**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 11/APR/2007

**MEMORANDUM**

SUBJECT: Trifloxystrobin: Human Health Risk Assessment for Section 3 Registration for the Proposed Uses on Grasses Grown for Seed. PC Code: 129112, Petition No: 6F7024, DP Num: 325826.

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ARIA/RIMUER Branch of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. RD of OPP has requested that ARIA evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result the from proposed use on grasses grown for seed in conjunction with the currently registered uses of the active ingredient trifloxystrobin.

Bayer CropScience has submitted a petition (PP#6F7024) to establish a new use for trifloxystrobin on grasses grown for seed as a broad-spectrum fungicide. The petitioner has requested tolerances on grass, forage and grass, hay. . In this document, ARIA has conducted an assessment of the human exposure and health risks resulting from this proposed use and all currently registered uses. The overall risk assessment, residue chemistry data review, and dietary risk assessment were provided by Debra Rate (ARIA). The non-dietary exposure/risk assessment was provided by Mark Dow (ARIA).

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## 1.0 Executive Summary

**Use Profile:**

***Background***

This document is an ARIA assessment to support a Section 3 request (PP#: 6F7024) for the establishment of a permanent trifloxystrobin tolerance in/on grasses grown for seed from its use as a broad-spectrum fungicide (i.e., 40 CFR §180.555). HED recently assessed the human exposure and health risks resulting from the use on specialty legume vegetables for a Section 18 registration (DP Num: 317330, B. O'Keefe, 16/AUG/2006). Also, other previous Section 3 petitions have resulted in the establishment of tolerances on crops including almonds, barley, carrots, celery, citrus, corn seed, field corn, hops, fruiting vegetables, oats, pecans, potatoes, rice, stone fruits, sweet corn, sugar beets, and wheat. The formulated end use products are labeled under the registered trade names Flint® Fungicide (EPA Reg. No. 264-777) and Absolute® 500 SC Fungicide (EPA Reg. No. 264-849).

No new hazard data have been submitted since the issuance of the last aggregate risk assessment. For full details on the hazard assessment and residential exposure assessment, see the following previous risk assessments: 1) HED Risk Assessment: Trifloxystrobin: HED Exposure/Risk Assessment to Support a Section 18 Request (05-FL-10 & 05-TN-10) for New Uses in/on Specialty Legume Vegetables. (DP Num: 317330, B. O'Keefe, 16/AUG/2006) and 2) HED Risk Assessment: Human Health Risk Assessment for Trifloxystrobin for New Section 3 Use on Soybeans (DP Num: 318618, B. O'Keefe, 07/AUG/2006). This document includes revised dietary (food and drinking water), occupational (handler and post-application), and aggregate assessments as they pertain to the requested new use.

***Proposed Uses***

Trifloxystrobin is a broad spectrum fungicide proposed in this Section 3 request specifically for use on grasses grown for seed. Trifloxystrobin is classified as an oximinoacetate fungicide in the strobilurin class. It acts by interfering with respiration in plant pathogenic fungi and is a potent inhibitor of spore germination and mycelial growth. It provides protective properties against a variety of pathogens in a variety of crops.

The trifloxystrobin product applied in the submitted magnitude of the residues in/on grass grown for seed study was Flint®, a water dispersible granule (WDG) formulation containing the active ingredient (ai) trifloxystrobin (50% ai). Trifloxystrobin is to be applied as a broadcast foliar spray by ground or aerial equipment. The proposed use pattern on grasses grown for seed allows for up to a maximum seasonal rate of 0.250 lb ai/A. There is a retreatment interval (RTI) of 21 days for this use. The petitioner is also seeking a registration for the use of Absolute® 500 SC, a suspension concentrate (FIC) and a multiple active ingredient (MAI) product, which contains 2.08 lb ai/gal of trifloxystrobin and 2.08 lb ai/gal of tebuconazole. The proposed use pattern of the Absolute® 500 on grasses grown for seed allows for up to the seasonal rate of 0.52 lb ai/A with a preharvest interval (PHI) of 4 days.

***Toxicity/Hazard***

The toxicological database is adequate for the purposes of risk assessment. HED and ARIA have a high degree of confidence in the toxicology database. Trifloxystrobin is of mild acute toxicity by oral, dermal, or inhalation routes of exposure, however it is a strong dermal sensitizer. Trifloxystrobin is a mild ocular and dermal irritant. The toxicology database is complete and there are no data gaps. For more information about the toxicology of trifloxystrobin, please see the HED's Hazard Identification Assessment Review Committee (HIARC) report (TXR # 0050612, S. Dapson, 01/APR/2002).

HIARC met on March 7, 2002 to re-evaluate the toxicology database for trifloxystrobin (HIARC Trifloxystrobin #3, S. Dapson, 01/APR/2002). The endpoint selected for acute dietary risk assessment was based on increased incidence of fused sternebrae #3 and #4 in fetuses observed in a developmental toxicity study in rabbits. The acute reference dose (RfD) or population-adjusted dose (PAD) is only to be used for females of childbearing age. No acute dietary endpoint was identified for the general population or other population subgroups. The endpoint for chronic dietary risk assessment was based on decreases in body weight, body weight gains, reduced food consumption, and histopathological lesions in the liver, kidneys and spleen of parental animals in a multi-generation reproduction study in rats. A chronic dog study in which increased incidence of clinical signs, increased mean liver weight and hepatocellular hypertrophy were observed is considered co-critical. The cPAD is applicable to all population subgroups.

Short- and intermediate-term dermal toxicity endpoints were based on increases in mean absolute and relative liver and kidney weights observed in a 28-day dermal toxicity study in rats. No long-term dermal exposure is expected based on the use pattern. Because a dermal toxicity study was used to determine the dermal endpoints, no dermal absorption adjustment is necessary. The endpoint chosen for assessment of short- and intermediate-term incidental oral risks (residential) is based on decreased pup body weights during lactation observed in a multi- generation reproductive toxicity study (the same study was chosen for the chronic dietary risk endpoint). The short-, intermediate- and long-term inhalation endpoints were based on reduced body weights, body weight gains, food consumption and food efficiency observed in parental animals in a multi-generation reproduction study in rats.

The toxicological database indicates that technical grade trifloxystrobin has moderate acute toxicity, falling into Toxicity Category 3 or 4 for all exposure routes. However, trifloxystrobin is a strong dermal sensitizer. Subchronic and chronic toxicity studies demonstrated that the target organs of trifloxystrobin are the liver, kidneys and spleen. Developmental effects were observed in developmental studies (fused sternebrae #3 and #4 observed in the rabbit), but only in the presence of maternal toxicity at the same lowest observable adverse effects level (LOAEL).

The cancer classification of trifloxystrobin was made by an *ad hoc* subcommittee of the Cancer Assessment Review Committee on May 27, 1999. The Committee determined that trifloxystrobin should be classified as a "Not Likely Human Carcinogen," based on the lack of evidence for carcinogenicity in rats and mice.

The trifloxystrobin toxicology database has been evaluated according to 2002 FQPA policies. The FQPA SF was reduced to 1x based on toxicological considerations by the FQPA Safety Factor Committee (HED Doc. No. 013545, B. Tarplee, 01/JUL/1999), the conservative residue assumptions used in the dietary and residential exposure risk assessments, and the completeness of the residue chemistry and environmental fate databases (DP Num: 317330, B. O'Keefe, 16/AUG/2006).

***Residue Chemistry***

In petition PP#6F7024, Bayer Crop Science is proposing the use of the 0.125 lb ai/A of trifloxystrobin (50% WDG) for broadcast foliar applications to grasses grown for seed at 21 day RTIs, for a maximum of 0.250 lb ai/A per season (0.280 kg ai/ha/season). The petitioner also requests the use of 0.125 lb ai/A of trifloxystrobin (2.08 lb/gal F1C) for broadcast foliar applications to grasses grown for seed at 21 day RTIs, for a maximum of 0.520 lb ai/A per season.

The qualitative nature of the residue in plants and animals is understood based on adequate metabolism studies conducted on apples, cucumbers, peanuts, sugar beets, wheat, goats, and laying hens. The HED Metabolism Assessment Review Committee (MARC) concluded that both trifloxystrobin and its free acid metabolite, CGA-321113, are of concern for both regulatory and risk assessment purposes in both plant and animal commodities. The MARC also determined that for animal commodities, the metabolite L7a (taurine conjugate of trifloxystrobin) in liver should be included in the risk assessment.

An adequate gas chromatography with nitrogen phosphorus detector (GC/NPD) method, Method AG-659A, is available for enforcing tolerances for the combined residues of trifloxystrobin and CGA-321113 in plant commodities. This method was used for analysis of samples from the grasses grown for seed field trial, and was adequately validated in conjunction with these analyses. The validated limit of quantitation (LOQ) is 0.01 ppm for each analyte (trifloxystrobin and CGA 321113) in grass forage, hay, and straw and 0.02 ppm for each analyte in seed screenings. Method AG 659A, modified to utilize liquid chromatography with mass spectroscopy/mass spectroscopy (LC/MS/MS), was also used for the analysis of trifloxystrobin and the acid metabolite CGA 321113 in oats and barley matrices.

The submitted grasses grown for seed field trial data are an adequate number in the appropriate regions for a regional registration (i.e. Northwest U.S.). Samples of grass forage, hay, straw and seed screenings were collected at the proposed PHI. Samples were analyzed using an adequate analytical method and the sample storage intervals are supported by the available storage stability data. Combined residues of trifloxystrobin and CGA-321113 (in parent equivalents) were <14 ppm in/on grass forage, hay, and straw, and <18 ppm in/on grass seed screenings.

The proposed use on grasses grown for seed will have no impact on the established tolerances of livestock commodities. However, new policies and changes to commodity tables require that a

new dietary burden be established which includes the proposed use and all previously established uses. The new methods for establishing a reasonable diet lowers the dietary burden of cattle (beef and dairy), poultry, and swine. Therefore, the established tolerances on livestock commodities are adequate for the proposed new use on grasses grown for seed. The dietary analysis presented in this memorandum utilizes tolerance level residues for all commodities [40 CFR §180.555], except for the residues of fat and meat byproducts of cattle, goats, horses, and sheep at 0.1 ppm and for residues of liver which are estimated to be 0.3 ppm in the dietary exposure analysis based on the combined residues of trifloxystrobin and CGA-321113 and Metabolite L7a.

The submitted studies support the calculated maximum residue limit (MRL) tolerances of trifloxystrobin (trifloxystrobin and CGA-321113) on grass, hay at 17 ppm and grass, forage at 12 ppm.

***Dietary Exposure (food/water)***
The Environmental Fate and Effects Division (EFED) determined estimated environmental drinking water concentrations (EDWCs) of trifloxystrobin in surface and ground water. The highest surface water EDWCs for acute exposure (92 ppb) and chronic exposure (140 ppb) were used in the dietary analyses. These estimates of residues in drinking water were incorporated directly into the DEEM-FCID model of the dietary risk assessment; i.e., into the food categories "water, direct, all sources" and "water, indirect, all sources."

The acute dietary exposure analysis for trifloxystrobin assumes 100% crop treated (CT) and tolerance level residues for each commodity. The acute dietary endpoint is applicable only to the population subgroup females 13-49 years old. An acute dietary endpoint for the general population including infants and children was not identified. The estimated dietary exposure (food and drinking water) for females 13-49 years old occupies less than 1% of the aPAD and does not exceed ARIA's level of concern.

Similarly, the chronic dietary exposure analysis for trifloxystrobin assumes 100% CT and tolerance level residues. The chronic dietary endpoint applies to all population subgroups including infants and children. The estimated dietary exposure (food and water) from trifloxystrobin does not exceed ARIA's level of concern for any population subgroup. Food and water exposure occupies <26% of the cPAD for the US population and the subgroup with the highest exposure, children 1-2 years old, occupies <81% of the cPAD. Therefore, these cPADs do not exceed ARIA's level of concern (LOC).

