(10)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 1/6/2005

SUBJECT: PP# 1F6342 -- **Human Health Risk Assessment for Clothianidin.** Proposal for Tolerance of Residues in/on Pome Fruit and the Use on Tobacco, Turf, and Ornamental Plants.

DP Barcode:	D304499	Decision No.:	304926
Chemical#:	044309	Class:	Insecticide
Trade Name:	Clutch® 50WDG	EPA Reg#:	3125-XXX
40 CFR:	§180.586	Chem Class:	chloronicotinyl

TO: Daniel Kenny, RM 01
Registration Division (7505C)

FROM: William Cutchin, Chemist
Science Information Management Branch (SIMB)
Health Effects Division (7509C)

Mark I. Dow, Ph.D., Biologist
Registration Action Branch 1 (RAB1)
Health Effects Division (7509C)

Alan Levy, Ph.D., Toxicologist
Registration Action Branch 2 (RAB2)
Health Effects Division (7509C)

and

Kelly Schumacher, Biologist
Registration Action Branch 2 (RAB2)
Health Effects Division (7509C)

THRU: Richard A. Loranger, Ph.D., Branch Senior Scientist
Registration Action Branch 2 (RAB2)
Health Effects Division (7509C)

MAR 16 2005

1.0 EXECUTIVE SUMMARY

General Background

Arvesta Corp. has requested the registration of clothianidin uses on pome fruit, tobacco, turf, and ornamental plants and a tolerance of 1.0 ppm for the pome fruit crop group. Clothianidin [*(E)*-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine] is a systemic insecticide belonging to the chloronicotinyl (CNI) class of chemicals, which enters the transpiration stream through the roots and cotyledons of newly germinating seedlings and protects below- and above-ground plant parts from insect damage. Clothianidin is a major metabolite of the insecticide, thiamethoxam, which is a broad spectrum insecticide possessing activity against sucking and chewing insects. Tolerances for thiamethoxam include residues of clothianidin in both plant and livestock commodities.

Clothianidin is registered as Poncho™ 600 FS for its established uses as a seed treatment on canola and corn. Tolerances have been established for the residues of clothianidin expressed as parent only on canola seed at 0.01 ppm; corn, field, forage at 0.10 ppm; corn, field, grain at 0.01 ppm; corn, field, stover at 0.10 ppm; corn, pop, grain at 0.01 ppm; corn, pop, stover at 0.10 ppm; corn, sweet, forage at 0.10 ppm; corn, sweet, kernel plus cob with husk removed at 0.01 ppm; corn, sweet, stover at 0.10 ppm; milk at 0.01 ppm; animal feed, nongrass at 0.02 ppm; grain, cereal, forage, fodder and straw at 0.02 ppm; grass, forage, fodder and hay at 0.02 ppm; soybean, forage at 0.02 ppm; and soybean, hay at 0.02 ppm.

The proposed uses are for clothianidin formulated from 0.5 to 50% ai as a granule, ARENA® 0.5 G; a water soluble granule, BELAY™ 16 WSG; or a water dispersible granule, CLUTCH™ 50 WDG. The products are to be applied to apples, pears, tobacco, turfgrass, and landscape ornamentals by ground-boom spray, ground broadcast spreaders, push-type drop, or broadcast spreaders using a single application at rates that vary from 0.05 - 0.4 lb ai/A with a 7-day PHI for apples and pears and a 14-day PHI for tobacco.

The most recent HED human health risk assessment for clothianidin was conducted in conjunction with the Section 3 requests for the uses on canola and corn (PP# 1F06315, DP Barcode: D288841, Y. Donovan, 5/01/03).

Hazard Assessment

Clothianidin does not appear to exhibit toxicity towards a consistent specific target organ. Decreases in body weight and body weight gain were observed in rats, dogs, and mice. In single dose studies, mice may be more sensitive than rats to neurotoxic effects. Transient signs of decreased spontaneous motor activity, tremors, and deep respirations were observed in mice at a dose level of 50 mg/kg with a No Observed Adverse Effect Level (NOAEL) of 25 mg/kg. Rats exhibited decreased arousal and decreased motor and locomotor activity at 100 mg/kg, the lowest dose tested. The acute toxicity study in mice was classified in Category II, whereas the acute study in rats was classified in Category IV. In longer term studies, dogs exhibited clinical signs of anemia. In the chronic feeding study in rats, adverse effects on the ovaries, liver, and kidney were observed. The only observed effects in mice following chronic dietary administration were

increases in vocalization and decreases in body weight and body weight gain. In the rat, administration via the oral route appears to be more toxic than via the dermal route. Although the NOAELs were similar for the subchronic and chronic feeding studies in the rat, a greater spectrum of effects were observed in the chronic study (decreased body weight, body weight gain and food consumption plus additional observations in the liver, ovary and kidney) versus the subchronic study (effects only on body weight and food consumption).

Clinical signs of neurotoxicity were exhibited in both rats and mice in acute neurotoxicity studies following exposure by gavage; however, no indications of neurotoxicity were observed following dietary exposure in the subchronic neurotoxicity study in rats. No quantitative or qualitative susceptibility was observed in fetuses in either of the developmental rat or rabbit studies; however, quantitative susceptibility was observed in the pups in both the reproduction and developmental neurotoxicity studies. The degree of concern for both of these studies is low because the observed effects are well characterized and there are clear NOAELs/ Lowest Observed Adverse Effect Level (LOAELs). In addition, the endpoint of concern identified in the reproduction study (decreased mean body weight gain and absolute thymus weights in pups, delayed sexual maturation, and an increase in still births) is being used for chronic dietary and short-, intermediate- and long-term non-dietary exposure risk assessments.

The Hazard Identification Assessment Review Committee (HIARC) classified clothianidin as not likely to be carcinogenic to humans. The mutagenicity studies gave mixed results. The HIARC has requested that the composition of the test materials used in the mutagenicity studies be investigated to determine whether or not the differences in composition may have affected the results from the studies.

Dose Response Assessment and Food Quality Protection Act (FQPA) Decision

The special FQPA safety factor is reduced to 1x because the existing data indicate that there are no residual uncertainties with regard to pre- and/or postnatal toxicity, conservative residue assumptions are used in the dietary risk assessments, and the residue chemistry and environmental fate databases are relatively complete (evaluated by the risk assessment team).

The HIARC noted evidence of potential effects on the immune system in several studies (decreased absolute and relative thymus and spleen weights). Juvenile rats in the reproduction study appeared to be more susceptible to these effects. Therefore, the HIARC recommended that testing be conducted to assess immune system function in adults and in young animals following exposure during the period of organogenesis. HIARC concluded that a 10X database uncertainty factor for the lack of a developmental immunotoxicity study is needed for clothianidin following both single and repeated dose studies (i.e., acute and chronic dietary exposure, short- and intermediate-term incidental oral exposure, and short-, intermediate-, and long-term dermal and inhalation exposure resulting from residential uses of clothianidin).

On November 14, 2002, the HIARC selected endpoints for acute and chronic dietary exposure, short- and intermediate-term incidental oral exposure, and short-, intermediate-, and long-term dermal and inhalation exposure. These are as follows:

Exposure Scenario	NOAEL	Dose or Target MOE*	Study/Effect
Acute dietary (females 13-50)	25 mg/kg/day	aRfD and aPAD = 0.025 mg/kg/day	Increased litter incidence of a missing lobe of the lung [developmental rabbit study, oral]
Acute dietary (general population)	25 mg/kg/day	aRfD and aPAD = 0.025 mg/kg/day	Transient signs of decreased spontaneous motor activity, tremors and deep respirations [Special Neurotoxicity/Pharmacology Study in Mice and Rats, oral]
Chronic dietary	9.8 mg/kg/day	cRfD and cPAD = 0.0098 mg/kg/day	Delayed sexual maturation, decreased mean body weight gain and absolute thymus weights in F_1 pups and increase in stillbirths [both generations in rat 2-generation reproduction study, oral]
Incidental oral (all durations)	9.8 mg/kg/day	Target MOE = 1000 (residential)	
Dermal (all durations) Absorption: 1%	9.8 mg/kg/day	Target MOE = 1000 (residential), 100 (occupational)	Delayed sexual maturation, decreased mean body weight gain and absolute thymus weights in F_1 pups and increase in stillbirths [both generations in rat 2-generation reproduction study, oral]
Inhalation (all durations) Absorption: 100%	9.8 mg/kg/day	Target MOE = 1000 (residential), 100 (occupational)	

* MOE = margin of exposure

Residential Exposure Estimates

Due to the proposed use patterns on turfgrasses, a number of residential or recreational post-application exposures are possible. In a residential setting, a "homeowner" may be exposed during lawn application. Further, the "homeowner" may also experience post-application dermal exposure. Toddlers may be exposed via "hand-to-mouth" oral exposures and/or dermal exposures. "Aggregated" exposures are presented for toddlers i.e., hand-to-mouth turf + hand-to-mouth soil + dermal post-application. The ExpoSac considers hand-to-mouth ingestion of granules to be episodic in nature, that is, a "one-time" event. Therefore the exposure from ingestion of granules is not combined with believed multiple exposures from "mouthing" of turf or soil or from post-application dermal exposure. The exposure estimate from toddler ingestion of granules is an MOE of 250 and therefore exceeds HED's level of concern. However, ingestion of granules is considered an episodic event and not a routine behavior. Because HED does not believe that this would occur on a regular basis, our concern for human health is related to acute poisoning rather than short or intermediate-term residue exposure. MOEs range from 1,300 for combined oral and dermal exposure for toddlers (treated turf + treated soil + dermal) to 8,900 for dermal exposures for adults (application + postapplication) adults.

