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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

Date: 12 November 2008

SUBJECT: Trifloxysulfuron-Sodium: Human Health Risk Assessment for the Requested Use on Sports Fields and Residential Turfgrass.

PC Code: 119009	DP Barcode: 352260
MRID No.: None	Registration No.: 100-1132
Petition No.: None	Regulatory Action: Section 3 Expanded Use
Assessment Type: Single Chemical, Aggregate	Registration Case No.: Not Applicable
TXR No.: None	CAS No.: 145099-21-4 (free sulfonylurea), 199119-58-9 (sodium salt), 290332-10-4 (sodium salt monohydrate)
Decision No.: 392450	40 CFR 180.591

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Note: Throughout this document, "trifloxysulfuron-sodium" refers, specifically, to the sodium salt and "trifloxysulfuron" refers to the free acid form of the molecule.

Conclusions

Based on highly conservative, health-protective assumptions, there are no human health considerations that would preclude granting the requested use of trifloxysulfuron-sodium on turfgrass. The database for trifloxysulfuron-sodium is essentially complete. Due to the new 40

Recvd in RAC 11/19/2008

CFR Part 158 data requirements, the Agency is requesting that an acceptable immunotoxicity study be completed as a condition of registration. No new or revised tolerances are associated with this action.

Action Requested

The petitioner, Syngenta Crop Protection, Inc., has requested that the registration for trifloxysulfuron-sodium, which is already registered for golf course turf, be amended to include residential turf as well as recreational fields.

Background

In September 2003, HED assessed the human health risks associated with requested uses of trifloxysulfuron-sodium on almond, citrus, cotton, sugarcane, tomato, and golf course turf (M. Doherty *et al.*, D284104). There were no risk concerns associated with those uses, and trifloxysulfuron-sodium was registered in the U.S. in 2003. The Agency has now been petitioned to expand the use on turf to include recreational fields and residential turf. This document updates the previous aggregate risk assessment to include the expanded use sites, to evaluate the effect, if any, of new pesticide registration data requirements (40 CFR Part 158), and to include drinking water as a source of exposure directly in the assessment as per current OPP policy. No new data have been submitted to support the requested use expansion.

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1.0 Executive Summary

HED has re-evaluated the database for trifloxysulfuron-sodium and found it to be essentially complete for purposes of evaluating the requested use expansion. Due to revisions in 40 CFR Part 158, there is now a requirement for an immunotoxicity study (OPPTS Guideline 870-7800). Although the lack of that study now represents a data gap, HED does not believe that a database uncertainty factor is warranted at this time. The existing toxicological data for trifloxysulfuron-sodium do not show any significant effects on immunological organs or function (some histopathological effects were noted in the spleen, thymus, and lymph nodes of dogs at higher dosing levels). Primarily, effects were seen in the kidneys, the urinary bladder, the liver, heart development, body weight gain, motor activity, and lung tissue at relatively high dose levels. The current hazard assessment, including the use of uncertainty factors, is believed to be protective of any immunotoxicity that may occur from exposure to trifloxysulfuron. The doses and endpoints for human health risk assessment have been revised from those presented in the most recent assessment for trifloxysulfuron (M. Doherty *et al.*, D284104, 24 Sept. 2003) and the hazard characterization has been updated.

Although there are no new sources of dietary exposure associated with the requested use expansion, HED has conducted a new dietary exposure assessment. As per current policy, the new assessment incorporated exposure via residues in drinking water directly into the dietary exposure model. The resulting dietary risk estimates are less than 1% of the population-adjusted dose (PAD) for all population subgroups and exposure durations; this is well below HED's level of concern, which is typically 100% of the PAD.

HED has completed occupational and residential exposure assessments to evaluate the requested uses. Since application of trifloxysulfuron-sodium may be made only by commercial or professional applicators, residential exposure is restricted to post-application activities on treated turf. Risk estimates for residential dermal and incidental oral exposures are well below HED's level of concern. Similarly, occupational risk estimates associated with application and well as post-application activities are below HED's level of concern.

HED has, in accordance with the Food Quality Protection Act, combined risk estimates from dietary and residential sources to derive aggregate risk estimates. These aggregate estimates are below HED's level of concern for all population subgroups. Therefore, HED has no aggregate human health risk concerns that would preclude granting the requested use expansions for trifloxysulfuron-sodium.

2.0 Physical/Chemical Properties Characterization

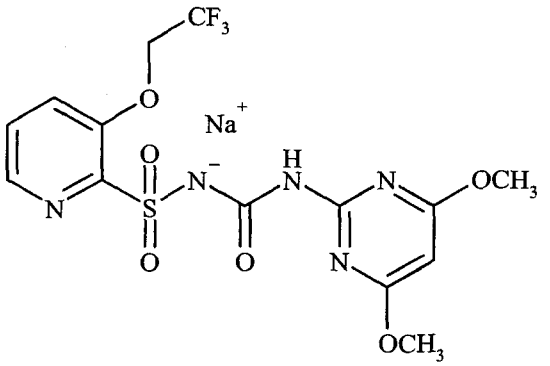
Table 2.1. Test Compound Nomenclature	
Compound Trifloxysulfuron-sodium	Chemical Structure 
Common name	Trifloxysulfuron-sodium
Company experimental name	CGA-362622
IUPAC name	N-[(4,6-dimethoxy-2-pyrimidinyl)carbamoyl]-3-(2,2,2-trifluoroethoxy)-pyridin-2-sulfonamide sodium salt
CAS name	N-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-3-(2,2,2-trifluoroethoxy)-2-pyridinesulfonamide sodium salt
CAS Registry Number	199119-58-9 (sodium salt); 290332-10-4 (sodium salt monohydrate); 145099-21-4 (free sulfonylurea)
End-use product/EP	Trifloxysulfuron 75% a.i., wettable granule formulation
Chemical Class	Sulfonylurea
Known Impurities of Concern	None

Table 2.2. Physicochemical Properties		
Parameter	Value	Reference
Molecular Weight	Monosodium salt: 459 Daltons Free acid: 437 Daltons	–
Melting point/range	173-175°C	MRIDs 45371904 and 45371910
pH	7.85 (saturated solution)	MRID 45371905
Density	1.63 g/cm^3 at 21°C	MRID 45371905
Water solubility (20°C)	63 mg/L at pH 5.06 5016 mg/L at pH 7.04 23.7 g/L at pH 7.71 38 g/L at pH 7.85	MRIDs 45371904 and 45371910
Solvent solubility (temperature not specified)	Methanol 39 g/L Ethanol 5.6 g/L Isopropanol 0.8 g/L Acetonitrile 5 g/L Acetone 12.4 g/L Ethyl acetate 595 mg/L	MRIDs 45371904 and 45371910
Vapor pressure (25 C)	<1 x 10^{-7} Pa	MRIDs 45371904 and 45371910
Dissociation constant, pKa	4.76 (acidic)	MRID 45371905
Octanol/water partition coefficient, logP_{OW} (25°C)	1.4 at pH 5.0 -0.42 at pH 7.0 -1.6 at pH 9.1	MRIDs 45371904 and 45371910
UV/visible absorption spectrum	not provided	—

Trifloxysulfuron-sodium is relatively soluble in water at neutral pH, but is significantly less soluble under acidic conditions, as would be expected given the compound's pKa value of 4.76 (Table 2.2). Data were not provided regarding solubility in basic solutions; however, based on the properties summarized in Table 2.2, solubility under basic conditions is expected to be similar to that in neutral aqueous media. This herbicide has a low vapor pressure at 25°C and dissipation via volatilization is not expected under normal conditions.

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

3.1.1 Database Summary

3.1.1.1 Sufficiency of studies/data

Based on the proposed use pattern, the toxicology database for trifloxysulfuron is adequate for risk assessment. There are acceptable studies available for endpoint selection that include: 1) subchronic oral toxicity studies in rats, mice, and dogs; 2) a chronic oral toxicity study in dogs and carcinogenicity studies in rats and mice; 3) developmental and reproduction studies in rats and a developmental study in rabbits; 4) acute and subchronic neurotoxicity studies in rats; and 4) a subchronic dermal toxicity study in rats. There is also a complete mutagenicity battery, as well as an acceptable metabolism study in the rat. A developmental neurotoxicity study is not required at this time. However, as part of the new EPA 158 guidelines, an immunotoxicity study in rats and/or mice is required (see Appendix II). Effects indicative of immunotoxicity were observed in subchronic toxicity studies in dogs (histopathology in thymus, spleen, and lymph nodes). However, these effects were not observed in other species (rats, mice, or rabbits) and not seen in any tested species as a result of chronic exposure. The doses and endpoints selected (along with traditional uncertainty factors) are considered protective of potential immunotoxicity. Therefore, an additional 10x database uncertainty factor is not warranted.

3.1.1.2 Mode of action, metabolism, toxicokinetic data

Trifloxysulfuron-sodium is a member of the sulfonylurea class of acetolactate synthase (ALS) inhibiting herbicides. It controls weeds by inhibiting a biochemical process which produces essential branched-chain amino acids necessary for plant growth. The inhibited enzyme system is acetolactate synthase (ALS).

