labelled material (6.1–7.1 mg eq./kg) than with Bu-^{14}C-labelled material (1.5–2.4 mg eq./kg) and were similar in immature and mature foliage. The majority of the radioactivity was extracted with ACN:H_2O, with higher extraction efficiency from samples treated with the Th-^{14}C label. Following treatment with Th-^{14}C-labelled material, 3.57 mg/kg and 4.34 mg/kg (67.5% and 70.6% TRR) was identified as TSA in immature and mature leaves, respectively. An additional 1.39 mg eq./kg and 0.41 mg eq./kg (17.8% and 6.6% TRR) in immature and mature leaves, respectively, was determined to be salts and/or other forms of TSA. Following treatment with Bu-^{14}C-labelled material, BSA occurred at 0.49 mg/kg (23.8% TRR) in immature leaves and at 0.49 mg/kg (37.6% TRR) in mature leaves. As with TSA, salts and other forms occurred for BSA and constituted, in total, 0.75 mg eq./kg (36.0% TRR) in immature foliage and 0.29 mg eq./kg (22.1% TRR) in mature foliage. Fluensulfone occurred at trace levels (0.009 mg/kg, 0.008 mg/kg) in immature lettuce from the Th-^{14}C and Bu-^{14}C treatments, respectively. Aside from BSA and TSA, no other metabolites of fluensulfone were identified.

Potato seed pieces were planted just prior to application of fluensulfone to soil at a rate of 4.04 kg ai/ha (Th-^{14}C) or 4.13 kg ai/ha (Bu-^{14}C). Immature (70 days after treatment) and mature (106 days after treatment) tubers were harvested and analysed. For immature and mature tubers, respectively, TRR were 0.32 and 0.44 mg eq./kg from the Th-^{14}C treatment and 0.22 and 0.17 mg eq./kg from the Bu-^{14}C treatment. Extraction with ACN:H_2O efficiently released residues: 91.9% TRR (Th-^{14}C, immature tuber), 91.7% TRR (Th-^{14}C, mature tuber), 76.9% TRR (Bu-^{14}C, immature tuber), and 79.1% TRR (Bu-^{14}C, mature tuber). Fluensulfone was found at trace levels (0.005 mg/kg) from both label treatments in mature tubers only. Otherwise, the only identified residues were BSA, TSA, and their salts and/or related compounds. BSA constituted 0.069 mg/kg (30.7% TRR) and 0.042 mg/kg (25.8% TRR) in immature and mature tubers, respectively. Salts and related forms of BSA provided an additional 0.041 mg eq./kg (17.8% TRR; immature tubers) and 0.035 mg eq./kg (21.4% TRR; mature tubers). TSA occurred at 0.21 mg/kg (63.0% TRR) and 0.31 mg/kg (65.3% TRR) in immature and mature tubers, respectively. Salts and related forms of TSA gave an additional 0.028 mg eq./kg (8.4% TRR; immature tubers) and 0.025 mg eq./kg (5.3% TRR; mature tubers).

Fluensulfone was extensively metabolised in all of the studies, with the only major residues being the BSA and TSA metabolites. A few chromatographic fractions contained radioactivity in excess of 10% TRR. Investigation of these fractions indicated that the residues were associated with

the BSA or TSA metabolites, as salts of the sulfonic acids or as related forms of the metabolites. The only major residues in the harvested matrices were the BSA and TSA metabolites and, with the exception of trace levels of fluensulfone in immature lettuce and mature potato, no parent compound was detected.

Environmental fate in soil

Fluensulfone is stable to hydrolysis under accelerated conditions (50 °C, pH 4, 7, 9) but is prone to photolysis [DT_{50} of 21days (Th-^{14}C) or 35 days (Bu-^{14}C) in soil], showing first-order kinetics. In an aerobic soil metabolism study, major residues following treatment with fluensulfone were BSA, TSA, and MeS, depending on the duration of incubation. Fluensulfone had DT_{50} estimates ranging from 7 to 17 days across six soils, all following first-order kinetics. BSA formed from fluensulfone generally accumulated for the first ca. 1 month of incubation followed by dissipation (DT_{50} 18–26 days). Residues of TSA accumulated continuously over the incubation period, reaching maxima of 49–74% of the applied radioactivity at the 120-day sampling. Residues of MeS began to be observed after the first 2–4 weeks of incubation, reaching a maximum of not more than 8% of the applied radioactivity; residues of MeS declined to 0% of the applied radioactivity between the 50 and 120-day sampling times, depending on the soil. In a separate study, the DT_{50} estimates for the TSA and MeS metabolites under aerobic soil conditions are 421 and 33 days, respectively. Field dissipation studies were not provided.