Dietary Exposure Estimates

Residue Chemistry

HED's Metabolism Assessment Review Committee (MARC) concluded that the nature of the residue has been adequately delineated and that parent only is the residue of concern to be used in risk assessment and the tolerance expression for primary crops. The metabolic profiles in the tested primary crops were similar in that the highest level residue was the parent, with the exception of mature sugar beet tops. The MARC concluded for livestock that parent and

metabolites TZNG, TZU, TZG, ATMG-Pyr (ruminants only) and ATC-Ac (poultry only) are the residues of toxicological concern to be included in the risk assessment, and that parent only is the residue of concern for the tolerance expression. For rotational crops, MARC determined that parent and metabolites TZNG and MNG are the residues of concern for risk assessment, while parent only is needed for the tolerance expression. For drinking water, parent only is the residue of concern. (See Reference 1 for metabolite structures.)

Residues of clothianidin were quantitated for apples and pears by Valent Method RM-39-A, which utilizes liquid chromatography/mass spectroscopy/mass spectroscopy (LC/MS/MS) analysis. Method validation and concurrent recovery data for apples and pears are considered acceptable. The limit of detection (LOD) is 0.005 ppm, and the limit of quantitation (LOQ) is 0.010 ppm. The method is similar to Method 00624, also a LC-MS/MS method, which was found acceptable by HED for data collection purposes and sent for petition method validation (PMV) by EPA's Analytical Chemistry Branch (ACB). ACB recommended that the registrant's plant and livestock methods be accepted for enforcement purposes without an EPA laboratory validation. Clothianidin and the metabolites TZG, MNG, TZNG, TZU, and ATMG-Pyr were not adequately recovered using any of the PAM I multiresidue methods.

The registrant has submitted adequate residue field trials, acceptable in data gathering method and number and geographic location, on the pome fruit representative crops, apples and pears. However, it was noted that adjuvants were not utilized, although they are allowed by the proposed label. There could be increased residues when adjuvants are included in the tank mix; therefore, the use of adjuvants should be removed from the label. Since pome fruits are not rotated, no rotational tolerances or restrictions are required for the proposed use.

Thirteen crop field trial studies were conducted in apples using a single application of Clutch® 50 WDG insecticide (50% clothianidin by weight) at application rates of 0.195 to 0.201 lb ai/A (0.219 to 0.225 kg ai/ha), 1x the proposed rate. The maximum residue in/on apples harvested 6 to 7 days following treatment was 0.199 ppm with a highest average field trial (HAFT) of 0.174 ppm. A residue decline study was conducted at one site and indicated that residues of clothianidin on treated apples decline with time. Apples treated with 3x the proposed rate of clothianidin were processed into apple juice and wet pomace by simulated commercial processing. Residues did not concentrate in either of the processed commodities. The concurrent storage stability demonstrated that clothianidin residues in apples stored frozen for the duration of the study did not degrade.

Seven crop field trial studies were conducted in pears using a single application of Clutch® 50 WDG insecticide (50 % clothianidin by weight) at application rates of 0.196 to 0.200 lb ai/A (0.220 to 0.224 kg ai/ha). The maximum residue in/on pears harvested 6 to 7 days following treatment was 0.176 ppm with a HAFT of 0.163 ppm. A residue decline study was conducted at one site and indicated that residues of clothianidin on treated pears decline with time. The concurrent storage stability demonstrated that clothianidin residues in pears stored frozen for the duration of the study did not degrade.

Clothianidin, radiolabelled at the nitroimino moiety, was applied to unfiltered cigarettes and smoked using a total recovery smoking apparatus (TRSA). Residues in smoke were

collected using a particulate filter and a series of gas dispersion traps. Extracts from the particulate filters and solutions from the dispersion traps were radioassayed by liquid scintillation counter (LSC). Those extracts containing >10% of the applied dose were analyzed by high pressure liquid chromatography (HPLC). The identity of clothianidin was confirmed by thin layer chromatography (TLC) for selected extracts and by HPLC/MS for cigarette extracts. The pyrolysis of clothianidin in cigarettes resulted in formation of approximately 50% of the applied dose as $^{14}CO_2$ recovered in the main stream (MS) and side stream (SS). The major component found in the butt and filter extracts was clothianidin, averaging 18% of the applied dose. The remaining 32% of the applied dose consisted of minor metabolites, each comprising ≤8% of the applied dose.

No Codex, Canadian, or Mexican maximum residue levels (MRLs) have been established for residues of clothianidin.

Dietary Exposure Analysis

Since clothianidin is a major metabolite of thiamethoxam, which has many registered uses and several pending uses, residues of clothianidin that would theoretically result from the metabolism of thiamethoxam are included in the analysis. The ratio of clothianidin to thiamethoxam in each commodity was multiplied by the respective thiamethoxam tolerance level to arrive at the theoretical maximum clothianidin residue level that would be present. Processing factors are DEEM (Version 7.76) default processing factors with the exception of the those on apple and pear juice, which are reduced to 0.14, the factor found in the apple processing study.

The acute analysis is a conservative, Tier 1 assessment that was based on tolerance level residues and the assumption of 100% crop treated for established and proposed clothianidin uses. For the commodities that have both thiamethoxam tolerances and established or proposed clothianidin tolerances (i.e., sweet corn, field corn, pop corn, canola, milk, and pome fruit), the proposed clothianidin tolerances are added to the residues that could result from use of thiamethoxam.

The chronic analysis is a somewhat conservative, Tier 2 assessment that was based on tolerance level residues and the assumption of 100% crop treated for established and proposed clothianidin uses, with the exception of anticipated residues (AR) for apples and pears. For the commodities that have both thiamethoxam tolerances and established or proposed clothianidin tolerances (i.e., sweet corn, field corn, pop corn, canola, and milk), the proposed clothianidin tolerances are added to the residues that could result from use of thiamethoxam. For apples and pears, the highest average field trial (HAFT) levels from the residue field trials were added to the residues that could result from use of thiamethoxam.

The acute and chronic dietary risk assessments were conducted using DEEM-FCID™ and Lifeline™ for the existing and proposed uses of clothianidin. The acute dietary exposure analysis is reported at the 95th percentile of exposure because the assessment incorporated 100% CT assumptions and tolerance-level residues. The estimated acute dietary exposure does not exceed 81% of the acute population adjusted dose (aPAD) for any population subgroup (most highly exposed subgroup, all infants <1 yr). The chronic analysis used 100% CT for all

commodities and tolerance level residues for all commodities except for the ARs used for apples and pears. The estimated chronic dietary exposure does not exceed 15% of the chronic population adjusted dose (cPAD) for any population subgroup (most highly exposed subgroup, children 1-2 yrs).

The HIARC determined that clothianidin is not likely to be a human carcinogen. As a result, a cancer dietary exposure analysis was not performed.

Drinking Water Exposure Estimates

EFED provided Tier I Estimated Drinking Water Concentrations (EDWCs) for clothianidin in surface water and in ground water for use in the human health risk assessments. The simulation model FIRST was used to calculate the surface water EDWCs, and the SCI-GROW model was used to calculate the groundwater EDWCs. It is assumed that the maximum application rate was at 0.4 lbs ai/A for turfgrass. This rate is the highest of all the proposed and existing uses. The EDWCs for clothianidin in surface waters is 7.29 ug/L for acute risk calculations and 1.35 ug/L for chronic risk and cancer risk calculations. Concentrations in ground water are not expected to exceed 5.84 ug/L. No monitoring data are available for clothianidin. Although clothianidin is a major metabolite of thiamethoxam in plants and in animals, it was not found in environmental fate studies. MARC's decision on residues of concern for thiamethoxam in drinking water is parent only. Therefore, significant exposure to clothianidin in drinking water due to thiamethoxam uses is not expected.

Aggregate Exposure Scenarios and Risk Conclusions

Acute Aggregate Risk (Food + Water)

Acute aggregate risk estimates do not exceed HED's level of concern. Using the conservative Tier I approach, the DEEM-FCID and Lifeline acute dietary risk estimates indicated that the acute exposures to clothianidin from food for the general U.S. population will utilize 18% of the aPAD. The most highly exposed population subgroup is all infants <1 yr, which utilizes 80% and 81% of the aPAD, as reported by DEEM-FCID and Lifeline, respectively. The calculated DWLOCs for acute exposure to clothianidin in drinking water range from 48 to 1500 ug/L. Both surface and ground water EDWCs were less than 7.29 ug/L, substantially less than the DWLOCs. Therefore, the acute aggregate risk associated with the proposed use of clothianidin does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Short- and Intermediate- Term Aggregate Risk (Residential + Food + Water)

The HIARC has determined that, for clothianidin, the toxicological effects are the same across oral, dermal, and inhalation routes of exposure and has selected the same endpoint and dose for short- and intermediate-term exposure scenarios. Therefore, the exposures are simply summed (combined/aggregated) for use in risk calculations. Combined residential exposure estimates range from an MOE of 1,300 for combined oral and dermal exposure to toddlers (treated turf + treated soil + dermal) to 8,900 for dermal exposure to adults (application +

postapplication) adults. The calculated short- and intermediate-term DWLOCs for short- and intermediate-term exposure to clothianidin in drinking water range from 8.7 to 320 ug/L. EDWCs generated by EFED for both surface and ground water were less than 5.84 ug/L, less than HED's calculated short- and intermediate-term DWLOCs. Therefore, the short- and intermediate-term aggregate risk associated with the proposed use of clothianidin does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Chronic Aggregate Risk (Food + Water)

Chronic aggregate risk estimates do not exceed HED's level of concern. Using the Tier 2 approach, the DEEM-FCID and Lifeline chronic dietary risk estimates indicated that the chronic exposures to clothianidin from food for the general U.S. population will utilize 6% of the cPAD, as reported by DEEM-FCID. The most highly exposed population subgroup is children 1-2 years old, which utilizes 15% of the cPAD, as reported by DEEM-FCID. The calculated DWLOCs for chronic exposure to clothianidin in drinking water range from 83 to 330 ug/L. Both surface and ground water EDWCs were less than 5.84 ug/L, substantially less than the DWLOCs. Therefore, the chronic aggregate risk associated with the proposed use of clothianidin does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Cancer

Clothianidin has been classified by HED HIARC as a "not likely human carcinogen." Therefore, a cancer risk assessment is not required.