***Residential Risk***
The existing residential uses of trifloxystrobin include turfgrass/ornamental disease control (Compass™). Because the FQPA requires consideration of aggregate exposure to all likely non-occupational uses, this assessment uses residential post-application contact with trifloxystrobin following Compass™ use on turfgrass as the most common and worst case contributor to such exposures. In a previous HED risk assessment (DP Num: 317330, B. O'Keefe, 16/AUG/2006),

the margins of exposure (MOEs) for applicable residential scenarios, i.e., post-application dermal (adult and toddler) and incidental oral (toddlers only) exposures from pesticide residues on lawns were calculated. Additionally, risk estimates from separate incidental oral exposures to toddlers were combined.

Risk from short-term incidental ingestion by toddlers is assessed by comparing these exposures to the 3.8 mg/kg/day no observable adverse effects level (NOAEL) identified from a two-generation reproduction study in rats (endpoint: decreases in pup body weight during lactation). Dermal exposures were compared to the NOAEL of 100 mg/kg/day from a 28-day dermal toxicity study in rats (endpoint: increases in mean absolute and relative liver and kidney weights).

The HED Standard Operating Procedures for Residential Exposure Assessments (Draft, December 18, 1997) were used as a guideline for performing the residential post-application assessment. Dermal risks were calculated for adults and children, while risks from incidental oral exposure were also calculated for children. Because the endpoints identified for dermal and incidental oral risks are based on different endpoints, exposures from these routes are not added together. The MOEs for dermal risk from post-application exposure are 1,300 for adults and 760 for children. The MOEs for children's risk from oral exposures range from 750 to 220,000. When incidental oral exposure from all possible residential sources are combined (ingestion of residues on turfgrass from hand-to-mouth activities, mouthing turfgrass and eating soil), the result is an MOE of 590. Therefore, all calculated residential post-application MOEs are greater than 100 on the day of application, and therefore do not exceed ARIA's level of concern.

***Aggregate Risk***

Acute, short-term, and chronic aggregate risk estimates resulting from aggregate exposure to trifloxystrobin in food and drinking water, and residential settings are below ARIA's level of concern. Intermediate-term exposure (1 to 6 months) to the parent trifloxystrobin is not expected to occur in residential settings due to its short half-life (about two days based on soil and aquatic metabolism studies). Therefore, an intermediate-term aggregate risk assessment was not performed.

For the acute aggregate risk scenario, food and drinking water exposures were taken into account in the dietary exposure assessment. The estimated dietary exposure (food and water) for females 13-49 years old occupies less than 1% of the aPAD. Therefore, acute aggregate risk is below ARIA's level of concern.

For the short-term (1 to 30 days) aggregate risk scenarios, food, drinking water and residential exposures are taken into account. Residential exposure for dermal and oral routes must be assessed separately, since dermal and oral endpoints were different and cannot be combined. The resulting MOEs for all short-term aggregate scenarios for adults and children are above 100, and therefore, do not exceed ARIA's level of concern.

For the chronic aggregate risk scenario, food, drinking water, and residential exposures were taken into account. In this case, chronic exposure in residential settings is not expected and the aggregate chronic assessment included food and drinking water only. Since the dietary exposure assessment already includes the highest chronic exposure from the drinking water modeling data, no further calculations are necessary. The general U.S. population and all population subgroups have exposure and risk estimates which are below ARIA's level of concern (i.e., the percentages of the chronic population adjusted doses (cPADs) are all below 100%). The aggregate chronic exposure to the U.S. population was <26% of the cPAD and the most highly exposed subgroup, children 1-2 years old, was at <81% of the cPAD. Therefore, chronic aggregate risk is below ARIA's level of concern.

***Occupational Exposure and Risk***

There is a potential for exposure to trifloxystrobin during mixing, loading, and application activities. Based on the proposed use pattern, ARIA believes the most highly exposed occupational pesticide handlers would be 1) mixer/loaders using open pour loading of water dispersible granules; 2) mixer/loaders using open-pour loading of liquids; 3) applicators using open-cab ground-boom spray equipment and 4) aerial applicators. Since the treatment blocks (i.e., areas treated) are relatively small compared to typical field crops such as cotton, corn, soybeans or wheat, ARIA believes pesticide handlers will be exposed to short-term duration (1 - 30 days) exposures but not to intermediate-term (1 - 6 months) duration exposures. Although multiple applications are possible, they are separated by 21 day RTIs. Therefore, it is unlikely that pesticide handlers would be exposed continuously for 30 days or more. Chronic exposures are not expected for handlers. Daily dermal and inhalation exposures were calculated separately.

All handler MOEs for short-term exposures are above the level of concern (LOC) MOE (100) with baseline personal protective equipment (PPE) (long-sleeved shirt, long pants, shoes and socks) and no protective gloves as well as baseline PPE and the use of protective gloves, except for mixer/loaders without protective gloves using open-pour loading of liquids in support of aerial operations. The lowest acceptable MOE is 5,100 for mixer/loaders for open-cab airblast applications. Because all MOEs, except for the one mentioned above, are above 100, these MOEs do not exceed ARIA's level of concern.

Because there are no transfer coefficient (TC) ($cm^2$/hr) data specific to the requested crops, ARIA is using a TC of 1,500 $cm^2$/hr, taken from small grains, as a screening level assessment to conservatively estimate post-application agricultural worker exposure. Also lacking compound specific dislodgeable foliar residue (DFR) data, ARIA will assume 20% of the application rate is available as DFR on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (07/MAY/1998 – Revised 07/AUG/2000). When calculations are made, the MOE associated with post-application agricultural worker exposure is 2,100 (DP Num: 333762, M. Dow, 08/NOV/2006). A MOE of 100 is adequate to protect agricultural workers from post-application exposures. Since the estimated MOE is >100, the proposed use does not exceed ARIA's level of concern.

The label for Flint® has a 12-hour restricted entry interval (REI). Technical-grade trifloxystrobin has a Toxicity Category III for Primary Eye Irritation (other Toxicity Categories are IV). Per the Worker Protection Standard (WPS), a 12-hr REI is required for chemicals classified under Toxicity Category III. Therefore, the REI of 12 hours appearing on the Flint® label is in compliance with the WPS. However, it is important to note that trifloxystrobin was found to be a strong dermal sensitizer. This warrants a requirement for gloves for mixers/loaders (even though trifloxystrobin is in Category IV for dermal toxicity). Also, double notification (i.e., verbal warnings as well as signs posted around treated fields) for post-application workers is recommended.

***Environment Justice***
Potential areas of environmental justice concern, 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," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

***Review of Human Research***
This risk assessment does not rely on any data from studies in which human subjects were intentionally exposed to a pesticide or other chemical.

***Additional Data Needs and Recommendations:***
The submitted studies support the recommended tolerances of trifloxystrobin (trifloxystrobin and CGA-321113) on grass, hay at 17 ppm and grass, forage at 12 ppm. Provided that the recommended Section B, label and Section F revisions are made, no residue chemistry deficiencies were noted in the subject petition (PP# 6F7024) that would preclude establishing permanent tolerances for trifloxystrobin on grass forage and hay.

1) The petitioner must submit a revised Section B and label to specify that the use on grasses grown for seed is a regional registration that includes only the Northwest U.S.

2) The Section F must be revised to change the proposed residues for grass, forage and grass, hay to match the recommended tolerances of 12 ppm and 17 ppm, respectively.

Provided the Section B (and label) and Section F are revised, ARIA recommends establishing permanent tolerances for the combined residues of trifloxystrobin and CGA-321113, expressed as parent, at 12 ppm in/on grass forage and 17 ppm in/on grass hay.

## 2.0 Ingredient Profile:

Trifloxystrobin is a broad spectrum fungicide for the control of a wide range of diseases in commercially important crops. Trifloxystrobin is classified as an oximinoacetate fungicide in the strobilurin class. It acts by interfering with respiration in plant pathogenic fungi and is a

potent inhibitor of spore germination and mycelial growth. It provides both curative and protective properties against a variety of pathogens in a variety of crops.

Trifloxystrobin belongs to the MAEs (β-methoxyacryl esters) class of fungicides, which are synthetic analogs of strobilurin A ((Fungicide Resistance Action Committee (FRAC) Group 11). In the U.S., trifloxystrobin is registered to Bayer CropScience and is marketed under the trade names FLINT®, GEM®, and STRATEGO®. For uses on food/feed crops, trifloxystrobin is formulated as a 50% WDG, a 4.17 lb/gal suspension concentrate (FlC), and a 1.04 lb/gal emulsifiable concentrate (EC). For use on grasses, a MAI FlC formulation is also being proposed which contains both trifloxystrobin and tebuconazole, each at 2.08 lb/gal. Bayer has submitted a petition (PP# 6F7024) proposing the use of the 50% WDG and the 2.08 lb/gal FlC on grass grown for seed.

## 2.1 Summary of Proposed Uses:

**Table 2.1. Summary of Directions for use for Trifloxystrobin on Grasses Grown for Seed.**

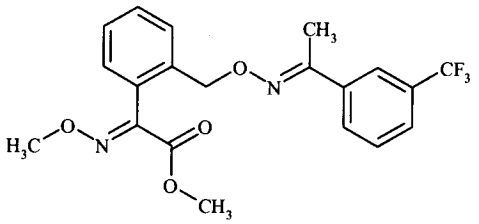
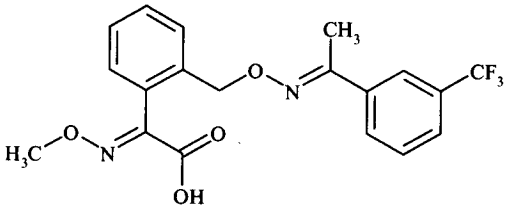
| Application Timing, Type and Equipment [1] | Formulation [EPA Reg. No.] | Single rate (lb ai/A) | Max. number of Appl. per Season | Max. Seasonal Application Rate (lb ai/A) | PHI (Days) | Use Directions and Limitations [2] |
|---|---|---|---|---|---|---|
| Broadcast foliar applications beginning at the first sighns of disease. Ground and aerial equipment | Flint® Fungicide 50 % WDG [264-777] | 0.125 | Not specified | 0.25 (8 oz product) | 0 | Minimum RTI is 21 days. Apply in a minimum of 5 and 10 gal/A for aerial and ground applications, respectively. |
| Broadcast foliar applications beginning at the first sighns of disease. Ground and aerial equipment | Absolute® 500 2.08 lb ai/gal FIC [264-849] | 0.125 | Not specified | 0.52 (32 oz product) | 4 | Minimum RTI is 21 days. Apply in a minimum of 10 and 20 gal/A for aerial and ground applications, respectively. Do not forage or cut green crop for feed purposes; however, after harvest of seed, the regrowth may be grazed 17 days following the last application. [4] Methylated seed oil or equivalent oil based product may be used as a spray adjuvant. |

[1] Ground applications of the 50% WDG can be made through the following types of irrigation equipment: hand move, solid set, wheel lines, and center pivot. However, the label for the 2.08 lb ai/gal FIC prohibits applications through irrigation equipment.
[2] The label for the 50% WDG specifies a plant-back interval (PBI) of 30 days for rotational crops with no primary uses, and the label for the 2.08 lb ai/gal FIC specifies a PBI of 120 days due to tebuconazole.
[3] This MAI formulation also includes tebuconazole at 2.08 lb ai/gal.
[4] The more restrictive feeding and grazing restrictions listed on the label for the 2.08 lb ai/gal FIC are based on tebuconazole residue data and reflect the current use directions for grasses grown for seeds listed on the label for a 3.6 lb ai/gal FIC formulation containing only tebuconazole (EPA Reg. No. 264-752).

***Conclusions:*** The petitioner must submit a revised Section B and label restricting the use of Flint® and Absolute® 500 on grasses grown for seed to the Northwest U.S.