Confined rotational crop studies were conducted with radish, lettuce, and wheat at plant-back intervals (PBIs) of 30, 120, and 360 or 390 days. Fluensulfone, radiolabelled as either the Th-^{14}C or Bu-^{14}C, was applied to soil at a rate of approximately 4 kg ai/ha. Lettuce was replanted at 390 days after application due to crop failure at the 360-day PBI. Following treatment with Th-^{14}C-labeled material, TRR generally declined sharply from 30 to 120 days and then remained relatively consistent between the 120 and the 360/390-day PBIs. (e.g., wheat hay: 27 mg eq./kg at 30-Day PBI, 9.4 mg eq./kg at 120-Day PBI, 10.8 mg eq./kg at 360-Day PBI) As with primary crops, the major residues were the BSA and TSA metabolites. A low level of the parent compound was observed in lettuce, radish root, radish foliage, and wheat forage, hay, and straw (but not grain). Fluensulfone, when found, was typically 1 to 2 orders of magnitude less than the BSA or TSA residue levels. In all cases, residues of fluensulfone and BSA were not quantifiable after the 120-day PBI whereas residues of TSA persisted at quantifiable levels for at least one year, ranging from 0.13 mg eq./kg (immature lettuce) to 11 mg eq./kg (wheat hay).

Overall, fluensulfone can be expected to dissipate rather rapidly in the environment, with a concomitant increase in residues of BSA, TSA, and, to a much lesser extent, MeS. BSA residues should then decline; however, TSA appears to be stable for an extended period. The Meeting concluded from the soil metabolism and confined rotational crop studies that TSA may accumulate in soils following repeated uses of fluensulfone and may occur in follow-on crops at plant-back intervals exceeding one year after treatment.

Methods of residue analysis

The Meeting received analytical methods for the analysis of fluensulfone, BSA, MeS, and TSA in plant and animal matrices. The methods are essentially identical for all samples and the LOQ for all matrices and analytes, defined as the lower limit of method validation, is 0.01 mg/kg.

Extraction of residues is accomplished with ACN:H_2O (1:1, v/v) or ACN (BSA and TSA in eggs only); the extract is then split for analysis of fluensulfone and MeS by one set of procedures and for analysis of BSA and TSA by a second set. For fluensulfone and MeS, there is no clean-up of the extract beyond filtration (except hexane partitioning for analysis of MeS in fatty/oily samples). Residues of fluensulfone and MeS are determined by reverse-phase LC-MS/MS in positive ion spray mode. For BSA and TSA, an aliquot of the initial extract is concentrated and then cleaned-up using C-18 SPE. Residues are determined by reverse-phase LC-MS/MS in negative ion spray mode.

The solvent used for extraction is the same as, or very similar to, that used in the metabolism studies and showed adequate extraction efficiency of incurred residues.

Testing of fluensulfone and the two sulfonic acid metabolites, BSA and TSA, through the FDA PAM multiresidue method protocols demonstrated that the compounds showed poor sensitivity, poor recovery, and/or poor chromatography. Overall, the results indicate that the FDA PAM multiresidue protocols are not suitable for the detection or enforcement of fluensulfone, BSA, or TSA residues in non-fatty foods.

Stability of residues in stored analytical samples

The Meeting received data depicting the stability of residues of fluensulfone, BSA, and TSA in tomato, pepper, cucumber, and melon. In addition, the stability of those analytes and MeS was investigated in frozen, stored tomato puree and paste. No dissipation of any analyte was observed during the storage periods for the various matrices. Stability was demonstrated in tomato raw agricultural commodity (RAC) for at least 469 days (approximately 15 months) and in tomato processed commodities for at least 181 days (approximately 6 months). For pepper, cucumber, and melon, residues were stable for at least 488 days (approximately 16 months).