Occupational Exposure Estimates

The requested uses of clothianidin include uses on pome fruit, turfgrass, landscape ornamental plantings, and tobacco. The formulations ARENA® 0.5 G (a 0.5 % granule) and CLUTCH™ 50 WDG (a 50 % water dispersible granule) are to be used on turfgrass found in commercial and public landscapes such as golf courses, home lawns, airports, cemeteries, parks, playgrounds, athletic fields, and commercial sod farms. BELAY™ 16 WSG (a 16 % water soluble granule), as well as CLUTCH™, will be used on tobacco. CLUTCH™ will be used on pome fruit.

Occupational Handler Exposure

Based upon the proposed use patterns, the most highly exposed occupational pesticide handlers are: 1) mixer/loader using open pour loading of granules in support of broadcast operations to commercial turf, 2) applicator using open cab ground boom spray equipment, 3) applicator using open-cab, granular, broadcast ground equipment, and 4) mixer/loader/applicator using walk behind push-type granular spreader. Repeat applications of clothianidin should not be applied consecutively. Typically, the acreage blocks to be treated for these proposed uses are expected to be relatively small, not requiring the volume of material or amount of time as might be required for large block crops such as corn, soybeans, cotton, or wheat. At the high rates of application, the number of repeat applications is low. Therefore, for these proposed uses, occupational pesticide handler exposures will typically be short-term (1 - 30 days).

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 Pesticide Handler's Exposure Database (PHED) (v. 1.1, 1998). For pesticide handlers, it is 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 "baseline" plus the use of protective gloves or other Personal Protective Equipment (PPE) as might be necessary. The proposed product labels involved in this assessment direct applicators and other handlers to wear long-sleeved shirt, long pants, waterproof gloves, and shoes and socks.

The HIARC identified dermal and inhalation endpoints for all durations: short-term (1 - 30 days), intermediate-term (1 - 6 months), and long-term (> 6 months). The NOAEL is the same for all durations, 9.8 mg a.i./kg bw/day, based upon a 2-generation rat reproduction study where the effects seen were decreased body weight gains, delayed sexual maturation, decreased absolute thymus weights in F_1 pups, and an increase in still births in both generations at the Lowest Observed Adverse Effect Level (LOAEL) of 31.2 mg a.i./kg bw/day. Since the dermal and inhalation endpoints are the same and have the same NOAEL, the exposures are simply summed (combined/aggregated) for use in risk calculation of MOE. Further, the risks estimated for short-term and intermediate-term exposures are coincidentally the same in this case. The HIARC identified a 1.0 % dermal absorption factor based upon a submitted dermal penetration study. The HIARC described clothianidin as "Not Likely" to be a human carcinogen; therefore, estimates of cancer risk are not necessary.

A MOE of 100 is adequate to protect occupational pesticide handlers. All estimated MOE's are > 100; therefore, the proposed uses do not exceed HED's level of concern for occupational handlers. The same endpoint and dose were selected for the short- and intermediate-term assessments. In addition, short- and intermediate-term exposures are equivalent; therefore, the estimated risks are the same.

Postapplication Exposure

There is a potential for agricultural workers to experience post-application exposure to pesticides 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. HED has also identified Transfer Coefficients (TC) (as cm^2/hr) relative to the various activities that express the amount of foliar contact over time, during each of the activities. Lacking compound specific dissipation data, HED assumes 20% of the application rate is available as foliar dislodgeable residue on the day of application. This is adapted from the Science Advisory Council For Exposure SOP No. 003 (7 May 1998 - Revised 7 August 2000). Foliar dislodgeable residues are assumed to decline 10% each day following application.

A MOE of 100 is adequate to protect agricultural workers from post-application exposures to clothianidin. The estimated MOE's are based upon conservative assumptions and are > 100; therefore, the estimated risks from post-application exposures do not exceed HED's level of concern.

Recommendations:

Regulatory Recommendations and Deficiencies

HED concludes that there is a reasonable certainty that no harm will result to the U.S. Population, including infants and children, from acute, short- and intermediate- term, and chronic aggregate exposure to clothianidin residues. The proposed label indicates that livestock should not be permitted to graze in treated orchards but does not specify a pre-grazing interval; the label should be revised to include a pre-grazing interval. Contingent on this label change and on the submissions of data to fulfill identified data gaps under Section 8.0, HED has no objection to the establishment of permanent tolerances for the residues of clothianidin, expressed as parent, in or on the following:

Pome Fruit ..... 1.0 ppm

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Clothianidin is a systemic insecticide belonging to the chloronicotinyl class of chemicals (CNI), which has an agonistic activity on the nicotinergic acetylcholine receptor (nACh-R). Clothianidin enters through the roots and cotyledons of newly germinating seedlings and protects below-and above-ground plant parts from insect damage.

TABLE 1. Clothianidin Nomenclature

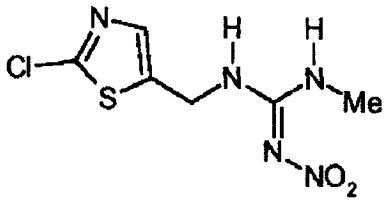
Compound	Chemical Structure
	
Common name	clothianidin
Company experimental name	TI-435, TM-444
IUPAC name	(*E*)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine
CAS name	[C(*E*)]-*N*-[(2-chloro-5-thiazolyl)methyl]-*N'*-methyl-*N''*-nitroguanidine
CAS #	205510-53-8 205510-92-5 210880-92-5
End-use product/EP	Poncho™ 600, ARENA® 0.5 G, CLUTCH™ 50 WDG, BELAY™ 16 WSG

TABLE 2. Clothianidin Physicochemical Properties

Parameter	Value
Melting point/range	176.8°C
pH	6.24 @ 23°C
Density	1.61 g/mL @ 20°C
Water solubility (20°C)	0.327 g/L
Solvent solubility (g/L at 25°C)	acetone 15.2 dichloromethane 1.32 ethyl acetate 2.03 heptane <0.00104 methanol 6.26 octanol 0.938 xylene 0.0128
Vapor pressure at 25°C	1.3×10^{-10} Pa
Dissociation constant (pK_a)	NA
Octanol/water partition coefficient Log(K_{ow})	0.7 @ 25°C

TABLE 2. Clothianidin Physicochemical Properties	
Paramcter	Value
UV/visible absorption spectrum	Max. 265.5 nm in acidic and neutral solution; max. 246.0 nm in basic solution
Henry's law constant	2.9×10^{-11} Pa × m³/mol at 20 °C

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Table 3. Acute Toxicity Profile - Clothianidin Technical, Intermediates, and Metabolites					
Test Material	**GDLN**	**Study Type**	**MRID**	**Results**	**Tox Category**
Technical	870.1100	Acute Oral - rat	45422621	LD_{50} > 5000 mg/kg	IV
BN0230M **Metabolite**	870.1100	Acute Oral - rat	45422628	Oral LD_{50} > 2000 mg/kg bw (♂+♀)	III
BN0335E2 **Metabolite**	870.1100	Acute Oral - rat	45422623	Oral LD_{50} > 2000 mg/kg (♂+♀)	III
MAI **Metabolite**	870.1100	Acute Oral - rat	45422629	Oral LD_{50} (♀) = 758 mg/kg. Males not more susceptible	III
Clothianidin-CCMT-**Adduct Intermediate**	870.1100	Acute Oral - rat	45422630	Oral LD_{50} > 2000 mg/kg (♂+♀)	III
Clothianidin-Hexahydropyrimidine **Intermediate**	870.1100	Acute Oral - rat	45422631	Oral LD_{50} > 2000 mg/kg (♂+♀)	III
Clothianidin-Triazan **Intermediate**	870.1100	Acute Oral - rat	45422632	Oral LD_{50} > 2000 mg/kg (♂+♀)	III
TMG **Metabolite**	870.1100	Acute Oral - rat	45422625	Oral LD_{50} ♂ < 550 mg/kg ♀ = 567 mg/kg bw	II
TZMU **Metabolite**	870.1100	Acute Oral - rat	45422624	Oral LD_{50} ♂ = 1424 mg/kg ♀ = 1282 mg/kg	III
TZNG **Metabolite**	870.1100	Acute Oral - rat	45422626	Oral LD_{50} ♂ > 1450 mg/kg ♀ = 1481 mg/kg	III

Table 3. Acute Toxicity Profile - Clothianidin Technical, Intermediates, and Metabolites

Test Material	GDLN	Study Type	MRID	Results	Tox Category
Technical	870.1100	Acute Oral - mouse	45422622	LD_{50} (M): 389 mg/kg bw (95% confidence limits = 380-475) LD_{50} (F): 465 mg/kg bw (95% confidence limits = 384-561) LD_{50} Combined: 425 mg/kg bw (95% confidence limits = 380-475)	II
Technical	870.1200	Acute Dermal - rat	45422634	LD_{50} > 2000 mg/kg	III
Technical	870.1300	Acute Inhalation	45422636	LC_{50} (M & F): > 5.538 mg/L	IV
Technical	870.2400	Primary Eye Irritation	45422701	Slightly irritating to the eye	IV
Clothianidin-CCMT-**Adduct Intermediate**	870.2400	Primary Eye Irritation	45422814	Not irritating to the eye	IV
Clothianidin-Triazan **Intermediate**	870.2400	Primary Eye Irritation	45422819	Not irritating to the eye	IV
Technical	870.2500	Primary Dermal Irritation	45422703	Not irritating to the skin	IV
Clothianidin-CCMT-**Adduct Intermediate**	870.2500	Primary Dermal Irritation	45422813	Not irritating to the skin.	IV
Clothianidin-Triazan **Intermediate**	870.2500	Primary Dermal Irritation	45422820	Not irritating to the skin.	IV
Technical	870.2600	Dermal Sensitization	45422705	Is not a sensitizer under conditions of study.	N/A
Clothianidin-CCMT-**Adduct Intermediate**	870.2600	Dermal Sensitization	45422815	Is not a sensitizer under conditions of study.	N/A
Clothianidin-Triazan **Intermediate**	870.2600	Dermal Sensitization	45422821	Is a sensitizer under the conditions of the study	N/A

