OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

MEMORANDUM

DATE: August 28, 2024

SUBJECT: **Sulfentrazone** – Human Health Risk Assessment for the Establishment of Tolerances for Residues in/on Pop Corn Commodities.

PC Code: 129081
CAS No.: 122836-35-5
Petition No.: NA
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: NA

Task Group No.: 00562132
Parent Case No.: 00561388
Registration Nos.: 279-3220, 279-3189
Regulatory Action: Section 3
Reg Review Case No.: 7231
40 CFR: §180.498

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The conclusions conveyed in this assessment were developed in full compliance with *EPA Scientific Integrity Policy for Transparent and Objective Science*, and EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions.* The full text of *EPA Scientific Integrity Policy for Transparent and Objective Science*, as updated and approved by the Scientific Integrity Committee and EPA Science Advisor can be found here: https://www.epa.gov/system/files/documents/2023-12/scientific_integrity_policy_2012_accessible.pdf. The full text of the EPA Scientific Integrity Program's *Approaches for Expressing and Resolving Differing Scientific Opinions* can be found here: https://www.epa.gov/scientific-integrity/approaches-expressing-and-resolving-differing-scientific-opinions.

In support of RD request, this document provides the HED's human health risk assessment conducted to support the establishment of tolerances for residues of sulfentrazone in/on pop corn commodities. The risk assessment, dietary risk assessment, and residue chemistry review were provided by George Kramer (RAB1), the hazard characterization was provided by Anwar Y. Dunbar (RAB1), the occupational/residential exposure (ORE) was provided by Joshua Godshall (RAB1), and the drinking water assessment was provided by Dena Barrett of the Environmental Fate and Effects Division (EFED).

The most recent human health risk assessment for sulfentrazone, conducted in support of application of sulfentrazone to chia; teff; mint; tree nut group 14-12; stalk and stem vegetable subgroup 22A; vegetable, *Brassica*, head and stem, group 5-16; and *Brassica*, leafy greens, subgroup 4-16B, was completed on 15-MAR-2018 (G. Kramer, *et al*., D443993).

Table of Contents

1.0 Executive Summary

Sulfentrazone is an aryl triazolinone herbicide used to control a variety of broadleaf weeds. Sulfentrazone acts by the same mechanism as the diphenyl ether herbicides in which membrane disruption is initiated by the inhibition of protoporphyrinogen oxidase (PPO) in the chlorophyll biosynthetic pathway and leads to the subsequent build-up of toxic intermediates. Plants emerging from soils treated with sulfentrazone turn necrotic and die shortly after exposure to light.

A tolerance is currently established under 40 CFR §180.498(a)(1) for the combined residues of sulfentrazone and its major metabolite, HMS (hydroxymethyl sulfentrazone), in/on soybean seed at 0.05 ppm. In addition, permanent tolerances are established under 40 CFR §180.498(a)(2) for the combined residues of sulfentrazone and its metabolites HMS and DMS (desmethyl sulfentrazone) in/on several food commodities; these established tolerances range from 0.15 ppm (various plant commodities) to 1.5 ppm (teff, straw). Tolerances for the combined residues of sulfentrazone and its metabolites HMS and DMS have been established under 40 CFR §180.498(c) in connection with regional registrations; these include tolerances for residues in/on succulent lima bean, succulent cowpea, and wheat grain at 0.15 ppm. Finally, tolerances are established under 40 CFR §180.498(d) for inadvertent and indirect combined residues of sulfentrazone and its metabolites HMS and DMS in/on cereal grain (excluding sweet corn) bran, forage, grain, hay, hulls, stover, and straw at 0.1-0.6 ppm as a result of the application of sulfentrazone to growing crops.

HED previously reviewed the registered use of sulfentrazone on field corn and recommended for the following tolerances for the combined residues of sulfentrazone and its metabolites HMS and DMS: corn, field, grain at 0.15 ppm and corn, field, stover at 0.30 ppm (Memo, G. Kramer, D286879, 10-JAN-2003). Subsequently, use on pop corn was added to the sulfentrazone label (same use pattern as field corn). RD has requested that HED recommend the tolerances required to support this use. No new data are available to support this action. By extrapolation from the field corn residue data, HED recommends for the establishment of the following tolerances for the combined residues of sulfentrazone and its metabolites HMS and DMS: corn, pop, grain at 0.15 ppm and corn, pop, stover at 0.3 ppm under §180.498(a)(2).

Exposure Profile: Humans may be exposed to sulfentrazone in food and drinking water since it may be applied directly to growing crops and following harvest, and application may result in sulfentrazone reaching surface and ground sources of drinking water. Based on the registered uses, there is no potential for residential handler or post-application exposure. However, adult and children non-occupational post-application exposures may occur from residues on turf due to spray drift resulting from applications made to adjacent areas. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, during application, and when re-entering treated fields.

Hazard Assessment and Dose Response Assessment: There have been no updates to the hazard assessment or endpoints for risk assessment for sulfentrazone. Toxicity reflective of disruption of heme synthesis (hematotoxicity) was observed in mice, rats, and dogs, and this was seen at about the same dose levels in the oral studies across species, except in the case of mice, where the effects were seen at a slightly higher dose. In addition, this hematotoxicity occurred around the same dose level from

short- through long-term exposure without increasing in severity.

Sulfentrazone caused developmental effects via the oral and dermal routes of exposure. Developmental effects, including decreased fetal body weights and reduced/delayed skeletal ossifications, were observed in both the oral and dermal developmental toxicity studies in the rat in the absence of maternal toxicity. In the two-generation reproduction study in rats, offspring effects, such as decreased body weights and decreased litter survival were observed at doses that were maternally toxic (decreased body weight during gestation in both generations).

In a route-specific 28-day dermal toxicity study in adult rabbits, there were no effects up to the highest dose tested (1000 mg/kg/day). In the route-specific 26-day inhalation study, there were portal-of-entry effects in the nasal passage and systemic effects, including decreased body weights and changes in numerous hematological parameters. Sulfentrazone is classified as “not likely to be carcinogenic to humans.”

The two-generation reproductive toxicity study in rats offspring no-observed adverse-effect level (NOAEL) = 14 mg/kg/day was selected for assessment of acute dietary (females 13-49 years old), chronic dietary, and incidental oral exposure scenarios. The offspring LOAEL is 33 mg/kg/day based on increased gestation duration, reduced pre-/postnatal litter and pup survival, reduced litter size, increased number of stillborn pups, and pup body-weight deficits throughout lactation in both generations of offspring observed in the two-generation reproductive toxicity study. The acute neurotoxicity (ACN) study (NOAEL = 250 mg/kg/day) was selected for assessment of acute dietary (all populations excluding females 13-49 years old) exposure. The LOAEL of 750 mg/kg/day is based upon an increased incidence of clinical signs, FOB findings, and decreased motor activity seen following a single oral administration in the rat ACN study. The dermal developmental toxicity study in rats (NOAEL = 100 mg/kg/day) was selected for assessment of dermal exposure (all durations). The LOAEL is based on developmental effects consisting of decreased fetal body weight; increased incidence of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubis; and reduced number of thoracic vertebral and rib ossification sites. The inhalation toxicity study in rats (no-observed adverse-effect concentration (NOAEC) is 0.256 mg/L) was selected for assessment of inhalation exposure (all durations). The lowest-observed adverse-effect concentration (LOAEC) is 1.71 mg/L for both sexes based on significant reductions in RBC parameters, including RBC count, HGB, Hct, MCV, MCH, and/or reticulocytes in male and female rats following 26 days of inhalation exposure to the test material. Portal-of-entry effects at this dose were also observed and manifested as an increased incidence of minimal nasal respiratory epithelial hyperplasia in both sexes. For all exposure scenarios except inhalation, a 100X uncertainty factor was applied [10X interspecies extrapolation; 10X for intraspecies variation; 1X FQPA SF (when applicable)]. For inhalation exposure scenarios, the interspecies factor was reduced from 10X to 3X due to the human-equivalent concentration calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences; therefore, a 30X uncertainty factor was applied [3X interspecies extrapolation; 10X for intraspecies variation; 1X FQPA SF (when applicable)].

Food Quality Protection Act (FQPA) Safety Factor (SF) Decision: The sulfentrazone risk assessment team concludes that the 10X FQPA SF should be reduced to 1X since the toxicology database is adequate for assessment of the registered uses, the selected endpoints are protective of the effects seen in the

neurotoxicity studies as well as the increased susceptibility to offspring observed in developmental and two-generation reproduction studies, and the conservative nature of the dietary and residential exposure analyses are unlikely to underestimate exposure [tolerance-level residues, 100% crop treated (PCT); use of 2012 Residential Standard Operating Procedures (SOPs)].

