UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: May 02, 2012

SUBJECT: Triflumizole: Human Health Risk Assessment for Registration Review

PC Code: 128879
Decision No.: 453462
Petition No.:
Risk Assessment Type: Registration Review
TXR No.:
MRID No.: NA

DP Barcode: D393221
Registration No.:
Regulatory Action: Registration Review
Case No.: NA
CAS No.: 68694-11-1
40 CFR: §180.476

FROM: Seyed Tadayon, Risk Assessor
John Liccione, Ph.D., Toxicologist
William Donovan, Ph.D., Chemist
Risk Assessment Branch V
Health Effects Division (7509P)
Office of Pesticide Programs

THROUGH: Linda Taylor, Senior Scientist
Donna Davis, Senior Scientist
Danette Drew, Senior Scientist
Michael Metzger, Branch Chief
Risk Assessment Branch V
Health Effects Division (7509P)
Office of Pesticide Programs

TO: Steven Snyderman, Chemical Review Manager
Risk Management and Implementation Branch III
Pesticide Re-evaluation Division (7508P)

This document provides the Health Effects Division's (HED's) risk assessment conducted in support of registration review for triflumizole. The emphasis of the present memo is on changes since the most recent assessments. The supporting documents are listed below.

Triflumizole – Human Health Risk Assessment. W. Cutchin, D363719, 4/1/09.
Triflumizole – Residue Chemistry Assessment. W. Cutchin, D346779, 10/1/08.
Triflumizole – Scoping Assessment. C. Eiden, D332497, 4/2/07.

Triflumizole – Drinking Water Assessment, C. Koper, D395021, 1/9/12.
Triflumizole – Dietary Exposure Assessment, W. Donovan, D397935, 3/28/12.
Triflumizole SLUA, BEAD, 9/2/11.
Triflumizole – Results of the MARC Meeting, J. Tyler, 3/12/02.

1.0 Executive Summary

Triflumizole is a broad spectrum, imidazole fungicide (group 3) that inhibits ergosterol biosynthesis in fungi. In the U.S., triflumizole is registered to Chemtura USA Corporation and is formulated as 50% water soluble packets (WS), 50% water dispersible granules (WDG), and as 480SC (suspension concentrate) at approximately 42% active ingredient (ai). It is registered for use on many agricultural crops, ornamentals in greenhouses/shade houses, interior scapes, and Christmas trees/conifers on nurseries and plantations. It is used as a pre-plant seed piece treatment on pineapples. Triflumizole can also be applied to trees, shrubs, and vines. There are no registrations on turf and garden vegetable uses.

HED reviewed the toxicity database for triflumizole, as well as the most recent risk assessment (DP 363719, Cutchin, W., 4-1-09), and concluded that no changes in point of departures (PODs), endpoints of concern or FQPA Safety Factors are warranted. Since the last risk assessment, an immunotoxicity study in mice was submitted and reviewed. The results of this study did not impact the overall risk assessment.

For plant commodities, the tolerance expression and risk assessments include parent and all metabolites containing the 4-chloro-2-trifluoromethylaniline moiety. For livestock commodities, the tolerance expression and risk assessments include parent, the metabolite 4-chloro-2-hydroxy-6-trifluoromethylaniline sulfate, and other metabolites containing the 4-chloro-2-trifluoromethylaniline moiety. The drinking water risk assessment includes parent and all metabolites containing the 4-chloro-2-trifluoromethylaniline moiety.

Adequate residue chemistry data have been provided for all crop uses of triflumizole. However, previously recommended changes to 40 CFR 180.476 are still needed (see Recommended Tolerances).

Revised dietary exposure assessments were conducted to incorporate updated percent crop treated information from the Biologic and Economic Analysis Division (BEAD) and updated estimated drinking water concentrations (EDWCs) from the Environmental Fate and Effects Division (EFED). Drinking water was incorporated directly in the dietary assessments.

The acute dietary (food + water) exposure assessments used tolerance level residues and 100% crop treated (CT) for all registered uses. These assessments demonstrate that the acute dietary risk estimates are not of concern for the general U.S. population (26% aPAD, 0.065598 mg/kg/day) and all population subgroups. Children 1-2 years old was the most highly exposed population subgroup at 39% aPAD and 0.096453 mg/kg/day. Exposure was equivalent to 0.068075 mg/kg/day or 68% of the aPAD for females 13-49 years old.

The chronic dietary exposure assessment used anticipated residues (ARs) from average field trial results and the most recent % CT information from BEAD. This assessment shows that the chronic dietary exposure estimates are not of concern for the general U.S. population (19% cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old at 32% cPAD. A cancer assessment was not performed because triflumizole is not carcinogenic.

HED has recently revised the Agricultural Re-entry Task Force (ARTF) and Pesticide Handler Exposure Database (PHED), and has conducted new occupational risk assessments for triflumizole. Based on this updated occupational exposure and risk assessment, HED is recommending the following label revisions:

When applying sprays with open cab air blast equipment on grapes, apple, pear and cherry, handlers must wear a chemical resistant hat to achieve the target MOE ≥ 300. The MOE with the current label PPE recommendations (single layer and glove) is 230. With the exception of hops and grapes, the post-application risk estimates did not exceed HED's LOC (i.e., MOEs ≥ 300) on day 0 using the highest relevant transfer coefficient. The Restricted Entry Interval (REI) for hops and grapes should be extended from the current REI (zero days) to 3 and 4 days respectively to achieve the target MOE ≥ 300. The MOEs on day zero are 200 for grapes and 270 for hops.

Data Deficiencies

HED has examined the toxicology and residue chemistry databases for triflumizole and found both to be complete.

Tolerance Considerations

Enforcement Analytical Method

Adequate plant and livestock analytical enforcement methods are available to enforce tolerances for residues of triflumizole (D346779, W. Cutchin, 10/1/08).

International Harmonization

Codex has not established Maximum Residue Limits (MRLs) for residues of triflumizole in/on various raw agricultural and processed commodities. Tolerance definitions are harmonized between Canada and the U.S. Additionally, all Canadian MRLs are harmonized with the corresponding US tolerance levels (see Appendix B).

Recommended Tolerances

HED recommends that the residue definition for the tolerance expression for triflumizole be modified in accordance with current policy on tolerance definitions (S. Knizner, 5/27/09), to read as follows for 40 CFR § 180.476(a)(1):

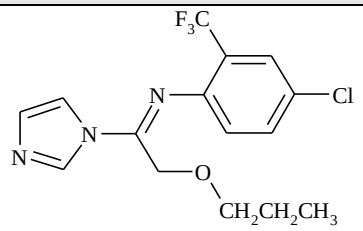
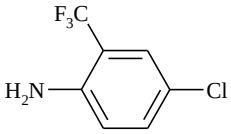
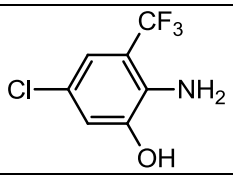
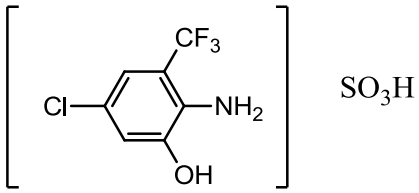
> *"Tolerances are established for residues of triflumizole (1-[(1E)-1-[[4-chloro-2-(trifluoromethyl)phenyl]imino]-2-propoxyethyl]-1H-imidazole), including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified is to be determined by measuring only those triflumizole residues convertible to 4-chloro-2-trifluoromethylaniline, expressed as the stoichiometric equivalent of triflumizole, in or on the commodity."*

Similarly, 40 CFR § 180.476(a)(2) should be revised to:

> *"Tolerances are established for residues of triflumizole (1-[(1E)-1-[[4-chloro-2-(trifluoromethyl)phenyl]imino]-2-propoxyethyl]-1H-imidazole), including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified is to be determined by measuring those triflumizole residues convertible to 4-chloro-2-trifluoromethylaniline plus the metabolite 4-chloro-2-hydroxy-6-trifluoromethylaniline sulfate, expressed as the stoichiometric equivalent of triflumizole, in or on the commodity."*

No changes to tolerance levels have occurred as a result of this registration review. However, some recommendations for changes made in a previous review are not currently reflected in the 40 CFR § 180.476 (D346779, W. Cutchin, 10/1/08). The following tolerances should be deleted from 180.476(a)(1): apple, dry pomace; apple, wet pomace; grape, dried pomace; grape, raisin, waste; and grape, wet pomace. The commodity listed as "cilantro, leaves" should be changed to "coriander, leaves." Also, the following tolerances should be deleted from 180.476(a)(2): cattle, meat; egg; goat, meat; hog, fat; hog, meat; hog, meat byproducts; horse, meat; milk; poultry, fat; poultry, meat; poultry, meat byproducts; and sheep, meat. Tolerance levels for the following commodities should be lowered from 0.5 to 0.10 ppm: fat of cattle, sheep, goat, and horse. Tolerance levels for the following commodities should be lowered from 0.5 to 0.20 ppm: meat byproducts of cattle, sheep, goat, and horse.