Table 4. Toxicity Profile of Clothianidin Technical		
Guideline No.	**Study Type**	**Results**
870.3100	90-Day oral toxicity rodents (rats)	**NOAEL**: 27.9/34.0 mg/kg/day (M/F) **LOAEL**: 202.0/254.2 mg/kg/day (M/F: decreased BW and BW gain).
870.3150	90-Day oral toxicity in nonrodents (dogs)	**NOAEL**: 19.3/42.1 mg/kg/day (M/F) **LOAEL**: 40.9/61.8 mg/kg/day (thinness, decreased body weight, body weight gain and anemia (1 M); decreased white blood cells, albumin, and total protein (F).
870.3200	21/28-Day dermal toxicity (rats)	**NOAEL**: 1000 mg/kg/day (HDT) **LOAEL**: >1000 mg/kg/day
870.3700	Prenatal developmental in rodents (rats)	**Maternal NOAEL**: 10 mg/kg/day **Maternal LOAEL**: 40 mg/kg/day (decreased body weight gain and food consumption). **Developmental NOAEL**: 125 mg/kg/day (HDT) **Developmental LOAEL**: cannot be established
870.3700	Prenatal developmental in nonrodents (rabbit)	**Maternal NOAEL**: 25 mg/kg/day **Maternal LOAEL**: 75 mg/kg/day (increased incidences of clinical signs (scant feces and orange urine), mortalities, decreased food consumption, early delivery, abortion, and decreased body weight gain) **Developmental NOAEL**: 25 mg/kg/day **Developmental LOAEL**: 75 mg/kg/day (premature deliveries, decreased gravid uterine weights, an increased litter incidence of a missing lobe of the lung and decreased litter average for ossified sternal centra per fetus).
870.3800	Reproduction and fertility effects (rat)	**Parental systemic NOAEL**: 31.2/36.8 mg/kg/day (M/F) **Parental systemic LOAEL**: 163.4/188.8 mg/kg/day (M/F) (decreased body weight, body weight gain and absolute and relative thymus weights). **Offspring systemic NOAEL**: 9.8/11.5 mg/kg/day (M/F) **Offspring systemic LOAEL**: 31.2/36.8 mg/kg/day (M/F: decreased body weight gains and delayed sexual maturation (M); decreased absolute thymus weights in F_1 pups of both sexes and an increase in stillbirths in both generations). **Reproductive NOAEL**: 31.2/188.8 mg/kg/day (M/F) **Reproductive LOAEL**: 163.4/not established mg/kg/day (M/F: decreased sperm motility, and increased number of sperm with detached heads in both generations).

Table 4. Toxicity Profile of Clothianidin Technical		
Guideline No.	**Study Type**	**Results**
870.4100a	Chronic toxicity rodents	See 870.4300
870.4100	Chronic toxicity dogs	**NOAEL**: 46.4/40.1mg/kg/day (M/F) **LOAEL**: not established/52.9 mg/kg/day (M/F: clinical evidence of anemia in females). Note: dose-related decreases in ALT activity observed in mid- and high-dose males and females.
870.4200	Carcinogenicity rats	See 870.4300
870.4200	Carcinogenicity mice	**NOAEL**: 171.4/65.1 mg/kg/day (M/F) **LOAEL**: 254.1/215.9 mg/kg/day (M/F: decreased body weight and body weight gain; decreased food consumption and food efficiency in males at the LOAEL). No evidence of carcinogenicity.
870.4300	Chronic feeding/Carcinogenicity rat	**NOAEL**: 82.0/32.5 mg/kg/day (M/F) **LOAEL**: 156.5/97.8 mg/kg/day (M/F, decreased body weight and food consumption and altered hepatocellular eosinophilic focus of the liver in both sexes; ovary interstitial gland hyperplasia and increased lymphohistiocytic infiltrate in females; and slightly increased incidences of pelvic mineralization and transitional cell hyperplasia in the kidney, mottled livers of males. No evidence of carcinogenicity.
870.5100	Gene Mutation bacterial reverse mutation assay **Parent**	Small, but significant increase in frequency of histidine revertants in TA1535 strain treated at 1500 and 5000 µg/plate +/-S9; still present but weaker in its absence. The positive response was only reproducible at 5000 µg/plate +/-S9. Clothianidin considered mutagenic under conditions of this test.

Table 4. Toxicity Profile of Clothianidin Technical		
Guideline No.	Study Type	Results
870.5100	Gene Mutation bacterial reverse mutation assay **Parent**	No mutagenic activity in bacteria (*Salmonella typhimurium* and *Escherichia coli*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **Parent**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **Parent**	Only TA 1535 tested. No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **BN0335E2 metabolite**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **TZMU metabolite**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **methyl guanidine intermediate**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **TZNG metabolite**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **TMG metabolite**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **BN0230M metabolite**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **MAI metabolite**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation bacterial reverse mutation assay **N-Methylnitroguanidin intermediate**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation - bacterial reverse mutation assay **TI 435-Triazan intermediate**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5100	Gene Mutation - bacterial reverse mutation assay **TI 435-CCMT-Adduct**	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5300	Gene Mutation - *in vitro* mammalian cell gene mutation test (L5178Y TK +/- mouse lymphoma cells) **Parent**	Increases in mutant frequency with and without S9 at dose levels that were cytotoxic. The observed response was primarily due to small colony formation, indicating clastogenic activity.

Table 4. Toxicity Profile of Clothianidin Technical		
Guideline No.	**Study Type**	**Results**
870.5300	Gene Mutation - *in vitro* mammalian cell gene mutation test (V79-HPRT Assay) **Parent**	No increase in mutant frequency under the conditions of the study.
870.5395	Cytogenetics - mammalian erythrocyte micronucleus test **Parent**	Clothianidin is considered to be neither clastogenic nor aneugenic under these test conditions.
870.5375	Cytogenetics - *in vitro* mammalian chromosome aberration test (CHL Cells) **Parent**	Significant increases in frequency of cells with structural aberrations. Predominant types were chromatid breaks and exchanges. There was, however, no clear indication of a dose-related response in either the presence or absence of S9 activation.
870.5500	Other Effects - DNA Repair Test in *Bacillus subtillis* **Parent**	No potential for DNA damage under these conditions.
870.5550	Other Effects - (UDS) in Mammalian Cells in Culture **Parent**	No evidence (or a dose related positive response) that UDS was induced.
870.6200	Acute neurotoxicity screening battery (rat)	**NOAEL**: not established **LOAEL**: 100 mg/kg (FOB: decreased arousal and decreased motor and locomotor activity).
870.6200	Subchronic neurotoxicity screening battery (rat)	**NOAEL**: 60.0/71.0 mg/kg/day (M/F) **LOAEL**: 177.0/200.1 mg/kg/day (M/F:slightly decreased food consumption, body weights and body weight gains).
870.6300	Developmental neurotoxicity (rat)	**Maternal NOAEL:** 42.9 mg/kg/day **Maternal LOAEL:** 142 mg/kg/day (decreased body weights, body weight gains, and food consumption) **Offspring NOAEL:** 12.9 mg/kg/day **Offspring LOAEL:** 42.9 mg/kg/day (decreased body weights, body weight gains, motor activity, and acoustic startle response in females)

Table 4. Toxicity Profile of Clothianidin Technical		
Guideline No.	**Study Type**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	Overall recovery: 95-100%. Readily absorbed and excreted within 96 hours following a single 2.5 mg/kg bw or repeated oral dose of 25 mg/kg bw, but at a dose of 250 mg/kg, absorption became biphasic and was saturated. Following single or multiple oral low doses (2.5 and 25mg/kg bw, respectively) of clothianidin, urinary excretion accounted for 89.2-94.6% of the administered radioactivity suggesting that a multiple exposure regimen did not affect the absorption/excretion processes. Urinary excretion unaffected following single 250 mg/kg dose. Excretion via the feces accounted for the remainder of the administered radioactivity in all treatment groups (3.8-8.6%). Rapid absorption and distribution of administered radioactivity to all organs and tissues followed by rapid excretion with reduction to background levels in most tissues and organs within 24 hours. Somewhat greater rate of absorption and elimination in females. Excretory patterns did not exhibit gender-related variability but reflected the delayed absorption in the high-dose group. Neither clothianidin nor metabolites appear to undergo significant sequestration. The metabolites identified (primarily oxidative demethylation products and cleavage products of the nitrogen-carbon bond between the nitroimino and thiazolyl moieties) were consistent with Phase I processes. Extraction efficiencies appeared to be excellent and most components in all of the matrices examined (urine, feces, and tissues) were adequately quantified and characterized. The available data, based upon studies using both the nitroimino- and the thiazolyl-2-labeled clothianidin, affirmed the metabolism pathway proposed by the investigators.
870.7485	Metabolism and pharmacokinetics (mouse)	Of the administered radioactivity, 98.7-99.2% was recovered. Readily absorbed and excreted within 168 hours following a single oral dose of 5 mg/kg body weight. Urine was the major route of excretion, accounting for 92.4-93.7% of the administered radioactivity. Feces accounted for 5.0-6.8% of the administered radioactivity. Within 24 hours, 89.0-91.7 % of the administered radioactivity was excreted in the urine and 4.9-6.2% was excreted in the feces. Residual radioactivity in any given tissue at 168 hours post-dose was considerably less than 1% of the administered dose. Therefore, neither clothianidin nor its metabolites appeared to exhibit potential for bioaccumulation. Excretory patterns did not exhibit gender-related variability. Both urinary and fecal metabolites were identified using TLC and radioautography in conjunction with known standards and were quantified by TLC/LSC . The major metabolites in both urine and feces were the parent compound (clothianidin) and TZNG [N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine] which resulted from N-demethylation of clothianidin. Extraction efficiencies were excellent and most components in the urine and feces were adequately quantified and characterized. Based on the data from the oral administration of [nitroimino-^{14}C]-clothianidin the metabolism pathway proposed by the investigators was supported.