3.1.2 Toxicological Effects

In subchronic and chronic feeding studies in mice, rats, and dogs, trifloxysulfuron-sodium generally caused decreased body weights and body weight gains, often accompanied by decreased food consumption. Decreased body weights, body weight gains and food consumption were also observed in female mice at the highest dose tested in an 18-month carcinogenicity study. No other treatment-related effects were observed in male or female mice at the highest dose tested in this study or in a 3-month feeding study. In a 2-year combined chronic toxicity/carcinogenicity study in rats, the most sensitive treatment-related effect was tubular atrophy in the kidneys of females, which developed in the second year of the study. In the same study at higher doses, Leydig cell hyperplasia of the testes also developed in the second year in

males. In 3-month and/or 28-day subchronic oral studies in rats, the following effects were also noted: decreased thymus weight and slight hypertrophy of thyroid follicular epithelium in males and slight histopathology in the liver in females (single cell necrosis, focal necrosis, inflammation and hepatocellular hypertrophy). In a 28-day dermal study in rats, the only treatment-related effect was decreased body weight gain in females at the limit dose of 1000 mg/kg/day. No effects were observed in males and no dermal irritation was noted in males or females.

In a 1-year chronic toxicity study in dogs, the following treatment-related effects were observed at the highest dose tested: decreased body weight gain and histopathology in the lungs of males (gray-white foci and fibrous thickening of the pleura) and increased incidence and severity of chronic inflammation in the urinary bladder of females. In 3-month and/or 28-day subchronic oral studies in dogs, the following effects were generally noted in both males and females: increased mortality (at high doses), clinical signs of toxicity (in moribund dogs), clinical chemistry changes (suggesting liver toxicity), liver toxicity (histopathological findings, increased glycogen, increased liver weights), signs of anemia (slight hematological changes with secondary effects in liver, spleen and bone marrow), and histopathological findings in lungs, kidney, thyroid, spleen, thymus and testes.

In the developmental toxicity study in rats at the limit dose of 1000 mg/kg/day, there was a decrease in maternal food consumption during treatment and a decrease in body weight gain during post-treatment. At the same dose, the offspring had a slight decrease in fetal body weights, an increase in minimal skeletal findings and an increase in poor/absent skeletal ossification. In the developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 100 mg/kg/day and the LOAEL was 250 mg/kg/day based on mortality and vaginal bleeding. In offspring at 100 mg/kg/day, one fetus had an abnormally shaped heart; at 250 mg/kg/day, three fetuses from two litters had this finding. Historical control data from the registrant did not describe any fetuses with this observation. In the 2-generation reproduction study in rats, decreases in body weights, body weight gains and food consumption were observed in the parental animals. At the same dose, the offspring showed decreases in body weight and body weight gain, decreases in spleen and thymus weights and an increase in vaginal patency. There was no effect on reproduction. There was no evidence of increased quantitative or qualitative susceptibility in the developmental toxicity study in rats or in the 2-generation reproduction study in rats. In the developmental toxicity study in rabbits, there was an increase in quantitative susceptibility based upon the presence of an abnormally shaped heart in one fetus at 100 mg/kg/day. Three additional fetuses from two litters at 250 mg/kg/day also had abnormally shaped hearts. The degree of concern for this finding was low beause there was a clear NOAEL for this effect, only 1 fetus had the effect at the LOAEL, and the effect was used as a toxicological endpoint in appropriate risk assessments. There are no residual uncertainties for pre-natal and/or post-natal toxicity.

In two acute neurotoxicity studies in rats, decreased motor activity was observed at the limit dose of 2000 mg/kg (only dose tested) in males and females on Day 1 in the first study and only in females in the second study. A NOAEL of 600 mg/kg was established for this effect in females. Microscopic examination revealed lesions in the nervous system of 2 males and 1 female at the dose of 2000 mg/kg in the first study. Microscopic examination of nervous system tissues was not performed in the second study. In a subchronic neurotoxicity study in rats, no neurologic effects were observed in either the males or females. In a 90-day feeding study and in a 28-day

feeding study in dogs, clinical signs of toxicity (including neurotoxic signs) were observed at high doses, but only in moribund dogs that subsequently died or were sacrificed in extremis. In none of the other toxicity studies on trifloxysulfuron-sodium was there any evidence of treatment-related neurotoxicity. Overall, there is not a concern for neurotoxicity resulting from exposure to trifloxysulfuron-sodium and a developmental neurotoxicity study in rats is not required.

In carcinogenicity studies in male and female rats and in male and female mice, trifloxysulfuron-sodium did not demonstrate any biologically significant evidence of carcinogenic potential. Trifloxysulfuron-sodium is classified as "not likely to be carcinogenic to humans."

Technical grade trifloxysulfuron-sodium did not demonstrate any mutagenic potential in a battery of 5 mutagenicity studies. There is not a concern for mutagenicity resulting from exposure to trifloxysulfuron-sodium. Results were negative without and with rat S-9 activation in a reverse gene mutation study using Salmonella typhimurium/Escherichia coli and in a forward gene mutation study using CHO cells at the HGPRT locus. In an *in vitro* chromosomal aberration study in CHO cells, trifloxysulfuron-sodium was negative when tested without and with rat S-9 activation. In an *in vivo* micronucleus study in mice using bone marrow cells, the results were negative and in an *in vitro* unscheduled DNA synthesis assay in primary rat hepatocyte cultures, results also were negative.

3.1.3 Dose-response

For acute dietary exposure (general population), an acute neurotoxicity study in rats is being used to calculate the acute reference dose (aRfD) of 6.0 mg/kg/day. The NOAEL of 600 mg/kg/day and the LOAEL of 2000 mg/kg/day are based on decreased motor activity and histopathological lesions (nervous system) in males and females. For acute dietary exposure in females (13-49), the aRfD is from the developmental toxicity study in rabbits. The NOAEL of 50 mg/kg/day and the LOAEL of 100 mg/kg/day are based on increased incidence of abnormally shaped hearts in fetuses. For chronic dietary exposure, the chronic RfD (cRfD) is from a combined chronic/carcinogenicity study in rats and is based on increased tubular atrophy in the kidneys at the LOAEL of 99.3 mg/kg/day (NOAEL = 23.7 mg/kg/day). A 2-generation reproduction study in rats is being used to select the dose and endpoint for assessing short-term incidental oral exposure. The offspring NOAEL of 79 mg/kg/day and the LOAEL of 631 mg/kg/day are based on decreases in pup weight. For intermediate-term incidental oral exposure, a chronic dog study is being used based on decreases in body weight, lung histopathology, and urinary bladder inflammation seen at the LOAEL of 121 mg/kg/day (NOAEL= 45 mg/kg/day). The developmental study in rabbits is being used for assessing short-term dermal and inhalation exposure, and the chronic dog is being used for assessing intermediate-term dermal and inhalation exposure.

3.1.4 FQPA

HED recommends the FQPA SF be reduced to 1X because there are no/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity, and the toxicological database is essentially complete (see section 3.4).

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

In metabolism studies in rats, trifloxysulfuron-sodium was rapidly and nearly completely absorbed and excreted within 48 hours. Urinary excretion was the primary route of elimination. Females excreted more of the administered dose (AD) in the urine than did males. There was no evidence for an enterohepatic circulation. Less than 0.30% of the AD remained in the tissues after 168 hours. Unchanged parent was eliminated almost entirely in the urine. Females excreted more unchanged parent in the urine than did males. With the exception of unchanged parent, the metabolite profile was similar between urine and feces. The primary metabolites in both urine and feces in all treated groups were Metabolites J (desmethyl parent) and K (5'-hydroxypyrimidine of parent). Other major metabolites included Metabolites F (formed from hydroxylation of the parent at the 5' position), X and N (glucuronide conjugates of F), A and D (additional desmethyl moieties). Several minor metabolites were also identified.

3.3 FQPA Considerations

3.3.1 Adequacy of the Toxicity Database

The toxicology database for trifloxysulfuron is adequate to characterize potential pre- and/or post-natal risk for infants and children. Acceptable/guideline studies for developmental toxicity in rats and rabbits and a 2-generation reproduction study in rats are available for FQPA assessment.

3.3.2 Evidence of Neurotoxicity

There were decreases in motor activity on Day 1 seen in males and females in an acute neurotoxicity study battery in rats (MRIDs 45372018, 45372020-22, 4537033) at 2000 mg/kg/day. Other effects included: minimal to moderate swelling of the cervical, thoracic and lumbar spinal cord in a single male, minimal to slight degeneration of the sciatic, tibial and plantar nerve fibers in another male and slight swelling of myelin in the thoracic area in one female. In another acute neurotoxicity study battery (MRIDs 45372018-19, 45372021-22), there were decreases in motor activity on Day 1 in females only. No neuropathological examination was conducted in the second study. No evidence of neurotoxicity, including neuropathology, was observed in a subchronic neurotoxicity study in rats at doses up to 967/1128 mg/kg/day (male/female).

Although there were possible neurotoxic signs noted in both sexes of dogs (470/457 mg/kg/day) on Day 12 (vomiting, recumbence, hunched posture, reduced activity, and weakness of hindlimbs), these effects were attributed to the moribund condition. In the only other treatment group at a dose of 343/312 mg/kg/day for males/females, similar, but less severe signs were noted in 1 of 2 males and 1 of 2 females on Day 11 and disappeared on Days 15 or 16. In a 28-day capsule study in dogs, none of these signs were reported at any dose (up to 500 mg/kg/day); however, the dogs in this study probably did not receive an accurate dose as test article was found in the feces. None of the neurotoxicity signs noted in the 28-day study or any other neurotoxic signs were reported in either the 90-day or 1-year dog studies.