Chemical Identity

Table 3.1 Trifumizole and Metabolite Nomenclature	
Chemical structure	
Empirical formula	$C_{15}H_{15}N_3OClF_3$
Common name	Triflumizole
IUPAC[1] name	(*E*)-4-chloro-α,α,α-trifluoro-*N*-(1-imidazol-1-yl-2-propoxyethylidene)-*o*-toluidine
CAS[2] name	1-[(1*E*)-1-[[4-chloro-2-(trifluoromethyl)phenyl]imino]-2-propoxyethyl]-1*H*-imidazole
CAS registry number	68694-11-1
End-use products (EPs)	Procure® 50WS; EPA Reg. No. 400-431 Procure® 480SC; EPA Reg. No. 400-518
Chemical class	Imidazole
Common moiety structure	
Common name	FA-1-1
IUPAC name	4-chloro-2-trifluoromethylaniline
Livestock common moiety structure	
Common name	FA-1-5
IUPAC name	4-chloro-2-hydroxy-6-trifluoromethylaniline
Livestock metabolite	
Common name	FA-1-5-S
IUPAC name	4-chloro-2-hydroxy-6-trifluoromethylaniline sulfate

[1] IUPAC = International Union of Pure and Applied Chemistry
[2] CAS = Chemical Abstracts Service

Physical/Chemical Characteristics

Triflumizole's physical and chemical properties are summarized below in Table 3.2.

Table 3.2. Physicochemical Properties of Triflumizole.		
Parameter	Value	Reference
Melting point/range	63.5°C	DEB# 6410, J. Smith, 1/7/92
pH	Not available	
Bulk Density	0.50-0.70 (at 20ºC)	
Water solubility (g/L at 20ºC)	0.0125 (at pH 5.9)	
Solvent solubility (g/100 mL at 20ºC)	Chloroform 222 Acetone 144 n-Hexane 1.76 Methanol 49.6 Xylene 63.9	
Vapor pressure (at 25ºC)	1.4×10^{-6} mmHg	
Dissociation constant, pK_a	3.7	
Octanol/water partition coefficient, $Log(K_{OW})$ at 25ºC	25	
UV/visible absorption spectrum	Not available	

Toxicology Assessment

The toxicology database for triflumizole is complete. The database of laboratory animal studies spans multiple routes of exposure (oral, dermal, inhalation) and animal species (rat, mouse, dog) and consists of studies ranging from a single exposure (acute) to subchronic and chronic exposures. Additionally, there are developmental toxicity studies in rats and rabbits, a rat reproductive toxicity study, an immunotoxicity study and acute and subchronic neurotoxicity studies. A summary of the current toxicity data available for triflumizole is included in the toxicity profile in Appendix A.

The liver is the primary target organ of triflumizole in the rat, mouse, and dog as evidenced by increased liver weight, hepatocyte fatty vacuolization, hypertrophy, inflammation, fatty degeneration, and necrosis. Specific subchronic effects included increased absolute and relative liver weights, accumulation of fat droplets, and slight hepatocyte centrilobular swelling. Chronic effects included hepatocyte fatty vacuolization; hepatocyte hypertrophy, focal inflammation, and necrosis; fatty degeneration; eosinophilic foci of hepatocyte alteration; hepatic nodules; bile duct hyperplasia; and hyaline degeneration/fibrosis of the bile duct. Liver effects were seen in rat and mouse subchronic and chronic/carcinogenicity studies.

Triflumizole is classified as not likely to be carcinogenic to humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern.

There was no evidence of neurotoxicity in the acute and subchronic neurotoxicity studies in the rat with triflumizole.
In oral rat developmental studies, fetal effects (decreased numbers of viable fetuses, increased dead or resorbed fetuses, increased numbers of late resorptions, decreased fetal body weight and

increased incidences of cervical ribs) were seen in the fetuses at the same doses at which maternal toxic effects were noted. Reproductive toxicity, manifested as increased gestation length, was increased at the high dose. There is no evidence for quantitative or qualitative susceptibility following *in utero* exposure or following pre-and post natal exposure.

Since the last risk assessment, an immunotoxicity dietary study in female BALB/c mice has been submitted and reviewed. The study revealed a significant decrease in the anti-SRBC IgM response at a dose level of 285.7 mg/kg/day. The NOAEL was 28.6 mg/kg/day. The results of the immunotoxicity study do not impact the point of departures (PODs) selected for dietary and non-dietary exposure risk assessments (W. Cutchin, D363719, 4/1/09).

The toxicological endpoint selected for dietary and non-dietary risk assessments are presented in Appendix A. Separate PODs were selected for females of child-bearing age (13-49) and the general population including infants and children. For females 13-49, a developmental endpoint was selected with a NOAEL 10 mg/kg/day and a LOAEL = 35 mg/kg/day. For the general population the POD was the NOAEL = 25 mg/kg/day and a LOAEL = 100 mg/kg/day at which functional observational battery (FOB) findings (neuromuscular impairment) and decreased locomotor activity were observed following a single exposure. An uncertainty factor of 100x (10x for inter-species extrapolation and 10x intra-species variation) was applied to derive the acute Reference Doses (RfD) for these population groups. The chronic dietary endpoint is based on liver toxicity observed at 3.5 mg/kg/day, the lowest dose tested in the combined chronic toxicity/carcinogenicity study in rats; a NOAEL was not established. An uncertainty factor of 300x (10x for inter-species extrapolation, 10x intra-species extrapolation and 3x for the use of a LOAEL (UF_L)) was used to derive the chronic RfD. An oral NOAEL of 3.5 mg/kg/day for offspring toxicity seen at 8.5 mg/kg/day from a two-generation reproduction study was used for assessing dermal and inhalation risk resulting from short-term exposures. A Margin of Exposure (MOE) of 100 is adequate for these exposure scenarios. An oral LOAEL of 3.5 mg/kg/day based on liver toxicity in the combined chronic toxicity/carcinogenicity was used for assessing dermal and inhalation risks resulting from intermediate- and long term exposures. Since a LOAEL was used, a MOE of 300 is required for these scenarios. An upper-bound estimate of dermal absorption of 3.5% was calculated by comparing the maternal LOAEL from the rat developmental study with the NOAEL from the rat dermal study. Since oral doses were used, dermal (3.5%) and inhalation (100%) absorption factors are used for route-to-route extrapolation.

The toxicology data base is complete and there are no residual uncertainty for pre-and post natal toxicity. The FQPA Safety Factor is reduced (1x) for acute dietary and short term (dermal and inhalation) exposure scenarios. However, a 3X FQPA Safety Factor is retained in the form of a LOAEL to NOAEL factor (UF_L) for assessing chronic dietary and intermediate- and long term dermal and inhalation risks from occupational use. The Agency has determined that a 3x for the use of a LOAEL (as opposed to the default 10x) is adequate based on the following weight of evidence considerations:

- The most sensitive endpoint in the target organ (liver) for this class of compounds (conazole fungicide) is used for assessing chronic risk.