Table 4. Toxicity Profile of Clothianidin Technical		
Guideline No.	Study Type	Results
870.7600	Dermal Penetration - monkey	Dermal absorption as the sum of urinary and fecal excretion and Cage/Pan/Chair Wash, Debris was 0.24 (± 0.11) as percent of dose. Adjustment of the direct absorption determination was not necessary because recovery from the dermal dose was >90%. A value of 1% dermal absorption was considered appropriate for use in risk assessment. This estimation takes into account any variability that would have likely occurred with testing several dose levels.
	Special Study: Neurotoxicity and pharmacology - mouse	**NOAEL**: 25 mg/kg/day (M/F) **LOAEL**: 50 mg/kg bw mg/kg/day (transient signs of decreased spontaneous motor activity, tremors, and deep respirations).

Clothianidin is a member of the chloronicotinyl class of chemicals and is a metabolite of the insecticide, thiamethoxam. Clothianidin induces some effects that are similar to other chemicals in its class, particularly effects on the liver, hematopoietic system, and kidneys.

Acute studies were conducted on the technical material, intermediates, and metabolites. With the exception of the TMG metabolite, most of the metabolites and intermediates appear to be of similar toxicity to the parent material in acute oral studies. The TMG metabolite appears to be more toxic. In addition, the clothianidin-Triazan Intermediate tested as a dermal sensitizer under the conditions of the study, whereas the parent was not a dermal sensitizer.

Acute neurotoxicity studies were conducted in both rats and mice following exposure to clothianidin by gavage. Comparing these two studies, mice appear to be more sensitive than rats to the acute neurotoxic effects of clothianidin when the compound is administered via oral gavage. In the acute neurotoxicity rat study, FOB effects, including decreased arousal and decreased motor and locomotor activity, were seen at the LOAEL on Day 0 in males. Effects at dose levels above the LOAEL in the rat study included tremors, slightly uncoordinated gait, effects on pupil response and righting reflex, decreases in body temperature, and ataxia. In the acute neurotoxicity study in mice, effects were also observed on Day 0 in males (no female mice were tested), but they occurred at lower dose levels than those that produced neurotoxic effects in rats. Effects seen at the LOAEL in this mouse study included transient signs of decreased spontaneous motor activity, tremors, and deep respirations. At higher dose levels, decreases in reactivity, grooming, and muscle tone; prone position; staggering gait; mydriasis; and hypothermia were observed in mice.

In rats only, a subchronic neurotoxicity study was conducted following dietary exposure to clothianidin. In contrast to the acute neurotoxicity study described previously, in which neurotoxic effects were observed after gavage exposure, no indications of neurotoxicity were noted in the subchronic study following dietary exposure. Slightly decreased food consumption, body weights, and body weight gains were the only observed effects in the subchronic neurotoxicity study.

In subchronic oral studies in rats and dogs, decreases in body weight and body weight gain were observed in both species. In addition, dogs also displayed decreased white blood cells, albumin, and total protein, as well as some anemia, and they appear to be more sensitive than rats to the effects of clothianidin following subchronic oral exposure. Following subchronic exposures, male dogs are more sensitive than females. No effects were observed up to the limit dose in the 28-day dermal study in rats.

Chronic feeding studies were conducted in the dog, rat, and mouse. Anemia was observed in the dog. In the rat, decreased body weight and food consumption, ovary interstitial gland hyperplasia, increased lymphohistiocytic infiltrate, and altered hepatocellular eosinophilic foci of the liver were observed in females; decreased body weight and food consumption, slightly increased incidences of pelvic mineralization, and transitional cell hyperplasia in the kidney, mottled livers, and altered hepatocellular eosinophilic foci in the liver were observed in male rats. In the mouse, decreases in body weight and body weight gain in females and increases in vocalization in both sexes were the only observed effects.

A comparison of the subchronic and chronic feeding studies in the rats shows that a wider spectrum of effects was observed in the chronic study, even though the NOAELs and LOAELs in these two studies were similar. Thus, it appears that there may be more toxicity in rats when exposure is over a longer period of time. In contrast, administration of clothianidin to the dog for a longer period of time does not appear to result in any additional effects or effects at lower dose levels.

In the developmental neurotoxicity study, toxicity in the offspring was observed at a lower dose level than the dose that caused toxicity in the maternal animals. Maternal effects included decreased body weights, body weight gains, and food consumption. Effects seen in the offspring included decreased body weights, body weight gains, motor activity, and acoustic startle response in the females.

No quantitative or qualitative susceptibility was observed in either of the developmental rat or rabbit studies. In the rat, no developmental toxicity was observed at the highest dose tested, although this dose level induced decreases in body weight gain and food consumption in the dams. In the rabbit, premature deliveries, decreased gravid uterine weights, an increase in litter incidence of a missing lobe of the lung, and a decrease in the litter average for ossified sternal centra per fetus were noted at a dose level in which maternal death, a decrease in food consumption, and clinical signs (scant feces and orange urine) were observed. Since the developmental effects observed in the rabbit study were seen in the presence of maternal toxicity, they are not considered to be qualitatively more severe than the maternal effects.

Quantitative susceptibility was observed in the two-generation reproduction study since the offspring NOAEL is lower than the parental NOAEL. The LOAEL for offspring toxicity is based on decreased body weight gains, delayed sexual maturation (males), decreased absolute thymus weights in F_1 pups of both sexes, and an increase in stillbirths in both generations. The parental systemic LOAEL is based on decreased absolute body weights and body weight gains with decreased absolute and relative thymus weights in both sexes.

In the rat chronic feeding/carcinogenicity study, an apparent increase in thyroid c-cell tumors was observed in females. In addition, an increased incidence of hepatocellular carcinomas in males was examined more closely. A statistical analysis revealed that the increase in thyroid c-cell tumors did not appear to be significant, especially when carcinomas and adenomas are combined. The increased incidence of hepatocellular carcinomas at the low and high doses were just outside historical control incidences for the same testing laboratory (only 2 studies) but were within the historical control range for the animal supplier. In addition, there was no dose-response. Finally, there was no continuum (i.e., no preneoplastic lesions and no adenomas). There was no evidence of an increase in tumors in mice. Therefore, clothianidin is classified as not likely to be carcinogenic to humans. Clothianidin is a major animal and plant metabolite of thiamethoxam. Thiamethoxam is not carcinogenic to male and female rats; however, dietary administration of thiamethoxam is associated with increased incidence of liver tumors in both sexes of mice. The fact that thiamethoxam induces liver tumors in mice and no tumors in rats supports the argument that clothianidin is not likely to be carcinogenic to humans because the apparent increases in tumors with clothianidin were in a different species (rats) and because the tumor of higher potential concern (thyroid) was not in the same target organ.

In the mutagenicity studies, none of the intermediates or metabolites appeared to have genotoxic potential under the conditions of the studies, but the studies for the technical material gave mixed results. Some of the batches of test material tested positively, and some tested negatively. The HIARC has requested that the composition of the test materials used in the mutagenicity studies be investigated to determine whether or not the differences in composition may have affected the results from the studies. Additional data on the composition of the materials has been submitted and is currently under review.

In some of the toxicological studies, there was evidence of possible effects on the immune system. Decreased absolute and adjusted thymus and spleen weights were observed in multiple studies. In addition, juvenile rats in the two-generation reproduction study appeared to be more susceptible to these effects. The thymus is involved in the production of T cells, whose function is to recognize and respond to foreign antigens. The spleen serves an important function in clearing the blood of infectious organisms. Therefore, the HIARC recommends a developmental immunotoxicity study.

In rats, clothianidin is readily absorbed and excreted within 96 hours following a single low dose or repeated low doses, but at a high dose, absorption became biphasic and was saturated. The studies suggest that a multiple exposure regimen did not affect the absorption/excretion processes. There was rapid absorption and distribution of administered radioactivity to all organs and tissues followed by rapid excretion with reduction to background levels in most tissues and organs within 24 hours. There was a somewhat greater rate of absorption and elimination in females. Excretory patterns did not exhibit gender-related variability but reflected the delayed absorption in the high-dose group. The metabolites identified (primarily oxidative demethylation products and cleavage products of the nitrogen-carbon bond between the nitroimino and thiazolyl moieties) were consistent with Phase I processes.

In mice, clothianidin is readily absorbed and excreted within 168 hours following a single low dose. Urine was the major route of excretion. Neither clothianidin nor its metabolites appeared to exhibit potential for bioaccumulation. Excretory patterns did not exhibit gender-related variability. The major metabolites in both urine and feces were the parent compound (clothianidin) and TZNG [N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine], which resulted from N-demethylation of clothianidin.