3.3.3 Developmental Toxicity Studies

In a developmental toxicity study in rats, maternal findings were limited to decreases in body weight gain and food consumption at the limit dose of 1000 mg/kg/day. The maternal LOAEL is 1000 mg/kg/day and the NOAEL is 300 mg/kg/day. In offspring, minor decreases in body weight, increased incidences of skeletal anomalies, and poor/absent skeletal ossification were observed at the LOAEL of 1000 mg/kg/day (NOAEL = 300 mg/kg/day).

In rabbits, mortality and vaginal/anal bleeding were seen at ≥ 250 mg/kg/day. Decreases in body weight gain, maternal food consumption, hemorrhagic contents of the cecum, large intestine, urinary bladder, uterus, and vagina, solid contents of the stomach, and fluid contents of the large intestines were also observed at 500 mg/kg/day. The maternal LOAEL is 250 mg/kg/day and the NOAEL is 100 mg/kg/day. At 500 mg/kg/day, only one animal survived to scheduled sacrifice. The surviving doe had four implantations, three of which ended in resorptions. The one surviving fetus had an asymmetrically shaped sternabrae # 6. At 100 mg/kg/day, an abnormally shaped heart was seen in one fetus; this anomaly was seen in two fetuses (different litters) in the 250 mg/kg/day group. The finding was not reported in the Registrant historical control data or in the Mid-Atlantic Reproduction and Teratology Association's (MARTA) historical control data. The developmental LOAEL is 100 mg/kg/day and the NOAEL is 50 mg/kg/day.

3.3.4 Reproductive Toxicity Study

In a 2-generation reproduction study in rats, decreases in body weight, body weight gain, and food consumption in males of both generations were observed at ≥ 8000 ppm (631 mg/kg/day). In P and F1 females, food consumption was decreased at ≥ 8000 ppm. Additionally at 12000 ppm (1029.6 mg/kg/day), decreases in body weight and body weight gain in P females were observed. The LOAEL for parental toxicity is 8000 ppm and the NOAEL is 1000 ppm (78.8/83.5 mg/kg/day [M/F]).

In pups, decreases in body weight were seen in males and females of both generations at ≥ 8000 ppm. Additionally at 8000 ppm, delayed sexual maturation (delayed vaginal opening) was noted in F1 female offspring. Absolute and relative spleen weights were decreased in F1 male pups and F1 and F2 female pups at ≥ 8000 ppm. Decreased spleen weights were also observed at ≥ 12000 ppm in F1 female pups, along with decreases in absolute and relative thymus weights. The LOAEL for offspring toxicity is 8000 ppm and the NOAEL is 1000 ppm. No evidence of reproductive toxicity was noted in the study.

3.3.5 Additional Information from Literature Sources

A literature search did not reveal information that would impact the risk assessment.

3.3.6 Pre-and/or Postnatal Toxicity

3.3.6.1 Determination of Susceptibility

No quantitative or qualitative evidence of increased susceptibility, as compared to adults, of rat fetuses to *in utero* or postnatal exposure to trifloxysulfuron was observed in the developmental toxicity study or the reproduction study in rats. There was an increase in quantitative

susceptibility in the rabbit developmental toxicity study based on abnormal heart shapes at a dose lower (100 mg/kg/day) than the dose of 250 mg/kg/day, which caused maternal effects (mortality as well as vaginal and/or anal bleeding).

3.3.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre- and/or Postnatal Susceptibility

The purposes of the Degree of Concern analysis are: (1) to determine the level of concern for the effects observed when considered in the context of all available toxicity data; and (2) to identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment. If residual uncertainties are identified, then HED determines whether these residual uncertainties can be addressed by an FQPA safety factor and, if so, the size of the factor needed.

There was an increase in quantitative susceptibility of fetuses in the developmental toxicity study in rabbits; however, the degree of concern regarding this finding is low. There is a clear NOAEL established for the effect, and the effect was characterized as an anomaly (rather than a malformation) and only one fetus had the effect. Additionally, the study and endpoint are used for risk assessment. There are no residual uncertainties or concerns for pre- and/or post-natal toxicity. Therefore, HED recommends the FQPA safety factor be reduced to 1x.

3.3.7 Recommendation for not requiring a Developmental Neurotoxicity Study

Although there were some neurotoxic signs noted in both sexes of dogs at a dose of 470/457 mg/kg/day for males/females in a 28-day range-finding dietary admix study, these effects were probably attributable to the moribund condition of the animals as all four were sacrificed on treatment day 12. In the only other treatment group at a dose of 343/312 mg/kg/day for males/females, similar, but less severe signs were noted in 1 of 2 males and 1 of 2 females on Day 11 and disappeared on Days 15 or 16. In a 28-day capsule study in dogs, none of these signs were reported at any dose (up to 500 mg/kg/day); however, the dogs in this study probably did not receive an accurate dose as test article was found in the feces. None of the neurotoxicity signs noted in the 28-day study or any other neurotoxic signs were reported in either the 90-day or 1-year dog studies.

In the two acute neurotoxicity studies in rats, decreased motor activity was observed only on Day 1 at the highest dose tested (2000 mg/kg, Limit Dose) in both sexes in one study and only in females on Day 1 of treatment in the other study. Of the neuropathological effects observed in 3 animals in this study (at the limit dose of 2000 mg/kg), the severity grade was only minimal to slight in 2 animals and minimal to moderate in only 1 animal. It was concluded that the findings in these 2 studies should not be of concern (HIARC, TXR 0052043). There were no neurological signs in any of the other studies (including a subchronic neurotoxicity study in rats and other subchronic or chronic studies in rats, mice or dogs). Therefore, based on the overall toxicity database and the weight of the evidence, a developmental neurotoxicity study is not warranted at this time.

3.4 FQPA Safety Factor for Infants and Children

HED recommends the FQPA SF be reduced to 1x after evaluating the toxicological and exposure data for trifloxysulfuron. This recommendation is based on the following:

- The toxicological data base is complete for FQPA assessment.
- There was no evidence of increased quantitative or qualitative susceptibility in the developmental toxicity study or 2-generation reproduction study in rats.
- Although there was evidence of increased quantitative susceptibility in the developmental toxicity study in rabbits, the degree of concern is low for the quantitative evidence of susceptibility seen in the study because there was a clear NOAEL for this effect, only one fetus had the effect at the LOAEL, and the effect is being used as a toxicological endpoint in appropriate risk assessments.
- There are no residual uncertainties for pre-natal and/or post-natal toxicity.
- The dietary food exposure assessment is based on assumptions designed to produce results that will not underestimate dietary exposure.
- The dietary drinking water assessment is based on values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.
- The residential/recreational exposure assessment will not underestimate postapplication exposures resulting from the use of trifloxysulfuron-sodium on turf.

3.5 Hazard Identification and Toxicity Endpoint Selection

3.5.1 Acute Reference Dose (aRfD) – General Population

Study Selected: Acute Neurotoxicity Studies in Rats (co-critical studies)
MRID No: 45372020 and 45372019
Dose and Endpoint for Risk Assessment: NOAEL= 600 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Acute RfD} = \frac{600\ mg\ /\ kg\ /\ day}{100\ (UF)} = \textbf{6 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors:
Two acute neurotoxicity studies are being used to select the dose and endpoint for establishing the general population aRfD of 0.237mg/kg/day. The LOAEL in the 2 acute neurotoxicity studies is 2000 mg/kg and is based on (1) decreased motor activity in males and females on Day 1 in the first study and only in females on Day 1 in the second study, and (2) histopathological lesions in the nervous system tissues of 2/10 male and 1/10 female rats in the first study. Since

nervous system tissues were not microscopically examined at dose levels below 2000 mg/kg, there is no NOAEL for these lesions in either study. Regarding these lesions, application of an additional 3X (due to the lack of a NOAEL) to the conventional Uncertainty Factor (UF) of 100 (10x for interspecies extrapolation and 10x for intraspecies variation) would have resulted in an aRfD of 6.6 mg/kg (LOAEL of 2000 mg/kg/UF of 300). An additional 3X (rather than 10X) would have been adequate because the lesions were observed in only 2/10 males and 1/10 females, all the lesions were morphologically different, none of the lesions was severe (mild/moderate in 1 male, minimal/slight in 1 male, and slight in 1 female), and lesions of nervous system tissues were not observed in the subchronic neurotoxicity study in rats or in any other subchronic or chronic studies in rats, mice or dogs or in developmental toxicity studies in rats and rabbits. Also, a developmental neurotoxicity study in rats was not required to be submitted. However, in the same 2 acute neurotoxicity studies, a NOAEL of 600 mg/kg was established for decreased motor activity in females and application of the standard UF of 100 resulted in an aRfD of 6.0 mg/kg (NOAEL of 600 mg/kg/UF of 100). Since the aRfD of 6.0 mg/kg is more conservative than the aRfD of 6.6 mg/kg (based on histopathology), it was selected to be the basis for the aRfD. This aRfD (6.0 mg/kg) is protective of all the effects observed in all the studies considered to be pertinent to determination of an aRfD for the general population (HIARC, TXR 0052043).