- There is low concern for the observed effects since the observed lesions (eosinophilic foci in male rats and fatty vacuolation and inflammation and necrosis in female rats) did not progress into malignancy.
- The available data does not show this chemical to be a potent toxicant following short and long-term dietary exposure since clear NOAELs were established in all the other studies such as the reproduction (3.5 m/k/d), subchronic rat (15.3 m/k/d), subchronic mouse (33.1 m/k/d); chronic dog 10 m/k/d) and the mouse carcinogenicity (16.2 m/k/d) studies.
- The extrapolated NOAEL of 1.2 mg/k/d (3.5/3 = 1.2) is supported by a comparable NOAEL (2.5 m/k/d) used for deriving the chronic RfD for a structurally-related chemical (Imazalil).

Based on these factors, the Agency is confident that the risk assessment would not under estimate dietary and non-dietary risks from chronic exposure to triflumizole.

Endocrine Disruption Screening Program

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Although triflumizole is not among the group of pesticide active ingredients on the initial list to be screened under the EDSP, it is included in a second lists of chemicals considered for Tier 1 screening. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients. For further information on the status of the EDSP, the policies and procedures, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Residue Chemistry Assessment

Adequate residue chemistry data have been provided for triflumizole. Field trials are of adequate number and geographic representation. Data analyses employed validated analytical methods and are supported by adequate storage stability data. Sufficient processing studies were submitted to elucidate the fate of triflumizole in processed commodities. Wet apple pomace and pineapple processed residue are the only livestock feedstuffs. As neither is fed to poultry or swine, all poultry and hog tolerances should be revoked. Finite residue levels of triflumizole are possible in fat and meat byproducts of ruminants, and these tolerances should be retained, but at lower levels than currently listed in 40 CFR 180.476. Lower livestock commodity tolerance levels are appropriate because of the lower dietary burden recently determined (D346779, W. Cutchin, 10/1/08). Confined rotational crops studies show that the metabolism of triflumizole in rotated crops is similar to that in primary crops, although relatively less parent and more metabolites were found. Results from the limited rotational crop field trials also indicated that the following current plant-back intervals are appropriate for rotated crops: 30 days for leafy and fruiting vegetables; 60 days for root and tuber vegetables; and 1 year for cotton, small cereal grains, and any other crops without registered uses for triflumizole.

Dietary Exposure Assessment

Revised dietary exposure assessments were conducted to incorporate updated percent crop treated information from BEAD and updated EDWCs from EFED. Drinking water was incorporated directly in the acute and chronic dietary assessments.

Drinking Water Residues
D395021, C. Koper, 1/9/12

EFED provided ground and surface water EDWCs for triflumizole. Updated EDWCs were provided to include the use on ornamentals. The highest ground water EDWCs were based on the aerial use pattern for cherries, consisting of 6 applications at 0.5 lb ai/A, with a 7-day retreatment interval (RTI). This same use pattern was selected for calculation of the chronic surface water EDWC; the acute surface water EDWC was modeled on the use pattern for ornamentals [FL nursery]: 3 applications at 1.0 lb ai/A, with a 7-day RTI. Modeled values were provided since there are no comprehensive monitoring data for triflumizole in ground or surface water.

Table 1 summarizes the maximum EDWCs for triflumizole. In order to account for degradates containing the 4-chloro-2-trifluoromethylaniline moiety, EFED used the total toxic residue approach to account for both triflumizole and the residues of concern. Detailed information on how the individual modeling input parameters were derived can be obtained from the "Tier I Estimated Drinking Water Concentrations for Triflumizole Including Degradates" memo (S. Ramasamy, March 3, 2002) (D281356).

Table 1.Summary of Estimated Surface Water and Groundwater Concentrations for Triflumizole.		
Scenario	Surface Water Conc., ppb [a]	Groundwater Conc., ppb [b]
Acute	**85**	3.1
Chronic (non-cancer)	**21**	3.1
Chronic (cancer)	15	3.1

[a] From the Tier II PRZM-EXAMS - Index Reservoir model.
[b] From the SCI-GROW model.
Bolded values selected for use in the dietary exposure assessments.

Percent Crop Treated Used in Dietary Assessment

Updated percent crop treated (%CT) information was provided by the Office of Pesticide Program's (OPP's) Biological and Economic Analysis Division (BEAD) for apples, cantaloupes, cherries, cucumbers, grapes, hazelnuts (filberts), honeydew melons, pears, pumpkins, squash, strawberries, and watermelons in a Screening Level Usage Analysis (SLUA) dated 02-SEP-2011. Although BEAD provided maximum and average %CT information, only the chronic dietary risk assessment required the percent crop treated refinement; therefore, only the average %CT values were utilized in the dietary exposure analysis.

Acute Dietary Risk Assessment
D397935, W. Donovan, 3/28/12

The results of the acute dietary risk analysis are reported in Table 2. The acute dietary (food + drinking water) exposure assessment used tolerance-level residues and 100% CT for all registered crops; thus, the acute dietary analysis may be considered an unrefined assessment. Drinking water was incorporated directly in the dietary assessment using the maximum concentration for surface water generated by the PRZM/EXAMS model. These assessments demonstrate that the acute dietary risk estimates (95^{th} percentile) are not of concern (<100% aPAD) for the general U.S. population (26% aPAD, 0.065598 mg/kg/day) and all population subgroups. Children 1-2 years old was the most highly exposed population subgroup at 39% aPAD and 0.096453 mg/kg/day. Exposure was equivalent to 0.068075 mg/kg/day or 68% of the aPAD for females 13-49 years old.

Chronic Dietary Risk Assessment
D397935, W. Donovan, 3/28/12

The results of the chronic dietary exposure analysis are reported in Table 2. The chronic dietary exposure assessment used anticipated residues (ARs; average field trial values) for most crops and tolerance level residues for hazelnuts. The assessment used % CT information for apples, cantaloupes, cherries, cucumbers, grapes, hazelnuts (filberts), honeydew melons, pears, pumpkins, squash, strawberries, and watermelons; and 100% CT for all other crops. Thus, the chronic dietary analysis may be considered a partially refined assessment. The chronic dietary (food + drinking water) risk assessment was conducted for the general U.S. population and various population subgroups. Drinking water was incorporated directly into the dietary assessment using the chronic (annual average) concentration for surface water generated by the PRZM/EXAMS model. This assessment concludes that the chronic dietary risk estimates are

below the Agency's level of concern (<100% cPAD) for the general U.S. population (19% cPAD) and all population subgroups. The most highly exposed population subgroup is children 1-2 years old at 32% cPAD.

Table 2. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Triflumizole.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer[a]	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.065598	26	0.002274	19	N/A	N/A
All Infants (< 1 year old)	0.041970	17	0.002517	22		
Children 1-2 years old	**0.096453**	**39**	**0.003785**	**32**		
Children 3-5 years old	0.086183	34	0.003259	28		
Children 6-12 years old	0.067224	27	0.002189	19		
Youth 13-19 years old	0.055321	22	0.001771	15		
Adults 20-49 years old	0.065771	26	0.002211	19		
Adults 50+ years old	0.060108	24	0.002236	19		
Females 13-49 years old	0.068075	**68**	0.002168	19		

[a] Because triflumizole is not a carcinogen, no cancer risk assessment was conducted.

Residential Risk Assessment

The registered non-occupational uses of triflumizole include a foliar spray by home owner and commercial applicators to landscape grown trees, shrubs and vines. Triflumizole is also registered for use on residential/non-commercially grown bearing apples, pears and grapes. Though not a restricted use pesticide, the product is intended for "commercial" use and "private residential" use. There are no registered uses on lawns or turf.