A dermal absorption study with monkeys is available. Dermal absorption, as the sum of urinary and fecal excretion and Cage/Pan/Chair Wash, Debris, was 0.24 (± 0.11) as percent of dose. Adjustment of the direct absorption determination was not necessary because recovery from the dermal dose was >90%. A value of 1% dermal absorption has been recommended as appropriate for use in risk assessment. This estimation takes into account any variability that would have likely occurred with testing several dose levels. The mouse single dose and rat single and multiple dose metabolism studies indicate that oral absorption is in the range of 90% or greater. Therefore, any extrapolation from the oral to the dermal route using the dermal absorption factor is not likely to grossly underestimate anticipated adverse effects.

3.2 FQPA Considerations

On November 14, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the potential for increased susceptibility of infants and children from exposure to clothianidin as required by the Food Quality Protection Act (FQPA) of 1996 according to the February 2002 OPP 10x Guidance Document. Although a complete complement of acceptable developmental, reproduction, developmental neurotoxicity, mammalian neurotoxicity, and special neurotoxicity studies is available and was reviewed at this meeting, the HIARC concluded that the toxicology database for clothianidin is not complete for FQPA purposes. Due to evidence of decreased absolute and adjusted organ weights of the thymus and spleen in multiple studies in the clothianidin data base, and since juvenile rats in the two-generation reproduction study appear to be more susceptible to these effects than adults, the HIARC recommended that testing be conducted to assess immune system function in adults and in young animals following exposure during the period of organogenesis.

The HIARC determined that no quantitative or qualitative susceptibility was observed in either the developmental rat or rabbit studies. No developmental toxicity was observed in the rat at dose levels which induced decreases in body weight gain and food consumption in the dams. In the rabbit, premature deliveries, decreased gravid uterine weights, an increase in litter incidence of a missing lobe of the lung, and a decrease in the litter average for ossified sternal centra per fetus were noted at a dose level in which maternal death, a decrease in food consumption, and clinical signs (scant feces and orange urine) were observed. The developmental effects in the rabbit study are not considered to be qualitatively more severe than the maternal effects.

In contrast, quantitative susceptibility was observed in both the reproduction and developmental neurotoxicity rat studies. In the reproduction study, offspring toxicity (decreased body weight gains, delayed sexual maturation in males, decreased absolute thymus weights in F_1 pups of both sexes, and an increase in stillbirths in both generations) was seen at a lower dose

than the dose that caused parental toxicity. In the developmental neurotoxicity study, offspring toxicity (decreased body weight gains, motor activity, and acoustic startle response) was seen at a lower dose than the dose that caused maternal toxicity.

Since there is quantitative evidence of increased susceptibility of the young following exposure to clothianidin in the 2-generation reproduction and developmental neurotoxicity studies in rats, HIARC next performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. When residual uncertainties are identified in a Degree of Concern Analysis, HIARC then examines whether these residual uncertainties can be addressed by a special FQPA safety factor and, if so, the size of the factor needed.

The results of the HIARC Degree of Concern Analysis for clothianidin are as follows. For the 2-generation reproduction study, HIARC determined that the level of concern is low because the observed effects are well characterized, there are clear NOAELs/LOAELs, and the endpoint of concern is the one that is being used for short, intermediate, and long term dietary and non-dietary exposure risk assessments. HIARC also determined that the degree of concern for the developmental neurotoxicity study is low because the observed effects are well characterized and there are clear NOAELs/LOAELs. Therefore, there are no residual uncertainties for pre- and/or postnatal toxicity.

Because there are no residual uncertainties regarding pre- and/or postnatal toxicity, the HIARC recommended that the special FQPA Safety Factor (SF) be reduced to 1x. The clothianidin risk assessment team evaluated the quality of the exposure data; based on these data, the team also recommended that the special FQPA SF be reduced to 1x. This recommendation is based on the following:

- There are no residual uncertainties for pre- and/or postnatal toxicity.
- The *acute* dietary food exposure assessment utilizes existing and proposed tolerance level residues and 100% CT information for all commodities. The *chronic* dietary food exposure assessment utilizes existing and proposed tolerance level residues, except for ARs for apple and pear, and 100% CT information for all commodities. By using these conservative assessments, actual and chronic exposures/risks will not be underestimated.
- The dietary drinking water assessment (Tier1 estimates) utilizes values generated by the FIRST model and associated modeling parameters which are designed to provide conservative, health-protective, high-end estimates of water concentrations.

HIARC evaluated the need for a database uncertainty factor for clothianidin in the absence of the developmental immunotoxicity study, and they determined that there is insufficient data to justify selection of an additional safety factor for the protection of infants and children lower than the default value of 10X for both single and repeated dose exposure scenarios. Therefore, a UF_{DB} of 10X will be applied to both single and repeated dose exposure

scenarios (i.e., acute and chronic RfDs, short- and intermediate-term incidental oral exposures, and short-, intermediate-, and long-term dermal and inhalation exposures resulting from residential uses of clothianidin) to account for the lack of the developmental immunotoxicity study with clothianidin.

3.3 Dose Response Assessment

Discussion of Toxicological Endpoints:

Acute dietary endpoints: The acute dietary endpoint for females in the 13 to 50 year age group is based on an increased litter incidence of a missing lobe of the lung. This endpoint is considered appropriate for this population subgroup because the observed developmental effects are presumed to occur following a single oral dose.

The acute dietary endpoint for the general population is based on transient signs of decreased spontaneous motor activity, tremors and deep respirations in the mouse following a single oral dose.

Chronic dietary endpoint: The chronic dietary endpoint is based on offspring effects in the 2-generation reproduction study: decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F_1 pups, and an increase in stillbirths in both generations.

Occupational/Residential endpoints: Endpoints of concern for assessing risks via the incidental oral, dermal, and inhalation exposure pathways are based on the offspring toxicity seen in the two generation reproduction study. An oral study (NOAEL) was selected for assessing dermal risks because of the concerns seen in the pups in the oral study, which are not evaluated in the available dermal toxicity study. The same critical study (i.e., oral) was also selected for assessing inhalation risks due to the concern for offspring toxicity and the lack of a repeated exposure inhalation study.

Table 5. Summary of Toxicological Dose and Endpoints for Clothianidin

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	Developmental NOAEL = 25 UF = 1000[a] **Acute RfD** = 0.025 mg/kg	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.025 mg/kg	Developmental rabbit study Developmental LOAEL = 75 mg/kg/day based on an increased litter incidence of a missing lobe of the lung.
Acute Dietary (General population)	NOAEL = 25 UF = 1000[a] **Acute RfD** = 0.025 mg/kg	FQPA SF = 1 **aPAD** = acute RfD / FQPA SF = 0.025 mg/kg	Special Neurotoxicity/Pharmacology Study in Mice and Rats LOAEL = 50 mg/kg based on transient signs of decreased spontaneous motor activity, tremors and deep respirations.

Table 5. Summary of Toxicological Dose and Endpoints for Clothianidin			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Chronic Dietary (All populations)	Offspring NOAEL= 9.8 UF = 1000[a] **Chronic RfD** = 0.0098 mg/kg/day	FQPA SF = 1 **cPAD** = chronic RfD / FQPA SF = 0.0098 mg/kg/day	2-Generation Reproduction Study Offspring LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F_1 pups and an increase in stillbirths in both generations.
Incidental Oral (All Durations)	NOAEL= 9.8 mg/kg/day	**Residential** LOC for MOE = 1000[a] **Occupational** = NA	2-Generation Reproduction Study Offspring LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F_1 pups and an increase in stillbirths in both generations.
Dermal (All Durations)	Oral study NOAEL= 9.8 mg/kg/day (dermal absorption rate = 1%)	**Residential** LOC for MOE = 1000[a] **Occupational** LOC for MOE = 100	2-Generation Reproduction Study Offspring LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F_1 pups and an increase in stillbirths in both generations.
Inhalation (All Durations)	Oral study NOAEL= 9.8 mg/kg/day (inhalation absorption rate = 100%)	**Residential** LOC for MOE = 1000[a] **Occupational** LOC for MOE = 100	2-Generation Reproduction Study Offspring LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F_1 pups and an increase in stillbirths in both generations.
Cancer (oral, dermal, inhalation)	**Classification: Not likely to be carcinogenic to humans**		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, LOC = level of concern, NA = Not Applicable

[a] Additional 10x database uncertainty factor for lack of a developmental immunotoxicity study.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (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 was scientific basis for

including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has 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).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, clothianidin may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

For clothianidin, effects which indicate potential endocrine disruption include changes in the ovaries and/or ovarian weights in the rat, dog, and mouse studies, changes in the testes and/or testicular weights in rodents and dogs, possible delayed sexual maturation in the reproduction and developmental neurotoxicity studies, increased adrenal weights with congestion, and increased thyroid weights with noted cysts and adenomas.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Arvesta Corporation has proposed the establishment of permanent tolerances for residues of clothianidin, (E)-N-[(2-chloro-5-thiazolyl)methyl]-N'-methyl-N''-nitroguanidine, in or on the following raw agricultural commodities: pome fruit at 1.0 ppm and for the use on tobacco, turf, and ornamental plants. Tolerances have previously been established for the residues of clothianidin expressed as parent only on canola seed at 0.01 ppm; corn, field, forage at 0.10 ppm; corn, field, grain at 0.01 ppm; corn, field, stover at 0.10 ppm; corn, pop, grain at 0.01 ppm; corn, pop, stover at 0.10 ppm; corn, sweet, forage at 0.10 ppm; corn, sweet, kernel plus cob with husk removed at 0.01 ppm; corn, sweet, stover at 0.10 ppm; milk at 0.01 ppm; animal feed, nongrass at 0.02 ppm; grain, cereal, forage, fodder and straw at 0.02 ppm; grass, forage, fodder and hay at 0.02 ppm; soybean, forage at 0.02 ppm; and soybean, hay at 0.02 ppm.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Table 6. Summary of Directions for Use of Clothianidin.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Apples						
Post bloom, airblast	CLUTCH™ 50 WDG [66330-XXX]	0.0625-0.094	2	0.2	7	10-14 day retreatment interval do not allow livestock to graze in treated orchards
Pears						
Post bloom, airblast	CLUTCH™ 50 WDG [66330-XXX]	0.125-0.2	1	0.2	7	do not allow livestock to graze in treated orchards
Tobacco						
ground-boom spray, soil drench and transplant treatment	CLUTCH™ 50 WDG BELAY™ 16 WSG ARENA® 0.5 G	0.05 - 0.4	3	0.4	14	12-hr reentry interval
Turf						
ground-boom spray, ground broadcast spreaders, push-type drop or broadcast spreaders	ARENA® 0.5 G	0.2 - 0.4	1	0.4	not indicated	12-hr reentry interval

It was noted that, although allowed by the proposed label, adjuvants were not utilized in the apple and pear field trials. There could be increased residues when adjuvants are included in the tank mix and, therefore, the use of adjuvants should be removed from the label.