Dietary Risk Estimates (Food + Drinking Water): Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID, ver. 4.02) which incorporates consumption data from United States Department of Agriculture (USDA) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA; 2005-2010). The unrefined acute and chronic analyses assumed tolerance-level residues, 100 PCT for all commodities, HED default processing factors, and modeled drinking water estimates. The resulting acute and chronic dietary risk estimates are not of concern to HED, and the subgroups with the greatest risk estimates utilized ≤7% of the acute population-adjusted dose (aPAD; females 13-49 years old) and ≤8% of the chronic population-adjusted dose (cPAD; all infants (<1 year old), respectively.

Residential (Non-Occupational) Exposure and Risk Assessment: The use on pop corn will not result in residential exposure; however, there are currently registered turf uses (e.g., residential turf, golf courses) that were assessed as part of Registration Review. The residential handler inhalation human-equivalent dose was updated in the previous assessment (G. Kramer, *et al*., D443993, 15-MAR-2018), however, as there are no residential inhalation exposures associated with this action, an updated quantitative assessment has not been conducted. All dermal and inhalation exposure risk estimates for residential handlers are not of concern [i.e., margins of exposure (MOEs) were ≥100 for dermal and ≥30 for inhalation risk] at baseline for all scenarios; MOEs were ≥560 for dermal and ≥1200 for inhalation risk. All residential post-application dermal risk estimates are also not of concern (i.e., MOEs ≥100); all MOEs were ≥610 for adults and ≥360 for children.

Aggregate-Risk Assessment: In accordance with FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. Acute, chronic, short-, and intermediate-term aggregate assessments were included in this risk assessment. An aggregate cancer risk assessment was not performed because sulfentrazone is not likely to be carcinogenic to humans. Acute and chronic aggregate risks are made up only of dietary (food and drinking water) sources; therefore, the exposure estimates provided in the dietary exposure analyses represent acute and chronic aggregate exposure, respectively. Short- and intermediate-term aggregate risks are made up of dietary and non-dietary sources of exposure from turf application. All aggregate sulfentrazone risk estimates are not of concern to HED.

Occupational Exposure and Risk Assessment: Occupational handler exposures are expected to occur from the use of sulfentrazone pop corn. However, as the application rate for pop corn (0.25 lb ai/A) is lower than the registered maximum application rate on high-acreage crops (0.375 lb ai/A) recently assessed during registration review (K. Lowe, D417171, 05-JUN-2014) and the resulting MOEs were not of concern, a quantitative assessment has not been conducted for this use. The occupational inhalation human-equivalent dose was updated in the previous assessment (G. Kramer, *et al*., D443993, 15-MAR-2018), which will minimally impact the risk estimates from registration review which were more protective and do not result in risk estimates of concern for corn.

Occupational post-application exposures are not anticipated for registered pop corn uses as all applications are to be made pre-emergent and therefore foliar contact is not expected. Therefore, for the soil-directed uses, post-application exposures and risks to occupational workers were not assessed.

Sulfentrazone is classified as Acute Toxicity Category III for acute oral, acute dermal, and acute inhalation toxicity. It is classified as Acute Toxicity Category III for eye irritation potential and Acute Toxicity Category IV for skin irritation potential. It is not a dermal sensitizer. Therefore, the acute toxicity categories for this chemical require a 12-hour restricted entry interval (REI) under 40 CFR 156.208(c)(2)(iii). Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for sulfentrazone at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for sulfentrazone.

Environmental Justice Considerations: Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]"

Review of Human Research: This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix D provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied (see Appendix D).

2.0 Risk Assessment Recommendations/Conclusions

HED has examined the toxicology and residue chemistry databases for sulfentrazone. There are no residue chemistry, residential, occupational, or toxicology data deficiencies that would preclude the establishment of the permanent tolerances listed in Table 2.2.2.

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

There is an adequate residue analytical method for the purposes of tolerance enforcement. A gas chromatography (GC) method for the determination of sulfentrazone and its metabolites DMS and HMS was previously submitted with a petition for a sulfentrazone tolerance for residues in/on soybeans (PP# 4F04407). A petition method validation (PMV) was successfully completed by the

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

Agency's Analytical Chemistry Laboratory (ACL). The limit of quantitation (LOQ) and limit of detection (LOD) were determined to be 0.05 ppm and 0.005-0.025 ppm, respectively. The method has been forwarded to the Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Methods Vol. II (PAM II).

The data requirements for multiresidue methods (MRMs) are fulfilled. The FDA MRMs are not suitable as enforcement methods since sulfentrazone residues of concern were not successfully recovered by the FDA MRMs.

2.2.2 Recommended and Established Tolerances

Table 2.2.2. Tolerance Summary for Sulfentrazone.

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Establish under 40 CFR §180.498(a)(2):			
Corn, pop, grain	-	0.15	Translation from field corn.
Corn, pop, stover	-	0.3	

2.2.3 International Harmonization

No Codex or Canadian maximum residue limits (MRLs) have been established for residues of sulfentrazone on pop corn. Therefore, harmonization of MRLs and U.S. tolerances is not an issue at this time.

2.3 Label Recommendations

None.

3.0 Introduction

3.1 Chemical Identity

The chemical structure and nomenclature of sulfentrazone and its metabolites are presented in Table 3.1.

Table 3.1. Nomenclature for Sulfentrazone and its Metabolites.

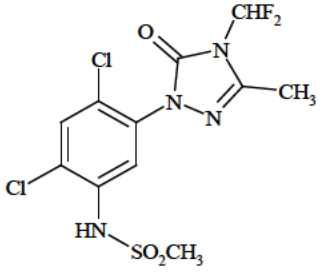
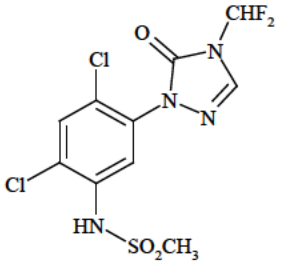
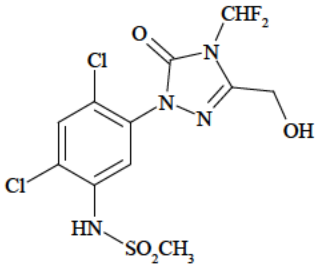
Chemical structure	
Common name	Sulfentrazone
Company experimental name	F6285; FMC 97285

Table 3.1. Nomenclature for Sulfentrazone and its Metabolites.	
IUPAC name	2',4'-dichloro-5'-(4-difluoromethyl-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)methanesulfonanilide
CAS name	*N*-(2,4-dichloro-5-(4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl)phenyl)methanesulfonamide
CAS registry number	122836-35-5
End-use product (EP)	4 lb/gal FlC formulation (Spartan® 4F Herbicide; EPA Reg. No. 279-3220) and 75% DF formulation (Spartan® Herbicide; EPA Reg. No. 279-3189)
Chemical structure of DMS metabolite	
Common name	3-desmethyl sulfentrazone; DMS
Chemical name	N-(2,4-dichloro-5-(4-(difluoromethyl)-4,5-dihydro-5-oxo-1H-1,2,4-triazol-1-yl)phenyl)methanesulfonamide
Chemical structure of HMS metabolite	
Common name	3-hydroxymethyl sulfentrazone; HMS
Chemical name	N-(2,4-dichloro-5-(4-(difluoromethyl)-4,5-dihydro-3-hydroxymethyl-5-oxo-1H-1,2,4-triazol-1-yl)phenyl)methanesulfonamide

3.2 Physical/Chemical Characteristics

In general, sulfentrazone is persistent and mobile. It has a 545-day aerobic soil half-life[2] and an average Koc coefficient of 45 mL/g. Additionally, it has a strong potential to leach into groundwater, as indicated in four completed small-scale prospective ground-water monitoring studies, and to move offsite to surface water. It has a low vapor pressure of 8×10^{-10} mm Hg. A detailed description of the physicochemical properties of sulfentrazone is provided in Appendix B.

3.3 Pesticide Use Pattern

Sulfentrazone corn uses are formulated as dry flowable (DF), and liquid products. Applications are to be made pre-emergent by chemigation, aerial, and groundboom equipment, at a single maximum application rate of 0.25 lb ai/A. Workers are required to wear baseline attire (i.e., long-sleeve shirt, long pants and shoes plus socks) along with personal-protection equipment (PPE) including chemical-resistant gloves when handling sulfentrazone products registered for use on corn (including pop corn). The REI is 12 hours as listed on the registered labels.

[2] 90th percentile upper confidence interval of the mean half-life.