3.5.2 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: Developmental Toxicity Study in Rabbits
MRID No: 45372005, 45372027
Dose and Endpoint for Risk Assessment: NOAEL= 50 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Acute RfD} = \frac{50\ mg\ /\ kg\ /\ day}{100\ (UF)} = \textbf{0.5 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors:
A developmental toxicity study in rabbits is being used to select the dose and endpoint for establishing the aRfD of 0.5mg/kg/day for females of child-bearing age. The abnormally shaped hearts observed at 100 mg/kg/day are considered treatment-related and to possibly have been induced by a single dose of the test material. Since these anomalies were observed *in utero*, this endpoint is applicable only to the population subgroup females 13-49 years old.

3.5.3 Chronic Reference Dose (cRfD)

Study Selected: Combined Chronic Toxicity/Carcinogenicity Study in Rats
MRID No: 45372010
Dose and Endpoint for Risk Assessment: NOAEL= 23.7 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

$$\textbf{Chronic RfD} = \frac{23.7\ mg\ /\ kg\ /\ day}{100\ (UF)} = \textbf{0.237 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors:
A combined chronic/carcinogenicity study in rats was used to select the dose and endpoint for establishing the cRfD of 0.237mg/kg/day. The 13-week feeding study in dogs (MRID 45372003, 45372028, 45372031), was also considered due to the treatment-related effects observed at the LOAEL of 164 mg/kg/day. Due to the spacing of doses in this study, the NOAEL is approximately 8 fold lower (19.6 mg/kg/day) and is considered to be unrealistic since a NOAEL of 45 mg/kg/day was determined in the 1-year feeding study in dogs. The LOAEL in the chronic dog study is 123 mg/kg/day (MRID 45372008).

3.5.4 Incidental Oral Exposure

Short-Term Incidental Oral (1-30 days)

Study Selected: 2-Generation Reproduction-Rat
MRID No: 45372007, 45372023
Dose and Endpoint for Risk Assessment: NOAEL= 79 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments about Study/Endpoint/Uncertainty Factors:
A 2-generation reproduction study in rats was used to select the dose and endpoint for short-term incidental oral exposure. The offspring NOAEL of 79 mg/kg/day is based on decreased pup body weights on Day 21 at the LOAEL of 631 mg/kg/day. This endpoint is based on offspring effects and is appropriate for the duration of exposure (1-30 days) and the population of concern (infants and children).

Intermediate-Term Incidental Oral (1-6 months)

Study Selected: Chronic Dog
MRID No: 45372008
Dose and Endpoint for Risk Assessment: NOAEL= 45mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factors:
A chronic toxicity study in dogs was used to select the dose and endpoint for intermediate-term incidental oral exposure. The NOAEL of 45 mg/kg/day is based on gray-white foci in the lungs, fibrous thickening of the lung pleura and decreased body weight gain in males and increased incidence and severity of chronic urinary bladder inflammation in females at the LOAEL of 121 mg/kg/day.

3.5.5 Dermal Absorption
A dermal absorption study is not available. The molecular weight of trifloxysulfuron-sodium is large and it is an ionic solid which is readily soluble in water. Additionally, it is closely related to other sulfonylurea herbicide chemicals. Thus, a more realistic (instead of 100% default) dermal absorption factor of 30% was estimated based on the structure-activity-relationships with other sulfonylurea pesticides.

Chemical	Dermal Absorption Factor	Reference
Triflusulfuron-methyl	27%	HIARC Report, 12/5/2001, TXR No. 0050332
Primisulfuron-methyl	30%	HIARC Report, 4/26/2002, TXR No. 0050694
Halosulfuron-methyl	75%	HIARC Report, 8/23/2002, TXR No. 0051076

3.5.6 Residential and Occupational Dermal Exposure

Short-Term Dermal Exposure (1-30 days)

Study Selected: Developmental Toxicity Study in Rabbits
MRID No: 45372005, 45372027
Dose and Endpoint for Risk Assessment: NOAEL= 50 mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factors:
A developmental study in rabbits was used to select the dose and endpoint for short-term dermal exposure. A dermal exposure study was submitted for trifloxysulfuron with decreases in body weight gain seen at 100 mg/kg/day. However, the developmental toxicity study in rabbits was selected for risk assessment due to the developmental effects observed at 100 mg/kg/day (NOAEL = 50 mg/kg/day). Since an oral NOAEL was selected, a dermal absorption factor of 30% was applied for risk assessment.

Intermediate-Term Dermal Exposure (1-6 months)

Study Selected: Chronic Dog
MRID No: 45372008
Dose and Endpoint for Risk Assessment: NOAEL= 45mg/kg/day
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability)
Comments about Study/Endpoint/Uncertainty Factors:
A chronic toxicity study in dogs was used to select the dose and endpoint for intermediate-term dermal exposure. The NOAEL of 45 mg/kg/day is based on gray-white foci in the lungs, fibrous thickening of the lung pleura and decreased body weight gain in males and increased incidence and severity of chronic urinary bladder inflammation in females at the LOAEL of 121 mg/kg/day. Since an oral NOAEL was selected, a dermal absorption factor of 30% was applied for risk assessment.

3.5.7 Residential and Occupational Inhalation Exposure

Short-Term Inhalation Exposure (1-30 days)

See short-term dermal exposure (section 3.5.6). The assumed inhalation absorption factor is 100%.

Intermediate-Term Inhalation Exposure (1-6 months)

See intermediate-term dermal exposure (section 3.5.6). The assumed inhalation absorption factor is 100%

3.5.8 Level of Concern for Margin of Exposure

Table 3.5.8 Summary of Levels of Concern for Risk Assessment.			
Route	Short-Term (1 - 30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Residential Exposure			
Incidental Oral	100	100	N/A
Dermal	100	100	N/A
Inhalation	100	100	N/A
Occupational (Worker) Exposure			
Dermal	100	100	N/A
Inhalation	100	100	N/A

3.5.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures.

Common toxicological effects (increased incidence of abnormally shaped hearts in fetuses) were selected for assessment of short-term exposures by the dermal and inhalation routes. The aggregate exposure risk assessment for these durations should be combined. Short-term incidental oral exposure cannot be combined due to a different toxicological endpoint (reduction in pup body weights and reduction in body weight gain).

Common toxicological effects (reduction in mean body weight gain and histopathology in lungs in males and chronic urinary bladder inflammation in females) were selected for assessment of intermediate-term oral, dermal (oral equivalent) and inhalation (oral equivalent) routes. The aggregate risk assessment for this exposure duration should also be combined.

3.5.10 Classification of Carcinogenic Potential

There was no evidence of carcinogenicity in cancer studies with mice and rats. Therefore, in accordance with EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), trifloxysulfuron is classified as "not likely to be carcinogenic to humans."

3.5.11 Summary of Toxicological Doses and Endpoints for Trifloxysulfuron for Use in Human Risk Assessments

Table 3.5a Toxicological Doses and Endpoints for Trifloxysulfuron for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population)	NOAEL = 600 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x Total UF=100x	Acute RfD =6 mg/kg/day aPAD = 6 mg/kg/day	Acute Neurotoxicity Studies in Rats. LOAEL = 2000 mg/kg based on decreased motor activity on Day 1 and histopathological lesions in nervous system tissues of males and females.
Acute Dietary (Females 13-49 years of age)	Developmental NOAEL = 50 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x Total UF=100x	Acute RfD =0.5 mg/kg/day aPAD = 0.5mg/kg/day	Developmental Toxicity Study in Rabbits. Developmental LOAEL=100 mg/kg/day based on increased incidence of abnormally shaped hearts in fetuses.
Chronic Dietary (All Populations)	NOAEL=23.7 mg/kg/day mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x Total UF=100x	Chronic RfD =0.237mg/kg/day cPAD = 0.237mg/kg/day	Combined Chronic/Carcinogenicity-Rat LOAEL = 99.3 mg/kg/day based on increased tubular atrophy in the kidneys of females.
Incidental oral-Short-Term (1-30 days)	Offspring NOAEL = 79 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x Total UF=100x	Residential LOC for MOE = 100	2-Generation Reproduction Study in Rats. Offspring LOAEL = 631/676 (M/F) mg/kg/day based on decreased pup body weights on Day 21.
Incidental oral-Intermediate-Term (1-6 months)	NOAEL = 45 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x Total UF=100x	Residential LOC for MOE = 100	1-Year Chronic Feeding Study in Dogs. LOAEL = 123/121 (M/F) mg/kg/day based on decreased body weight gain and histopathology in lungs in males and chronic urinary bladder inflammation in females.
Dermal-Short-Term (1-30 days)	Oral study NOAEL= 50 mg/kg/day	UF_A=10x UF_H=10x DAF=30 %	Occupational LOC for MOE = 100	Developmental Toxicity Study in Rabbits. LOAEL = 100 mg/kg/day based on increased incidence of abnormally shaped hearts in fetuses.
Dermal-Intermediate-Term (1-6 months)	Oral study NOAEL= 45 mg/kg/day	UF_A=10x UF_H=10x DAF=30 %	Occupational LOC for MOE = 100	1-Year Chronic Feeding Study in Dogs. LOAEL = 123/121 (M/F) mg/kg/day based on decreased body weight gain and histopathology in lungs in males and chronic urinary bladder inflammation in females.
Cancer (oral, dermal, inhalation)	Classification: "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. N/A = not applicable.