Based on the available plant metabolism studies, HED's MARC concluded that, for the currently proposed uses, the nature of the residue has been adequately delineated and that parent only is the residue of concern to be used in risk assessment and the tolerance expression for primary crops. However, future new uses on root crops and/or leafy vegetables will require analysis of metabolite TMG and parent in field trials (see Reference 1 for structures of metabolites). Alternatively, the registrant may submit additional metabolism data, preferably side-by-side thiazol- and nitroimino- radiolabeled studies. The metabolic profiles in the tested primary crops were similar in that the highest level residue was the parent, with the exception of mature sugar beet crops. Based on the submitted goat and hen metabolism studies, the MARC

concluded for ruminants that parent, TZNG, TZU, TZG, and ATMG-Pyr are the residues of toxicological concern to be included in the risk assessment, and parent only is the residue of concern for the tolerance expression. For poultry, with future new uses where higher residues in poultry feed items are found, parent, TZNG, TZU, TZG, and ATG-Ac are residues of concern to be analyzed in a feeding study and included in the risk assessment. Parent only is needed for the tolerance expression. With respect to the nature of the residue in rotational crops, MARC determined that parent, TZNG, and MNG are the residues of concern for risk assessment, while parent only is needed for the tolerance expression (Reference 3, HED MARC D282449, Y. Donovan, 04/25/03).

Table 7. Summary of MARC Decisions and Analytical Method Detections for Clothianidin

Matrix	Residues of Concern For Risk Assessment	Analytes Detected by Data Collection Method	Residues of Concern For Tolerance Expression	Analytes Detected by Enforcement Method
Plants	Parent only	Parent only	Parent	Parent only
Livestock (Cattle)	Parent, TZU, TZG, TZNG, ATMG-Pyr	Parent, TZU, TZG, ATMG-Pyr	Parent	Parent, TZU, TZG, ATMG-Pyr
Livestock (Poultry)	Parent, TZU, TZG, TZNG, ATG-Ac	N/A	Parent	N/A
Rotational crops	Parent, TZNG, MNG	Parent, TZNG	Parent	Parent only
Water	Parent only	N/A	N/A	N/A

Clothianidin, (E)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine, radiolabelled at the nitroimino moiety, was applied to unfiltered cigarettes at approximately 43 ppm and smoked using a total recovery smoking apparatus (TRSA). Residues in smoke were collected using a particulate filter and a series of gas dispersion traps. Extracts from the particulate filters and solutions from the dispersion traps were radioassayed by LSC. Those extracts containing >10% of the applied dose were analyzed by HPLC. The identity of clothianidin was confirmed by TLC for selected extracts and by HPLC/MS for cigarette extracts. The pyrolysis of clothianidin in cigarettes resulted in formation of approximately 50% of the applied dose as $^{14}CO_2$ recovered in the main stream (MS) and side stream (SS). The major component found in the butt and filter extracts was clothianidin, averaging 18% of the applied dose. No major known metabolites were formed at >8% of the applied dose.

Residue data on apples and pears were obtained using the Valent analytical method RM-39-A for determining the residue of clothianidin in/on RACs and processed fractions. Macerated samples were extracted via homogenization with acetonitrile/water 2:1 (v:v). This sample extract mixture was vacuum-filtered into a round-bottom flask, and the extract filtrate was then brought to volume with acetonitrile (ACN). An aliquot of the filtrate was concentrated to the aqueous remainder via rotary vacuum evaporator. To this aqueous sample extract was added de-ionized water and then the solution was put through a ChemElut® CE-1020 cartridge column, which was then washed with hexane. The hexane wash was discarded. The purified extract was

eluted from the column with hexane/ethyl acetate 1:1 (v:v). This resultant eluate was evaporated to dryness via rotary vacuum evaporator, then reconstituted in ACN/0.05% aqueous acetic acid 1:4 (v:v) for analysis. The analysis was conducted by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) using a C18 column and quantitated using an external standard calibration technique.

Three product ions arise from the precursor ion in the MS/MS analyzer. The LC/MS/MS system chromatographic responses of clothianidin in solvent were linear over the calibration standards' range of 0.010 ppm to 0.500 ppm. The validated LOQ and LOD were 0.010 ppm and 0.005 ppm, respectively. Control interferences in apples and pears were all less than 0.005 ppm. Method validation and concurrent recovery data for apples and pears were considered acceptable. Concurrent recoveries of clothianidin were analyzed by spiking untreated samples of apples and pears at levels from 0.010 to 0.500 ppm. Recoveries of clothianidin ranged from 72% to 121% in apples and 62% to 97% in pears.

Previously, Method 00552 was used for data gathering and was proposed as an enforcement method to determine residues of clothianidin in plant commodities. Briefly, residues were extracted with ACN/water, filtered, and the filtrate was concentrated for cleanup through a ChemElut column eluted with cyclohexane/ethyl acetate. Residues were analyzed by HPLC using a C18 column, a gradient mobile phase of acidic water and ACN, with confirmation and quantitation by MS/MS. Residues of clothianidin were quantitated by external standard calibration. A modification of the method has been submitted (M001) which adds the use of an internal standard, d_3-clothianidin, for quantitation. The validated LOQ, without using internal standard quantitation, is 0.02 ppm for corn plant, cob, grain, and straw; rape forage, straw, and seed; sugar beet tops and root; sunflower plant and seed; and wheat forage, grain, and straw. With the use of the internal standard, the validated LOQ is 0.01 ppm for corn grain, rape seed and sugar beet root, and 0.02 ppm for wheat straw. Only the internal standard method has a validated LOQ (0.01 ppm). A successful ILV has been completed with corn grain along with adequate radiovalidation data for apple, corn forage, stover, and grain. No interferences were observed in any of the studies, including an interference study which investigated 133 compounds. The method is similar to Method 00624, also a LC-MS/MS method, which was found acceptable by HED for data collection purposes and sent to EPA's Analytical Chemistry Branch (ACB) for Agency validation. Upon review of the method, ACB recommended that the registrant's non-internal standard plant and livestock methods be accepted for enforcement purposes without further EPA laboratory validation. Clothianidin and the metabolites TZG, MNG, TZNG, TZU, and ATMG-Pyr were not adequately recovered using any of the PAM I multiresidue methods.

Thirteen crop field trial studies were conducted in apples using a single application of Clutch® 50 WDG insecticide (50% clothianidin by weight) at application rates of 0.195 to 0.201 lb ai/A (0.219 to 0.225 kg ai/ha). The maximum residue in/on apples harvested 6 to 7 days following treatment was 0.199 ppm with a highest average field trial (HAFT) of 0.174 ppm. A residue decline study was conducted at one site and indicated that residues of clothianidin on treated apples decline with time. Residues in apple juice were reduced by a factor of 0.14x. The

concurrent storage stability demonstrated that clothianidin residues did not degrade in apples stored frozen for the duration of the studye.

Seven crop field trial studies were conducted in pears using a single application of Clutch® 50 WDG insecticide (50 % clothianidin by weight) at application rates of 0.196 to 0.200 lb ai/A (0.220 to 0.224 kg ai/ha). The maximum residue in/on pears harvested 6 to 7 days following treatment was 0.176 ppm with a HAFT of 0.163 ppm. A residue decline study was conducted at one site and indicated that residues of clothianidin on treated pears decline with time. The concurrent storage stability demonstrated that clothianidin residues did not degrade in pears stored frozen for the duration of the study.

Table 8. Summary of Residues from the Crop Field Trials with Clothianidin.

Crop Matrix	Applic. Rate lb ai/A (kg ai/ha)	PHI (days)	Residues (ppm)				
			Min.	Max	HAFT	Mean	Std. Dev.
Apple (proposed use = 0.2 lb ai/A total application rate, 7-day PHI)							
Fruit	0.195-0.201 (0.219-0.225)	38144	<0.005	0.199	0.174	0.1	0.1
Pear (proposed use = 0.2 lb ai/A total application rate, 7-day PHI)							
Fruit	0.196-0.200 (0.220-0.224)	38144	0.041	0.176	0.163	0.11	0

A processing study was conducted on apples treated at 3x the proposed rate, which produced raw fruit with quantifiable residues of clothianidin. The study was conducted using simulated commercial practices. The processing study is supported by adequate storage stability data, and the residue data were obtained using an adequate data gathering method that determined the residue of concern, parent. The results of the processing study indicate that residues of clothianidin are reduced during the formation of apple juice (0.14x) and wet apple pomace (0.24x). Separate tolerances for clothianidin on apple processed commodities are not required.