Table 3.3. Summary of Directions for Use of Sulfentrazone.						
Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Corn (field and pop)						
Pre-emergent Soil directed; aerial, groundboom; chemigation	Dry Flowable: [Spartan® 4F Herbicide; EPA Reg. No. 279-3220) Liquid: [Spartan® Herbicide; EPA Reg. No. 279-3189]	0.25	1	0.25	NA	Pre-emergence applications only

3.4 Anticipated Exposure Pathways

Based on the registered sulfentrazone application scenarios, dietary exposure is an anticipated exposure pathway as residues of sulfentrazone may be found in/on crops, livestock commodities, and drinking water. There are registered residential uses of sulfentrazone and potential for spray drift, so there is exposure in residential and non-occupational settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is also potential for post-application exposure for workers re-entering treated sites. This risk assessment considers all of the aforementioned exposure pathways based on the existing uses of sulfentrazone.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it was considered in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm

workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

There have been no updates to the hazard or dose response assessments for sulfentrazone. This is an abbreviated hazard characterization for sulfentrazone. The toxicology database for sulfentrazone is complete and adequate for hazard characterization, toxicity endpoint selection, and FQPA SF evaluation. There are no new data or changes to the endpoints or selected points of departure (PODs) since the last human health risk assessment. The last complete hazard characterization for sulfentrazone was completed by Kramer *et al*. (D443993, 15-MAR-2018).

Sulfentrazone belongs to a class of herbicides that inhibit PPO in target photosynthetic organisms, ultimately resulting in disruption of chlorophyll biosynthesis. In mammals, PPO is also an important enzyme in heme biosynthesis and its inhibition can lead to toxic effects associated with disruption of heme utilization (e.g., red blood cells). Some of the effects reported for sulfentrazone in mammals are consistent with PPO inhibition.

4.1 Safety Factor for Infants and Children (FQPA Safety Factor)

The RAB1 risk assessment team recommended that the FQPA SF be reduced to 1X for all exposure scenarios. The toxicity database is complete and dietary and residential exposure analyses are unlikely to underestimate exposure. Although effects were seen in neurotoxicity studies and there is evidence of susceptibility to offspring in developmental and two-generation reproduction studies, the effects are well characterized with clearly established NOAEL/lowest-observed adverse-effect level (LOAEL) values and selected endpoints are protective for the observed effects.

4.1.1 Completeness of the Toxicology Database

The existing toxicology database for sulfentrazone is adequate for FQPA evaluation. Developmental toxicity studies in rats and rabbits, a two-generation reproduction study in rats, and neurotoxicity studies in rats are available for FQPA consideration.

4.1.2 Evidence of Neurotoxicity

In the ACN and SCN studies, observed effects included changes in motor activity and FOB parameters, clinical signs, and body weight decrements. There is low concern for neurotoxicity since: 1) effects were seen at relatively high doses; 2) effects occurred in the absence of neuropathology; 3) there is no evidence of neurotoxicity in other available studies in the toxicity database; 4) effects are well-characterized with clearly established NOAEL/LOAEL values; and 5) the selected PODs are protective of these effects.

4.1.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There was evidence for increased (quantitative and qualitative) susceptibility following oral and dermal exposures in the developmental toxicity studies in rats and the reproduction studies in rats. Although

developmental toxicity was observed at lower doses than maternal toxicity in both studies in the rat, the concern is low based on the following considerations: 1) the toxicology database for assessing pre- and postnatal susceptibility is complete; 2) there are clear NOAELs and LOAELs for the developmental effects observed via both the oral and dermal routes; 3) the PODs used for assessing dietary and dermal exposure risks are based on developmental and/or offspring toxicity; 4) the portal-of-entry effects seen in the 26-day inhalation study are protective of the developmental toxicity; and 5) there are no residual uncertainties for pre-and/or postnatal toxicity.

4.1.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary and residential exposure analyses are conservative in nature. The dietary exposure assessment used tolerance-level residues and assumed 100% CT. The residential exposure assessment uses the 2012 Residential SOPs and is considered health-protective.

4.2 Toxicity Endpoints and Point of Departure Selections

4.2.1 Dose-Response Assessment

Table 4.2.4 summarizes the toxicological doses and endpoints selected for residential dietary/non-dietary and occupational risk assessment. There have been no changes since the last risk assessment for sulfentrazone (G. Kramer, *et al*., D443993, 15-MAR-2018).

Acute Dietary Endpoint (Females 13 - 49 years old): The acute dietary endpoint for females 13-49 years old is based on increased gestation duration, reduced pre-/postnatal litter and pup survival, reduced litter size, increased number of stillborn pups, and pup body-weight deficits throughout lactation in both generations of offspring observed in the two-generation reproductive toxicity study in rats at the LOAEL of 33 mg/kg/day. The developmental effects were reported in the presence of mild maternal toxicity (decreased body weight and body-weight gain, particularly in F_1 females). Reduced prenatal viability, reduced litter size, and increased number of stillborn pups were conservatively considered single-dose effects and, therefore, relevant for the acute dietary (females aged 13-49) exposure scenario in order to protect against potential exposure of pregnant females. It should be noted that the fetal body-weight deficits and retardation in skeletal development (including decreased numbers of caudal vertebral and metacarpal ossification sites) reported in the oral rat prenatal developmental toxicity study were also evaluated for this acute dietary endpoint. However, it was concluded that such effects are unlikely due to a single-dose effect and are more appropriate for a repeated-exposure scenario. Furthermore, EPA has not traditionally considered delays in ossification (and related fetal body-weight deficits) to be single-dose effects. Other effects that may be attributable to a single dose that are applicable for this population, such as increased resorptions, decreased implantations and abortions, were seen at higher doses; therefore, this study is also protective of these effects. The conventional 100-fold uncertainty factor (10X inter-, and 10X intraspecies) was applied to the NOAEL (14 mg/kg bw/day). The FQPA SF was reduced to 1X (see Section 4.1). Thus, the acute reference dose (aRfD) and aPAD are equivalent at 0.14 mg/kg bw/day.

Acute Dietary Endpoint (General population, including infants and children): The acute dietary endpoint

for the general population, including infants and children, is based upon an increased incidence of clinical signs, FOB findings, and decreased motor activity at the LOAEL of 750 mg/kg bw seen following a single oral administration in the rat ACN study. There were no other effects observed attributable to a single-dose applicable to this population. The aRfD and aPAD are equivalent at 2.5 mg/kg bw based on the NOAEL of 250 mg/kg from the ACN study and a 100-fold uncertainty factor (10X interspecies, 10X intraspecies, 1X FQPA).

Chronic Dietary Endpoint (All populations): The chronic dietary endpoint is based on increased gestation duration, reduced pre-/postnatal litter and pup survival, and pup body-weight deficits throughout lactation in both generations of offspring observed at the LOAEL of 33 and 40 mg/kg/day in males and females, respectively, in the rat two-generation reproductive toxicity study. This LOAEL is based on developmental toxicity, the most sensitive endpoint, and is protective of developmental and chronic effects seen in other studies. The chronic reference dose (cRfD) and cPAD are equivalent at 0.14 mg/kg bw/day based on the NOAEL of 14 mg/kg/day in the two-generation reproductive toxicity study and a 100-fold uncertainty factor (10X interspecies, 10X intraspecies, 1X FQPA).

Incidental Oral Endpoint (Short- and intermediate-term): This endpoint is based on offspring toxicity observed in the rat two-generation reproductive toxicity study in the form of reduced pre-/postnatal litter and pup survival, and pup body-weight deficits throughout lactation in both generations of offspring observed at the LOAEL of 33 and 40 mg/kg/day in males and females, respectively (lowest NOAEL = 14 mg/kg/day for males). The effects seen in the offspring are appropriate for the population (infants and children) and durations (short- and intermediate-term) of concern. The LOC for incidental oral risk estimates is for MOEs less than 100, which includes the 10X inter- and 10X-intraspecies factors. The FQPA SF was reduced to 1X (see Section 4.1).

Dermal Endpoints (Short- and intermediate-term): The dermal developmental toxicity study in rats was selected to assess dermal exposures (NOAEL = 100 mg/kg/day). The LOAEL is based on developmental effects consisting of decreased fetal body weight; increased incidence of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubis; and reduced number of thoracic vertebral and rib ossification sites. There were no effects seen up to the highest dose tested in the dermal toxicity study in rabbits; however, there was quantitative sensitivity observed in the database. Since a developmental dermal toxicity study is available, it was selected to evaluate dermal exposures. This endpoint is appropriate since the developmental effects were seen after repeated exposure via the dermal route, and it is conservative for children and males. The LOC for occupational and non-occupational dermal risk estimates is for MOEs less than 100, which includes the 10X inter- and 10X intraspecies factors. The FQPA SF was reduced to 1X (see Section 4.1).