Residential Handler Exposure

Residential short-term (1-30 days) dermal and inhalation exposures are expected for triflumizole handler activities associated with use on ornamental plants. The results of the residential handler exposure and risk assessment are presented in Appendix C. The total short-term margins of exposure (MOEs) are not of concern (i.e. an MOE $\geq$ 100) with baseline attire (shorts, short-sleeves, shoes and socks). For triflumizole the dermal and inhalation endpoints are based on the same toxicological effect, therefore the MOEs are combined to determine a total risk estimates.

Post-Application Exposure

Post-application exposure from triflumizole use on landscape ornamentals is expected to be negligible based on the following factors: 1) Children young enough to exhibit hand-to-mouth behavior would not typically play in ornamental beds or tree plots; 2) If present, leaf to skin residue transfer would be negligible because of the minimal frequency and duration of contact. Based on the low frequency of application and low likelihood for significant post-application exposure, there are no residential risk concerns for post-application exposure. Therefore, a quantitative post-application residential exposure and risk assessment was not conducted.

Aggregate Risk Assessment

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

Acute Aggregate Risk

In examining acute aggregate risk, HED has assumed that the only pathway of exposure relevant to the acute time frame is dietary exposure. Therefore, the acute aggregate risk is comprised of exposures to triflumizole residues in food and drinking water and is equivalent to the acute dietary risk estimates summarized in Table 2 above. The acute risk estimates are well below HED's level of concern for all population subgroups.

Short-Term Aggregate Risk

The residential handler exposure from applying triflumizole using a hand held pump sprayer was the exposure scenario with the highest estimated risk, and was therefore combined with the chronic dietary exposure for adults (General US population), to estimate the highest aggregate exposure and risk. Despite the numerous conservative assumptions in developing these estimates, the MOE is above the LOC of 100, and is not of concern (Table 3).

Table 3. Short-Term and/or Intermediate Term Aggregate Risk Calculations

Population	Short- or Intermediate-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Adult Male	3.5	100	0.035	0.002274	0.025	0.027	130

[1] The LOC is based on the standard inter- and intra- species uncertainty factors totaling 100. The FQPA Safety Factor has been reduced to 1X.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Residential Exposure = [Dermal exposure + Inhalation Exposure].
[4] Total Exposure = Avg Food + Drinking Water Exposure + Residential Exposure.
[5] Aggregate MOE = NOAEL of 3.5 mg/kg/day/ (Avg Food + Drinking Water Exposure + Residential Exposure)

Intermediate-Term Aggregate Risk

There are no current residential uses which result in intermediate-term exposure. Therefore, an intermediate-term aggregate risk assessment was not performed nor required.

Chronic Aggregate Risk

In examining chronic aggregate risk, HED has assumed that the only pathway of exposure relevant to this time frame is dietary exposure. Therefore, chronic aggregate risk is comprised of exposures to triflumizole residues in food and drinking water and is equivalent to the chronic dietary risk summarized in Table 2 above. The chronic risk estimates are below HED's level of concern for all population subgroups. Because triflumizole is not a carcinogen, no cancer risk assessment was conducted.

Occupational Risk Assessment

Short-/Intermediate-term Handler Risk

Triflumizole products can be applied to apples, pears, cherries, cucurbit vegetables, grapes, strawberries, hazelnuts, brassica leafy greens and for pre-plant treatment of pineapple seed pieces for foliar disease control via airblast, groundboom, aircraft, dip tank, or chemigation. Handler exposure is expected to be short- or intermediate-term based on information provided on the labels. The labels state that all handlers must wear the proper personal protective equipment (PPE): a long-sleeved shirt, long pants, chemical resistant gloves, shoes, and socks. Based on this assessment, triflumizole's labels need to be amended to include a requirement to wear chemical resistant hat for application with open cab air blast equipment in order to meet the target MOE of 300. The MOE with the current label PPE recommendations (single layer and glove) is 230.

The maximum application rate for each exposure scenario is presented as the worst case scenario. All handler scenarios (mixer/loader, applicator, and flagger) are considered to be short and intermediate-term. Both short- and intermediate-term total (dermal and inhalation) MOEs were above the target exposure levels of 100 and 300, respectively, and therefore do not exceed HED's level of concern (Appendix C).

Short-/Intermediate-Term Post-Application Risk

HED default assumptions, triflumizole-specific DFR data (MRID # 45375401) and the revised Agricultural Re-entry Task Force (ARTF) data base were used in assessing post application activities. With the exception of hops and grapes, the intermediate-term post-application risk estimates did not exceed HED's LOC (i.e., MOEs $\geq$ 300) on day 0 using the highest relevant transfer coefficient. For hops and grapes the intermediate-term post-application risk estimates did not exceed HED's LOC (i.e., MOEs $\geq$ 300) on days 3 and 4, respectively. The activities with the highest estimated risk are mechanically assisted harvesting for hops and girdling for grapes. The MOE's on day zero are 200 for grapes and 270 for hops.

Inhalation Postapplication Risk

Although a quantitative occupational postapplication inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than postapplication exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of occupational postapplication inhalation exposure scenarios. Since handler inhalation exposure is not of concern, post-application inhalation exposure is not of concern.

Restricted Entry Interval

For hops and grapes the intermediate-term post-application risks did not exceed HED's LOC (i.e., MOEs ≥ 300) on days 3 and 4, respectively. The MOE's on day zero are 200 for grapes and 270 for hops. This is a change from the previous risk assessment due to revised ARTF data which was used to calculate exposure and risk at various reentry intervals. The activities with the highest estimated risk are mechanically assisted harvesting for hops and girdling for grapes. For the remaining crops the intermediate-term post-application risks did not exceed HED's LOC (i.e., MOEs ≥ 300) on day zero. The label REIs are currently based on the acute toxicity of technical chemical material. Under the Worker Protection Standard WPS, active ingredients classified as acute toxicity category III or IV for acute dermal and primary skin irritation are assigned a 12-hour REI. Thus, with the exception of hops and grapes the 12-hour REI on the triflumizole label is acceptable. The post-application occupational exposure exceeds the Agency's level of concern for hops and grapes at day zero (MOE = 200 for grape and 270 for hops , Target MOE = 300); therefore, the current REI of zero days (for hops and grapes) must be extended to 3 and 4 days respectively to achieve risks below the Agency levels of concern (MOEs of ≥ 300).

Appendix A. Toxicity Profile and Endpoint Selection

Acute Toxicity Profile – Triflumizole				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [rat]	00144463	LD_{50} = 1362 mg/kg	III
870.1200	Acute dermal [rat]	00144465	LD_{50} > 5000 mg/kg	IV
870.1300	Acute inhalation [rat]	00144466	LC_{50} > 3.2 mg/L	IV
870.2400	Acute eye irritation [rabbit]	00144467	Slight ocular irritant	III
870.2500	Acute dermal irritation [rabbit]	00144468	Not a dermal irritant	IV
870.2600	Skin sensitization [Guinea pig]	00144469	Mild dermal sensitizer	N/A

Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	45498001 (1980) Acceptable/guideline 0, 20, 200, 2000 ppm M: 0, 1.4, 15.3, or 176.5 mg/kg/day F: 0, 1.8, 17.2, or 217.9 mg/kg/day	NOAEL = Males: 15.3 mg/kg/day; Females: 17.2 mg/kg/day LOAEL = Males: 176.5 mg/kg/day; Females: 217.9 mg/kg/day based on increased kidney and liver weights and the accumulation of fat droplets in the liver.
870.3100	90-Day oral toxicity rodents (mouse)	45498002 (1980) Acceptable/guideline 0, 20, 200, 2000 ppm M: 0, 3.2, 33.1, or 380.7 mg/kg/day F: 0, 4.2, 42.6, or 466.2 mg/kg/day	NOAEL = Males: 33.1 mg/kg/day; Females: 42.6 mg/kg/day LOAEL = Males: 380.7 mg/kg/day; Females 466.2 mg/kg/day based on reduced growth.
870.3150	90-Day oral toxicity (nonrodents)	NA	NA
870.3200	21/28-Day dermal toxicity (rat)	41706601 (1990) Acceptable/guideline 0, 10, 100, or 1000 mg/kg/day 6 hr/day, 7 d/week	NOAEL ≥1000 mg/kg/day LOAEL = not identified
870.3250	90-Day dermal toxicity	NA	NA
870.3465	90-Day inhalation toxicity	NA	NA
870.3700a	Prenatal develop-mental in rodents (rat)	00157075 (1986) Acceptable/non-guideline (complimentary) F:0 or 3 mg/kg/day	Must be considered with MRID 45458001 LOAELs/NOAELs not assigned

Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700a	Prenatal developmental in rodents (rat)	00164384 (1986) Acceptable/non-guideline (repeat) F: 0, 3, 7, or 35 mg/kg/day	Must be considered with MRID 45458001 LOAELs/NOAELs not assigned
870.3700a	Prenatal developmental in rodents (rat)	45458001 (1983) Acceptable/non-guideline F: 0, 10, 35, or 120 mg/kg/day	**Maternal** NOAEL = 10 mg/kg/day LOAEL = 35 mg/kg/day based on decreased body weight gain and food consumption,; increased placental weight, and increased maternal spleen and liver weights. **Developmental** NOAEL = 10 mg/kg/day LOAEL = 35 mg/kg/day based on decreased numbers of viable fetuses, increased dead or resorbed fetuses, increased numbers of late resorptions, decreased fetal body weight,and increased incidences of cervical ribs.
870.3700b	Prenatal developmental in nonrodents (rabbit)	00156546 (1985) Acceptable/guideline F: 0, 50, 100, or 200 mg/kg/day	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight gains, food consumption, and placental weights. **Developmental** NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day based on decreased 24-hour survival, decreased placental weights, and increased fetal and litter incidences of lumbar ribs.
870.3700b	Prenatal developmental in nonrodents (rabbit)	40752003 (1988) Unacceptable/guideline F: 0, 5, 25, or 50 mg/kg/day	Must be considered with MRID 00156546 **Maternal** NOAEL = 50 mg/kg/day LOAEL = not identified **Developmental** NOAEL = 50 mg/kg/day LOAEL = not identified
870.3800	Reproduction and fertility effects (rat)	00162176 (1986) 00156548 (1984) 40301602 (1987) Acceptable/guideline with MRID 156547 0, 30, 70, or 170 ppm P: 0, 1.5, 3.5, or 8.5 mg/kg/day	**Parental/Systemic** NOAEL = 8.5 mg/kg/day LOAEL = not established **Reproductive** NOAEL = 3.5 mg/kg/day (reproductive NOAEL), based upon increased gestation length in the dams of F_{1a}, F_{2a}, and F_{3a} intervals at the LOAEL of 8.5 mg/kg/day. **Offspring** NOAEL = 3.5 mg/kg/day LOAEL = 8.5 mg/kg/day based on decreased pup weights, survival indices, and litter sizes in both F_3 litters, reduced litter size in the F_{1a} litter, increased total-litter mortality in the F_{3a}litter, and developmental effects in the F_{1b} and F_{2b} progeny.

Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100a	Combined chronic toxicity/carcinogenicity (rats)	00156545 (1984) Acceptable/guideline 0, 100, 400, or 1600 ppm M: 0, 3.5-3.7, 14.1-15.1, or 59.4-62.0 mg/kg/day F: 0, 4.5-4.6, 18.0-18.1, or 77.0-78.0 mg/kg/day	LOAEL = 3.5 mg/kg/day, based on liver toxicity (eosinophilic foci in male rats and fatty vacuolation and inflammation and necrosis in female rats). NOAEL is <3.5 mg/kg/day because the lowest dose tested is the LOAEL
870.4100b	Chronic toxicity (dog)	00149848 (1984) Acceptable/guideline 0, 100, 300, or 1000 ppm M: 0, 3.33, 10.00, or 34.10 mg/kg/day F: 0, 3.27, 10.69, or 35.17 mg/kg/day	NOAEL = Males: 10.00 mg/kg/day; Females: 10.69 mg/kg/day LOAEL = Males: 34.10 mg/kg/day; Females: 35.17 mg/kg/day based on increased alkaline phosphatase activity and a mild, macrocytic anemia in males, increased absolute and relative liver weights in both sexes, and on macroscopic findings in the liver of both sexes.
870.4200	Carcinogenicity (rat)	NA; see 870.4300	NA
870.4300	Chronic Toxicity/ Carcinogenicity (mouse)	00156544 (1984) Acceptable/guideline 0, 100, 400, or 1600 ppm M: 0, 16.2, 67.4, or 296.1 mg/kg/day F: 0, 21.7, 86.1, or 362.2 mg/kg/day	NOAEL = Males: 16.2 mg/kg/day; Females: 21.7 mg/kg/day LOAEL = Males: 67.4 mg/kg/day; Females: 86.1 mg/kg/day based on microscopic lesions of the liver. **No evidence of carcinogenicity**
870.5100	Bacterial reverse mutation	40494409 (1987) Acceptable seven concentrations ranging from 5 to 5000 µg/plate	Negative with or without S9 activation at 5000 µg/plate and less.
870.5100	Bacterial reverse mutation	45502203 (1983) Acceptable concentrations ranging from 8 to 8000 µg/plate	Negative with or without S9 activation at 8000 µg/plate and less.
870.5375	*In vitro* mammalian chromosome abberation (CHL)	40494408 (1987, 1988) Acceptable 5 to 40 µg/mL	Negative with or without S9.
870.5395	*In vitro* mammalian cytogenetics (mouse bone marrow)	00160620 (1986) Acceptable M&F: 160, 533 and 1600 mg/kg (single oral dose)	Negative. Not clastogenic for the production of micronuclei in bone marrow polychromatic erythrocytes in mice at single oral doses up to 1600 mg/kg.
870.5500	DNA damage/repair *REC* assay	45502204 (1983) Unacceptable concentrations range from 24 to 24,000 mg/disk	Negative. No evidence of DNA damage up to 24,000 mg/disk. Study is unacceptable because a metabolic activation system was not used.
870.5550	UDS in primary rat hepatocytes	45502205 (1984) Acceptable 12.5 to 30 µg/mL	Negative. No evidence of unscheduled DNA synthesis up to cytotoxic concentrations.

Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.6200a	Acute neurotoxicity screening battery	46202502 (year)	NOAEL = 25 mg/kg/day LOAEL = 100 mg/kg/day, based on FOB findings (neuromuscular impairment, as evidenced by decreased hind-and fore-limb grip strength, impaired gait and mobility, abnormal righting reflex) and decreased locomotor activity
870.6200b	Subchronic neurotoxicity screening battery	46202502, 46259401 Acceptable/guideline	NOAEL = 2000 ppm (133.3 mg/kg bw/day), HDT.
870.6300	Developmental neurotoxicity	NA	NA
870.7485	Metabolism and pharmacokinetics (rat)	40789101 (1988) Acceptable/guideline with 41606201 and 41606202 M&F: 10 mg/kg as single oral dose	Following oral treatment of rats with [phenyl-U-^{14}C]-NF-114, no sex-related differences were observed in absorption, metabolism, distribution or excretion. Maximum concentrations of radioactivity in plasma were attained within 1 hour of dosing in both sexes. Low levels of radioactivity were detectable in all tissue, organ, and blood samples. Radioactivity in urine accounted for 69.5-74.4% of the dose and feces accounted for 21.7-21.9% of the dose. Based on the metabolite profile, the metabolism in rats primarily involves oxidation to FM-8-1 and FA-1-5, followed by sulfation and glucuronidation.
870.7485	Metabolism and pharmacokinetics (rat)	41606201 (1983) 41606202 (1984) Acceptable/guideline with 40789101 M&F: 10 or 300 mg/kg as single oral dose	Following oral treatment of rats with [phenyl-U-^{14}C]-NF-114, approximately 93.8-100.6% of the administered dose was recovered. Urine was the major route of excretion. Low levels of radioactivity were detectable in all tissue, organ, and blood samples collected 2 days (10 mg/kg group) or 4 days (300 mg/kg group) post-dose with tissue concentrations generally higher in males than females. The metabolite profile in the excreta was quantitatively and qualitatively similar between the sexes and dose groups. Based on the metabolite profile, the biotransformation of NF-114 in rats primarily involved oxidation of parent to FM-8-1 and FA-1-5, followed by conjugation yielding sulfate and glucuronic acid conjugates.
870.7600	Dermal penetration	NA	NA