Definition of the residue

Studies depicting the nature of the residues in animals consistently show fluensulfone to be cleaved at the sulfonyl moiety, presumably via glutathione conjugation, resulting in both halves of the molecule having a sulfonyl functional group. With the exception of poultry fat, fluensulfone was not observed in any animal commodity. In livestock, the majority of the radiolabel was excreted. Retained fluensulfone is extensively metabolized, with the radioactivity being associated primarily with sugars, amino acids, and fatty acids. MeS and butene sulfinic acid were identified in livestock studies, but were observed only in excreta. In the rats, significant residues were thiazole mercapturate, thiazole glucuronide, BSA, TSA, and butene sulfinic acid. MeS, observed in some field trial samples, was not identified in the rat metabolism study.

Based on the livestock metabolism studies, a residue definition potentially suitable for enforcement by the typical criteria is possible only for poultry fat and poultry liver, which were the only matrices in the animal metabolism studies with quantifiable residues of a fluensulfone-specific compound (fluensulfone in fat and TSA in liver). Although fluensulfone was a major residue in poultry fat (up to 55% TRR), the available residue data indicate that quantifiable residues of the parent compound are not expected in plants; thus exposure to fluensulfone via livestock diets is unlikely, making the parent compound an unsuitable marker for enforcement in any livestock commodity. The other potential marker, TSA, occurred only as a minor component in poultry liver (2.7% TRR). Based on the results of the metabolism studies and on the residue profiles observed in crop metabolism studies, confined rotational crop studies, and supervised residue trials, the Meeting determined that a residue definition for livestock commodities is not necessary.

In both plant and rotational crop metabolism studies, fluensulfone appears to follow the same glutathione-mediated pathway observed in livestock; however, in plants quantifiable residues of the BSA and TSA metabolites were consistently observed. Parent fluensulfone was identified only at trace levels in immature lettuce, mature potato, and rotational lettuce, radish foliage, and wheat hay, forage and straw at short PBIs (30 days). In target crops, BSA ranged from 0.071–1.24 mg/kg (43.6–68.1% TRR) and TSA ranged from 0.17–4.75 mg/kg (66.6–85.3% TRR). In rotational crops, BSA was detected in all matrices except wheat grain at the 30-day PBI (0.004–1.4 mg/kg) and in most matrices at the 120-day PBI (0.001–0.43 mg/kg), and was undetected (< 0.001 mg/kg) by the 360/390-day PBI, except wheat straw at 0.012 mg/kg. In contrast, TSA was detected in all rotational crop matrices at all PBIs, ranging from 0.086 mg/kg to 16 mg/kg across all samples.

In crop field trials, fluensulfone was detected in only one sample (summer squash at 0.017 mg/kg). Across all crops, residues of BSA ranged from < 0.01 to 0.27 mg/kg and TSA ranged

from < 0.01 to 0.71 mg/kg. MeS ranged from < 0.01 to 0.08 mg/kg and was less than both BSA and TSA in the corresponding sample. In all trials with only pre-plant applications (per GAP), MeS was < 0.01 mg/kg in all samples of cantaloupe, pepper, and tomato. Although MeS was not found in the plant or rotational crop metabolism studies, it was observed in supervised residue trials in cucumber (< 0.01–0.079 mg/kg) and summer squash (< 0.01–0.050 mg/kg).

The Meeting determined that fluensulfone is not a suitable marker for compliance with MRLs in crops. Both BSA and TSA are suitable markers based on results of supervised field trials. The confined rotational crop study, however, demonstrates a potential for TSA to carry over into succeeding crops. Therefore, given that quantifiable residues of fluensulfone are not expected in plant commodities, that a separate analysis is required for the analysis of fluensulfone and BSA/TSA, and that residues of TSA may occur from previous crop cycle treatments with fluensulfone, the Meeting determined that BSA is the most suitable marker for MRL compliance. A validated method exists for analysis of BSA in plant commodities. The Meeting defined the BSA metabolite as the residue definition for compliance in plants.