## 2.2 Structure and Nomenclature:

**Table 2.2. Nomenclature of Trifloxystrobin and its Regulated Metabolite.**

| | |
|---|---|
| Compound |  |
| Common name | Trifloxystrobin |
| Company experimental names | BO17211 or CGA-279202 |
| Molecular weight | 408.4 |
| IUPAC name | Methoxyimino-{2-[1-(3-trifluoromethyl-phenyl)-ethylideneaminooxymethyl]-phenyl}-acetic acid methyl ester |
| CAS name | (E,E)-α-(methoxyimino)-2-[[[[1-[3-(trifluoromethyl)phenyl]ethylidene]amino]oxy] methyl]-benzeneacetic acid methyl ester |
| CAS # | 141517-21-7 |
| End-use products/EP | Flint® Fungicide (50% WDG, EPA Reg. No. 264-777)<br>Absolute 500 SC Fungicide (2.08 lb/gal FlC; EPA Reg. No. 264-849), which also contains 2.08 lb/gal of tebuconazole |
| Regulated Metabolite |  |
| Common Name | Trifloxystrobin acid |
| Company Code | CGA-321113 |
| Molecular weight | 394 |
| CAS name | (alpha,E)-alpha-(methoxyimino)-2-[[[[1-[3-(trifluoromethyl)phenyl]ethylidene]amino]oxy]methyl]-benzeneacetic acid |
| CAS # | 252913-85-2 |

## 2.3 Physical and Chemical Properties:

**Table 2.3. Physicochemical Properties of Trifloxystrobin.**

| Parameter | Value | | Reference |
|---|---|---|---|
| Melting point | 72.9°C | | D254920, A. Smith, 23/APR/1999 |
| pH | 7.7 at 25°C (1% w/w, aqueous dispersion) | | |
| Density | 1.36 g/cm3 at 21°C | | |
| Water solubility | 0.00061 g/L at 25°C | | |
| Solvent solubility (g/L at 25°C) | methanol 76<br>acetone >500 | dichloromethane >500<br>toluene 500 | |

| | | | |
|---|---|---|---|
| | ethyl acetate >500<br>n-hexane 11 | n-octanol 18 | |
| Vapor pressure (at 25°C) | $3.4 \times 10^{-6}$ Pa | | |
| Dissociation constant, pKa | None noted at pH 2-12 | | |
| Octanol/water partition coefficient, Log P(ow) | 4.5 at 25°C | | |
| UV/visible absorption | 250.7 nm | | |

## 3.0 HAZARD CHARACTERIZATION

A detailed hazard characterization is available in the following reference:

*TRIFLOXYSTROBIN- 3rd Report of the Hazard Identification Assessment Review Committee,* S. Dapson, HED Document: TXR # 0050612, 01/APR/2002.

All toxicological data requirements for trifloxystrobin technical have been satisfied, except for the study, Acute Neurotoxicity – Rat, which was submitted but determined to be not acceptable. However, the HIARC determined that, based on a weight-of-the-evidence review of the available data, a developmental neurotoxicity study with trifloxystrobin in rats was not required. ARIA and HED have a high degree of confidence in the toxicology database. Acute data requirements for all end-use products have been satisfied.

### 3.1 Hazard Profile

The toxicological database indicates that technical grade trifloxystrobin has moderate acute toxicity and is a strong dermal sensitizer. Trifloxystrobin falls into Toxicity Category IV for acute oral and dermal toxicity. All toxicological data requirements, have been satisfied. An acute neurotoxicity study was requested by the HIARC, because the submitted study was unacceptable; however, the study was never required as a core data requirement. The acute toxicity of trifloxystrobin technical is summarized in Table 4 below.

**Table 3.1 Acute Toxicity of Trifloxystrobin Technical**

| Guideline No. | Study Type | MRID # | Results | Toxicity Category |
|---|---|---|---|---|
| 870.1100 | Acute Oral | 44496622<br>44496623 | $LD_{50} > 5$ g/kg | IV |
| 870.1200 | Acute Dermal | 44496626<br>44496627 | $LD_{50} > 2$ g/kg | IV |
| 870.1300 | Acute Inhalation | 44496630 | $LC_{50} > 4.65$ mg/L | IV |
| 870.2400 | Primary Eye Irritation | 44496632 | mild irritant | III |

| Table 3.1 Acute Toxicity of Trifloxystrobin Technical | | | | |
|---|---|---|---|---|
| Guideline No. | Study Type | MRID # | Results | Toxicity Category |
| 870.2500 | Primary Skin Irritation | 44496635 | mild irritant | IV |
| 870.2600 | Dermal Sensitization | 44496637<br>44496638 | strong sensitizer | N/A |

The cancer classification of trifloxystrobin was made by an *ad hoc* subcommittee of the Cancer Assessment Review Committee on May 27, 1999. The Committee determined that trifloxystrobin should be classified as a "Not Likely Human Carcinogen." Due to the classification, no cancer risk assessment was performed.

## 3.2 FQPA Considerations

On March 7, 2002, HED's HIARC evaluated the potential for increased susceptibility of infants and children from exposure to trifloxystrobin according to the February 2002 OPP 10x guidance document. The HIARC concluded that the toxicology database was complete for Food Quality Protection Act (FQPA) purposes and that there are no residual uncertainties for pre-/post-natal toxicity (S. Dapson, 01/APR/2002). Based on the hazard data, the FQPA Safety Factor Committee (B. Tarplee, 01/JUL/1999) recommended the FQPA Safety Factor (SF) be reduced to 1x. The trifloxystrobin risk assessment team evaluated the quality of the exposure data; and, based on these data, also recommended that the FQPA SF be reduced to 1x. The recommendation is based on the following:

- There is no indication of increased susceptibility of rat or rabbits to trifloxystrobin. In the developmental and reproduction toxicity studies, effects in the fetuses/offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity;
- The HIARC determined that a developmental neurotoxicity study in rats is not required;
- Although an acute neurotoxicity study is required (the submitted study was unacceptable), based on a weight-of-the-evidence review of the available data, the lack of an acute neurotoxicity study does not impact HED's ability to make an FQPA safety factor decision;
- The acute and chronic dietary food exposure assessments utilize existing and proposed tolerance level residues and 100% crop treated information for all commodities. By using these screening-level assessments, actual exposures/risks will not be underestimated;
- The exposure assessments will not underestimate the potential dietary (food and drinking water) or non-dietary exposures for infants and children from the use of trifloxystrobin;
- The dietary drinking water assessment utilizes water concentration values generated by model and associated modeling parameters, which are designed to provide conservative, health protective, high-end estimates of water concentrations, which are not likely to be exceeded; and
- The residential post-application assessment is based upon the residential SOPs. The assessment is based upon surrogate study data. These data are reliable and are not expected to underestimate risk to adults or children. The residential SOPs are based upon reasonable "worst-case" assumptions and are not expected to underestimate risk.

## 3.3 Toxicity Endpoint Selection

On April 1, 2002, HIARC re-evaluated the toxicology data base for trifloxystrobin, established RfDs, PADs, and selected the toxicological endpoints for occupational/residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to trifloxystrobin as required by the FQPA of 1996. Toxicological endpoints for use in risk assessment are presented in Table 3.3 below.

**Table 3.3 Summary of Toxicological Doses and Endpoints for Trifloxystrobin 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 Females 13-49 only | NOAEL = 250 mg/kg/day | UFA=10x<br>UFH=10x<br>FQPA SF=1x<br>($UF_{DB}$) | Acute RfD = acute NOAEL / Safety Factors = 2.5 mg/kg/day<br><br>aPAD = acute NOAEL / Safety Factors = 2.5 mg/kg/day | Developmental Toxicity-Rat<br>LOAEL = 500 mg/kg/day, based upon increased fetal skeletal anomalies. |
| Acute Dietary General Population including infants and children | There were no appropriate toxicological effects attributable to a single exposure (dose) observed in oral toxicity studies including maternal effects in developmental studies in rats and rabbits. Therefore, a dose and endpoint were not identified for this risk assessment. | | | |
| Chronic Dietary all populations | Parental NOAEL= 3.8 mg/kg/day | UFA=10x<br>UFH=10x<br>FQPA SF=1x<br>($UF_{DB}$) | Chronic RfD = chronic NOAEL / Safety Factors = 0.038 mg/kg/day<br><br>cPAD = chronic NOAEL / Safety Factors = 0.038 mg/kg/day | Two-Generation reproduction study-Rat<br>LOAEL = 55.3 mg/kg/day, based upon decreases in body weight, body weight gains, reduced food consumption and histopathological lesions in the liver, kidneys and spleen. |
| Short- (1-30 days) and Intermed-Term (1- 6 months) Oral | Offspring NOAEL= 3.8 mg/kg/day | NA | **LOC for MOE** = 100 (Residential, includes the FQPA SF) | Two-Generation reproduction study-Rat<br>LOAEL = 55.3 mg/kg/day, based upon reduced pup body weights during lactation. |
| Short- (1-30 days) and Intermed-Term (1-6 months) Dermal | Dermal study NOAEL= 100 mg/kg/day | NA | **LOC for MOE** = 100 (Occupational)<br><br>**LOC for MOE** = 100 (Residential, includes the FQPA SF) | 28-Day Dermal Toxicity Study-Rat<br>LOAEL = 1000 mg/kg/day, based upon increases in mean absolute and relative liver and kidney weights. |
| Long-Term Dermal (> 6 months) | Oral study NOAEL= 3.8 mg/kg/day (dermal absorption rate = 33%) | NA | **LOC for MOE** = 100 (Occupational)<br><br>**LOC for MOE** = 100 (Residential, includes the FQPA SF) | Two-Generation reproduction study-Rat<br>LOAEL = 55.3 mg/kg/day, based upon decreases in body weight, body weight gains, reduced food consumption and histopathological lesions in the liver, kidneys and spleen. |
| Short- (1-30 days), Intermed-(1- 6 months) and Long-Term (> 6 months) Inhalation | Oral study NOAEL= 3.8 mg/kg/day (inhalation absorption rate = 100%) | NA | **LOC for MOE** = 100 (Occupational)<br><br>**LOC for MOE** = 100 (Residential, includes the FQPA SF) | Two-Generation reproduction study-Rat<br>LOAEL = 55.3 mg/kg/day, based upon decreases in body weight, body weight gains, reduced food consumption and histopathological lesions in the liver, kidneys and spleen. |

| Table 3.3 Summary of Toxicological Doses and Endpoints for Trifloxystrobin for Use in Dietary and Non-Occupational Human Health Risk Assessments | |
|---|---|
| Cancer (oral, dermal, inhalation) | Trifloxystrobin is classified as "Not Likely Human Carcinogen" based on the lack of evidence of carcinogenicity in mouse and rat cancer studies. |

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (intraspecies). $UF_H$ = potential variation in sensitivity among members of the human population (interspecies). $UF_L$ = use of a LOAEL to extrapolate a NOAEL. $UF_S$ = use of a short-term study for long-term risk assessment. $UF_{DB}$ = to account for the absence of key data (i.e., lack of a critical study). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. NA = not applicable.

## 3.4 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 the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases 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).

The submitted data (acute, subchronic, chronic, developmental and reproduction) for trifloxystrobin do not indicate a potential for endocrine disruption, however; when the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, trifloxystrobin may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

# 4.0 Public Health and Pesticide Epidemiology Data

There is no new public health or pesticide epidemiology data to report at this time.

# 5.0 Dietary Exposure/Risk Characterization

## 5.1 Pesticide Metabolism and Environmental Degradation

### 5.1.1 Metabolism in Primary Crops

The qualitative nature of the residue in plants is adequately understood, based on acceptable metabolism studies conducted on apples, cucumbers, peanuts, sugar beet, and wheat (MARC memo. 15/JUN/1999; DP Num: 287242, L. Cheng, 08/OCT/2003). The HED MARC has determined that the total toxic residue, both for regulatory and risk assessment purposes, is trifloxystrobin and the free form of its acid metabolite CGA-321113. No new information has been reviewed (DP Num: 325826, D. Rate, 10/APR/2007; DP Num: 317330, B. O'Keefe, 16/AUG/2006)

### 5.1.2 Metabolism in Rotational Crops

An adequate confined rotational crop study is available (DP Num: 254208, F. Ives, 22/JUL/1999) reflecting the application of $^{14}$C-trifloxystrobin at 2.0 lb ai/A. The previously submitted confined rotational crop studies were deemed adequate. Total radioactive residues (expressed as trifloxystrobin equivalents) accumulated at levels greater than 0.01 ppm in/on the following rotational commodities planted in silt loam soil that has been treated with [$^{14}$C]trifloxystrobin (GP or TFMP label) at 2.0 lb ai/A (2x the maximum proposed seasonal rate): turnip leaves (0.011-0.064 ppm); turnip roots (0.005-0.018 ppm); spinach (0.016-0.264 ppm); wheat forage (0.021-0.282 ppm); wheat straw (0.042-0.200 ppm); and wheat grain (0.029-0.069 ppm). Total radioactive residues in/on commodities from the TFMP-label treatment were higher than the GP-label treatment.