Inhalation Endpoints (Short- and intermediate-term): The short- and intermediate-term inhalation endpoints were derived from the route specific 26-day inhalation study in rats where the NOAEC is 0.256 mg/L. The lowest-observed adverse-effect concentration (LOAEC) is 1.71 mg/L for both sexes based on significant reductions in RBC parameters, including RBC count, HGB, Hct, MCV, MCH, and/or reticulocytes in male and female rats following 26 days of inhalation exposure to the test material. Portal-of-entry effects at this dose were also observed and manifested as an increased incidence of minimal nasal respiratory epithelial hyperplasia in both sexes. Human-equivalent concentrations and doses were calculated based on this subchronic inhalation study. Human-equivalent concentrations

were derived from this study based upon an increased incidence of minimal nasal respiratory epithelial hyperplasia in both sexes, which is considered a portal-of-entry effect. See Table 4.2.4.3. The LOC is 30 for occupational inhalation exposure scenarios which includes the following UFs: interspecies (3X), and intraspecies (10X). The interspecies factor was reduced from 10X to 3X due to the human-equivalent concentration calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. For details regarding the calculation of the human-equivalent concentrations and human-equivalent doses, see the last risk assessment (G. Kramer, *et al*., D443993, 15-MAR-2018).

4.2.2 Recommendation for Combining Routes of Exposures for Risk Assessment

The Agency must consider risks from individual routes of exposure (oral, dermal, and inhalation) and perform combined exposure and risk assessments if a common toxicity endpoint is established across different routes of exposure. Since the same effects (fetal/offspring body-weight deficits) were observed in the studies selected to evaluate dermal and incidental oral exposures, exposure from these routes should be combined.

4.2.3 Summary of Points of Departure and Toxicity Endpoints Used in Human-Health Risk Assessment

Table 4.2.3.1. Summary of Toxicological Doses and Endpoints for Sulfentrazone for Use in Residential and Dietary Human Health Risk Assessment.

Exposure Scenario	POD	Uncertainty/ FQPA SFs	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49)	NOAEL = 14 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	aRfD = aPAD = 0.14 mg/kg/day	Two-generation Reproductive Toxicity Study - Rat Offspring Toxicity LOAEL = 33 (M) and 40 (F) mg/kg/day based on reduced prenatal viability (fetal & litter), reduced litter size, increased no. of stillborn pups, reduced pup and litter postnatal survival, and decreased pup body weights throughout lactation.
Acute Dietary (General population including infants and children)	NOAEL = 250 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	aRfD =aPAD = 2.5 mg/kg/day	ACN Study - Rat LOAEL = 750 mg/kg/day based on increased incidence of clinical signs and FOB parameters and decreased motor activity.
Chronic Dietary (all populations)	NOAEL = 14 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	cRfD = cPAD = 0.14 mg/kg/day	Two-generation Reproductive Toxicity Study - Rat Offspring Toxicity LOAEL = 33 (M) and 40 (F) mg/kg/day based on reduced prenatal viability (fetal & litter), reduced litter size, increased no. of stillborn pups, reduced pup and litter postnatal survival, and decreased pup body weights throughout lactation.
Short- (1-30 days) and Intermediate-Term (1-6 months) Incidental Oral	Offspring NOAEL = 14 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE < 100	Two-Generation Reproductive Toxicity Study - Rat Offspring Toxicity LOAEL = 33 (M) and 40 (F) mg/kg/day based on reduced

Table 4.2.3.1. Summary of Toxicological Doses and Endpoints for Sulfentrazone for Use in Residential and Dietary Human Health Risk Assessment.				
Exposure Scenario	**POD**	**Uncertainty/ FQPA SFs**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
				prenatal viability (fetal & litter), reduced litter size, increased no. of stillborn pups, reduced pup and litter postnatal survival, and decreased pup body weights throughout lactation.
Short- (1-30 days), Intermediate- (1-6 months) Dermal	NOAEL = 100 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE < 100	Dermal Developmental Study - Rat LOAEL = 250 mg/kg/day based on decreased fetal body weight; increased incidences of fetal skeletal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites.
Short- (1-30 days), Intermediate- (1-6 months) Inhalation	Portal-of-entry NOAEL = 0.256 mg/L	UF_A = 3X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE < 30	Inhalation Toxicity Study – Rat Portal-of-entry LOAEL = 1.71 mg/L based on an increased incidence of minimal nasal respiratory epithelial hyperplasia in male and female rats.
Cancer (oral, dermal, inhalation)	**Classification:** Sulfentrazone is classified as "not likely to be carcinogenic to humans."			

NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Table 4.2.3.2. Summary of Toxicological Doses and Endpoints for Sulfentrazone for Use in Occupational Human-Health Risk Assessment.				
Exposure Scenario	**POD**	**Uncertainty/ FQPA SFs**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Short- (1-30 days), Intermediate- (1-6 months) Dermal	NOAEL = 100 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE < 100	Dermal Developmental Study - Rat LOAEL = 250 mg/kg/day based on decreased fetal body weight; increased incidences of fetal skeletal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubes; and reduced number of thoracic vertebral and rib ossification sites.
Short- (1-30 days), Intermediate- (1-6 months) Inhalation	Portal-of-entry NOAEL = 0.256 mg/L	UF_A = 3X UF_H = 10X	Occupational LOC for MOE < 30	Inhalation Toxicity Study – Rat Portal-of-entry LOAEL = 1.71 mg/L based on an increased incidence of minimal nasal respiratory epithelial hyperplasia in male and female rats.
Cancer (oral, dermal, inhalation)	**Classification:** Sulfentrazone is classified as "not likely to be carcinogenic to humans."			

NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

Table 4.2.3.3. Calculated Inhalation Human-Equivalent Concentrations and Doses for Sulfentrazone.						
Population	Scenario	Duration Adjustment		Human-Equivalent Concentration		Human-Equivalent Dose (mg/kg/day)
		hours/day	days/week	mg/L	mg/m^3	
Occupational	Handler	8	5	0.041	40.9	3.87

* Toxicity duration adjustment from 6 hours per day/5 days per week exposure in the subchronic rat inhalation study (MRID 49253902). Human-equivalent concentrations calculated using duration adjustments, when applicable, and a systemic regional deposited dose ratio (RDDR) of 0.213, which was obtained with a mass median aerodynamic diameter (MMAD) of 2.3 µm and a geometric standard deviation (GSD) of 2.0 µm from the lowest dose tested (0.256 mg/L), as well as the combined sex body weight of 236 g from the Agency's inhalation guidance document (J. Whalan *et al*., March 6, 1998).

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

The HED Metabolism Assessment Review Committee (MARC) determined that the parent compound, sulfentrazone, and the metabolite HMS [*N*-(2,4-dichloro-5-(4-(difluoromethyl)-4,5-dihydro-3-hydroxymethyl-5-oxo-1*H*-1,2,4-triazol-yl)phenyl)methanesulfonamide)] are the residues of concern in soybean seed, and that sulfentrazone and its metabolites HMS and DMS [(*N*-2,4- dichloro-5-[4-(difluoromethyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl)phenyl)methanesulfonamide] are the residues of concern in other primary crops and rotational crops (Memo, G. Kramer, 14-JUN-1996; D226434). HED has concluded that the results of the rotational crop metabolism studies may be translated to support preemergent uses on all types of crops. Additionally, sulfentrazone and its metabolites HMS and DMS were identified as the residues of concern in meat, milk, poultry, and eggs. The HED MARC concluded that parent and 3-carboxylic acid sulfentrazone are the residues of concern for the drinking water assessment (Memo, G. Kramer *et al.*, D288713, 10-APR-2003).

The residues of concern in primary crops, rotational crops, livestock, and drinking water, as identified by the MARC, are shown in Table 5.1 below.

Table 5.1. Residues of Concern in Crops, Livestock, and Drinking Water.		
Matrix	Tolerance Expression	Residues for Risk Assessment
Primary Crops, except soybean seed	sulfentrazone, HMS, DMS (free and conjugated)	sulfentrazone, HMS, DMS (free and conjugated)
Soybean, seed	sulfentrazone, HMS	sulfentrazone, HMS
Rotational Crops	sulfentrazone, HMS, DMS (free and conjugated)	sulfentrazone, HMS, DMS (free and conjugated)
Livestock	sulfentrazone, HMS, DMS	sulfentrazone, HMS, DMS
Water	not applicable	sulfentrazone, 3-carboxylic acid sulfentrazone

5.2 Food Residue Profile

HED previously reviewed the registered use of sulfentrazone on field corn and recommended for the following tolerances for the combined residues of sulfentrazone and its metabolites HMS and DMS: corn, field, grain at 0.15 ppm and corn, field, stover at 0.30 ppm (Memo, G. Kramer, D286879, 10-JAN-2003). Subsequently, use on pop corn was added to the sulfentrazone label (same use pattern as field corn). RD has requested that HED recommend the tolerances required to support this use. No new data are available to support this action. By extrapolation from the field corn residue data, HED recommends for the establishment of the following tolerances for the combined residues of

sulfentrazone and its metabolites HMS and DMS: corn, pop, grain at 0.15 ppm and corn, pop, stover at 0.3 ppm under §180.498(a)(2).

5.3 Water Residue Profile

Drinking water residues provided by EFED (Memo, M. Barrett, D415627, 21-MAY-2014) were incorporated directly into the acute and chronic dietary analyses as "water, direct, all sources" and "water, indirect, all sources." The estimated drinking water concentrations (EDWCs) were Tier 1 estimates for ground water using the Pesticide Root Zone Model-Ground Water (PRZM-GW) model version 1.07 (Screening Concentration in Ground Water) and surface water using the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) model.