Regarding the toxicity of the BSA, TSA, and MeS metabolites, the JMPR has concluded that TSA is unlikely to be of any toxicological relevance; data are insufficient at this time to make a definitive toxicological determination regarding the relevancy of BSA and MeS.

For BSA, the JMPR has determined that the ADI and ARfD for fluensulfone could be used as a screening evaluation of exposure to BSA. Based on a comparison of toxicity data between BSA and fluensulfone, the evaluation may be made directly, without a correction for molecular weight. If additional uses are considered in the future, the use of the fluensulfone points of departure to evaluate exposure to BSA may need to be re-evaluated.

For MeS, the JMPR has determined that the IEDI (0.07 µg/kg bw/day) for MeS should be compared to the Cramer class III TTC value of 1.5 µg/kg bw/day and that the IESTI (3.2 µg/kg bw/day)[1] should be compared to the single-exposure TTC for Cramer class III compounds of 5 µg/kg bw proposed by EFSA. The IESTI is somewhat refined in that for melon, the specific HR (0.01 mg/kg) from melon field trials was used rather than the HR for the fruiting vegetables, Cucurbits group (0.053 mg/kg). On the basis of these comparisons, the Meeting concluded that MeS is not considered to be a relevant metabolite for the crops under consideration. If additional uses are considered in the future, this conclusion may need to be re-evaluated.

Given the residue profile in crops and taking into consideration the available information on the toxicities of the metabolites, the Meeting determined that the residue definition for dietary exposure from crops is BSA. In lieu of BSA-specific toxicological points of departure, dietary intake estimates for BSA should be compared to the ADI and ARfD for fluensulfone, with no correction for molecular weight.

Definition of the residue for compliance with the MRLs and dietary intake for plant commodities: *BSA {3,4,4-trifluorobut-3-ene-1-sulfonic acid}*.

Definition of the residue for compliance with the MRLs and for dietary intake for animal commodities: *Not necessary*

Results of supervised residue trials on crops

Fluensulfone is registered in the USA for use on cucurbit vegetables and on fruiting vegetables. For all crops, the cGAP is an application to the soil at 2.8 kg ai/ha made seven days prior to transplanting crops into the field. Application may be made by broadcast spray to the soil, by banded spray, or by

[1] The estimate of 3.2 µg/kg bw is refined, using the observed HR for melon (0.01 mg/kg) rather than the HR for the fruiting vegetables, Cucurbits group (0.053 mg/kg), which resulted in a maximum dietary intake estimate of 5.3 µg/kg bw.

drip irrigation. The applied material must be mechanically incorporated 15–20 cm into the soil profile for spray applications or by sufficient volume for drip irrigation application.

The Meeting received supervised residue trial data for cucumber, summer squash, cantaloupe, pepper, and tomato. The trials were conducted in North America (USA and Canada). All trials were conducted at a target application rate of 3.9 kg ai/ha, which reflects a nominal exaggeration of 39% relative to the cGAP. Therefore, the Meeting decided to scale residue values for all analytes from trials otherwise meeting the cGAP to an application rate of 2.8 kg ai/ha. Residues scaled to < 0.01 mg/kg were maintained at < 0.01 mg/kg. Reported values are field trial averages unless otherwise noted.

Residues of fluensulfone were < 0.01 mg/kg in all samples.

Fruiting vegetables, Cucurbits

In cucumber, mean field trial residues of BSA (unscaled) from independent field trials treated 7 days prior to transplant (n=7) were: < 0.01, 0.01 (2), 0.063, 0.07, 0.17, and 0.219 mg/kg.

Application rates for these trials ranged from 3.72 kg ai/ha to 4.11 kg ai/ha. Scaled to an application rate of 2.8 kg ai/ha, the residues of BSA are: < 0.01 (3), 0.041, 0.045, 0.114, and 0.137 mg/kg.

In summer squash, mean field trial residues of BSA (unscaled) from independent field trials treated 7 days prior to transplant (n=8) were: < 0.01, 0.05, 0.06, 0.082, 0.186, 0.196, 0.214, and 0.247 mg/kg.