The study adequately characterized/identified the majority of radioactive residues in/on all commodities harvested from all plantback intervals. The predominant metabolite identified was trifluoroacetic acid (20.1-93.6% TRR). HED does not consider this residue to be of concern at the 0.2 ppm levels observed. Intact parent was identified only as a minor (0.001 ppm) component. The following additional metabolites were detected at low concentrations (<0.01 ppm each): CGA-279202, CGA-331409, CGA-357261, CGA-357262, CGA-321113, CGA-373465, CGA-373466, CGA-320299, and phthalic acid.

### 5.1.3 Metabolism in Livestock

The qualitative nature of the residue in livestock is adequately understood based on acceptable studies conducted on goats and laying hens. The MARC has determined that the total toxic residue, both for regulatory and risk assessment purposes, is trifloxystrobin and the free form of its acid metabolite CGA-321113. Additionally, metabolite L7a (taurine conjugate of trifloxystrobin) in the liver should be included in risk assessment.

### 5.1.4 Analytical Methodology

An adequate GC/NPD method (Method AG-659A) is available for enforcing tolerances for the combined residues of trifloxystrobin and CGA-321113 in plant and livestock commodities. This

method was validated by the Agency (DP Num: 265003, L. Cheng, 13/APR/2000) and forwarded to FDA for inclusion in PAM Vol. II.

In the current grass field trials, samples of forage, hay, straw, and seed screenings were analyzed for residues of trifloxystrobin and CGA-321113 using a LC/MS/MS method (Bayer Report No. 200177; MRID 45205301). This method uses the same extraction procedures as the current GC/NPD tolerance enforcement method, but uses different clean up procedures and detection by LC/MS/MS.

The LC/MS/MS method was adequately validated using control samples fortified with each analyte at 0.01 and 15 ppm for forage, hay and straw and at 0.02 and 15 ppm for seed screenings. Average recoveries from all grass commodities were 82-99% for trifloxystrobin and 82-95% for CGA-321113, with standard deviations of ± 8-19%. The LC/MS/MS method used in the grass field trials was determined adequate for collecting data on residues of trifloxystrobin and CGA-321113 in/on grass commodities.

### 5.1.5 Multiresidue Methods

The regulated residues were tested in accordance with the PAM, Volume I, Appendix II. Trifloxystrobin gave adequate responses through protocol C, and was completely recovered from fortified apple samples when analyzed through protocols D and E. Acid metabolite CGA-321113 was recoverable through protocol B and residues from apples fortified with CGA-321113 were completely recovered through Section 402 E2/C1 (extraction with methylene chloride). These data were forwarded to FDA.

### 5.1.6 Storage Stability

Adequate storage stability data are available indicating that trifloxystrobin and CGA-321113 are stable at -20°C for at least 24 months in cucumbers, potatoes, grapes, and wheat (forage, grain and straw) and for at least 18.6 months in peanut nutmeats, hay and oil (DP Num: 254221, 254213, 254218, 254217; L. Cheng; 06/APR/2000). These data will support the current grass field trails, in which samples of forage, hay, straw and seed screening were stored at <-15°C for up to 14.9 months prior to analysis.

### 5.1.7 Magnitude in Plants

Bayer Crop Science submitted crop field trials supporting the use of trifloxystrobin (50% WDG or 2.08 lb ai/gal FlC) on grasses grown for seed (MRID No. 46727801). The results from this study are discussed below and summarized in Table 5.1.7.

| Table 5.1.7. Summary of Residue Data for Grass Field Trials using a 50% WDG Formulation of Trifloxystrobin.. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Matrix | Total Rate lb ai/A (kg ai/ha) | PHI (days) | Total Trifloxystrobin Residues (ppm) [1] | | | | | | |
| | | | n | Min. | Max. | HAFT [2] | Median | Mean | Std. Dev. |
| **Grasses grown for seed (0.5 lb ai/A/season, 0-day PHI) [3]** | | | | | | | | | |
| Forage | 0.497-0.505 (0.557-0.566) | 0 | 10 | 3.38 | 8.43 | 7.70 | 5.84 | 5.67 | 1.73 |
| Hay | 0.497-0.505 (0.557-0.566) | 0 | 10 | 5.35 | 13.00 | 10.78 | 9.28 | 9.08 | 2.25 |
| Straw | 0.487-0.526 (0.546-0.589) | 0 | 10 | 5.91 | 13.89 | 11.69 | 10.51 | 10.00 | 2.52 |
| Seed Screenings | 0.487-0.526 (0.546-0.589) | 0 | 10 | 5.34 | 17.36 | 16.88 | 13.69 | 12.85 | 3.93 |

[1]The combined trifloxystrobin residues are trifloxystrobin + CGA-321113. The validated LOQ for trifloxystrobin and CGA-321113 is 0.01 ppm in forage, hay and straw, and 0.02 ppm for seed screenings, for combined LOQs of 0.02 or 0.04 ppm.
[2]HAFT = Highest Average Field Trial.
[3]The use rate is the maximum being proposed for the 2.08 lb ai/gal FlC formulation.

**Grasses grown for seed.** Bayer CorpScience submitted data from five grass field trials conducted during 2002 in EPA growing Regions 11 and 12. Each test site included a control plot and two treated plots, one for the harvest of forage and hay and the other for the harvest of mature straw and seed screenings. Trifloxystrobin (50% WDG) was applied to treated plots as four broadcast foliar applications at 0.105-0.137 lb ai/A/application, for a total of 0.487-0.526 lb ai/A/season. The initial application was made at the 2nd leaf to four node stage for the forage/hay plots and at the early boot to late boot stage for the straw/seed plots. Subsequent applications were made at RTIs of 19-22 days. All applications were made using ground equipment at spray volumes of 19-33 gal/A, and included the use of a non-ionic surfactant at 0.125% v/v. Single control and duplicate treated samples of grass forage, hay, straw, and seed screenings were collected from all tests immediately following the final application (0 days after treatment (DAT)); and in one test, samples of forage, hay, straw, and seed screening samples were also harvested at 7, 14, and 21 DAT to examine residue decline. Samples were stored frozen from collection to analysis for up to 14.9 months, an interval supported by available storage stability data.

Residues of both trifloxystrobin and CGA-321113, expressed in parent equivalents, were >LOQ in/on all treated samples of grass forage, hay, straw and seed screenings harvested at 0 DAT, with parent accounting for the majority of the total residues. At 0 DAT, combined trifloxystrobin and CGA-321113 residues were 3.38-8.43 ppm in/on forage, 5.35-13.0 ppm in/on hay, 5.91-13.89 ppm in/on straw, and 5.34-17.36 ppm in/on seed screenings. Average combined residues were 5.67 ppm in/on forage, 9.08 ppm in/on hay, 10.0 ppm in/on straw, and 12.85 ppm in/on seed screenings.

In the residue decline trial, combined residues in forage, hay and straw declined from 0 to 7 DAT, but remained relatively steady from 7 to 21 DAT. For seed screenings, combined residues declined steadily from 0 to 14 DAT, but were similar between 14 and 21 DAT.

The available field trial data, based on the number and geographic distribution, are adequate for a regional registration (i.e. Northwest U.S.). The appropriate samples were collected at the proposed PHIs. The samples were analyzed using an adequate analytical method and the sample storage intervals are supported by available storage stability data.

The field trial data will support the use of up to four broadcast foliar applications of trifloxystrobin (WDG or FlC) to grasses grown for seed. The data support a maximum single application rate of 0.125 lb ai/A, at minimum RTIs of 21 days, for a maximum of 0.5 lb ai/A/season. The data also support a PHI of 0 days for both grass forage and hay.

### 5.1.8 Magnitude in Meat, Milk, Poultry, and Eggs

The dietary burdens for trifloxystrobin residues in livestock diets were recently calculated in conjunction with a petition for use of trifloxystrobin on soybeans (DP Num: 318624, L. Cheng, 27/JUN/2006). The calculated dietary burdens under this earlier petition were 19.95 ppm for beef and dairy cattle, 3.29 ppm for swine and 3.32 ppm for poultry. Since the soybean data were reviewed, the Agency has revised its guidance on calculating potential residues in livestock diets and updated the types and percentages of feedstuffs listed in Table 1 of Guideline 860.1000 (Agency memo OCT/2006).

The only new feedstuffs associated with the current petition are grass forage and hay; grass straw and seed screenings are no longer considered to be significant feedstuffs. However, as explained below, grass, hay is removed from feedstuffs and grass, forage is not added to the diets of livestock. Considering the existing and recommended tolerances for trifloxystrobin on livestock feedstuffs and the recent guidance on constructing a reasonably balance diet (RBD) for livestock, the dietary exposure of livestock to trifloxystrobin residues was recalculated to be 0.78 ppm for beef cattle, 0.79 ppm for dairy cattle, 0.40 ppm for swine and 0.74 ppm for poultry (Table 5.1.8).

**Table 5.1.8. Livestock Dietary Burdens for *Trifloxystrobin* [a].**

| | | | | % Diet [b] | | | | Dietary Contribution - Residue (ppm) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Feedstuff** | **Type** | **Tolerance, ppm** | **% Dry Matter** | **Beef** | **Dairy** | **Poultry** | **Swine** | **Beef** | **Diary** | **Poultry** | **Swine** |
| | | | | | | | | | | | |
| **almond hulls** | R | 3.0 | 90 | - | 5 | - | - | - | 0.17 | - | - |
| **aspirated grain fractions** | R | 5.0 | 85 | 5 | - | - | - | 0.29 | - | - | - |
| **wheat hay** | R | 0.2 | 88 | 10 | 10 | - | - | 0.02 | 0.02 | | |
| | R | 0.2 | 40 | - | 30 | - | - | - | 0.15 | - | - |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **corn, field, forage (silage)** | | | | | | | | | | | |
| **Grass /nongrass/ cereal grain, forage/silage/hay** | R | | | | | | | | | | |
| | | | | | | | | | | | |
| **beet, sugar, dried pulp** | CC | 0.4 | 88 | 5 | 5 | - | - | 0.02 | 0.02 | - | - |
| **beet, sugar, molasses** | CC | 0.2 | 75 | 5 | 5 | - | - | 0.01 | 0.01 | | |
| **rice, grain** | CC | 3.5 | 88 | 10 | 10 | 20 | 10 | 0.40 | 0.40 | 0.70 | 0.35 |
| **Corn, field, grain /other grains/grain milled byproducts)** | CC | 0.05 | 88 | 50 | 20 | 55 | 75 | 0.03 | 0.01 | 0.03 | 0.04 |
| | | | | | | | | | | | |
| **soybean seed** | PC | 0.04 | 89 | 15 | 15 | 20 | - | 0.007 | 0.007 | 0.008 | - |
| **peanut meal** | PC | 0.04 | | - | - | 5 | 15 | - | - | 0.002 | 0.006 |
| | | | | | | | | | | | |
| **Totals (Dietary Burden)** | | | | 100 | 100 | 100 | 100 | **0.78** | **0.79** | **0.74** | **0.40** |

[a] All data are based on Table 1 Feedstuffs (October 2006), a revision of feedstuffs data found in Table 1 (180.1000 OPPTS Test Guidelines). Residue levels for beef and dairy are corrected for moisture content and are determined by formula: tolerance / %DM x % in diet. Residue levels for poultry and swine are considered "as-is" and are determined by formula: tolerance x % in diet. R: roughage; CC: carbohydrate concentrate; PC: protein concentrate.

[b] Typical compositions of daily rations for the animals of choice for Table 1 data follow the guidelines explained in Appendix I.