For surface water, the highest acute (peak) sulfentrazone TTR value is 37.3 ppb, and the 10-year average value is 5.3 ppb. For ground water, the highest daily (peak) sulfentrazone TTR value is 134 ppb, and the post-breakthrough-average value is 98 ppb. EFED has confirmed that these values remain appropriate for risk assessment purposes (E-mail, M. Barrett, 30-AUG-2017).

Table 5.3. Estimated Tier 1 Concentrations of Sulfentrazone and 3-Carboxylic Acid Sulfentrazone in Drinking Water Due to the Use of Sulfentrazone.

Scenario	Surface Water (ug/L)		Groundwater (ug/L)	
	Acute	Chronic	Acute	Chronic
FL Sugarcane	37.3	3.2	-	-
LA Corn	31.3	5.3	-	-
Delmarva Sw. corn	-	-	134	98

EDWCs of 0.134 ppm and 0.098 ppm were used in the acute and chronic analyses, respectively.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

The acute and chronic analyses employed tolerance-level residues for all commodities and HED default processing factors. As was done in the previous dietary assessments, the established tolerance (40 CFR §180.498(a)(2)) for succulent vegetable soybean is greater than the 40 CFR §180.498(a)(1) tolerance for soybean seed; therefore, the succulent vegetable soybean tolerance of 0.15 ppm was used for soybean seed as a conservative assumption.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic assessments assumed 100 PCT for all commodities.

5.4.3 Acute Dietary Risk Assessment

The acute food plus drinking water risk estimates are below HED's level of concern [<100% of the aPAD)] at the 95th percentile of the exposure distribution for the U.S. general population (<1% aPAD). The aPAD is lower for females 13 to 49 years old. Although all infants (<1 year old) old had the highest

exposure estimate (resulting in a risk estimate of 1.1% aPAD), the population subgroup with the highest risk estimate (6.4% aPAD) was females 13 to 49 years old.

5.4.4 Chronic Dietary Risk Assessment

The chronic risk estimates are below HED's level of concern for the U.S. general population [<100% of the cPAD)], and all population subgroups. The population subgroup with the greatest exposure and risk estimate (7.6% cPAD) was all infants (<1 year old).

5.4.5 Cancer Dietary Risk Assessment

A cancer dietary assessment was not conducted because sulfentrazone is classified as "not likely to be carcinogenic to humans."

5.4.6 Summary Table

Table 5.4.6. Summary of Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk for Sulfentrazone.[1]

Population Subgroup	95th Percentile			cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
	aPAD (mg/kg/day)	Exposure (mg/kg/day)	%aPAD			
General U.S. Population	2.5	0.010786	<1.0	0.14	0.003828	2.7
All Infants (<1 year old)		0.028504	1.1		**0.010605**	**7.6**
Children 1-2 years old		0.021085	<1.0		0.009173	6.6
Children 3-5 years old		0.016276	<1.0		0.007314	5.2
Children 6-12 years old		0.010887	<1.0		0.004473	3.2
Youth 13-19 years old		0.008132	<1.0		0.003062	2.2
Adults 20-49 years old		0.009055	<1.0		0.003382	2.4
Adults 50-99 years old		0.007919	<1.0		0.003192	2.3
Females 13-49 years old	0.14	**0.009024**	**6.4**		0.003312	2.4

[1] The populations with the greatest risk estimates are bolded.

6.0 Residential Exposure and Risk Characterization

There are no proposed residential uses for sulfentrazone at this time, therefore a quantitative residential handler/post-application risk assessment has not been conducted. However, there are registered residential uses that have been previously assessed (K. Lowe, 05-JUN-2014; D417171) that are applicable for aggregate.

Table 6.0 reflects the residential risk estimates that are recommended for use in the aggregate assessment for sulfentrazone.

- The recommended residential exposure for use in the adult short-term aggregate assessment reflects dermal exposure from applications to turf via backpack sprayer.
- The recommended residential exposure for use in the children 1 < 2 years old short-term aggregate assessment reflects dermal and hand-to-mouth exposures from post-application exposure to turf applications.

Table 6.0. Recommendations for the Residential Exposures for the Sulfentrazone Aggregate Assessment.									
Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation[3]	Oral	Total	Dermal	Inhalation[3]	Oral	Total
Short-term									
Adult	Handler – MLA liquids via backpack	0.18	N/A	N/A	**0.18**	560	N/A	N/A	**560**
Child 11 < 16 years old	Post-application exposure from golfing (liquid formulation)	0.013	N/A	N/A	**0.013**	7,800	N/A	N/A	**7,800**
Child 6 < 11 years old	Post-application exposure from golfing (liquid formulation)	0.015	N/A	N/A	**0.015**	6,600	N/A	N/A	**6,600**
Child 1 < 2 year old	Post-application exposure from activities on turf (liquid formulation)	0.28	N/A	0.0057	**0.28**	360	N/A	2,500	**310**

[1] Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + incidental oral (where applicable).
[2] MOE = the MOEs associated with the highest residential doses.
[3] Inhalation risk estimates were not combined with dermal or oral risk estimates in this assessment since the toxicological effects in the inhalation toxicological study were portal-of-entry and different from those seen in the studies selected to evaluate dermal and incidental oral exposures.

7.0 Aggregate Exposure and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

7.1 Acute Aggregate Risk

Acute aggregate risk results from exposure to residues in food and drinking water alone. The acute dietary exposure analysis included both food and drinking water. Therefore, acute aggregate risk is equivalent to the acute dietary risk, as discussed in Section 5.4, above. All risk estimates are not of concern.

7.2 Short- and Intermediate-Term Aggregate Risk

Short- and intermediate-term aggregate exposure takes into account short- and intermediate-term residential exposure plus chronic exposure to food and water (considered to be a background exposure level). Sulfentrazone is currently registered for uses that could result in short- and intermediate-term residential exposure. For short- and intermediate-term exposures, incidental oral and dermal exposure

risk assessments are appropriate to aggregate due to similarities in the toxicity endpoints observed in studies selected to evaluate incidental oral and dermal exposures. The short- and intermediate-term incidental oral and dermal exposures are combined with chronic dietary (food and water) exposure for determination of aggregate short- and intermediate-term exposures.

The backpack scenario for mixing and loading liquids is the exposure scenario with the greatest exposure for adults; therefore, the exposure estimates for this scenario are protective of other exposure scenarios. Children 1-2 years old represent the population subgroup for children with the greatest exposure; therefore, the exposure estimates for children 1-2 years old are protective of other children population subgroups. The LOC is 100 for incidental oral and dermal assessments; therefore, MOEs <100 are risk estimates of concern.

Tables 7.2.1 and 7.2.2 summarize the short-term aggregate exposures and risk estimates for 1-2 year olds and adults. The aggregate short-term MOEs are >100 for adults and children; therefore, aggregate exposures to sulfentrazone are not of concern to HED. The PODs used for short- and intermediate-term assessments are the same and intermediate-term exposures are no higher than short-term exposures; therefore, the short-term assessment is representative of both short- and intermediate-term aggregate assessments.

Table 7.2.1. Short-Term Aggregate Risk Calculations for Children 1-2 Years Old.

Population	LOC	Background Dietary + Incidental Oral Exposures			Residential Exposures		Aggregate MOE (food, water, and residential)[4]
		Chronic Food and Water Exposure (mg/kg/day)	Incidental Oral Exposure (mg/kg/day)[1]	Oral MOE[2]	Dermal Exposure (mg/kg/day)	Dermal MOE[3]	
Children 1-2 years old	100	0.009173	0.0057	940	0.28	360	260

[1] Short-term Incidental Oral Exposure = Hand-to-mouth exposure.
[2] Oral MOE = NOAEL (14 mg/kg/day) ÷ (chronic food/water exposure + incidental oral exposure).
[3] Dermal MOE = NOAEL (100 mg/kg/day) ÷ (dermal exposure).
[4] Aggregate MOE = 1/[(1/oral MOE) + (1/dermal MOE)].

Table 7.2.2. Short-Term Aggregate Risk Calculations for Adults.

Population	Dietary Exposure[1]		Dermal Residential Exposure[2]		Aggregate MOE (food, water, and residential)[3]
	Chronic Food and Water Exposure (mg/kg/day)	MOE	Dermal Exposure (mg/kg/day)	MOE	
Adults 20-49 years old	0.003382	4100	0.18	560	490

[1] MOE dietary = [(short-term oral NOAEL = 14 mg/kg/day)/(chronic dietary exposure)].
[2] MOE dermal = [(short-term dermal NOAEL = 100 mg/kg/day)/(high-end dermal residential exposure)].
[3] Aggregate MOE = 1/[(1/dietary MOE) + (1/dermal MOE) + (1/inhalation MOE)].