Table 3.5b Summary of Toxicological Doses and Endpoints for Trifloxysulfuron for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal-Short-Term (1-30 days)	Oral study NOAEL= 50 mg/kg/day	UF_A=10x UF_H=10x DAF=30 %	Occupational LOC for MOE = 100	Developmental Toxicity Study in Rabbits. LOAEL = 100 mg/kg/day based on increased incidence of abnormally shaped hearts in fetuses.
Dermal-Intermediate-Term (1-6 months)	Oral study NOAEL= 45 mg/kg/day	UF_A=10x UF_H=10x DAF=30 %	Occupational LOC for MOE = 100	1-Year Chronic Feeding Study in Dogs. LOAEL = 123/121 (M/F) mg/kg/day based on decreased body weight gain and histopathology in lungs in males and chronic urinary bladder inflammation in females.
Inhalation Short-Term (1-30 days)	Oral study NOAEL= 50 mg/kg/day	UF_A=10x UF_H=10x IAF=100%	Occupational LOC for MOE = 100	Developmental Toxicity Study in Rabbits. LOAEL = 100 mg/kg/day based on increased incidence of abnormally shaped hearts in fetuses.
Inhalation Intermediate-Term (1-6 months)	Oral study NOAEL= 45 mg/kg/day	UF_A=10x UF_H=10x IAF=100%	Occupational LOC for MOE = 100	1-Year Chronic Feeding Study in Dogs. LOAEL = 123/121 (M/F) mg/kg/day based on decreased body weight gain and histopathology in lungs in males and chronic urinary bladder inflammation in females.
Cancer (oral, dermal, inhalation)	Classification: "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). MOE = margin of exposure. LOC = level of concern. IAF=inhalation absorption factor.

3.6 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

4.0 Public Health and Pesticide Epidemiological Data

None.

5.0 Exposure Assessment

5.1 Summary of Uses

Trifloxysulfuron-sodium is a low-application-rate herbicide belonging to the sulfonylurea class of chemicals. Like other herbicides in this class, trifloxysulfuron-sodium acts by inhibiting the plant enzyme acetolactate synthase, resulting in reduced production of branched-chain amino acids. The leaves of susceptible plants typically turn yellow, red, or purple several days after application. Complete plant death occurs 1-3 weeks after application, depending on the species and environmental conditions. Use patterns for trifloxysulfuron-sodium are presented in Table 5.1.

Table 5.1. Summary of Directions for Use of Trifloxysulfuron-Sodium (75% WG formulation, EPA File Symbol 100-RRGE).

Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Almond					
Postemergence Directed to soil Ground Equip.	0.019	3	0.056	3	For use as a tank mix with glyphosate formulations registered for use on almonds. The minimum retreatment interval is 30 days. Application to newly established groves (<2 years old) is prohibited.
Citrus					
Postemergence Directed to soil Ground Equip.	0.019	3	0.056	14	For use as a tank mix with glyphosate formulations registered for use on citrus. The minimum retreatment interval is 30 days. Application to newly established groves (<2 years old) is prohibited.
Cotton (picker varieties only)					
Early postemergence Over-the-top (minimum of 5 true leaves) Ground Equip.	0.005-0.007	Not specified (NS)	0.019	60	Use limited to AL, AR, FL, GA, LA, MS, NC, SC, TN, VA, the boot heel area of MO and portions of OK and TX, excluding the high plains region of West TX and OK. Tank mixing with any other herbicides or additives (other than surfactant) or with insecticides containing malathion, profenofos, or emamectin benzoate is prohibited.

Table 5.1. Summary of Directions for Use of Trifloxysulfuron-Sodium (75% WG formulation, EPA File Symbol 100-RRGE).

Applic. Timing, Type, and Equip.	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Postemergence (8 inches in height to layby) Directed spray Ground Equip.	0.007-0.012	NS	0.019	60	Use limited to AL, AR, AZ, CA, FL, GA, LA, MS, NC, SC, TN, VA, the boot heel area of MO and portions of OK and TX, excluding the high plains region of West TX and OK. The minimum retreatment interval is 14 days. Applications are to be directed to minimize contact with cotton leaves. Applications may be made alone or as a tank mix with glyphosate (to Roundup Ready® cotton varieties only), Caparol® (prometryn), Dual Magnum® (metolachlor), MSMA, Staple® (pyrithiobac-sodium), Cotoran® (fluometuron), or Buctril® (bromoxynil, BXN cotton varieties only). Tank mixing with insecticides containing malathion, profenofos, or emamectin benzoate is prohibited.
Sugarcane					
Early postemergence (up to 24" tall) Over-the-top Ground Equip.	0.014	3	0.070	100	Use limited to FL, LA, and TX on ratoon sugarcane only. The minimum retreatment interval is 14 days. Applications may be made alone or as a tank mix with atrazine or asulam.
Postemergence (18" tall up to layby) Directed spray Ground Equip.	0.014-0.028	3	0.070	100	Use limited to FL, LA, and TX on plant or ratoon sugarcane. The minimum retreatment interval is 14 days. Applications may be made alone or as a tank mix with atrazine or asulam.
Tomato (transplanted tomatoes in FL only)					
Preemergence (pre-transplant) Ground	0.007	1 (+ 1 post-emergence)	0.014	45	Use limited to FL. Mechanical incorporation of product into the soil is to be avoided.
Postemergence Over-the-top or directed Ground Equip.	0.007-0.014	1 (+1 pre-emergence)	0.014	45	Use limited to FL. Application is to be made prior to fruit set.
Turf					
Postemergence Broadcast Ground Equip.	0.005 - 0.026	Not specified; 3 implied	0.080	N/A	12-month rotational restriction to anything other than turf grasses.

5.2 Dietary Exposure/Risk Pathway

5.2.1 Residue Profile

(M. Doherty, D284480, 8/25/03; MARC Report, TXR No. 0052100, 8/25/03)

There are no new residue chemistry data associated with the requested use expansion. The following summary of the residue chemistry database is derived from the above citations.

Tolerances for trifloxysulfuron are listed in 40 CFR 180.591. Currently, there are no established maximum residue limits (MRLs) for trifloxysulfuron in Canada, Mexico, or Codex and international harmonization is not an issue (Appendix III).

The nature of the residues in plants and animals is adequately understood; the terminal residue of concern in plants and animals is trifloxysulfuron. In water, residues of concern include trifloxysulfuron as well as the metabolites CGA-053052, CGA-382997, and CGA-368732 (see Section 5.2.2 for more details). Trifloxysulfuron-sodium was found to be extensively metabolized in plants. The foliage of plants was found to have the highest residues, with very low residues in the edible portions of the crops. Trifloxysulfuron-sodium was found to be less extensively metabolized in livestock, although similar metabolites were found.

The available analytical methodology is considered to be adequate for tolerance enforcement. The method uses acetonitrile extraction and HPLV/UV detection. The limit of quantitation (LOQ) is 0.01 ppm for each plant substrate. Multiresidue methods currently in use by the FDA are not successful at extracting or quantitating residues of trifloxysulfuron.

Based on the results of the livestock metabolism studies and on the anticipated dietary burdens to livestock, there is no expectation of finite residues of trifloxysulfuron in livestock matrices [i.e., 40 CFR 180.6(a)(3)]. Livestock feeding studies have not been submitted for trifloxysulfuron and none are required at this time.

Confined rotational crop and field rotational crop studies showed residues of trifloxysulfuron to be < 0.01 ppm in all matrices. The label lists a number of rotational crop restrictions which are, presumably, in place due to phytotoxicity concerns.

5.2.2 Water Exposure/Risk Pathway

(S. Termes, D276988, 8/20/03)

No drinking water monitoring data are available for trifloxysulfuron. Therefore, the water resource assessments are based solely on model-estimated exposure concentrations. Estimates were only performed for parent trifloxysulfuron-sodium. Exposure concentrations were estimated for uses on almonds, citrus, cotton, sugar cane, tomato, and turf. The application rates, frequency and number of applications vary between crops and were taken from the proposed labels for products containing trifloxysulfuron as the active ingredient.

In estimating residues of trifloxysulfuron-sodium in water, the highest application rates, frequency, number and shortest application interval were selected to represent the use pattern that would represent the high-end of possible exposure. The turf use has the highest seasonal application rate (0.080 lb ai/A) and sugarcane has the highest per application rate (0.028 lb ai/A). Tomato use has the lowest seasonal application rate (0.014 lb ai/A) and fewest applications (2). Trifloxysulfuron-sodium can be applied up to three times for the other uses. It was assumed that all applications were made by ground spray to soil, except for turf, where a ground spray to foliage was considered. The sugarcane use pattern was used to model residues in water.