An adequate cattle feeding study is available for trifloxystrobin (DP Num: 254208 and 257888, F. Ives, 22/JUL/1999). In this study, groups of three cows were dosed orally with trifloxystrobin at levels equivalent to 2, 6, and 20 ppm in the diet for 28-30 days and tissues were analyzed for trifloxystrobin and CGA-321113. Based on the recalculated dietary burden, these dosing levels are equivalent to approximately 2.5x, 7.7x, and 25x feeding levels for beef and dairy cattle. Residues of trifloxystrobin and CGA-321113 were each <LOQ in milk and muscle from the 20 ppm dosing level (25x); therefore milk and muscle samples from the 2 and 6 ppm dose groups were not analyzed. In addition, residues of trifloxystrobin were <0.02 ppm (<LOQ) in kidney and liver from all three dose groups and in fat from the 2 and 6 ppm dose groups; however, trifloxystrobin was detected at <0.02-0.05 ppm in omental fat and at <0.02–0.06 ppm in perirenal fat from the 20 ppm dose group. Residues of CGA-321113 were not detected in fat from all three dose groups or in liver and kidney from the 2 and 6 ppm dose groups. However, CGA-321113 was detected in kidney (<0.02–0.02 ppm) and liver (<0.02–0.09 ppm) at the 20 ppm feeding level.

Current tolerances for combined trifloxystrobin residues at 0.05 ppm in meat, meat-byproducts, and fat of cattle, goats, horses, and sheep were recommended to increase to 0.1 ppm (DP Num:

318624, L. Cheng, 27/JUN/2006). Based on the above feeding study and a dietary burden of ~0.78 ppm for cattle, quantifiable residues of trifloxystrobin or CGA-32113 are unlikely to exceed the current tolerances. Therefore, the existing tolerances for trifloxystrobin residues in cattle commodities should remain unchanged. Since the tolerance values will remain unchanged they are expected to provide a conservative estimate for dietary risk. Therefore, for the dietary risk assessment, a value of 0.2 ppm (19.95 (previous Maximum Theoretical Dietary Burden (MTDB)) / 100 X 0.98 (Metabolite L7a from feeding study) should be added for Metabolite L7a on top of the recommended tolerance level for liver (i.e. 0.3 ppm), as previously handled (DP Num: 332107, B. Hanson, 30/NOV/2006).

Based on the recent revisions to Reference Table 1 (860.1000), the estimated dietary burden for swine to trifloxystrobin residues has been substantially reduced from ~3.3 ppm to 0.40 ppm. Therefore, the 2, 6, and 20 ppm feeding levels in the available cattle feeding study would be equivalent to 5x, 15x, and 50x the dietary burden for swine. Considering the above residue data for cattle muscle, fat, liver and kidney from the 6 and 20 ppm dose groups, quantifiable residues of trifloxystrobin or CGA-32113 are unlikely to exceed current tolerances in hog meat, meat byproducts, or fat [40 CFR §180.6(a)(2)]. Therefore, the existing tolerances for trifloxystrobin residues in hog commodities should remain unchanged.

An adequate poultry feeding study is also available for trifloxystrobin (DP Num: 254221, L. Cheng, 06/APR/2000). In this study, groups of 15 hens were administered trifloxystrobin at dietary levels of 1.5, 4.5, and 15 ppm for 28 days. These exposures are equivalent to 2.7x, 8x, and 27x the recalculated dietary burden for poultry (0.74 ppm). At the 15 ppm dose level, residues of trifloxystrobin and CGA-321113 were both <LOQ (<0.02 ppm) in eggs at all sampling intervals and in skin with attached fat, peritoneal fat, muscle, and liver at the end of the study. As residues of trifloxystrobin and CGA-321113 were <LOQ (<0.02 ppm) in all poultry commodities at the 20x dose level, quantifiable residues are unlikely to exceed the current tolerance levels in eggs and poultry tissues [40 CFR §180.6(a)(2)]. Therefore, the existing tolerances for trifloxystrobin residues for eggs and poultry fat, meat, and meat byproducts should remain unchanged.

### 5.1.9 Confined and Field Rotational Crops

An adequate confined rotational crop study is available (DP Num: 254208, F. Ives, 22/JUL/1999) reflecting the application of $^{14}$C-trifloxystrobin at 2.0 lb ai/A (4x the proposed rate for grasses). Based on the data from the primary plant metabolism studies and the confined rotational crop study, the MARC concluded that the residue of concern in plants, including rotational crops, is parent and its free acid metabolite CGA-321113.

Adequate limited field rotational crop studies are also available (DP Num: 254213, L. Cheng, 06/APR/2000) reflecting the application of trifloxystrobin (WDG) to primary crops of squash or cucumbers as four foliar applications a rates totaling 1.0 lb ai/A/ season (2x the proposed maximum seasonal rate for grass). In these two field trials, rotational crops of lettuce, turnips,

and wheat were planted at 30- and 120-day plant-back intervals, and samples of the appropriate RACs were collected and analyzed for residues of trifloxystrobin and CGA-321113. At both test locations, residues of trifloxystrobin and CGA-321113 were <0.02 ppm (<LOQ) in all RAC samples from crops planted 30 days after the last application; therefore no analysis was conducted on the 120-day PBI samples.

With regards to the proposed use on grass, the rotational crop data support the 30-day PBI listed on the label for the 50% WDG. The label for the 2.08 lb ai/gal FlC, which is a MAI including tebuconazole, specifies a more restrictive 120-day PBI based on tebuconazole data.

### 5.1.10 Pesticide Metabolites and Degradates of Concern

**Table 5.1.10. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression**

| Matrix | | Residues included in Risk Assessment | Residues included in Tolerance Expression |
|---|---|---|---|
| Plants | Primary Crop | Trifloxystrobin and CGA-3211113 | Trifloxystrobin and CGA-3211113 |
| | Rotational Crop | Trifloxystrobin and CGA-3211113 | Trifloxystrobin and CGA-3211113 |
| Livestock | Ruminant | Trifloxystrobin; CGA-3211113; and Metabolite L7a in liver and meat byproducts | Trifloxystrobin and CGA-3211113 |
| | Swine | Trifloxystrobin and CGA-3211113 | Trifloxystrobin and CGA-3211113 |
| | Poultry | Trifloxystrobin and CGA-3211113 | Trifloxystrobin and CGA-3211113 |
| Drinking Water | | Trifloxystrobin and CGA-3211113 | Not Applicable |

### 5.1.11 Drinking Water Residue Profile

The proposed use rate of trifloxystrobin on grasses grown for seed is less than or equal to the use rates previously used in the screening models to determine residues of water. As such, no new EDWCs were calculated for this risk assessment (personal communication with S. Syslo).

The drinking water residues incorporated directly into the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) and summarized in the following memoranda: "*Drinking water and aquatic exposure concentrations from human health risk and ecological exposure assessments, respectively, from the use of trifloxystrobin as a seed treatment (10 crops) or for foliar application for use on barely, oats, soybeans, and sweet corn,*" DP Num: 309489, 314187, 315580, 318621, 316623, 319463, 316090, 316091, J. Wolf, 13/Dec/2005.

Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources." The EDWCs used in the dietary assessment are expected to be conservative.

In the earlier assessments, the Agency used FIRST and SCI-GROW screening models to determine the EDWCs of trifloxystrobin in surface and ground water, respectively. Trifloxystrobin is immobile in soil. It degrades and transforms rapidly in soil and aquatic environments. The primary degradate is CGA-321113. EDWCs were calculated for total trifloxystrobin residues (parent trifloxystrobin plus the major degradate CGA-321113) using EFED's FIRST model for surface water and the SCI-GROW model for ground water. EFED's interim method for drinking water estimates for pesticides used in rice paddies was also used to generate EDWCs.

The use site with the highest application rate is turf, with a maximum label rate of 1.078 lb ai/A/yr (three applications at 0.359 lb ai/A/yr). EDWCs were also provided for rice paddies that may be treated with trifloxystrobin.

For turf, the surface water EDWC is 92 ppb for the peak value (acute) and 50 ppb for the chronic value. The ground water screening concentration to be used for both acute and chronic assessments is 3.4 ppb. These values represent upper-bound estimates of the concentrations of total residues of trifloxystrobin that might be found in surface water and ground water from use on turf at the maximum application rate.

To estimate surface water concentrations for use on rice, an interim rice paddy model was used. EFED provided estimates of total trifloxystrobin residues (parent plus degradates) and for parent only. The parent only estimate is 48 ppb and the total parent plus degradates estimate is 140 ppb. EFED recommended using the total estimate for chronic risk assessment and the parent only estimate for acute risk assessment. EFED explained that the acute estimate is for parent only since trifloxystrobin is expected to require at least one day to degrade, and the chronic estimate includes parent plus degradates to account for potential degradation. HED recognizes that it is unrealistic to expect the quantity of residues to increase over time (i.e., to go from 48 to 140 ppb); therefore, these values should be viewed as very conservative. Further, the rice estimates are considered overestimates due to the nature of the assumptions built into the model.

The highest estimates for acute exposure (92 ppb from use on turf) and chronic exposure (140 ppb from use on rice) were used in the dietary analysis.

**Table 5.1.11. Summary of Estimated Surface Water and Groundwater Concentrations for Trifloxystrobin.**

| | Trifloxystrobin | |
|---|---|---|
| | Surface Water Conc., ppb [a] | Groundwater Conc., ppb [b] |
| Acute | 92 (turf) | 3.4 (turf) |

**Table 5.1.11. Summary of Estimated Surface Water and Groundwater Concentrations for Trifloxystrobin.**

| | Trifloxystrobin | |
|---|---|---|
| | Surface Water Conc., ppb [a] | Groundwater Conc., ppb [b] |
| Chronic (non-cancer) | 140 (rice) | 3.4 (turf) |
| Chronic (cancer) | NA | NA |

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on interim rice paddy model.

[b] From the SCI-GROW model assuming a maximum seasonal use rate of 1.078 lb ai/A/yr, a Koc of 124.0 mL/g, and a half-life of 282.75 days.

### 5.1.12 Proposed Tolerances

The Agency has determined that the tolerance expression for primary and rotational crops should include parent trifloxystrobin and its free acid metabolite, CGA-321113. Permanent tolerances are established for the combined residues of trifloxystrobin and CGA-321113 in/on various plant and livestock commodities ranging from 0.04-30.0 ppm [40 CFR §180.555(a)]. The tolerances proposed for grass forage and hay by the petitioner are listed in Table 5.1.12, along with the Agency's recommended tolerance levels.

The recommended tolerance levels for grass forage and hay were determined using recent Agency Guidance (*Guidance for Setting Pesticide Tolerances Based on Field Trial Data* SOP), as residues in all samples of these commodities were above the LOQ. The appropriate tolerances for grass forage and hay were calculated to be 12 and 17 ppm, respectively. Although residue data were also provided for grass straw and seed screenings, tolerances are not required on these commodities as the Agency no longer considers them to be significant livestock feedstuffs.

Based on the available cattle and poultry feeding studies and the recalculated dietary burdens for beef cattle (0.78 ppm), dairy cattle (0.79 ppm), swine (0.40 ppm), and poultry (0.74 ppm), the current tolerances for livestock commodities are adequate. Based on the available data and new dietary modeling, the current tolerances for livestock commodities should remain unchanged.

There are currently no Canadian MRLs for trifloxystrobin, but Codex and Mexican MRLs have been established for trifloxystrobin in/on various commodities. The residue definition for both Codex and Mexican MRLs includes only parent compound in plant commodities, but the definition for Codex MRLs in livestock commodities includes parent and the acid metabolite, CGA321113. Therefore, harmonization in plant commodities is not possible at this time as the current U.S. tolerance definition includes the combined residues of trifloxystrobin and its free acid metabolite. Harmonization of the tolerance level in meat byproducts of cattle, goats, and sheep is not possible at this time as the U.S. tolerance in meat byproducts reflects higher potential exposures to various feedstuffs.

| Table 5.1.12.Tolerance Summary for Trifloxystrobin | | | |
|---|---|---|---|
| Crop Commodity | Proposed Tolerance (ppm) | Recommended Tolerance (ppm) | Comments (*Correct Commodity Definition*) |
| Grass, forage | 10 | 12 | |
| Grass, hay | 14 | 17 | |

## 5.2 Dietary Exposure and Risk

HED is currently using new methods and procedures for incorporating estimated drinking water concentrations directly into calculation of exposure/risk. Rather than using a Drinking Water Level Of Comparison (DWLOC), estimated drinking water concentrations (e.g., PRZM-EXAMS, FIRST or SCI-GROW predictions) are directly entered into the exposure model (e.g., DEEM, Calendex, CARES, Lifeline) to assess the contributions from drinking water. Using this approach, aggregation of food and water exposure pathways for single chemical aggregate acute, chronic and cancer risk assessment is most often performed using DEEM and Lifeline Models.