Subchronic, Chronic and Other Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Hepatic enzyme induction	Special studies	40830401 (1988) Acceptable/nonguideline M&F: 0 or 200 mg/kg/day as oral dose for five consecutive days	The study provides evidence that triflumizole induces hepatic microsomal enzymes when administered orally. However, no correlation between the increased enzyme activities and hepatic lesions observed following chronic administration was made since no histopathology was performed.
870.7800	Immunotoxicity	48086101 Acceptable/guideline	LOAEL = 2000 ppm (285.7 mg/kg/day) based on significant decrease in the anti-SRBC IgM response. NOAEL = 200 ppm (28.6 mg/kg/day).

Summary of Toxicological Doses and Endpoints for Triflumizole for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Acute Dietary (General Population, including Infants and Children)	NOAEL= 25 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Acute RfD = 0.25 mg/kg/day aPAD = 0.25 mg/kg/day	Acute Neurotoxicity Study – Rat LOAEL = 100 mg/kg/day based on FOB findings (neuromuscular impairment) and decreased locomotor activity.
Acute Dietary (Females 13-49 years of age)	NOAEL = 10 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Acute RfD = 0.1 mg/kg/day	Developmental Toxicity Study – Rat Developmental LOAEL = 35 mg/kg/day based on decreased numbers of viable fetuses, increased dead or resorbed fetuses, increased numbers of late resorptions, decreased fetal body weight, and increased incidences of cervical ribs.
Chronic Dietary (All Populations)	LOAEL=3.5 mg/kg/day	UF_A= 10x UF_H= 10x FQPA:UF $_{LOAEL \rightarrow NOAEL}$ = 3x	Chronic RfD = 0.0117 mg/kg/day cPAD = 0.0117mg/kg/day	Combined Chronic Toxicity/Carcinog. Study - Rat Based on liver toxicity (eosinophilic foci in male rats and fatty vacuolation and inflammation and necrosis in female rats).
Dermal Short-Term (1-30 days)	NOAEL= 3.5 mg/kg/day	UF_A= 10x UF_H= 10x	Residential and Occupational LOC for MOE = 100	Multi-generation Reproduction Study - Rat LOAEL = 8.5 mg/kg/day based on decreased pup body weight, mortality, reduced litter size and increased incidence of hydroureter and space between the body wall and organs were observed at 8.5 mg/kg/day (NOAEL = 3.5 mg/kg/day). In addition, gestation length was increased in the dams of F_{1a}, F_{2a}, and F_{3a} intervals at the LOAEL of 8.5 mg/kg/day (NOAEL = 3.5 mg/kg/day).
Dermal Intermediate- and Long-Term (1-6 months and 6 months and longer)	LOAEL= 3.5 mg/kg/day	UF_A= 10x UF_H= 10x $UF_{LOAEL \rightarrow NOAEL}$= 3x	Residential and Occupational LOC for MOE = 300	Combined Chronic Toxicity/Carcinog. Study - Rat Based on liver toxicity (eosinophilic foci in male rats and fatty vacuolation and inflammation and necrosis in female rats).

Summary of Toxicological Doses and Endpoints for Triflumizole for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Inhalation Short- Term (1-30 days)	NOAEL= 3.5 mg/kg/day	UF_A= 10x UF_H= 10x	Residential and Occupational LOC for MOE = 100	Multi-generation Reproduction Study - Rat LOAEL = 8.5 mg/kg/day based on decreased pup body weight, mortality, reduced litter size and increased incidence of hydroureter and space between the body wall and organs were observed at 8.5 mg/kg/day (NOAEL = 3.5 mg/kg/day). In addition, gestation length was increased in the dams of F_{1a}, F_{2a}, and F_{3a} intervals at the LOAEL of 8.5 mg/kg/day (NOAEL = 3.5 mg/kg/day).
Inhalation Intermediate- and Long-Term (1-6 months and 6 months and longer)	LOAEL= 3.5 mg/kg/day	UF_A= 10x UF_H= 10x $UF_{LOAEL \rightarrow NOAEL}$= 3x	Residential and Occupational LOC for MOE = 300	Combined Chronic Toxicity/Carcinog. Study - Rat Based on liver toxicity (eosinophilic foci in male rats and fatty vacuolation and inflammation and necrosis in female rats).
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Appendix B: International Harmonization

Summary of US and International Tolerances and Maximum Residue Limits : Triflumizole (PC Code 128879)				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR §180.476 Plant: parent compound triflumizole, 1-(1-((4-chloro-2-(trifluoromethyl)phenyl)imino)-2-propoxyethyl)-1 H -imidazole, and its metabolites containing the 4-chloro-2-trifluoromethylaniline moiety, calculated as stoichiometric equivalent of the parent compound.		1-[1-[[4-chloro-2-(trifluoromethyl)phenyl]imino]-2- propoxyethyl]-1H-imidazole, including metabolites containing the 4-chloro-2-trifluoromethylaniline moiety, expressed as triflumizole		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Apple	0.5	0.5		
Apple, dry pomace	2.0			
Apple, wet pomace	2.0			
Brassica,head and stem, subgroup 5A	8.0			
Brassica, leafy greens, subgroup 5B	40			
Canistel	2.5			
Cherry, sweet	1.5	1.5		
Cherry, tart	1.5	1.5		
Cilantro, leaves	35			
Grape	2.5	2.5		
Grape, dried pomace	15			
Grape, raisin, waste	10			
Grape, wet pomace	15			
Hazelnut	0.05			
Hop, dried cones	50			
Leafy greens subgroup 4A, except spinach	35			
Mango	2.5			
Papaya	2.5			
Pear	0.5	0.5		
Pineapple	4.0			
Sapodilla	2.5			
Sapote, black	2.5			
Sapote, mamey	2.5			
Star apple	2.5			
Strawberry	2.0	2.0		
Swiss chard	18			
Turnip,greens	40			
Vegetable, cucurbit, group 9	0.5	0.5 balsam apples, balsam pears, cantaloupes, chayote fruit, Chinese cucumbers, Chinese waxgourds, citron melons, cucumbers, edible gourds (other than those listed in this item), muskmelons (other than those listed in this item) pumpkins, summer squash, watermelons, west Indian gherkins, winter squash		

Summary of US and International Tolerances and Maximum Residue Limits : Triflumizole (PC Code 128879)				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR §180.476 Livestock: parent compound triflumizole, 1-(1-((4-chloro-2-(trifluoromethyl)phenyl)imino)-2-propoxyethyl)-1 H -imidazole, the metabolite 4-chloro-2-hydroxy-6-trifluoromethylaniline sulfate, and other metabolites containing the 4-chloro-2-trifluoromethylaniline moiety, calculated as the parent compound		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Cattle, fat	0.5			
Cattle, meat	0.05			
Cattle, meat byproduct	0.5			
Egg	0.05			
Goat, fat	0.5			
Goat, meat	0.05			
Goat, meat byproduct	0.5			
Hog, fat	0.5			
Hog, meat	0.05			
Hog, meat byproduct	0.5			
Horse, fat	0.5			
Horse, meat	0.05			
Horse, meat byproduct	0.5			
Milk	0.05			
Poultry, fat	0.05			
Poultry, meat	0.05			
Poultry, meat byproduct	0.1			
Sheep, fat	0.5			
Sheep, meat	0.05			
Sheep, meat byproduct	0.5			
Completed: : M. Negussie; 02/16/2012				