Application rates for these trials ranged from 3.80 kg ai/ha to 4.14 kg ai/ha. Scaled to an application rate of 2.8 kg ai/ha, the residues of BSA are: < 0.01, 0.032, 0.038, 0.051, 0.115, 0.12, 0.133, and 0.149 mg/kg.

In melon, mean field trial residues of BSA (unscaled) from independent field trials treated 7 days prior to transplant (n=8) were: < 0.01 (3), 0.021, 0.025, 0.032, 0.049, and 0.064 mg/kg.

Application rates for these trials ranged from 3.85 kg ai/ha to 4.11 kg ai/ha. Scaled to an application rate of 2.8 kg ai/ha, the residues of BSA are: < 0.01 (3), 0.013, 0.016, 0.019, 0.030, and 0.040 mg/kg.

Noting that the GAP in the USA is for the cucurbit vegetables crop group, which is equivalent to the Codex fruiting vegetables, Cucurbit group, and that the BSA residue data from cucumbers, summer squash, and melons are not significantly different by the Kruskal-Wallis test, the Meeting determined that the residues from the trials are similar and is estimating a group maximum residue level for fruiting vegetables, Cucurbits based on the following scaled BSA residue data set (n=23): < 0.01 (7), 0.013, 0.016, 0.019, 0.030, 0.032, 0.038, 0.040, 0.041, 0.045, 0.051, 0.114, 0.115, 0.120, 0.133, 0.137, and 0.149 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg for BSA on fruiting vegetables, Cucurbits; the HR is 0.16 mg/kg (from a single sample) and the STMR is 0.032 mg/kg.

Fruiting vegetables, other than Cucurbits

In chilli pepper, mean field trial residues of BSA (unscaled) from independent field trials treated 7 days prior to transplant (n=3) were: 0.040, 0.041, and 0.184 mg/kg.

Application rates for these trials ranged from 3.98 kg ai/ha to 4.10 kg ai/ha. Scaled to an application rate of 2.8 kg ai/ha, the residues of BSA are: 0.025, 0.025, 0.116 mg/kg.

In sweet peppers, mean field trial residues of BSA (unscaled) from independent field trials treated 7 days prior to transplant (n=8) were: 0.048, 0.055, 0.063, 0.070, 0.073, 0.082, 0.136, and 0.232 mg/kg.

Application rates for these trials ranged from 3.84 kg ai/ha to 410 kg ai/ha. Scaled to an application rate of 2.8 kg ai/ha, the residues of BSA are: 0.030, 0.034, 0.041, 0.045 (2), 0.050, 0.083, and 0.146 mg/kg.

In tomato, mean field trial residues of BSA (unscaled) from independent field trials treated 7 days prior to transplant (n=20) were: < 0.01 (3), 0.013, 0.023, 0.026, 0.029, 0.034, 0.042, 0.072, 0.074, 0.078, 0.087, 0.088, 0.094, 0.173, 0.198, 0.231, 0.269, and 0.273 mg/kg.

Application rates for these trials ranged from 3.64 kg ai/ha to 4.12 kg ai/ha. Scaled to an application rate of 2.8 kg ai/ha, the residues of BSA are: < 0.01 (4), 0.014, 0.016, 0.018, 0.021, 0.026, 0.045, 0.046, 0.049, 0.054, 0.055, 0.061, 0.108, 0.132, 0.140, 0.168, and 0.169 mg/kg;

Noting that the GAP in the USA is for the fruiting vegetables crop group, which is equivalent to the Codex group fruiting vegetables, other than Cucurbits except sweet corn and mushroom, and that the residue data from sweet pepper, chilli pepper, and tomato are not significantly different by the Kruskal-Wallis test, the Meeting determined that the residues from the trials are similar and is estimating a group maximum residue level for fruiting vegetables, other than Cucurbits except sweet corn and mushroom based on the following scaled BSA residue data set: (n=31): < 0.01 (4), 0.014, 0.016, 0.018, 0.021, 0.025, 0.025, 0.026, 0.030, 0.034, 0.041, 0.045 (3), 0.046, 0.049, 0.050, 0.054, 0.055, 0.061, 0.083, 0.108, 0.116, 0.132, 0.140, 0.146, 0.168, and 0.169 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg for BSA on fruiting vegetables, other than Cucurbits except sweet corn and mushroom; the HR is 0.17 mg/kg (from a single sample) and the STMR is 0.045 mg/kg.