### 5.2.1 Acute Dietary Exposure/Risk

An acute dietary assessment assuming tolerance level residues and 100% crop treated was performed for trifloxystrobin. The acute dietary risk assessment for trifloxystrobin shows that for all included commodities, the acute dietary risk estimates are below ARIA's level of concern (i.e. <100% acute population adjusted doses (aPAD)). There were no appropriate toxicological effects attributable to a single exposure (dose) for the general population; therefore, a dose and endpoint were not identified for this risk assessment. The acute PAD for females 13-49 years was 2.5 mg/kg/day. The highest estimate for acute surface water exposure (92 ppb) was used in this analysis. Ground water sources were not included in this assessment, as the EDWCs for this water source are minimal in comparison to surface water. For food and drinking water, the exposure to females 13-49 yrs old was 0.017 mg/kg/day, which utilized <1% of the aPAD at the 95$^{th}$ percentile.

### 5.2.2 Chronic Dietary Exposure/Risk

A chronic dietary assessment assuming tolerance level residues and 100% crop treated was also conducted. The chronic dietary risk assessment shows that for all included commodities, the chronic dietary risk estimates are below ARIA's level of concern (i.e. <100% chronic population adjusted doses (cPAD). The highest estimate for chronic surface water exposure (140 ppb) was used in this analysis; ground water sources were minimal in comparison to surface water. For the U.S. population the exposure for food and water utilized 26% of the cPAD. The chronic dietary risk estimate for the highest reported exposed population subgroup, children 1-2 years old, is 81% of the cPAD.

| Table 5.2.2. Result of Acute and Chronic Dietary Exposure and Risk Estimates for Trifloxystrobin. | | | |
|---|---|---|---|
| Population Subgroup | PAD, mg/kg/day | DEEM-FCID | |
| | | Exposure, mg/kg/day | % PAD |
| **Acute Dietary Estimates 95th Percentile of Exposure)** | | | |
| Females 13-49 yrs | 2.5 | 0.017357 | <1 |
| **Chronic Dietary Estimates** | | | |
| U.S. Population | 0.038 | 0.009809 | 26 |
| All infants (< 1 yr) | 0.038 | 0.023782 | 63 |
| Children 1-2 yrs | 0.038 | 0.030808 | 81 |
| Children 3-5 yrs | 0.038 | 0.022468 | 59 |
| Children 6-12 yrs | 0.038 | 0.012246 | 32 |
| Youth 13-19 yrs | 0.038 | 0.007450 | 20 |
| Adults 20-49 yrs | 0.038 | 0.007687 | 20 |
| Adults 50+ yrs | 0.038 | 0.007759 | 20 |
| Females 13-49 yrs | 0.038 | 0.007530 | 20 |
| **Cancer Dietary Estimate** | | | |
| U.S. Population | Classified as a "Not Likely Human Carcinogen." | | |

### 5.2.3 Cancer Dietary Risk

The HIARC classified trifloxystrobin as a "not likely carcinogen"; therefore, quantification of human cancer risk is not required and a cancer dietary assessment was not performed.

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Trifloxystrobin's residential uses include disease control in turfgrass and ornamentals (Compass®). Up to three applications may be made in a season, with the shortest interval between applications being 5-7 days. Because FQPA requires consideration of aggregate exposure to all likely non-occupational uses, this assessment uses non-occupational postapplication contact with trifloxystrobin following Compass® use on turfgrass as the most common and worst case contributor to such exposures.

### 6.1 Residential Postapplication Exposure

There is potential for dermal (adults and children) and incidental oral exposure (children only) during post-application activities. The following post-application exposure scenarios resulting from lawn treatment were previously assessed: (1) dermal exposure from pesticide residues on lawns, (2) incidental non-dietary ingestion of pesticide residues on lawns from hand-to-mouth transfer, (3) incidental non-dietary ingestion of residues from object-to-mouth activities (pesticide-treated turfgrass), and (4) incidental non-dietary ingestion of soil from pesticide-treated residential areas. Post-application exposures from various activities following lawn treatment are considered to be the most common and significant in residential settings. An exposure/risk assessment was previously performed using applicable toxicological endpoints selected by the HIARC (01/APR/2002). The proposed new use does not alter the previous residential risk assessment, therefore a new residential assessment was not performed (DP Num: 264570, J. Arthur, 06/AUG/2001).

The HED Standard Operating Procedures for Residential Exposure Assessments (Draft, December 18, 1997) were used as a guideline for performing the residential postapplication assessment. Also used in the assessment were interim changes to these SOPs which were adopted by the HED Exposure Science Advisory Council regarding standard values, including, for turf transferable residues, turf transfer coefficients and hand-to-mouth activities (Policy 11, February 22, 2001). The exposure and risk estimates for the four residential exposure scenarios are assessed for the day of application (day "0"), because it is assumed that adults and toddlers could contact the lawn immediately after application. On the day of application, it was assumed that 5 percent of the application rate is available from the turfgrass as transferable residue (20 percent for object-to-mouth activities).

The NOAEL of 100 mg/kg/day from a 28-day dermal toxicity study in rats (endpoint: increases in mean absolute and relative liver and kidney weights) was used for determining short-/intermediate-term dermal risk to adults and toddlers, and the NOAEL of 3.8 mg/kg/day from a two-generation reproduction study in rats (endpoint: decreases in pup body weight during lactation), for determining short-/intermediate-term incidental ingestion risk to toddlers.

Adult and children's dermal exposure and risk from treated lawns is summarized in Table 6.1.1. The Short-/Intermediate-Term MOEs for adults and children are 1300 and 760, respectively.

Children's risk from oral hand-to-mouth activities on treated lawns is summarized in Table 6.1.2. The Short-/Intermediate-Term MOE for children is 750.

Children's risk from object-to-mouth (turfgrass) from treated lawns is summarized in Table 6.1.3. The Short-/Intermediate-Term MOE for children is 3000.

Children's risk from incidental ingestion of soil from treated lawns is summarized in Table 6.1.4. The Short-Intermediate-Term MOE for children is 220,000.

Since the short-/intermediate-term MOEs are above 100, they DO NOT exceed ARIA's level of concern. Chronic or long-term exposure is not expected.

**TABLE 6.1.1.** Dermal Exposure and Risk for Adults and Children from Treated Lawns

| Subgroup exposed | Application Rate (lb ai/A) | Fraction of ai Available | Turf Transferable Residue[1] ($ug/cm^2$) | Dermal Transfer Coefficient ($cm^2/hr$) | Exposure Time (hrs/day) | Absorption Factor | Body Weight (kg) | Daily Dose[2] (mg/kg /day) | Short-Term MOE[3] |
|---|---|---|---|---|---|---|---|---|---|
| Adult | 0.34 | 0.05 | 0.19 | 14,500 | 2 | 1 | 70 | 0.079 | 1300 |
| Children | 0.34 | 0.05 | 0.19 | 5,200 | 2 | 1 | 15 | 0.13 | 760 |

[1] Turf Transferable Residue ($ug/cm^2$) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 $A/cm^2$
[2] Daily Dose = (Turf Transferable Residue x 1E-3 mg/ug x Dermal Transfer Coefficient x Exposure Time)/Body weight
[3] Short & Intermediate-Term Dermal MOE = Short & Intermediate-Term Dermal NOAEL (100 mg/kg/day) /Daily Dose

**TABLE 6.1.2.** Oral Hand-to-Mouth Exposure and Risk for Children from Treated Lawns

| Application Rate (lb ai/A) | Fraction of ai Available | Turf Transferable Residue[1] ($ug/cm^2$) | Exposure Time (hrs/day) | Extraction by saliva | Hand Surface Area ($cm^2$/event) | Frequency (events/ hr) | Body Weight (kg) | Daily Dose[2] (mg/kg/ day) | Short-Term MOE[3] |
|---|---|---|---|---|---|---|---|---|---|
| 0.34 | 0.05 | 0.19 | 2 | 0.5 | 20 | 20 | 15 | 0.0051 | 750 |

[1] Turf Transferable Residue (ug/cm2) = Application rate (lb ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm2
[2] Daily Dose = (Turf Transferable Residue (ug/cm2) x Extraction by Saliva x Hand Surface Area (cm2/event) x Frequency (events/hr) x 1E-3 mg/ ug x ET (hrs/day)] / [Body Weight (kg)]
[3] Intermediate-Term Oral MOE = Intermediate-Term Oral NOAEL (3.8 mg/kg/day) /Daily Dose

**TABLE 6.1.3.** Oral Object-to-Mouth (Turfgrass) Exposure and Risk for Children from Treated Lawns

| Application Rate (lb ai/A) | Fraction of ai Available | Grass Residue[1] ($ug/cm^2$) | Surface Area Mouthed ($cm^2$/day) | Body Weight (kg) | Daily Dose[2] (mg/kg/ day) | Short-Term MOE[3] |
|---|---|---|---|---|---|---|
| 0.34 | 0.2 | 0.76 | 25 | 15 | 0.0013 | 3000 |

[1] Grass residue (ug/cm2) = [Application Rate (lbs ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm2]
[2] Daily Dose = [Grass residue (ug/cm2) x Surface Area Mouthed (cm2/day) x 1E-3 mg/ug] / [Body Weight (kg)]
[3] Intermediate-Term Oral MOE = Intermediate-Term Oral NOAEL (3.8 mg/kg/day) /Daily Dose

**TABLE 6.1.4.** Exposure and Risk for Children from Ingestion of Soil from Treated Lawns

| Application Rate (lb ai/A) | Fraction of ai Available | Soil Residue[1] (ug/g) | Ingestion Rate (g/day) | Body Weight (kg) | Daily Dose[2] (mg/kg/day) | Short-Term MOE[3] |
|---|---|---|---|---|---|---|
| 0.34 | 1.0 | 2.6 | 100 | 15 | 0.000017 | 220,000 |

[1] Soil residue (ug/g) = [Application Rate (lbs ai/A) x Fraction of ai Available x 4.54E+8 ug/lb x 2.47E-8 A/cm$^2$ x 0.67 cm$^3$/g soil]
[2] Daily Dose = [Soil residue (ug/g) x Ingestion rate (mg/day) x 1E-6 g/ug] / [Body Weight (kg)]
[3] Intermediate-Term Oral MOE = Intermediate-Term Oral NOAEL (3.8 mg/kg/day) /Daily Dose

## 6.2 Combined Exposure

DP Num: 318618, B. O'Keefe, 07/AUG/2006

The FQPA requires residential exposures that could reasonably be expected to occur on the same day be combined and compared to the appropriate toxicity endpoint. Because trifloxystrobin is not applied by residential handlers, the only multiple-residential exposure scenarios involve children's exposure from dermal and oral routes following turfgrass treatment by a pest control operator (PCO). For incidental oral exposure to toddlers in residential settings, the three scenarios that would reasonably be expected to occur on the same day are toddler's incidental ingestion of residues on turf from hand-to-mouth activities, mouthing turfgrass and eating soil. These daily exposures, when combined, total 0.0064 mg/kg/day. When the combined exposure is compared to the short-term incidental oral NOAEL (3.8 mg/kg/day), the MOE = 590. Because the toxicity endpoints for dermal and oral exposure are not the same, the combining of risks for these different routes of exposure is not done.

Therefore, the combined risk from incidental oral exposures anticipated for toddlers (i.e., MOE = 590) DOES NOT exceed ARIA's level of concern.