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Appendix C. Residential and Occupational Exposure and Risk Estimates for Triflumizole

Table 1: Short-Term Residential Handler Exposure and Risk Estimates for Triflumizole

Exposure Scenario	Target MOE	Dermal Unit Exposure	Inhalation Unit Exposure	Maximum Application Rate [a]	Amount Treated or Handled Daily [b]	Dermal		Inhalation		Total
						Dose [c]	MOE [d]	Dose [e]	MOE [f]	MOE[g]
Mixer/Loader/Applicator										
M/L/A Broadcast Hand Held Pump Sprayer (Gardens)	100	38	0.0027	1 (lb ai/A)	1 A	0.017	210	0.000034	100,000	210
M/L/A Broadcast Application Hand Held Pump Sprayer (Fruit Trees and Ornamentals)	100	56	0.0038	1 (lb ai/A)	1 A	0.025	140	0.000048	7,4000	140
M/L/A Spot Treatment Hand Held Pump Sprayer for (Gardens)	100	38	0.0027	1 (lb ai/A)	0.023 A	0.00038	9,200	7.8E-07	4,500,000	9,100
M/L/A Spot Treatment Hand Held Pump Sprayer (Fruit Trees and Ornamentals)	100	56	0.0038	1 (lb ai/A)	0.023 A	0.00056	6,200	0.0000011	3,200,000	6,200
M/L/A Hand Held Pump Sprayer (Gardens)	100	38	0.0027	0.0025 (lb ai/gal)	5 gal	0.00021	17,000	4.2E-07	8,300,000	17,000
M/L/A Hand Held Pump Sprayer (Fruit Trees and Ornamentals)	100	56	0.0038	0.0025 (lb ai/gal)	5 gal	0.00031	11,000	5.9E-07	5,900,000	11,000

a. Based on registered labels
b. Exposure Science Advisory Council Policy #9.1
c. Dermal Dose = Dermal Unit Exposure (mg/kg) x Application Rate (lb ai/A or gal) x Amount Treated or Handled (A or gallons/day) x DAF (3.5%)/BW (80 kg)
d. Dermal MOE = Dermal NOAEL (3.5 mg/kg/day)/Dermal Dose (mg/kg/day)
e. Inhalation Dose = Inhalation Unit Exposure (mg/kg) x Application Rate (lb ai/A or gal) x Amount Treated or Handled (A or gallons/day) /BW (80 kg)
f. Inhalation MOE = Inhalation NOAEL (3.5 mg/kg/day)/ Inhalation Dose (mg/kg/day)
g Total MOEs =1/[(1/Dermal MOE) + (1/Inhalation MOE)]. Level of concern = 100

Table 2: Short-/Intermediate- Occupational Exposure and Risk Estimates for Triflumizole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure [1] mg /lb ai	Inhalation Unit Exposure [1] mg /lb ai	Application Rate [2] lb ai/A	Amount Treated Daily [3] Acre or Gallon	Dermal		Inhalation		Total
		Mitigation Level	Mitigation Level			Dose [4]	MOE [5]	Dose [6]	MOE [7]	MOE [8]
Mixer/Loader										
Mixing/Loading Liquids for Aerial Applications	Broccoli; Chinese Broccoli, Brussels Sprouts, Cabbage, Chinese Cabbage (Napa), Chinese Mustard Cabbage, Cauliflower, Cavalo Broccoli, And Kohlrabi, Cucumber, Gherkin, Gourds, Melons, Pumpkin, Squash ,Apples, Pear, Cherry Leafy Greens(except spinach)	0.22 (single layer/no glove	0.000219	0.25	350	0.0084	420	0.00024	15,000	400
	Hops	0.0376 single layer/glove		0.375		0.0022	1,600	0.00036	9,700	1,400
	Strawberry	0.22 (single layer/no glove		0.125		0.0042	830	0.00012	29,000	810
	Hazelnut			0.19		0.0064	550	0.00018	19,000	530
Mixing/Loading Liquids for Chemigation Applications	Strawberry			0.125		0.0042	830	0.00012	29,000	810
	Broccoli; Chinese Broccoli, Brussels Sprouts, Cabbage, Chinese Cabbage (Napa), Chinese Mustard Cabbage, Cauliflower, Cavalo Broccoli, And Kohlrabi], Cucumber, Gherkin, Gourds, Melons, Pumpkin, Squash, Leafy green (except spinach)			0.25	350	0.0084	420	0.00024	15,000	400
Mixing/Loading Liquids for Groundboom Applications	Broccoli; Chinese Broccoli, Brussels Sprouts, Cabbage, Chinese Cabbage (Napa), Chinese Mustard Cabbage, Cauliflower, Cavalo			0.25	80	.0019	1,800	0.000055	64,000	1,800

Table 2: Short-/Intermediate- Occupational Exposure and Risk Estimates for Triflumizole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure [1] mg /lb ai	Inhalation Unit Exposure [1] mg /lb ai	Application Rate [2] lb ai/A	Amount Treated Daily [3] Acre or Gallon	Dermal		Inhalation		Total
		Mitigation Level	Mitigation Level			Dose [4]	MOE [5]	Dose [6]	MOE [7]	MOE [8]
	Broccoli, And Kohlrabi, Cucumber, Gherkin, Gourds, Melons, Pumpkin, Squash									
	Strawberry			0.125		0.00096	3,600	0.000027	130,000	3,500
Mixing/Loading Liquids for Airblast Applications	Apples, Pear, Cherry			0.5	40	0.0019	1,800	0.000055	64,000	1,800
	Canistel, Mango, Papayas, Sapodilla, Sapote, Star apple			0.31		0.0012	2,900	0.000034	100,000	2,900
	Hazelnut (filbert)			0.19		0.00073	4,800	0.000021	170,000	4,700
	Hops			0.375		0.0014	2,400	0.000041	85,000	2,400
	Grape			0.25		0.00096	3,600	0.000027	130,000	3,500
	Pineapple			0.005/lb/gal	100 gals	0.00048	73,000	0.0000014	2,600,000	71,000
Mixing/Loading Wettable Powders (WSP) for Aerial Applications	Apples, Pear	0.0098 (single layer/no glove with water soluble packages	0.00024	0.5	350	0.00075	4,700	0.00053	6,700	2,700
Mixing/Loading Wettable Powders for Airblast Applications	Grape	0.17 Single layer/glove	0.0434	0.5	40	0.0015	2400	0.0109	320	300
Mixing/Loading Wettable Powders for Airblast Applications	Apples, Pear	0.17 single layer/glove	0.0434	0.25		0.0007	4700	0.0054	650	600

Table 2: Short-/Intermediate- Occupational Exposure and Risk Estimates for Triflumizole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure [1] mg /lb ai	Inhalation Unit Exposure [1] mg /lb ai	Application Rate [2] lb ai/A	Amount Treated Daily [3] Acre or Gallon	Dermal		Inhalation		Total
		Mitigation Level	Mitigation Level			Dose [4]	MOE [5]	Dose [6]	MOE [7]	MOE [8]
Mixing/Loading Wettable Powders (WSP) for Aerial Applications	Apples, Pear, Cherry	0.0098 water soluble packages	0.00024	0.5	350	0.00075	4,700	0.00053	6,700	2,700
	Cucumber, Gherkin, Gourds, Melons, Pumpkin, Squash, Strawberries			0.25		0.00038	9,300	0.00026	13,000	5,500
	Hazelnut			0.19		0.00029	12,000	0.0002	18,000	7,200
	Hops			0.375		0.00056	6200	0.00039	8,900	3,700
Mixing/Loading Wettable Powders(WSP) for Airblast Applications	Grape			0.5	40	0.000086	41,000	0.00006	58,000	24,000
	Hazelnut			0.19		0.000033	110,000	0.000023	150000	63,000
	Apples, Pear, Cherry			0.50		0.000086	41000	0.00006	58,000	24,000
Mixing/Loading Wettable Powders (WSP) for Groundboom Applications	Cucumber, Gherkin, Gourds, Melons, Pumpkin, Squash, Strawberries			0.25	80	0.000086	41000	0.00006	58,000	24,000
Mixing/Loading Wettable powder (WSP) via Dip	Pineapple			0.005lb ai/gal	100gals	0.000021	160,000	0.000015	230,000	96,000
Mixing/Loading Dry Flowables for Airblast Applications	Apples, Pear	0.227	0.00896	0.25	40	0.0010	3,500	0.0011	3,100	1,700