The residues of concern in drinking water are parent trifloxysulfuron, CGA-053052, CGA-382997, and CGA-368732. In order to account for the potential residues of these breakdown products in water, HED has assumed that these metabolites occur at the maximum percent of the

applied parent compound observed in ^{14}C-environmental fate studies. Those values are 61% of the a.i. for CGA-053052 (hydrolysis at pH 5 after 30 days), 54% of the a.i. for CGA-382997 (aerobic soil metabolism after 365 days), and 53% of the a.i. for CGA-368732 (hydrolysis at pH 7 after 30 days). The conversion factor to go from parent compound to all residues of concern is, therefore, 2.68. This assumption results in overestimated levels of the total residues of concern since it assumes that all of the compounds occur simultaneously, ignoring the kinetics of their formation and dissipation. These total-residue estimated environmental concentrations (EECs) have been used directly in the dietary assessment (see below) to estimate dietary exposure to trifloxysulfuron from food and drinking water. The surface water estimates were used for acute (0.01026 ppm) and chronic (0.00083 ppm) assessments.

Table 5.2.1. Summary of Estimated Surface and Ground Water Concentrations for Trifloxysulfuron-sodium and Associated Residues of Concern.

Exposure Duration	Trifloxysulfuron-sodium		Trifloxysulfuron-sodium + CGA-053052 + CGA-382997 + CGA-368732 [a]	
	Surface Water Conc., ppb [b]	Ground Water Conc., ppb [c]	Surface Water Conc., ppb	Ground Water Conc., ppb
Acute	3.83	0.032	10.26	0.086
Chronic (non-cancer)	0.31	0.032	0.83	0.086

[a] Assumes worst-case factors, relative to trifloxysulfuron-sodium, of 0.61 for CGA-053052, 0.54 for CGA382997, and 0.53 for CGA-368732; as provided in the MARC Report (TXR No. 0052100, 8/25/03). The conversion factor for trifloxysulfuron-sodium to all residues of concern is 2.68.
[b] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on sugarcane grown in Florida.
[c] From the SCI-GROW model assuming a maximum seasonal use rate of 0.0788 lb ai/A, a K_{oc} of 29, and a half-life of 29.84 days.

5.2.3 Acute and Chronic Dietary Exposure and Risk

(M. Doherty, D355841, 6 November 2008)

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model DEEM-FCID™ (Version 2.03), which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. The analyses were completed to evaluate a request to expand the use sites to include sports fields and residential turf. Although these use sites do not alter the dietary exposure estimates that were completed in August 2003, the assessment is being re-done in order to include residue estimates for drinking water as described above.

Both the acute and chronic assessments are based on tolerance-level residues and assume 100% crop treated. Residue estimates for drinking water are from models designed to produce high-end results. For these reasons, the assessments should be considered highly conservative with respect to human health. Even with these assumptions, risk estimates for all population subgroups are less than 1% of the population-adjusted dose (PAD) for both acute and chronic analyses Table 5.3). Typically, HED is concerned when risk estimates exceed 100% of the PAD.

Table 5.3. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Trifloxysulfuron.						
Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.000677	< 1	0.000074	< 1	N/A	
All Infants (< 1 year old)	0.002046	< 1	0.000085	< 1		
Children 1-2 years old	0.001324	< 1	0.000196	< 1		
Children 3-5 years old	0.001114	< 1	0.000166	< 1		
Children 6-12 years old	0.000741	< 1	0.000107	< 1		
Youth 13-19 years old	0.000589	< 1	0.000071	< 1		
Adults 20-49 years old	0.000574	< 1	0.000058	< 1		
Adults 50+ years old	0.000513	< 1	0.000059	< 1		
Females 13-49 years old	0.000592	< 1	0.000060	< 1		

6.0 Residential Exposure/Risk Pathway

(S. Wang, D353060, 22 Aug 2008)

6.1 Applicator Exposure

The proposed use of trifloxysulfuron-sodium on turf is restricted to commercial or professional applicators only (pers. comm. Fred Pearson, July 23, 2008). Hence, non-occupational or residential handler's exposure/risk assessment is not required.

6.2 Post-Application Exposure

Based on the SOPs for Residential Exposure Assessment and the uses specified in the proposed labels, the following residential post-application exposure scenarios are evaluated:

- Dermal Dose from pesticide residues on treated turf for homeowners and golfers,
- Oral Dose from hand-to-mouth activity from treated turf,
- Oral Dose from object-to-mouth activity from treated turf, and
- Oral Dose from soil ingestion activity from treated turf.

The exposure and risk estimates for these activities are presented in Table 6.2. All MOEs are greater than 100 and therefore reflect risk estimates that are below HED's level of concern. An aggregate MOE that combines dermal and oral exposures for toddlers has not been derived because of different toxicological effects via these routes (see Section 3.5.9).

Table 6.2. Post-Application Exposures to Trifloxysulfuron-sodium.				
Exposure Scenario	Application Rate (lb ai/A)	TTR_0 or SR_0 ($\mu g/cm^2$ or $\mu g/g$)	Exposure Estimate (mg/kg/day)	MOE[2]
Recreational				
Golfing	0.025	0.014	0.00014	360,000
Residential				
Dermal Exposure (Adults)	0.025	0.014	0.0020	25,000
Dermal Exposure (Toddlers)	0.025	0.014	0.0029	17,000
Hand to Mouth Activity (Toddlers)	0.025	0.014	0.00037	210,000
Object to Mouth Activity (Toddlers)	0.025	0.056	0.000093	850,000
Soil Ingestion (Toddlers)	0.025	0.1878	0.0000012	66,000,000
Aggregate Oral (Toddlers)			0.0004642	170,000

[1] From D353060 (S. Wang, 22 Aug 08)
[2] MOE = NOAEL (50 mg/kg/day, dermal or 79 mg/kg/day, oral) ÷ Exposure Estimate

6.3 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents living in close proximity to spraying operations. This situation is particularly the case with aerial application. However, to a lesser extent, spray drift resulting from the ground application of trifloxysulfuron-sodium could also be a potential source of exposure. The Agency has been working with the Spray Drift Task Force (a membership of U.S. pesticide registrants), EPA Regional Offices, State Lead Agencies for pesticide regulation, and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, and is developing a policy on how to apply appropriately the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast, and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift risks associated with pesticide application.

7.0 Aggregate Risk Assessments

In accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. 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. For trifloxysulfuron, there is the potential for dietary as well as residential/recreational exposure. Aggregate risk estimates for the various exposure durations are detailed below.

7.1 Acute Risk

For trifloxysulfuron, the only source of exposure appropriate for consideration in an acute aggregate assessment is dietary exposure; therefore, the acute aggregate risk estimates are

equivalent to the acute dietary risk estimates discussed in Section 5.2.3 and are below HED's level of concern for all population subgroups.

7.2 Short-Term Risk

Short-term exposures may result from recreational and residential activities on trifloxysulfuron-treated turf. In estimating short-term aggregate risk, HED has combined chronic dietary (food + drinking water, Table 5.3) exposure estimates with non-dietary oral exposures resulting from residential/recreational activities (Table 6.1). Due to different toxicological endpoints being used for assessing dermal and oral exposures, only oral routes of exposure are appropriate for combining in the aggregate risk estimates (see Section 3.5.9). The behavior resulting in residential oral exposures are only applicable to infants and young children; therefore, the recreational/residential component for older population subgroups is zero (Table 7.1) The resulting aggregate risk estimates are below HED's level of concern (i.e., MOEs are greater than 100) for all population subgroups.

Table 7.1. Short-Term Aggregate Exposure and Risk Estimates for Trifloxysulfuron.

Population Subgroup	Exposure Estimates, mg/kg/day			MOE[1]
	Chronic Dietary	Recreational/Residential	Total	
General U.S. Population	0.000074	Not applicable	0.000074	1,000,000
All Infants (< 1 year old)	0.000085	0.0004642	0.0005492	140,000
Children 1-2 years old	0.000196	0.0004642	0.0006602	110,000
Children 3-5 years old	0.000166	0.0004642	0.0006302	120,000
Children 6-12 years old	0.000107	Not applicable	0.000107	730,000
Youth 13-19 years old	0.000071	Not applicable	0.000071	1,100,000
Adults 20-49 years old	0.000058	Not applicable	0.000058	1,300,000
Adults 50+ years old	0.000059	Not applicable	0.000059	1,300,000
Females 13-49 years old	0.000060	Not applicable	0.000060	1,300,000

[1] MOE = NOAEL (79 mg/kg/day) ÷ Exposure Estimate

7.3 Intermediate-Term Risk

Based on the use sites and patterns for trifloxysulfuron, there are no non-dietary, residential exposure pathways that are considered to be appropriately evaluated by an intermediate-term aggregate assessment. A quantitative intermediate-term aggregate risk assessment has not been completed.

7.4 Chronic Risk

Based on the use sites and patterns for trifloxysulfuron, the only source of exposure appropriate for consideration in a chronic aggregate assessment is dietary exposure; therefore, the chronic aggregate risk estimates are equivalent to the chronic dietary risk estimates discussed in Section 5.2.3 and are below HED's level of concern for all population subgroups.

7.5 Cancer Risk

Trifloxysulfuron-sodium has been classified as "Not likely to be carcinogenic to humans." Therefore, cancer risk from exposure to trifloxysulfuron-sodium is not a concern.