## 6.3 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for trifloxystrobin. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, 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, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply 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 with specific products with significant risks associated with drift.

It is noted that the 1.078 lb ai/A application rate for turf was modeled to estimate postapplication residential exposure of toddlers. As this rate is equal to or higher than many of agricultural application rates, this scenario is protective of any exposure of farm children via spray drift from agricultural trifloxystrobin applications.

## 7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate trifloxystrobin 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 and ARIA have considered both the route and duration of exposure.

## 7.1 Acute Aggregate Risk

An acute dietary assessment assuming tolerance level residues and 100% crop treated was performed for trifloxystrobin. The acute dietary risk assessment for trifloxystrobin shows that for all included commodities, the acute dietary risk estimates are below ARIA's level of concern (i.e. <100% acute population adjusted doses (aPAD)). There were no appropriate toxicological effects attributable to a single exposure (dose) for the general population; therefore, a dose and endpoint were not identified for this risk assessment. The acute PAD for females 13-49 years was 2.5 mg/kg/day. The highest estimate for acute surface water exposure (92 ppb) was used in this analysis. Ground water sources were not included in this assessment, as the EDWCs for this water source are minimal in comparison to surface water. For food and drinking water, the exposure to females 13-49 yrs old was 0.017357 mg/kg/day, which utilized <1% of the aPAD at the 95$^{th}$ percentile.

## 7.2 Short-Term Aggregate Risk

DP Num: 318618, B. O'Keefe, 07/AUG/2006

The short-term aggregate risk assessment estimates risks likely to result from 1- to 30-day exposure to trifloxystrobin residues from food, drinking water, and residential pesticide uses. High-end estimates of residential exposure are used in the short-term assessment, while average values are used for food and drinking water exposure (i.e. chronic exposures).

Different endpoints were identified by HIARC for short-term incidental oral and dermal risk assessment (the basis for the oral endpoint is reduced pup body weights and the dermal endpoint is based on increases in liver and kidney weights). Therefore, it is not possible to combine dietary/incidental oral exposure with dermal exposure.

Short-term aggregate risk assessments were conducted for the following scenarios: 1) adults (dermal residential + dietary food and drinking water exposures); 2) children 1-2 years (dermal residential + dietary food and drinking water exposures); and 3) children 1-2 years (incidental oral + dietary food and drinking water exposures). Adult and child risk from dermal exposure is summarized in Table 6.1.1 in Section 6.1. A short-term aggregate risk assessment is required for infants and children because there are residential postapplication oral exposure scenarios. Toddlers' incidental oral exposure is assumed to include hand-to-mouth exposure, object-to-

mouth exposure and exposure through incidental ingestion of soil. See Tables 6.1.2-6.1.4 in Section 6.1 for short-term exposure and risk estimates from incidental oral sources for children. Table 7.2 summarizes short-term aggregate risks. All short-term aggregate risk estimates result is MOEs greater than 100. Therefore, ARIA does not consider short-term aggregate risk to be a concern.

**Table 7.2. Short-Term Aggregate Risk (Food, Water and Incidental Exposure)**

| Population | Short-Term Scenario | | | | | |
|---|---|---|---|---|---|---|
| | NOAEL mg/kg/day | LOC MOE[1] | Average Food + Water Exposure mg/kg/day | Residential Oral Exposure[2] mg/kg/day | Residential Dermal Exposure[2] mg/kg/day | Aggregate MOE (food and residential)[3] |
| US Population | 100 | 100 | 0.009809 | NA | 0.079 | 1100 |
| Children (1-2 years) | | | 0.030808 | NA | 0.1308 | 620 |
| Children (1-2 years) | 3.8 | 100 | 0.030808 | 0.00642 | NA | 102 |

[1] The level of concern (LOC) MOE is 100, based on inter- and intra-species safety factors totaling 100.
[2] Residential Exposure = [Incidental exposure from all possible sources]. No residential oral exposure is expected for adults.
[3] Aggregate MOE = [NOAEL (mg/kg/day) ÷ (Avg Food Exposure + Residential Exposure)].
NA = Not Applicable

## 7.3 Intermediate-Term Aggregate Risk

An intermediate-term aggregate risk assessment (1 to 6 months of exposure to trifloxystrobin residues from food, drinking water, and residential pesticide uses) is not expected to occur based on the short soil half-life (about 2 days). Therefore, an intermediate-term aggregate risk assessment was not performed.

## 7.4 Long-Term Aggregate Risk

Because there are no long-term (chronic) exposures due to residential use, long-term aggregate risk is solely due to chronic dietary risk and risk contributed from drinking water. Section 5.2.2 describes the long-term aggregate risk (chronic dietary and drinking water).

## 7.5 Cancer Risk

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the HIARC classified trifloxystrobin as a "not likely" human carcinogen. Therefore, a cancer dietary exposure analysis was not performed.

# 8.0 Cumulative Risk Characterization/Assessment

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 trifloxystrobin and any other substances and trifloxystrobin does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that trifloxystrobin has 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 Office of Pesticide Programs 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/Risk Pathway

DP Num: 333762, M. Dow, 08/NOV/2006

### 9.1 Short-/Intermediate-/Long-Term Handler Risk

Based upon the proposed use pattern, ARIA believes the most highly exposed occupational pesticide handlers would be 1) mixer/loaders using open pour loading of water dispersible granules; 2) mixer/loaders using open-pour loading of liquids; 3) applicators using open-cab ground-boom spray equipment and 4) aerial applicators.

Since the treatment blocks (i.e., areas treated) are relatively small compared to typical field crops such as cotton, corn, soybeans or wheat, ARIA believes pesticide handlers will be exposed to short-term duration (1 - 30 days) exposures but not to intermediate-term (1 - 6 months) duration exposures. Although multiple applications are possible, they are separated by 21 day RTIs. Therefore, it is unlikely that pesticide handlers would be exposed continuously for 30 days or more.

Private (i.e., grower) applicators may perform all functions, that is, mix, load and apply the material. The HED ExpoSAC SOP Number 12 (29 March 2000) directs that although the same individual may perform all those tasks, they shall be assessed separately. The available exposure data for combined mixer/loader/applicator scenarios are limited in comparison to the monitoring of these two activities separately. These exposure scenarios are outlined in the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (August 1998). HED has adopted a methodology to present the exposure and risk estimates separately for the job functions in some scenarios and to present them as combined in other cases. For equipment types such as fixed-wing aircraft, ground-boom tractors, or air-blast sprayers, the applicator exposures are assessed and presented separately from those of the mixers and loaders. By separating the two job functions, HED determines the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

No chemical specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). For pesticide handlers, it is HED standard practice to present estimates of dermal exposure for "baseline" that is, for workers wearing a single layer of work clothing consisting of a long-sleeved shirt, long pants, shoes plus socks and no protective gloves as well as for "baseline" and the use of protective gloves or other PPE as might be necessary. The product label directs applicators and other handlers must wear long-sleeved shirt, long pants, shoes plus socks and chemical-resistant gloves made of any waterproof material.

The PHED does not contain data for water dispersible granules. However it does contain data regarding dry flowable formulations. As a surrogate, RD uses the unit exposure data for a dry flowable formulation which is expected to result in similar exposures.

The HED recently conducted an exposure/risk assessment for trifloxystrobin (DP Num: 317330, B. O'Keefe, 16/AUG/2006). The current risk assessment uses toxicological endpoints cited in the March 7, 2002 HED HIARC report. Relative to the assessment herein, the HIARC identified a short-term duration (1 - 30 days) dermal toxicological endpoint from a 28-day dermal toxicity study in the rat. The toxic effects seen were increases in mean absolute and relative liver and kidney weights. The NOAEL is 100 mg ai/kg bw/day. Since the dermal endpoint is identified from a dermal study, there is no adjustment for dermal absorption. Although ARIA does not expect intermediate-term duration (1 - 6 months) exposures, the short-term and intermediate-term dermal endpoints are the same. Therefore, in the event that there might be intermediate-term exposures, the estimates of risk are adequate to account for intermediate-term exposures.

The HIARC also identified a short-term inhalation toxicological endpoint from a 2-generation reproduction study in the rat. The effects seen were decreases in body weight, body weight gains, reduced food consumption and histopathological lesions in the liver, kidneys and spleen in the dams. Since the toxic effects are maternal effects (i.e., not fetal effects) a 70 kg bw is used to calculate exposure.

The dermal and inhalation toxicological endpoints are identified from different studies (dermal versus reproduction) and cite different toxicological effects. Therefore, dermal and inhalation exposures are not combined. The Margins of Exposure (MOE) are presented separately for dermal and inhalation exposure.

The Cancer Assessment Review Committee (CARC) has classified trifloxystrobin as a "Not Likely Human Carcinogen" therefore a cancer risk assessment is not necessary. See Table 9.1 for a summary of exposures and risks to occupational pesticide handlers

**Table 9.1. Summary of Exposure & Risk for Occupational Handlers Applying Trifloxystrobin to Grasses Grown for Seed**

| Unit Exposure[1] mg ai/lb handled | Applic. Rate[2] lb ai/unit | Units Treated[3] | Avg. Daily Dose[4] mg ai/kg bw/day | MOE[5] |
|---|---|---|---|---|
| *Mixer/Loader - Open-pour Loading of Water Dispersible Granule* supporting aerial operations | | | | |
| Dermal:<br>SLNoGlove 0.066 LC<br>SLWithGlove 0.066 HC<br>Inhal. 0.00077 HC | 0.125<br>lb ai/A | 350 A | Dermal:<br>SLNoGlove 0.0413<br>SLWithGlove 0.0413<br>Inhal. 0.000481 | <br>2,400<br>2,400<br>7,900 |
| *Mixer/Loader - Open-pour Loading Liquids* supporting aerial operations | | | | |
| Dermal:<br>SLNoGlove 2.9 HC<br>SLWithGlove 0.023 HC<br>Inhal. 0.0012 HC | 0.125<br>lb ai/A | 350 A | Dermal:<br>SLNoGlove 1.81<br>SLWithGlove 0.0144<br>Inhal. 0.00075 | <br>55<br>7,000<br>5,100 |
| *Applicator - Ground-boom - Open-cab* | | | | |
| Dermal:<br>SLNoGlove 0.014 HC<br>SLWithGlove 0.014 MC<br>Inhal. 0.00074 HC | 0.125<br>lb ai/A | 200 A | Dermal:<br>SLNoGlove 0.005<br>SLWithGlove 0.005<br>Inhal. 0.00026 | <br>20,000<br>20,000<br>14,000 |
| *Aerial Applicator* | | | | |
| Dermal:<br>SLNoGlove 0.0050 HC<br><br>Inhal. 0.000068 HC | 0.125<br>lb ai/A | 350 A | Dermal:<br>SLNoGlove 0.00313<br><br>Inhal. 0.0000425 | <br>32,000<br><br>89,000 |

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Dermal exposure: SLNoGlove = single layer of work clothing (long pants long sleeved shirt, shoes plus socks) and No protective gloves; SLWithGlove = single layer of work clothing AND the use of protective gloves. Inhal. = Inhalation. Units = mg ai/pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence.
2. Applic. Rate. = Taken from the proposed amendment to the Flint label and from the proposed Absolute label
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. ExpoSAC; Revised 5 July 2000;
4. Average Daily Dose (ADD) = Unit Exposure * Applic. Rate * Units Treated ÷ Body Weight (70 kg)
5. MOE = Margin of Exposure = NOAEL ÷ ADD. Dermal NOAEL = 100 mg ai/kg bw/day, Inhalation NOAEL = 3.8 mg ai/kg bw/day.

## 9.2 Short-/Intermediate-/Long-Term Postapplication Risk

It is possible for agricultural workers to have post-application exposure to pesticide residues during the course of typical agricultural activities. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application agricultural activities that may occur and which may result in post-application exposures to pesticide residues. HED has also identified Transfer Coefficients (TC) ($cm^2/hr$) relative to the various activities which express the amount of foliar contact over time, during each of the activities identified.