Table 2: Short-/Intermediate- Occupational Exposure and Risk Estimates for Triflumizole.										
Exposure Scenario	Crop or Target	Dermal Unit Exposure [1] mg /lb ai	Inhalation Unit Exposure [1] mg /lb ai	Application Rate [2] lb ai/A	Amount Treated Daily [3] Acre or Gallon	Dermal		Inhalation		Total
		Mitigation Level	Mitigation Level			Dose [4]	MOE [5]	Dose [6]	MOE [7]	MOE [8]
Applicator										
Applying Sprays via Aerial Equipment	Broccoli; Chinese Broccoli, Brussels Sprouts, Cabbage, Chinese Cabbage (Napa), Chinese Mustard Cabbage, Cauliflower, Cavalo Broccoli, And Kohlrabi, Cucumber, Gherkin, Gourds, Melons, Pumpkin, Squash ,Apples, Pear, Cherry , Leafy Greens(except spinach) , strawberry	0.005 eng. control	0.000068	0.25	350	0.00019	18,000	0.000074	47,000	13,000
	Hops			0.375		0.00029	12,000	0.00011	31,000	8,800
	Hazelnut			0.19		0.00015	24,000	0.000057	62,000	17,000
Applying Sprays via Groundboom Equipment	Broccoli; Chinese Broccoli, Brussels Sprouts, Cabbage, Chinese Cabbage (Napa), Chinese Mustard Cabbage, Cauliflower, Cavalo Broccoli, And Kohlrabi, Cucumber, Gherkin, Gourds, Melons, Pumpkin, Squash , Strawberry	0.0786 open cab	0.00034	0.25	80	0.0007	5,100	0.000085	41,000	4,500
Applying Sprays via Open Cab Air blast Equipment	Apples, Pear, Cherry, grape	0.215 glove/chemical resistant hat	0.00471	0.5	40	0.0019	1,900	0.0012	3,000	1,100
	Canistel, Mango, Papayas, Sapodilla, Sapote, Star apple			0.31		0.0012	3,000	0.00073	4,800	1,800
	Hazelnut (filbert)			0.19		0.00071	4,900	0.00045	7,800	3,000
Flagger										

Table 2: Short-/Intermediate- Occupational Exposure and Risk Estimates for Triflumizole.										
Exposure Scenario	Crop or Target	Dermal Unit Exposure [1] mg /lb ai	Inhalation Unit Exposure [1] mg /lb ai	Application Rate [2] lb ai/A	Amount Treated Daily [3] Acre or Gallon	Dermal		Inhalation		Total
		Mitigation Level	Mitigation Level			Dose [4]	MOE [5]	Dose [6]	MOE [7]	MOE [8]
Flagging for Aerial Sprays Applications	All Crops	0.011	0.00035	0.5	350	0.0084	4,200	0.0077	4,600	2,200
Mixer/loader/Applicator										
Mixing/Loading /App Mixing/Loading /App Wettable Powder with Mechanically-pressurized Handgun (ORETF)	Ornamentals	1.3 single layer/glove	0.0039	0.005lb ai/gal	1000gals	0.0028	1200	0.0002	11000	1100
	Orchard crops			0.5	40 acres	0.011	310	0.0010	3600	300

[1] PHED/ORETF (level of mitigation: Baseline, PPE, Eng. Controls)
[2] Based on registered or proposed label
[3] Exposure Science Advisory Council Policy #9.1
[4] Dermal Dose = Dermal Unit Exposure (mg/kg) x Application Rate (lb ai/acre or gal) x Amount Treated (A/day) x DAF (3.5%)/BW (80kg)
[5] Dermal MOE = Dermal NOAEL (3.5 mg/kg/day)/Dermal Dose (mg/kg/day)
[6] Inhalation Dose = Dermal Unit Exposure (mg/kg) x Application Rate (lb ai/acre or gal) x Amount Treated (A/day) /BW (80kg)
[7] Inhalation MOE = Inhalation NOAEL (3.5 mg/kg/day)/ Inhalation Dose (mg/kg/day)
[8] Total MOE = 1/ (1/Dermal MOE + 1/Inhalation MOE)

Applicator with open cab air blast equipment on grapes, apple, pear and cherry must wear a chemical resistant hat to achieve the target MOE ≥ 300. The MOE with the current label PPE recommendations (single layer and glove) is 230.

Table 3: Dermal Post-application Exposure and Risk Using Chemical-Specific DFR Data.

Crop Group	Proposed Crop	Highest Transfer Coefficient for Crop (cm^2/hr) and Associated Activity	Days after Treatment	Study Test Site	Chemical-specific DFR[a] (ug/cm^2)		Dermal Dose[b] (mg/kg/day)		Short-Term MOE[c]	Intermediate-Term MOE[c]
					Short - Term	Intermediate-Term	Short - Term	Intermediate-Term		
Deciduous tree fruit	Apple, Pear, Cherry	Thinning fruit (3600)	0	CA	0.563	0.130	0.014	0.003	250	1100
Evergreen tree fruit	Canistel, Mango, Papayas, Sapodilla, Sapote, Star apple	Thinning fruit (3600)	0	CA			0.009	0.002	400	1700
Brassica	Broccoli; Chinese Broccoli, Brussels Sprouts, Cabbage, Chinese Cabbage (Napa), Chinese Mustard Cabbage, Cauliflower, Cavalo Broccoli, And Kohlrabi	Hand harvesting (4200)	0	CA			0.0083	0.0019	420	1800
Cucurbit vegetables	Cucumber, Gherkin, Gourds, Melons, Pumpkin, Squash	Irrigation (1900)	0	CA			0.0037	0.0009	930	4000

Table 3: Dermal Post-application Exposure and Risk Using Chemical-Specific DFR Data.

Crop Group	Proposed Crop	Highest Transfer Coefficient for Crop (cm^2/hr) and Associated Activity	Days after Treatment	Study Test Site	Chemical-specific DFR[a] (ug/cm^2)		Dermal Dose[b] (mg/kg/day)		Short-Term MOE[c]	Intermediate-Term MOE[c]
					Short - Term	Intermediate-Term	Short - Term	Intermediate-Term		
Leafy vegetable	Leafy Vegetable (except spinach)	Hand weeding (4200)	0	CA			0.0083	0.0019	420	1800
Berry low	Strawberry	Irrigation (1900)	0	CA			0.004	0.001	930	4000
Tree nut	Hazelnut (filbert)	Thinning (3600)	0				0.005	0.001	650	2800
Bunch and bundle	Hops	Mechanically assisted harvesting	Day 3 S/T Day 2 I/T	CA			0.0295	0.016	120	330
Vine/trellis	Grapes	Girdling, turning	Day 4 S/T Day 2 I/T	CA			0.0761	0.0113	110	310

a. Chemical-specific DFR = day zero predicted grape vine DFR data(0.563 ug/cm^2) for short –term exposure estimate and predicted grape vine average 30 days residue (0.130 ug/cm^2) data for intermediate-term exposure estimate for all crops.

b. Dermal Dose = [DFR (ug/cm^2) x TC (cm^2/hr) x 0.001 mg/ ug x DAF (3.5%) x 8 hrs/day] ÷ body weight (80 kg).

c. MOE = NOAEL (3.5 mg/kg/day)/ Dermal Dose (mg/kg/day).

The MOEs on day zero are 200 for grapes and 270 for hops.