8.0 Cumulative Risk

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 for trifloxysulfuron and any other substances, and trifloxysulfuron does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA assumed that trifloxysulfuron does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure

(S. Wang, D353060, 22 Aug 2008)

Based on the product use information, there is a potential for occupational exposure from handling (mixing/loading/applying) trifloxysulfuron-sodium for the proposed use. Both dermal and inhalation exposures are expected to be significant for these activities. There is also the potential for post-application occupational exposure from entering areas previously treated with trifloxysulfuron-sodium. Inhalation exposure is not expected to be significant based on the compound's low vapor pressure and dilution by outdoor air.

No chemical-specific data for assessing human exposures during pesticide handling activities were submitted to the Agency in support of the registration of trifloxysulfuron-sodium. Therefore, HED used surrogate data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 (8/98) to assess occupational exposure scenarios. Defaults established by the HED Science Advisory Council for Exposure (Exposure SAC) were used for acres or gallons treated per day and body weight. All MOEs for the handlers are greater than 100 at the baseline level (130,000 ~ 610,000; Tables 9.1 and 9.2) and therefore, they do not exceed HED's level of concern.

The occupational post-application exposures/risks were calculated using activity-specific transfer coefficient (Tc) values from the HED Exposure SAC Policy Number 3.1. All post-application MOEs calculated on the day of application are greater than 100 (5,400~ 180,000; Table 9.3). The technical material has a Toxicity Category III or IV, and the 12-hour Restricted Entry Interval (REI) appearing on the proposed label is in compliance with the Worker Protection Standard (WPS).

Table 9.1. Non-Cancer Short-Term Risk for Trifloxysulfuron-Sodium Handlers.

Exposure Scenario (Scenario #)	Mitigation Level[a]	Dermal Unit Exposure[b] (mg/lb ai)	Inhalation Unit Exposure[c] (µg/lb ai)	Crop	Application Rate (lb ai/A)	Amount Treated[d] (A/day)	Daily Dermal Dose[e] (mg/kg/day)	Daily Inhalation Dose[f] (mg/kg/day)	Combined Daily Dose[g]	Total MOE[h]
Mixer/Loader										
Dry Flowables for Ground-boom application (1)	Baseline	0.066	0.77	Turfgrass	0.025	40	0.00033	0.000013	0.00034	150,000
Applicator										
Sprays with Ground-boom (2)	Baseline	0.014	0.74	Turfgrass	0.025	40	0.00007	0.000012	0.000082	610,000
Mixer/Loader/Applicator										
Sprays with Back Pack Sprayer (3)	Baseline	2.5	30	Turfgrass	0.0004 lb ai/gal soln	40 gallons	0.0002	0.000008	0.00021	240,000

a Baseline consists of long-sleeve shirt, long pants, shoes, and socks and no respirator. PPE consists of long-sleeve shirt, long pants, shoes, socks, chemical-resistant gloves, and no respirator.
b Baseline Dermal Unit Exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, and open cab tractors, as appropriate.
c Baseline Inhalation Exposure represents no respiratory protection, open mixing/loading, and open cab tractors, as appropriate.
d Daily acres treated values are from EPA estimates of acreage that could be treated or volume handled in a single day for each exposure scenario of concern, based on the application method and formulation/packaging type.
e Daily dermal dose (mg/kg/d) = [unit dermal exposure (mg/lb ai) * application rate (lb ai/acre) * daily acres treated* dermal absorption rate (30%)] / body weight (60 kg).
f Daily inhalation dose (mg/kg/d) = [unit exposure (µg/lb ai) * (1mg/1000 µg) conversion * application rate (lb ai/acre) * daily acres treated] / body weight (60 kg).
g Combined daily dose = daily dermal dose + daily inhalation dose.
h Total MOE = NOAEL (50 mg/kg/d) / combined daily dose. UF = 100.

Table 9.2. Non-Cancer Intermediate-Term Risk for Trifloxysulfuron-Sodium Handlers.										
Exposure Scenario (Scenario #)	Mitigation Level[a]	Dermal Unit Exposure[b] (mg/lb ai)	Inhalation Unit Exposure[c] (µg/lb ai)	Crop	Application Rate (lb ai/A)	Amount Treated[d] (A/day)	Daily Dermal Dose[e] (mg/kg/day)	Daily Inhalation Dose[f] (mg/kg/day)	Combined Daily Dose[g]	Total MOE[h]
Mixer/Loader										
Dry Flowables for Ground-boom application (1)	Baseline	0.066	0.77	Turfgrass	0.025	40	0.00033	0.000013	0.00034	130,000
Applicator										
Sprays with Ground-boom (2)	Baseline	0.014	0.74	Turfgrass	0.025	40	0.00007	0.000012	0.000082	550,000
Mixer/Loader/Applicator										
Sprays with Back Pack Sprayer (3)	Baseline	2.5	30	Turfgrass	0.0004 lb ai/gal soln	40 gallons	0.0002	0.000008	0.00021	220,000

a Baseline consists of long-sleeve shirt, long pants, shoes, and socks and no respirator. PPE consists of long-sleeve shirt, long pants, shoes, socks, chemical-resistant gloves, and no respirator.
b Baseline Dermal Unit Exposure represents long pants, long sleeved shirt, no gloves, open mixing/loading, and open cab tractors, as appropriate.
c Baseline Inhalation Exposure represents no respiratory protection, open mixing/loading, and open cab tractors, as appropriate.
d Daily acres treated values are from EPA estimates of acreage that could be treated or volume handled in a single day for each exposure scenario of concern, based on the application method and formulation/packaging type.
e Daily dermal dose (mg/kg/d) = [unit dermal exposure (mg/lb ai) * application rate (lb ai/acre) * daily acres treated * dermal absorption rate (30%)] / body weight (60 kg).
f Daily inhalation dose (mg/kg/d) = [unit exposure (µg/lb ai) * (1mg/1000 µg) conversion * application rate (lb ai/acre) * daily acres treated] / body weight (60 kg).
g Combined daily dose = daily dermal dose + daily inhalation dose.
h Total MOE = NOAEL (45.3 mg/kg/d) / combined daily dose. UF = 100.

Table 9.3. Post-application Exposure and Risk for Trifloxysulfuron-Sodium Workers.

Crop	Application Rate (lb ai/A)	Work Activity	Transfer Coefficients[a] (cm^2/hr)	Post-application Day[b]	DFR[c] ($\mu g/cm^2$)	Daily Dose[d] (mg/kg/day)	MOE [e]
Turfgrass	0.025	Mowing	500	0	0.014	0.00028	180,000
		Transplanting, hand weeding	16,500	0	0.014	0.0093	5,400

a Transfer coefficient from Science Advisory Council for Exposure: Policy Memo #003 "Agricultural Transfer Coefficients," May 7, 1998.
b Day after treatment represents approximately 12 hours following application when sprays have dried.
c DFR = Application Rate (lb ai/acre) x Fraction of active ingredient that remains on the foliage when sprays have dried (0.05) x 4.54E8 µg/lb x 24.7E-9 acre/cm^2.
d Daily dose = DFR (µg/cm^2) x TC (cm^2/hr) x conversion factor (1 mg/1,000 µg) x exposure time (8 hrs/day) x dermal absorption (0.3) / body weight (60 kg).
e MOE = NOAEL (50 mg/kg/day) / daily dose (mg/kg/day).

10.0 Data Needs and Label Requirements

10.1 Toxicology

OPPTS 870.7800 – Immunotoxicity. As part of the revised 40 CFR Part 158, this study is required for registration of a pesticide. HED recommends that submission of an acceptable immunotoxicity study be made a conditions of the requested registration.

10.2 Residue Chemistry

None.

10.3 Occupational and Residential Exposure

None.

Table 10.1. Tolerance Summary for Trifloxysulfuron-sodium

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments (correct commodity definition)
There are no tolerances associated with this action			

Appendix I – Toxicity Profile Tables for Trifloxysulfuron-sodium.

Table I.1. Acute Toxicity Profile - Trifloxysulfuron-sodium

Test Material	GDLN	Study Type	MRID	Results	Tox Category
Technical	870.1100	Acute Oral - rat	45371922	LD_{50} > 5000 mg/kg	IV
Technical	870.1100	Acute Oral - mouse	45371923	LD_{50} > 5000 mg/kg	IV
Technical	870.1200	Acute Dermal - rat	45371925	LD_{50} > 2000 mg/kg	III
Technical	870.1300	Acute Inhalation	45371927	LC_{50} (M & F): > 5.03 mg/L	IV
Technical	870.2400	Primary Eye Irritation	45371929	Moderate irritation to the eye	III
Technical	870.2500	Primary Dermal Irritation	45371931	Mild irritation to the skin	IV
Technical	870.2600	Dermal Sensitization (Buehler)	45371933	Negative	N/A
Technical	870.2600	Dermal Sensitization (Maximization)	45371934	Negative	N/A

Table I.2. Toxicity Profile of Trifloxysulfuron-sodium Technical Grade Active Ingredient.