The TCs used in this assessment are from an interim TC Standard Operating Procedure (SOP) developed by HED's ExpoSAC using proprietary data from the ARTF database (SOP # 3.1). It is the intention of HED's ExpoSAC that this SOP will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further

analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

HED has not identified TC's specifically for grasses grown for seed. However, there are TC's identified for the culture of grasses such as the small grains i.e., barley, oats, wheat and rye. As with the small grains, harvesting of grasses grown for seed is mechanical. There are few, if any, cultural activities requiring worker contact with the growing crop. For the small grains, the highest TC (1,500 $cm^2$/hr) is associated with scouting a crop at full stages of foliar development or with irrigation activities at full stages of development. It is unlikely that there would be greater worker exposures associated with grasses grown for seed.

Therefore, as a screening level assessment, ARIA herein uses the TC of 1,500 $cm^2$/hr for a conservative estimate of agricultural worker exposure to post-application residues of trifloxystrobin.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 20% of the application rate is available as dislodgeable foliar residue on day zero after application. This is adapted from the ExpoSAC SOP No. 003 (7 May 1998 - Revised 7 August 2000).

The following convention may be used to estimate post-application exposure.

Average Daily Dose (ADD) (mg ai/kg bw/day) = DFR $\mu g/cm^2$ * TC $cm^2$/hr * hr/day * 0.001 mg/$\mu$g * 1/70 kg bw

and where:

Surrogate Dislodgeable Foliar Residue (DFR) = application rate * 20% available as dislodgeable residue * $(1\text{-}D)^t$ * $4.54 \times 10^8$ $\mu g/lb$ * $2.47 \times 10^{-8}$ $A/cm^2$.

0.125 lb ai/A * 0.20 * $(1\text{-}0)^0$ * $4.54 \times 10^8$ $\mu g/lb$ * $2.47 \times 10^{-8}$ $A/cm^2$ = 0.28 $\mu g/cm^2$, therefore,

0.28 $\mu g/cm^2$ * 1,500 $cm^2$/hr * 8 hr/day * 0.001 mg/$\mu$g ÷ 70 kg bw = 0.048 mg/kg bw/day.

MOE = NOAEL ÷ ADD then 100 mg/kg bw/day ÷ 0.048 mg/kg bw/day = 2,081

A MOE of 100 is adequate to protect agricultural workers from post-application exposures. Since the estimated MOE is > 100, the proposed use does not exceed ARIA's level of concern.

**Table 9.2. Summary of Occupational Postapplication Risks for Trifloxystrobin.**

| Crops | Activities | Maximum Application Rate (lb ai/acre) | MOE at Day 0 | Restricted Entry Interval (REI) in Hours (Target MOE= 100) | |
|---|---|---|---|---|---|
| | | | | Short-term | Intermediate-term |
| Grasses Grown for Seed | Harvesting and Scouting | 0.125 | 2,100 | 12 | 12 |

## 9.3 Restricted Entry Interval (REI)

Trifloxystrobin is classified in Acute Toxicity Category III for primary eye irritation. It is classified in Category IV for acute dermal toxicity, acute inhalation toxicity, primary skin irritation and it is not a dermal sensitizer. Based upon the acute toxicity characteristics, the interim Work Protection Standard (WPS) restricted entry interval (REI) of 12 hours is adequate to protect agricultural workers from post-application exposures to trifloxystrobin. The Flint® Fungicide label lists a REI of 12 hours.

The proposed Absolute label lists a 24 hour REI due assumedly to its combination with tebuconazole.

In the 2006 O'Keefe assessment, (DP Num: 317330, B. O'Keefe, 16/AUG/2006) it is noted "that trifloxystrobin was found to be a strong dermal sensitizer. This warrants a requirement for gloves for mixers/loaders (even though trifloxystrobin is in Category IV for dermal toxicity). Also, double notification (i.e., verbal warnings as well as signs posted around treated fields) for postapplication workers was recommended. The ARIA team recommends that the labels should be confirmed or amended as may be appropriate.

## 10.0 Tolerance Summary

The tolerance expression for trifloxystrobin in/on plants (40 CFR 180. 555) is the combined residues of trifloxystrobin, (benzeneacetic acid, (*E,E*)-α-(methoxyimino)-2-[[[[1-[3-(trifluoromethyl) phenyl]ethylidene]amino]oxy] methyl]-methyl ester) and the free form of its acid metabolite CGA–321113 ((*E,E*)-methoxyimino-[2-[1-(3-trifluoromethylphenyl)-ethylideneaminooxymethyl]-phenyl] acetic acid.

**Table 10.0. Tolerance Summary for Trifloxystrobin**

| Crop Commodity | Proposed Tolerance (ppm) | Recommended Tolerance (ppm) | Comments *(Correct Commodity Definition)* |
|---|---|---|---|
| Grass, forage | 10 | 12 | |
| Grass, hay | 14 | 17 | |

There are currently no Canadian MRLs for trifloxystrobin. Codex and Mexican MRLs have been established for trifloxystrobin in/on various commodities; however, there are no MRLs for the commodities associated with the proposed use of trifloxystrobin in/on grasses grown for seed. Also, the residue definition for both Codex and Mexican MRLs includes only parent compound in plant commodities, but

the definition for Codex MRLs in livestock commodities includes parent and the acid metabolite, CGA321113. Therefore, harmonization in plant commodities is not possible at this time as the current U.S. tolerance definition includes the combined residues of trifloxystrobin and its free acid metabolite. Harmonization of the tolerance level in meat byproducts of cattle, goats, and sheep is not possible at this time as the U.S. tolerance in meat byproducts reflects higher potential exposures to various feedstuffs.

## 11.0 Data Needs and Label Recommendations

### 11.1 Toxicology

No additional data is required.

### 11.2 Residue Chemistry

1) The petitioner must submit a revised Section B and label which restricts the use on grasses grown for to only the Northwest U.S.

2) The Section F must be revised to change the proposed residues for grass, forage and grass, hay to match the recommended tolerances of 12 ppm and 17 ppm, respectively.

### 11.3 Occupational and Residential Exposure

As mentioned above, because trifloxystrobin was found to be a strong dermal sensitizer. This warrants a requirement for gloves for mixers/loaders (even though trifloxystrobin is in Category IV for dermal toxicity). Also, double notification (i.e., verbal warnings as well as signs posted around treated fields) for postapplication workers was recommended. The ARIA team recommends that the labels should be confirmed or amended as may be appropriate.

## 12.0 References:

DP Num: 317330, B. O'Keefe, 16/AUG/2006
DP Num: 318618, B. O'Keefe, 07/AUG/2006
TXR # 0050612, HIARC Trifloxystrobin #3, S. Dapson, 01/APR/2002
Cancer Assessment Review Committee on May 27, 1999
HED Doc. No. 013545, B. Tarplee, 01/JUL/1999
DP Num: 333762, M. Dow, 08/NOV/2006
FQPA Safety Factor Committee (B. Tarplee, 01/JUL/1999)
DP Num: 244009, M. Rust, 02/SEP/1999.
MARC memo. 15/JUN/1999
DP Num: 287242, L. Cheng, 08/OCT/2003
DP Num: 254208, F. Ives, 22/JUL/1999

DP Num: 265003, L. Cheng, 13/APR/2000
DP Num: 254221, 254213, 254218, 254217; L. Cheng; 06/APR/2000
46727801.der, D. Rate, 28/FEB/2007
DP Num: 325826, D. Rate, 10/APR/2007
DP Num: 318624, L. Cheng, 27/JUN/2006
DP Num: 254208 and 257888, F. Ives, 22/JUL/1999
DP Num: 332107, B. Hanson, 30/NOV/2006
DP Num: 254221, L. Cheng, 06/APR/2000
DP Num: 254208, F. Ives, 22/JUL/1999
DP Num: 254213, L. Cheng, 06/APR/2000
DP Num: 321998, W. Cutchin, 28/SEP/2005
DP Num: 322584, W. Cutchin, 14/NOV/2005
DP Num: 333762, M. Dow, 08/NOV/2006

Appendix: Toxicity Profile:

| Table A.1 Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID#(s)** | **Results** |
| 870.3100 | Subchronic-Feeding-Rat | 44496701 | **NOAEL = 500 ppm (30.6-32.8 mg/kg/day).** Decreased body weight (males), hypertrophy of hepatocytes (males), and pancreatic atrophy observed at the **LOAEL of 2000 ppm (127-133 mg/kg/day).** |
| 870.3100 | Subchronic-Feeding-Mouse | 44496641 | **NOAEL = 500 ppm (76.9-110 mg/kg/day).** Increased liver weights and necrosis of hepatocytes observed at the **LOAEL of 2000 ppm (315-425 mg/kg/day).** |
| 870.3150 | Subchronic-Feeding-Dog | 44496702 | **NOAEL = 30 mg/kg/day.** Increased liver weight and hepatocyte hypertrophy in males observed at the **LOAEL of 150 mg/kg/day.** |
| 870.3200 | 28-Day Dermal Toxicity-Rat | 44496703 | **NOAEL = 100 mg/kg/day.** Increased liver and kidney weight observed at the **LOAEL of 1000 mg/kg/day.** |
| 870.3700 | Developmental Toxicity-Rat | 44496708 | **Maternal NOAEL = 10 mg/kg/day.** Decreased body weight gain and food consumption observed at the **Maternal LOAEL of 100 mg/kg/day.** **Developmental NOAEL = 1000 mg/kg/day.** No developmental effects observed. **Developmental LOAEL = >1000 mg/kg/day.** |
| 870.3700 | Developmental Toxicity-Rabbit | 44496709 | **Maternal NOAEL = 10 mg/kg/day.** Decreased body weights and body weight gain, food consumption and efficiency observed at the **Maternal LOAEL of 50 mg/kg/day.** **Developmental NOAEL = 250 mg/kg/day.** Skeletal anomolies observed at the **Developmental LOAEL of 500 mg/kg/day.** |
| 870.3800 | Reproductive Toxicity-Rat | 44496710 | **Parental NOAEL = 50 ppm (3.8 mg/kg/day).** Decreased body weight and weight gain, decreased food consumption, liver, kidney and spleen effects observed at the **Parental LOAEL of 750 ppm (55.3 mg/kg/day).** **Reproductive NOAEL = 1500 ppm (110.6 mg/kg/day).** **Reproductive LOAEL = >1500 ppm (110.6 mg/kg/day).** |
| 870.4100 | Chronic-Feeding-Dog | 44496704 | **NOAEL = 5 mg/kg/day.** Increased clinical signs, increased liver weight and hepatocellular hypertrophy observed at the **LOAEL of 50 mg/kg/day.** |
| 870.4200 | Carcinogenicity-Mouse | 44496705 | **NOAEL = 300 ppm (39.4 mg/kg/day).** Liver effects observed at the **LOAEL of 1000 ppm (131.1 mg/kg/day).** |
| 870.4300 | Chronic Toxicity/ Carcinogenicity-Rat | 44496711 | **NOAEL = 250 ppm (9.81-11.37 mg/kg/day).** Decreased body weight and body weight gain observed at the **LOAEL of 750 ppm (29.7-34.5 mg/kg/day).** |
| 870.5100 | Gene Mutation - *Salmonella* | 44496712<br>44496715<br>44496716<br>44496717 | **Negative** |
| 870.5300 | Gene Mutation | 44496713 | **Positive** |

| Table A.1 Subchronic, Chronic and Other Toxicity Profile | | | |
|---|---|---|---|
| **Guideline No.** | **Study Type** | **MRID#(s)** | **Results** |
| | in Chinese Hamster Cultured V-79 | | |
| 870.5385 | Structural Chromosome Aberration - Micronucleus - mouse | 44496714 | **Negative** |
| 870.5385 | Structural Chromosome Aberration - Cytogenetics - Chinese Hamster | 44496718 | **Negative** |
| 870.5500 | DNA Repair-Rat hepatocytes | 44496719 | **Negative** |
| 870.6200 | Acute Oral Neurotoxicity - Rat | 44496640 | NOAEL and LOAEL could not be determined. |
| 870.7485 | Metabolism-Rat | 44496722<br>44496821 | Tissue half-lives ranged from 13 to 42 hours. Highest residues were found in liver, kidneys, spleen and blood. Parent compound was extensively metabolized to approximately 35 metabolites. |