7.3 Chronic Aggregate Risk

The chronic aggregate risk assessment results from long-term exposure to residues in food and drinking water, as there are no residential scenarios that result in long-term exposure. The chronic dietary exposure analysis included both food and drinking water and, therefore, the chronic aggregate risk assessment is equivalent to the chronic dietary risk assessment discussed in Section 5.4, above. All risk estimates are not of concern.

7.4 Cancer Aggregate Risk

An aggregate cancer risk assessment was not performed because sulfentrazone is not likely to be carcinogenic to humans.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

HED conducts human health spray drift assessments to determine potential risk from indirect exposure to pesticides that may drift during or immediately after an application. Pesticide applications made in the form of a spray and applied aerially or via airblast or groundboom may result in pesticide drift and deposition in non-target areas adjacent to the application site.

On July 15th, 2024, the Agency updated its practice on spray drift[3] to include chemical-specific spray drift assessments for proposed uses through Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) registration actions (e.g., Section 3 new active ingredient and/or new use registrations, label amendments, Section 18 emergency exemptions, etc). Historically, chemical-specific spray drift assessments have only been routinely incorporated within human health draft risk assessments (DRAs) for registration review; as of July 15th, 2024, new active ingredients seeking initial U.S. registration and any future new uses will be subject to the consideration of a chemical-specific spray drift assessment. Additionally, registration actions submitted to the Agency for active ingredients which have had a human health DRA completed during the registration review process will also be subject to consideration of spray drift within the risk assessment. Registration actions submitted for active ingredients without an initial completed spray drift assessment, whether within a DRA or at the time of initial US registration, will not be subject to the consideration of a chemical-specific spray drift assessment for the proposed uses. These active ingredients will be assessed for spray drift during the subsequent registration review process to ensure that all uses are considered concurrently prior to any new use evaluations. During registration review, the Agency will continue to evaluate each pesticide for the potential for spray drift in accordance with the most up-to-date science and policy.

Sulfentrazone has had a comprehensive spray drift evaluation as part of a completed human health DRA during Registration Review (G. Kramer, *et al.*, D410365, 05-JUN-2014). Therefore, any subsequent or proposed new uses are being considered for a spray drift assessment.

The most recent quantitative spray drift assessment for sulfentrazone was conducted in June 2014 and resulted in no risk estimates of concern (K. Lowe, D417171, 05-JUN-2014). The conclusions from the June 2014 spray drift assessment on turf are considered protective of the use on pop corn for the following reasons:

- The single maximum application rate is lesser than those previously assessed,
- The dermal and incidental oral endpoints/PODs remain unchanged, and
- A quantitative spray drift assessment for sulfentrazone is not required because the maximum application rate for a crop/target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate (0.375 lb ai/A) for any sulfentrazone products.

[3] *Implementing Chemical Specific Human Health Spray Drift Analysis for Pesticide Registration Action.* Available online: https://www.regulations.gov/document/EPA-HQ-OPP-2013-0676-0124.

Therefore, an updated quantitative spray drift assessment was not conducted for the use on pop corn.

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from the FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides).

During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for sulfentrazone.

10.0 Cumulative Exposure and Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to sulfentrazone and any other substances. For the purposes of this action, therefore, EPA has not assumed that sulfentrazone has a common mechanism of toxicity with other substances.

In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis.[4] This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[5] and conducting cumulative risk assessments (CRA)[6].

Sulfentrazone is a N-phenyltriazolinone PPO inhibitor. As part of the ongoing process to review registered pesticides, the Agency intends to apply this framework to determine if the available toxicological data for sulfentrazone suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure and Risk Characterization

11.1 Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and

[4] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework

[5] Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)

[6] Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)

exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

The quantitative exposure/risk assessment for occupational handlers resulting from registered applications to corn (including pop corn) were assessed in 2014 for registration review (ORE memo: K. Lowe, D417171, 05-JUN-2014). A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessment. Each assumption and factor is detailed in the 2014 ORE memo for registration review.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

The occupational handler exposure and risk estimates indicate that the short- and intermediate-term dermal and inhalation MOEs are not of concern to HED (i.e., MOEs $\geq$ 100 for dermal and MOEs $\geq$ 30 for inhalation), as long as label directed PPE (baseline attire plus chemical-resistant gloves) are worn for the highest application rate for mixing/loading liquids and dry flowables for aerial application to high-acreage crops.

11.2 Occupational Post-Application Exposure and Risk Estimates

11.2.1 Occupational Post-Application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from FIFRA SAP in December 2009, and received the SAP's final report on March 2, 2010. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for sulfentrazone.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure, and all of the occupational handler scenarios resulted in inhalation risk estimates that were not of concern at baseline (i.e., all inhalation MOEs without a respirator ≥ the LOC). Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

11.2.2 Occupational Post-Application Dermal Exposure/Risk Estimates

Most of the registered uses for sulfentrazone, including all corn (and pop corn), are soil-directed preplant or preemergent uses where no crop foliage is present. Currently, HED has no transfer coefficients or other data to assess post-application dermal exposures to soil by occupational workers.

In general, such exposures are considered to be negligible. Therefore, for the soil-directed uses, post-application exposures and risks to occupational workers were not assessed.

Restricted Entry Interval

The REI specified on the registered labels are based on the acute toxicity of sulfentrazone. Sulfentrazone is classified as acute toxicity category III for acute oral, acute dermal, and acute inhalation toxicity. It is classified as toxicity category III for eye irritation potential and category IV for skin irritation potential. It is not a dermal sensitizer. Short- and intermediate-term post-application risk estimates were not a concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2) (iii), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irrigation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to sulfentrazone.

12.0 References

Preliminary Human Health Risk Assessment for Registration Review
G. Kramer, *et al.*, 05-JUN-2014; D410365

Most-Recent Human Health Risk Assessment
G. Kramer, *et al.*, 15-MAR-2018; D443993

ORE Memo
K. Lowe, D417171; 05-JUN-2014

Dietary Memo
G. Kramer, 129081_TG00562132_CHEMD_2024-08-28

Chemistry Memo
G. Kramer, 10-JAN-2003; D286879

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food uses for sulfentrazone are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1. Toxicological Data Requirements for Sulfentrazone.

Study	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 28-Day Dermal	yes	yes
870.3465 28-Day Inhalation	yes[1]	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700a Dermal Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	no	--
870.6100b 90-Day Neurotoxicity (hen)	no	--
870.6200a ACN Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Develop. Neurotoxicity	no	--
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	--
870.7800 Immunotoxicity	yes	yes

[1] HED's Hazard Science and Policy Council (HASPOC) used a weight of evidence approach to recommend that subchronic inhalation toxicity data are required at this time (TXR 0050684, D. Smegal, 02-MAR-2012).

A.2 Toxicity Profiles

Table A.2. Acute Toxicity Profile – Sulfentrazone.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral (rat)	41911605 (94.0% a.i.)	LD_{50} = 3034.4 (2101.9 – 3966.8) mg/kg (M) LD_{50} = 2688.9 (2008.1 – 3369.8) mg/kg (F) LD_{50} = 2854.8 (2282.5 – 3427.1 mg/kg (C)	III
	Acute Oral (mouse)	41911606 (94.0% a.i.)	LD_{50} = 751.9 (644.7 – 859.1) mg/kg (M) LD_{50} = 701.8)579.6 – 823.9) mg/kg (F) LD_{50} = 711.0 (586.0 – 836.3 mg/kg (C)	III
870.1200	Acute Dermal (rat)	50365110 (97.78% a.i.)	$LD_{50} \geq$ 5000 mg/kg (M & F)	IV
	Acute Dermal (rabbit)	41991607 (94.0% a.i.)	LD_{50} > 2000 mg/kg (M & F)	III
870.1300	Acute Inhalation (rat)	50365111 (97.78% a.i.)	$LC_{50} \geq$ 5.13 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	50365112 (97.78% a.i.)	Mildly irritating	III
870.2500	Primary Skin Irritation (rabbit)	50365113 (97.78% a.i.)	Non-irritating	IV
870.2600	Dermal Sensitization (mouse)	50365114 (97.78% a.i.)	Not considered a dermal Sensitizer (LLNA)	N/A
	Dermal Sensitization (guinea pig)	51603517 (96.95% a.i.)	Not a sensitizer (GPMT)	N/A