Guideline No.	Study Type	Results
870.3100	90-Day oral toxicity rodents (rats)	**NOAEL**: 507/549 mg/kg/day (M/F) **LOAEL**: 1052/1128 mg/kg/day (M/F): M = decreased body weight, decreased body weight gain, equivocal increased testicular atrophy at end of recovery phase; F = decreased body weight, decreased body weight gain, equivocal slightly increased histopathology in liver (single cell necrosis, focal necrosis, inflammation, hepatocellular hypertrophy).
870.3100	90-Day oral toxicity rodents (mice)	**NOAEL**: 1023/1507 mg/kg/day (M/F) **LOAEL**: >1023/>1507 mg/kg/day (M/F): M = not attained; F = not attained
870.3150	90-Day oral toxicity in nonrodents (dogs)	**NOAEL**:19.8/19.6 mg/kg/day (M/F) **LOAEL**: 164.2/167.3 mg/kg/day (M/F): M = decreased body weight gain (20%), slight hematological effects, clinical chemistry changes suggesting hepatotoxicity, decreased thymus weight, thymic atrophy, increased glycogen in liver, hemorrhage in mesenteric lymph nodes; F = decreased body weight gain (44%), anemia with extramedullary hematopoiesis in liver/spleen and myeloid hyperplasia in bone marrow, clinical chemistry changes suggesting hepatotoxicity, decrease thymus weight, thymic atrophy and hyaline tubular change in kidney.
870.3200	21/28-Day dermal toxicity (rats)	**NOAEL**: 1000/100 mg/kg/day (M/F) **LOAEL**: >1000/1000 mg/kg/day(M/F): M = not attained; F = decreased body weight gain. No dermal irritation M/F.
870.3700	Prenatal developmental in rodents (rats)	**Maternal NOAEL**: 300 mg/kg/day **Maternal LOAEL**: 1000 mg/kg/day based on decreased food consumption during treatment, decreased body weight gain during post-treatment. **Developmental NOAEL**: 300 mg/kg/day **Developmental LOAEL**: 1000 mg/kg/day based on slight decrease in fetal weight, increased skeletal anomalies, increased poor/absent skeletal ossification.
870.3700	Prenatal developmental in nonrodents (rabbit)	**Maternal NOAEL**: 100 mg/kg/day **Maternal LOAEL**: 250 mg/kg/day based on increased mortality, increased vaginal/anal bleeding. **Developmental NOAEL**: 50 mg/kg/day

Table I.2. Toxicity Profile of Trifloxysulfuron-sodium Technical Grade Active Ingredient.		
Guideline No.	Study Type	Results
		Developmental LOAEL: 100 mg/kg/day based on abnormally shaped heart (one fetus at 100 mg/kg/day and 3 fetuses from 2 litters at 250 mg/kg/day).
870.3800	Reproduction and fertility effects (rat)	**Parental systemic NOAEL**:78.8/83.5 mg/kg/day (M/F) **Parental systemic LOAEL**:631/676 mg/kg/day (M/F) based on decreased body weight and gain as well as decreased food consumption. **Offspring systemic NOAEL**:78.8/83.5 mg/kg/day (M/F) **Offspring systemic LOAEL**: 631/676 mg/kg/day (M/F):decreased pup weight and weight gain, decreased spleen weight, thymus weight and increased vaginal patency. **Reproductive NOAEL**:968/1030 mg/kg/day (M/F) **Reproductive LOAEL**:>968/1030 (M/F)
870.4100a	Chronic toxicity rodents (rat)	See 870.4300
870.4100	Chronic toxicity dogs	**NOAEL**: 51.1/45.3 mg/kg/day (M/F) **LOAEL**: 123/121 mg/kg/day (M/F): M = gray-white foci in lungs, fibrous thickening of lung pleura, equivocal decreased body weight gain; F = equivocal increased incidence and severity of chronic urinary bladder inflammation.
870.4200	Carcinogenicity rats	See 870.4300
870.4200	Carcinogenicity mice	**NOAEL**:854/112 mg/kg/day (M/F) **LOAEL**:>854/818 mg/kg/day (M/F): M = not determined; F = decreased body weight, body weight gain and food consumption. Negative for carcinogenicity in M and F.
870.4300	Chronic feeding/Carcinogenicity rats	**NOAEL**: 82.6/23.7 mg/kg/day (M/F) **LOAEL**: 429/99.3 mg/kg/day (M/F): M = decreased body weight and gains, decreased food consumption and increased Leydig cell hyperplasia in testes; F = increased tubular atrophy in kidneys. At 500 mg/kg/day decreased body weight, body weight gain, food consumption and increased tubular atrophy in kidneys. Negative for carcinogenicity in M and F.
870.5100	Gene Mutation bacterial reverse mutation assay (S. typhimurium/E. coli)	Negative without and with S-9 activation.
870.5300	In vitro mammalian cell forward gene mutation assay (CHO cells/HGPRT locus)	Negative without and with S-9 activation.
870.5375	In vitro mammalian cytogenetics assay in CHO cells	Negative without and with S-9 activation.
870.5395	Cytogenetics - mammalian erythrocyte micronucleus test in the mouse	Negative at single oral doses up to 5000 mg/kg.
870.5500	In vitro unscheduled DNA synthesis (primary rat hepatocytes)	Negative response up to 250 µg/mL. Cytotoxicity at ≥15.63 µg/mL.
870.6200	Acute neurotoxicity screening battery (rat)	**NOAEL**:<2000 mg/kg/day (M/F) **LOAEL**: 2000 mg/kg/day (M/F): M&F = decreased motor activity on day 1, histopathological lesions in nervous system tissues.
870.6200	Acute neurotoxicity	**NOAEL**: 2000/600 mg/kg/day (M/F)

Table I.2. Toxicity Profile of Trifloxysulfuron-sodium Technical Grade Active Ingredient.		
Guideline No.	Study Type	Results
	screening battery (rat)	**LOAEL**: > 2000/2000 mg/kg/day (M/F): M = not attained; F = decreased motor activity on day 1
870.6200	Subchronic neurotoxicity screening battery (rat)	**NOAEL**:112/553 mg/kg/day (M/F) **LOAEL**:472/1128 mg/kg/day (M/F): M = decreased body weight, body weight gain and food consumption.; F = decreased body weight.
870.6300	Developmental neurotoxicity (rat)	No study performed.
870.7485	Metabolism and pharmacokinetics (rat)	Rapidly absorbed and exceted. Most (>87%) of the administered dose (AD) was excreted within 24 hours. After 7 days, very little (≤0.3% of AD) remained in the tissues. Urine was the primary route of excretion in males (50-61% of AD) and in females (70-80% of AD). Unchanged parent in males (11-20% of AD) and in females (37-47% of AD) was excreted almost entirely in the urine and only trace amounts were found in the feces. With the exception of the parent, the metabolite profile was similar between the urine and feces. The 2 primary metabolites in both urine and feces were Metabolite J (desmethyl parent, up to 26% of AD) and Metabolite K (5'hydroxy-pyrimidine of parent, up to 19% of AD). Other metabolites were Metabolites X, N, F, A and D, each up to 8.2% of the AD in males and up to 4.7% of the AD in females. Several minor metabolites were also identified as Metabolite Q, Metabolite P, guanidine, CGA-382997 and CGA-368732 (each ≤4.4% of the AD).
870.7485	Biliary Metabolism (rat)	In bile duct cannulated rats, absorption was 84-88% of the Administered Dose (AD) at 48 hours. Nearly all of the AD was excreted within 48 hours. Excretion in urine ranged from 58-76%, in bile from 5-27%, and in feces was about 6% of the AD. There was no evidence for an enterohepatic circulation. Biotransformation was similar to that in the conventional rat metabolism study. The metabolite profiles in urine, bile fluid and feces were all similar.
870.7600	Dermal Penetration (rat)	No study performed.

Appendix II – Rationale for Toxicology Data Requirements

Guideline Number: 870.7800 **Study Title: Immunotoxicity**
Rationale for Requiring the Data
The immunotoxicity study is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.
Practical Utility of the Data
How will the data be used? Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have these data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

Appendix III – International Residue Limits

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: N-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-3-(2,2,2-trifluoroethoxy)-2-pyridinesulfonamide, monosodium salt]	Common Name: Trifloxysulfuron-sodium	X Proposed tolerance ☐ Reevaluated tolerance ☐ Other	Date: 11/12/02

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above ☐ No Codex proposal step 6 or above for the crops requested	Petition Number: PP#1F06280 DP Barcode: D284480 Other Identifier:
Residue definition (step 8/CXL): N/A	Reviewer/Branch: M. Doherty/RAB2
	Residue definition: Trifloxysulfuron-sodium and metabolites converted to parent equivalents

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Almond Hulls	0.01
		Almond Nut Meat	0.01
		Citrus	0.01
		Cottonseed	0.05
		Cotton By-Products	1.0
		Sugarcane	0.01
		Tomatoes	0.01

Limits for Canada	Limits for Mexico
X No Limits ☐ No Limits for the crops requested	X No Limits ☐ No Limits for the crops requested
Residue definition: N/A	Residue definition: N/A

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)

Notes/Special Instructions: S.Funk, 11/11/08.

13544

R163908

Chemical Name: 2-Pyridinesulfonamide, N-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-3-(2,2,2-trifluoroethoxy)-, monosodium salt, monohydrate

PC Code: 119009
HED File Code: 14000 Risk Reviews
Memo Date: 11/12/2008
File ID: 00000000
Accession #: 000-00-0127

HED Records Reference Center
11/21/2008