Based on the maximum residue level of fruiting vegetables, other than Cucurbits except sweet corn and mushroom (0.3 mg/kg) and a dehydration factor of 7, the Meeting estimated a maximum residue level of 2 mg/kg for BSA in chilli pepper (dry), an HR of 1.2, and an STMR of 0.32.

Fate of residues during processing

High-temperature hydrolysis

The Meeting received a study investigating the high-temperature hydrolysis of fluensulfone, BSA, MeS, and TSA. Samples of aqueous buffered solutions were spiked with fluensulfone, BSA, MeS, or TSA at ca. 1 mg/L and put under conditions simulating pasteurisation (90 °C, pH 4, 20 min.); baking, brewing, boiling (100 °C, pH 5, 60 min); and sterilisation (120 °C, pH 6, 20 min.). Solutions were analysed by HPLC-MS/MS prior to and after processing. All four analytes were shown to be stable under all three conditions, with overall recoveries ranging from 87 to 118% of the initial concentration.

Residues after processing

The Meeting received data depicting the concentration/dilution of residues during processing of tomato into canned, juice, puree, paste, wet and dry pomace, peeled, and sun-dried processed commodities. Processed commodities were derived using simulated commercial practices. Of the three studies that were submitted, two were suitable for deriving processing factors (in one study, all residues were < 0.01 mg/kg). In those two studies, residues of fluensulfone were < 0.01 mg/kg in all samples and processing factors for the parent compound could not be derived.

Crop	Processed commodity	BSA processing factors	Best processing factor estimate (average)	STMR-P, mg/kg	HR-P, mg/kg
Tomato	RAC	--	--	STMR=0.045	HR=0.17
	Canned	0.33	0.33	0.015	0.056

Crop	Processed commodity	BSA processing factors	Best processing factor estimate (average)	STMR-P, mg/kg	HR-P, mg/kg
	Dry pomace	6.6, 9.3, 17	11	0.50	1.9
	Peeled	0.33	0.33	0.015	0.056
	Sundried	1.67, 2	1.8	0.081	0.31
	Juice	0.67, 0.83	0.75	0.034	0.13
	Paste	1, 1, 3.54	1.8	0.081	0.31
	Puree	0.67, 1.38	1.0	0.045	0.17
	Wet pomace	0.66, 3, 4	2.6	0.12	0.44

Based on the maximum residue estimate for fruiting vegetables, other than Cucurbits except sweet corn and mushroom (0.3 mg/kg) and the processing factor of 1.8 for both dried tomato and tomato paste, the Meeting recommends a maximum residue level of 0.5 mg/kg for BSA in dried tomato and 0.5 mg/kg for BSA in tomato paste.

Residues in animal commodities

The Meeting has determined that residue definitions for compliance and dietary intake are not necessary for animal commodities and that residues in animal commodities are not expected.

RECOMMENDATIONS

Definition of the residue for compliance with the MRLs and dietary intake for plant commodities: *3,4,4-trifluorobut-3-ene-1-sulfonic acid (BSA)*. Note that for dietary intake, exposure estimates should be compared to the ADI and ARfD for fluensulfone, with no correction for molecular weight.

Definition of the residue for compliance with the MRLs and for dietary intake for animal commodities: *Not necessary.*

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of BSA were calculated for the 17 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current Meeting. The ADI for fluensulfone is 0–0.01 mg/kg bw. The calculated IEDIs for BSA were 0–3% of the maximum fluensulfone ADI. The Meeting concluded that the long-term intakes of residues of BSA, when fluensulfone is used in ways that have been considered by the JMPR, are unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intakes (IESTI) of BSA were calculated for food commodities and their processed commodities using HRs/HR-Ps or STMRs/STMR-Ps estimated by the current Meeting. The ARfD for fluensulfone is 0.3 mg/kg bw. The calculated maximum IESTI for BSA was 7% of the fluensulfone ARfD for all commodities. The Meeting concluded that the short-term intake of residues of BSA, when fluensulfone is used in ways that have been considered by the JMPR, is unlikely to present a public health concern.