Note: It is recognized that some studies in the sulfentrazone database have conservative NOAEL/LOAEL values that are based on effects that are not considered adverse according to current HED policy and practices (e.g., decreases in body-weight gain without a corresponding decrease in absolute bodyweight). These updates, however, would result in higher NOAEL/LOAEL values and would not impact the selected endpoints. Consequently, given the current risk picture for sulfentrazone, the Agency did not find it necessary to update these studies at this time.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Sulfentrazone.		
Guideline No./ Study Type	**MRID No. (year)/Classification/ Doses**	**Results**
870.3100 90-Day oral toxicity (rat)	43004601 (1990) Acceptable/Guideline 0, 300, 1000, 3000, & 7000 ppm, M: 0, 3.3, 6.7, 19.9, 65.8, 199.3, & 534.9 mg/kg/day F: 0, 4, 7.7, 23.1, 78.1, 230.5, & 404.3 mg/kg/day	Systemic Toxicity NOAEL = 19.9 mg/kg/day in males and 23.1 mg/kg/day in females. Systemic Toxicity LOAEL = 65.8 mg/kg/day in males and 78.1 mg/kg/day in females, based on clinical signs of anemia (reduced Hct, HGB, MCV, and MCH values during treatment).
870.3100 90-Day oral toxicity (mice)	43616517 (1993) Acceptable/Guideline 0, 50, 100, 300, 550, 1000, & 3000 ppm M: 0, 10.3, 17.8, 60, 108.4, & 194.4 mg/kg/day F: 0, 13.9, 29, 79.8, 143.6, & 257 mg/kg/day	Systemic Toxicity NOAEL = 60 mg/kg/day in males and 79.8 mg/kg/day in females. Systemic Toxicity LOAEL = 108.4 mg/kg/day in males and 143.6 mg/kg/day in females, based on decreased body weights, body-weight gains, red blood cells, HGB, Hct, and severity of splenic micropathology (increased incidence and severity of extramedullary hematopoiesis). Four-week recovery period reversed all the treatment related effects except extramedullary hematopoiesis; however, severity was reduced.
870.3150 90-Day oral toxicity (dog)	42932102 (1992) Acceptable/Guideline 0, 300, 800 & 2000 ppm M/F: 0/0, 10/10, 28/28, & 57/73 mg/kg/day	Systemic Toxicity NOAEL = 28 mg/kg/day for males and females. Systemic Toxicity LOAEL = 57/73 mg/kg/day (M/F), based on decreased body weights (7-10%) and body-weight gains during first 5 weeks of study; decreased HGB, Hct, MCV, and MCH concentration, and increased absolute liver weights and alkaline phosphatase levels, and microscopic changes in the liver and spleen (pigmented sinusoidal microphages in the liver, swollen centrilobular hepatocytes and pigmented reticuloendothelial cells in the spleen).
870.3200 28-Day dermal toxicity (rabbit)	44248301 (1996) Acceptable/Guideline 0, 10, 30, 100, 300, & 1000 mg/kg/day	Systemic and Dermal Toxicity NOAEL = 1000 mg/kg/day (highest dose tested or HDT). Systemic and Dermal Toxicity LOAEL was not established.
870.3465 26-Day inhalation toxicity with 28 days of recovery (rat)	49253902 (2013) Acceptable/Non-Guideline 0, 0.085, 0.256, and 1.71 mg/L (0, 20, 40, and 600 mg/kg/day [M/F])	NOAEL = 0.256 mg/L. LOAEL = 1.71 mg/L based on significant reduction in RBC parameters, including RBC count, HGB, Hct, MCV, MCH, and/or reticulocytes in male and female rats following 26 days of inhalation exposure to the test material. Portal-of-entry NOAEL = 0.256 mg/L. Portal-of-entry LOAEL = 1.71 mg/L based on an increased incidence of minimal nasal respiratory epithelial hyperplasia in male and female rats.
870.3700a Prenatal Developmental (rat)	42932104 (1992) Acceptable/Guideline 0, 1, 10, 25, & 50 mg/kg/day	Maternal NOAEL = 25 mg/kg/day. Maternal LOAEL = 50 mg/kg/day, based upon increased relative splenic extramedullary hematopoiesis. Developmental NOAEL = 10 mg/kg/day. Developmental LOAEL = 25 mg/kg/day, based upon decreased mean fetal weights, and retardation in skeletal development evidenced by an increased number of litters with any variation and by decreased number of caudal vertebral and metacarpal ossification sites.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Sulfentrazone.		
Guideline No./ Study Type	**MRID No. (year)/Classification/ Doses**	**Results**
870.3700 Prenatal developmental (rat)	43651003 (1992) Acceptable/Non-Guideline 0, 25, & 50 mg/kg/day Study was conducted to evaluate external and cardiac abnormalities.	Maternal NOAEL = 25 mg/kg/day. Maternal LOAEL = 50 mg/kg/day, based on decreased mean body weights during gestation, and decreased litter size. Developmental NOAEL = 25 mg/kg/day. Developmental LOAEL = 50 mg/kg/day, based on significant reductions in the number of implantations and percentage of live fetuses, increase in the percentage of early resorptions, and decreased fetal body weights. Supplemental study to the 1992 Developmental-Toxicity Study in Rats (MRID 42932104).
870.3700 Prenatal dermal developmental (rat)	MRID 42932105 (1992) Acceptable/Guideline 0, 5, 25, 50, 100, & 250 mg/kg/day	Maternal NOAEL >250 mg/kg/day. Maternal LOAEL was not established. Developmental NOAEL = 100 mg/kg/day. Developmental LOAEL = 250 mg/kg/day, based on decreased fetal body weight; increased incidence of fetal variations: hypoplastic or wavy ribs, incompletely ossified lumbar vertebral arches, and incompletely ossified ischia or pubis; and reduced number of thoracic vertebral and rib ossification sites.
870.3700b Prenatal Developmental (rabbit)	MRID 42932106 (1993) Acceptable/Guideline 0, 100, 250, & 375 mg/kg/day	Maternal NOAEL = 100 mg/kg/day. Maternal LOAEL = 250 mg/kg/day, based on increased early abortions, clinical signs (hematuria and decreased feces), and reduced body-weight gain. Developmental NOAEL = 100 mg/kg/day. Developmental LOAEL = 250 mg/kg/day, based on increased early resorptions, decreased live fetuses per litter, and decreased fetal weights.
870.3800 Two-Generation reproduction and fertility effects (rat)	43345408 (1994) Acceptable/Guideline 0, 200, 500, & 700 ppm M/F: 0, 14/16, 33/40, & 46/56 mg/kg/day	Parental Toxicity NOAEL =14 (M) and 16 (F) mg/kg/day. Parental Toxicity LOAEL = 33 (M) and 40 (F) mg/kg/day based on decreased maternal body weight/body-weight gain during gestation in both generation (P & F_1) and reduced premating body-weight gain in second-generation (F_1) males. Reproductive Toxicity NOAEL = 14 (M) and 16 (F) mg/kg/day. Reproductive Toxicity LOAEL = 33 (M) and 40 (F) mg/kg/day, based on increased duration of gestation in females and degeneration and/or atrophy of the germinal epithelium of the testes and oligospermia and intratubular degenerated seminal material in the epididymis of F_1 males. Offspring Toxicity NOAEL = 14 (M) and 16 (F) mg/kg/day. Offspring Toxicity LOAEL = 33 (M) and 40 (F) mg/kg/day, based on reduced prenatal viability (fetal & litter), reduced litter size, increased no. of stillborn pups, reduced pup and litter postnatal survival and decreased pup body weights throughout lactation.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Sulfentrazone.		
Guideline No./ Study Type	**MRID No. (year)/Classification/ Doses**	**Results**
870.3800 One-Generation reproduction and fertility effects (rat)	43869101(1995) Acceptable/Non-guideline 0, 50, 100, 200, & 500 ppm F_0 M/F: 0, 3.9/4.1, 7.8/13.4, 16/16, & 40/43 mg/kg/day F_1 M/F: 0/0, 4.5/5.0, 9.2/10.1, 18/20, & 45/51 mg/kg/day	Systemic/Developmental Toxicity NOAEL = 20 (F) mg/kg/day. Systemic/Developmental Toxicity LOAEL = 51 (F) mg/kg/day, (F_1 females), based on decrease in pre-mating body-weight gain (10%). Offspring and Reproductive Toxicity NOAEL = 16 mg/kg/day (M/F) mg/kg/day. Offspring and Reproductive Toxicity LOAEL F_1 = 40 (M/F) mg/kg/day, based on reduced gestation day-20 fetal weights; decreased postnatal day 0, 4, and 7 pup weights; decreased pup survival; delayed vaginal patency; reduced epididymal, prostate, and testicular weights. Additional information supports the conclusions reached in the two-generation reproduction study (MRID 43345408).
870.4100b Chronic toxicity (dog)	43345406 (1994) Acceptable/Guideline 0, 300, 800, and 1800 ppm M/F: 0, 9.9/10.4, 24.9/29.6, & 61.2/61.9 mg/kg/day	Systemic Toxicity NOAEL = 24.9/29.6 mg/kg/day for males/and females. Systemic Toxicity LOAEL = 61.2/61.9 mg/kg/day (M/F), based upon compensated normochromic microcytosis.
870.4200 Carcinogenicity rodents (mouse)	43345407 (1994) Acceptable/Guideline 0, 300, 600, 1000, & 2000 ppm M/F: 0, 46.6/58.0, 93.9/116.9, 160.5/198.0, & 337.6/407.1 mg/kg/day	Systemic Toxicity NOAEL = 93.9 mg/kg/day for males and 116.9 mg/kg/day for females. Systemic Toxicity LOAEL = 160.5 mg/kg/day for males and 198.0 mg/kg/day for females, based on dose-related decreases in HGB and Hct by study termination. No evidence of carcinogenicity.
870.4300 Combined chronic toxicity/carcinogenicity rodents (rat)	43345409 (1994) Acceptable/Guideline M: 0, 600, 1000, 2000, & 3000 ppm F: 0, 300, 600, 1000 & 2000 ppm M/F: 0/0, 24.3/20, 40/36.4, 82.8/67, & 123.5/124.7 mg/kg/day	Systemic Toxicity NOAEL = 40 mg/kg/day for males and 36.4 mg/kg/day for females. Systemic Toxicity LOAEL = 82.8 mg/kg/day for males and 67 mg/kg/day for females, based on dose-related decreased body weights (11 & 19%), body-weight gains (13 & 26%), food consumption (13 & 19%), HGB, Hct, MCV, and MCH. Increased nucleated red blood cells and reticulocytes in bone of females at 124.7 mg/kg/day. No evidence of carcinogenicity.
870.5100 Gene Mutation: Ames assay Gene Mutation: HGPRT	41911611 (1986) Acceptable/Guideline *Salmonella typhimurium* strains TA1535, TA1538, TA1537, TA98, and TA100 were exposed to sulfentrazone technical (95.5%) at concentrations of 100-10,000 ug/plate with or without S9 activation (both trials).	No evidence of compound-induced cytotoxicity was evident either in presence or in absence of S9 activation. The positive controls induced the expected mutagenic responses in the appropriate tester strain. Sulfentrazone was considered not mutagenic under any test condition.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Sulfentrazone.		
Guideline No./ Study Type	**MRID No. (year)/Classification/ Doses**	**Results**
870.5300 *In vitro* mammalian cell gene mutation assay (mouse lymphoma)	43004604 (1992) Acceptable/Guideline Mouse lymphoma (L5178Y $TK^{+/-}$ CHO) cells were exposed to sulfentrazone technical (94.2%) in non-activated dose ranges of 424-1308 ug/mL (Trial 1) and 1308-3000 ug/mL (Trial 2); With S9 activation dose ranges of 424-1407 ug/mL (Trial 1) and 915-1800 ug/mL (Trial 2).	In a forward gene-mutation assay, sulfentrazone at precipitating levels were equivocally positive in the absence of S9 activation. This response was not repeated at doses up to 1800 g/mL in the presence of S9 activation.
870.5395 Mammalian erythrocyte micronucleus test	43004605 (1992) Acceptable/Guideline Groups of 5 male and 5 female ICR mice received single intraperitoneal injection of 85, 170, and 340 mg/kg sulfentrazone technical (94.2%). Test material was administered in corn oil and bone marrow cells harvested at 24, 48, and 72 hours post-dosing. Cyclophosphamide at 30 mg/kg was used as positive control.	The test was negative in mice administered single intraperitoneal doses of 85-340 mg/kg. The 340 mg/kg dose was estimated to be approximately 80% of the LD50/7. No evidence of a cytotoxic effect on the target organ and no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow cells.
870.5450 Dominant lethal assay - rodent	44248302 (1996) Acceptable/Guideline In dominant lethal assay, male rats were dosed at 0, 100, 225, or 450 mg/kg/day for 5 days and mated to untreated females sequentially for 10 weeks to determine the level of fetal deaths due to dominant lethal mutations.	There were no significant differences from negative controls in the proportion of early dead: total implants, and (total) dead: total implants. Based on the results, sulfentrazone is considered negative for inducing dominant lethal mutations in pre-meiotic, meiotic, and post-meiotic germ cells of male rats under conditions of this assay up to the estimated maximum tolerable dose (MTD).
870.6200 ACN Study	43345405 (1994) Acceptable/Guideline 0, 250, 750, & 2000 mg/kg	Systemic Toxicity NOAEL = 250 mg/kg/day. Systemic Toxicity LOAEL = 750 mg/kg/day, based upon increased incidence of clinical signs, FOB findings, and decreased motor activity which was reversed by day 14 post dose. No evidence of neuropathology at any dose.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile for Sulfentrazone.		
Guideline No./ Study Type	**MRID No. (year)/Classification/ Doses**	**Results**
870.6200 SCN Study	43345405 (1994) Acceptable/Guideline 0, 500, 2500, or 5000 ppm (0/0, 30/37, 150/180, or 265/292 mg/kg/day [M/F])	NOAEL = 500 ppm (30/37 mg/kg/day). LOAEL = 2500 ppm (150/180 mg/kg/day) based on increased incidence of clinical signs (M&F), decreased body weight, body-weight gain, and food consumption (F), and increased motor activity at week 13 only (F). No evidence of neuropathology at any dose.
870.7485 Metabolism and pharmacokinetics (rat)	43345410 (1994) Acceptable/Guideline Phenyl-^{14}C sulfentrazone (98% pure.) was administered to Sprague-Dawley rats (five animals/sex/dose) by gavage as a single dose at levels of 50 and 500 mg/kg, or as a single dose of 50 mg/kg following a 14-day pretreatment with non-radioactive sulfentrazone (50 mg/kg/day).	Sulfentrazone was readily absorbed and 84 to 104% of the administered dose was excreted in urine and feces within 72 hours. There were no major sex differences in the pattern of excretion. Almost all the radioactivity in the urine was HMS (84-104% of the administered dose). In the feces, HMS accounted for 1.26-2.55% of the administered dose. The proposed metabolic pathway appeared to be conversion of the parent compound mainly to HMS (excreted in the urine). A small amount of HMS was also converted to sulfentrazone 3-carboxylic acid (excreted in the urine and feces).
870.7800 Immunotoxicity (rat)	48748601 (2012) Acceptable/Guideline 0, 500, 1000, or 2000 ppm (0, 42, 87, or 163 mg/kg/day[F])	Systemic NOAEL = 1000 ppm (87 mg/kg/day). Systemic LOAEL = 2000 ppm (163 mg/kg/day) based on reduced body weight, and increased absolute and relative spleen weights. Immunotoxicity NOAEL = 2000 ppm (equivalent to 163 mg/kg/day). Immunotoxicity LOAEL was not established.
Published literature	47749201 (2009) De Castro, *et al*., (2007) Acceptable/non-guideline 0, 25, or 50 mg/kg bw/day	Dose-dependent, statistically significant delayed ear opening, decreased grip response and rearing frequency, and increased surface righting reflex reaction time observed at ≥25 mg/kg/day; no effect on maternal body weight (only parameter tested in dams) during gestation. The results of this non-guideline study were published in the open literature. Due to limitations in study conduct and reporting of the statistical analysis, the study is of limited value in risk assessment.

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical Properties of Technical Grade Sulfentrazone.		
Parameter	Value	Reference
Melting range	120-122 ºC	D288712, G. Kramer, G. Reddy, and L. Liu, 06-MAR-2003
pH	4.78 at 23 ºC	
Density	0.53 g/cm^3	
Water solubility	4.0 x 10^2 µg/g	
Solvent solubility	18.6% w/w in acetonitrile	
Vapor pressure	8 x 10^{-10} mm Hg	
Dissociation constant, pK_a	6.56	
Octanol/water partition coefficient, Log(K_{OW})	1.49 at pH 5	
UV/visible absorption spectrum	Not available	

Appendix C. International Residue Limit Status Sheet.

Table C.1. Summary of US and International Tolerances and Maximum Residue Limits.

Residue Definition:

U.S. 40 CFR § 180.498(a)(2): Tolerances are established for the combined residues of the free and conjugated forms of sulfentrazone, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of sulfentrazone (*N*-[2,4-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1*H*-1,2,4-triazol-1-yl]phenyl]methanesulfonamide) and its metabolites HMS (*N*-(2,4-dichloro-5-(4-(difluoromethyl)-4,5-dihydro-3-hydroxymethyl-5-oxo-1*H*-1,2,4-triazol-1-yl)phenyl)methanesulfonamide) and DMS (*N*-(2,4-dichloro-5-(4-(difluoromethyl)-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl)phenyl)methanesulfonamide, calculated as the stoichiometric equivalent of sulfentrazone

Canada -

Codex -

Other[1] -

Commodity	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S.	Canada	Codex	Other
Corn, pop, grain	0.15	-	-	
Corn, pop, stover	0.3	-	-	

Completed: G. Kramer; 6/3/2024 using Global MRL and Pesticides | CODEXALIMENTARIUS FAO-WHO

Appendix D. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the pesticide handlers exposure database (PHED 1.1); and the agricultural handlers exposure task force (AHETF) database; are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency websites : http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure.

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