A previously submitted cattle feeding study indicated that at the highest dose level, 2.56 mg/kg feed (about 6.9X of the dietary burden for dairy cattle and about 9.8X for beef cattle), residues of parent and all metabolites were below the LOQ of 0.02 ppm for tissues. It was concluded that no tolerance is needed for meat and meat by-products. For milk, the highest residue level of parent clothianidin is 0.012 ppm, while each metabolite was below the LOQ of 0.01 ppm. Based on the goat metabolism study, parent clothianidin accounts for about 50% of the TRR in milk.

The only animal feed item associated with this action is wet apple pomace. Although HED is recommending that a tolerance of 1.0 ppm be established on raw apples (as a member of the pome fruit crop group) from the proposed use, HED does not consider that residue level appropriate for apple pomace in the livestock dietary burden calculation for two reasons. First, a processed food study determined that clothianidin residues are reduced by a factor of 0.24x on

wet apple pomace as a result of simulated commercial processing (MRID: 45480402, W. Drew, 4/21/04). Second, the HAFT of the apple crop field trials, 0.174 ppm (MRID: 45480402, W. Drew, 4/10/04), is well below the RAC tolerance. Therefore, a residue level of 0.2 ppm will be used for pomace. Replacing the lowest contributor to the clothianidin dietary burden of cattle from the previous calculations, corn grain, and using the calculated total residue and % dry matter (DM) for wet apple pomace will result in a dietary burden of 0.43 ppm for both beef and dairy cattle. The highest dose level of cattle feeding study outlined above is 6.0x higher than the calculated beef and dairy cattle burden.

Since the dietary burden including the use on apples is calculated to be 0.43 ppm for beef and dairy cattle and the cattle feeding study indicated that at the highest dose level, 2.56 mg/kg feed (about 6.0x for both beef and dairy cattle dietary burden), residues of parent and all metabolites were below the LOQ of 0.02 ppm for tissues, no tolerance is needed for meat, fat, and meat by-products. Since for milk, the highest clothianidin residue level found in the feeding study was 0.012 ppm, while each metabolite was below the LOQ of 0.01 ppm, the established 0.01 ppm tolerance for milk is adequate. The previous conclusion regarding the lack of a need for poultry and egg tolerances is still applicable since there are no significant poultry feed items from pome fruit.

Current status sheets available to HED indicate that no Codex, Canadian, or Mexican maximum residue levels (MRLs) have been established for residues of clothianidin.

4.2.2 Acute Dietary

Acute Dietary Exposure and Risk. aPAD = acute RfD = 0.025 mg/kg bwt/day.

The acute analysis is a conservative, Tier 1 assessment which is based on tolerance-level residues and the assumption of 100% crop treated for established and proposed clothianidin uses. Clothianidin is a major metabolite of thiamethoxam which has many registered uses and several pending uses. Residues of clothianidin that would theoretically result from the metabolism of thiamethoxam are included in the analysis. The residues of both clothianidin and thiamethoxam were measured in thiamethoxam crop field trials and animal feeding studies that were reviewed and accepted by EPA. The ratio of clothianidin to thiamethoxam in each commodity was multiplied by the respective thiamethoxam tolerance level to arrive at the theoretical maximum clothianidin residue level that would be present. These maximum clothianidin residues are used in the acute analysis. For the commodities that have both thiamethoxam tolerances and proposed clothianidin tolerances (i.e., sweet corn, field corn, pop corn, canola, and milk), the proposed clothianidin tolerances are added to the residues that result from use of thiamethoxam. Processing factors are DEEM (Version 7.76) default processing factors with the exception of those on apple and pear juice, which are reduced to 0.14, the factor found in the apple processing study.

As this is a Tier 1 assessment, dietary exposure and risk at the 95th percentile of exposure are reported. The general U.S. population and all population subgroups have exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the acute population

adjusted doses (aPADs) are all below 100%). The most highly exposed population subgroup is all infants <1 yr, which utilizes 80% and 81% of the aPAD, as reported by DEEM-FCID and Lifeline, respectively (Table 9).

Table 9. Results of Acute Dietary Exposure Analysis Using both DEEM FCID and Lifeline At the 95th Percentile[1]

Population Subgroup	aPAD (mg/kg/day)	DEEM		LifeLine	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.025	0.004608	18	0.004511	18
All Infants (< 1 year old)	0.025	0.020018	80	0.020197	81
Children 1-2 years old	0.025	0.014988	60	0.015766	63
Children 3-5 years old	0.025	0.012197	49	0.012194	49
Children 6-12 years old	0.025	0.006700	27	0.006595	26
Youth 13-19 years old	0.025	0.002965	12	0.002822	11
Adults 20-49 years old	0.025	0.002839	11	0.003383	14
Adults 50+ years old	0.025	0.003394	14	0.003567	14
Females 13-49 years old	0.025	0.003046	12	0.003661	15

[1] Percentage Acute PAD (% aPAD) = $\frac{\text{Exposure X 100}}{\text{aPAD}}$

4.2.3 Chronic Dietary

Chronic Dietary Exposure and Risk cPAD = chronic RfD = 0.0098 mg/kg bwt/day.

The chronic analysis is a somewhat conservative, Tier 2 assessment that is based on tolerance level residues and the assumption of 100% crop treated for established and proposed clothianidin uses with the exception of anticipated residues (AR) for apples and pears. To account for thiamethoxam sources of clothianidin, the ratio of clothianidin to thiamethoxam in each commodity was multiplied by the respective thiamethoxam tolerance level to arrive at the theoretical maximum clothianidin residue level that would be present. These maximum clothianidin residues are used in the chronic analysis. With the exception of apples and pears, for the commodities that have both thiamethoxam tolerances and proposed clothianidin tolerances (i.e., sweet corn, field corn, pop corn, canola, and milk), the proposed clothianidin tolerances are added to the residues that result from use of thiamethoxam. For apples and pears, the highest average field trial (HAFT) levels from the residue field trials were added to the residues that result from use of thiamethoxam. Processing factors are DEEM (Version 7.76) default processing factors with the exception of those on apple and pear juice, which are reduced to 0.14, the factor found in the apple processing study.

The general U.S. population and all population subgroups have exposure and risk estimates which are below HED's level of concern (i.e., the percentages of the chronic

population adjusted doses (cPADs) are all below 100%). The most highly exposed population subgroup is children 1-2 yrs at 15% and 14% of the cPAD, as reported by DEEM-FCID and Lifeline, respectively (Table 10).

Table 10. Results of Chronic Dietary Exposure Analysis Using both DEEM-FCID and Lifeline[1]

Population Subgroup	cPAD (mg/kg/day)	DEEM		LifeLine	
		Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.0098	0.000552	6	0.000514	5
All Infants (< 1 year old)	0.0098	0.001304	13	0.001264	13
Children 1-2 years old	0.0098	0.001457	15	0.001392	14
Children 3-5 years old	0.0098	0.001191	12	0.001125	11
Children 6-12 years old	0.0098	0.000718	7	0.000622	6
Youth 13-19 years old	0.0098	0.000404	4	0.000374	4
Adults 20-49 years old	0.0098	0.000431	4	0.000443	5
Adults 50+ years old	0.0098	0.000485	5	0.000460	5
Females 13-49 years old	0.0098	0.000434	4	0.000486	5

[1] Percentage Chronic PAD (% cPAD) = $\frac{\text{Exposure X 100}}{\text{cPAD}}$

4.2.4 Cancer Dietary

The HIARC determined that clothianidin is not likely to be a human carcinogen. Therefore, a cancer dietary exposure analysis was not performed.

4.3 Water Exposure/Risk Pathway

The fate and disposition of clothianidin in the environment suggest that it is persistent and mobile, stable to hydrolysis, and has potential to leach to ground water, as well as runoff to surface waters. The high persistence of clothianidin (aerobic soil metabolism and terrestrial field dissipation half-lives ranging from half a year to several years) may cause accumulation of the chemical in soils following repeated uses.

EFED provided Tier I Estimated Drinking Water Concentrations (EDWCs) for clothianidin in surface water and in ground water for use in human health risk assessments. The simulation model FIRST was used to calculate the surface water EDWCs and the SCI-GROW model was used to calculate the groundwater EDWC. No clothianidin monitoring data were available. Although clothianidin is a major metabolite of thiamethoxam in plants and in animals, it was not found in environmental fate studies. Therefore, exposure to clothianidin in drinking water due to thiamethoxam uses is not expected. MARC's decision on residues of concern for thiamethoxam in drinking water is parent only. For the simulation models, the application rate of 0.4 lbs ai/A for turfgrass was used. This rate is the highest of all the proposed and existing uses.

The EDWCs for clothianidin in surface waters are 7.29 ug/L for acute risk calculations and 1.35 ug/L for chronic risk and cancer risk calculations. Clothianidin EDWCs in ground water are not expected to exceed 5.84 ug/L.

Table 11. Estimated Tier 1 concentrations of clothianidin in drinking water.

Chemical	Surface Water (ug/L)		Groundwater (ug/L)
	Acute	Chronic	Acute and Chronic
Clothianidin	7.29	1.35	5.84

4.4 Residential Exposure/Risk Pathway

Due to the proposed use patterns on turfgrasses, a number of residential or recreational post-application exposures are possible. In a residential setting, a "homeowner" may be exposed during application of the material to his or her lawn. Further, the "homeowner" may also experience post-application dermal exposure. Toddlers may be exposed via "hand-to-mouth" oral exposures and/or dermal exposures. These estimated exposures and risks are also presented. "Aggregated" exposures are presented for toddlers (i.e., hand-to-mouth turf + hand-to-mouth soil + dermal post-application). The ExpoSAC considers hand-to-mouth ingestion of granules to be episodic in nature, that is, a "one-time" event. Therefore the exposure from ingestion of granules is not combined with believed multiple exposures from "mouthing" of turf or soil or from post-application dermal exposure. Golfers may be exposed to post-application exposures, and estimates of adult and adolescent golfers are presented.

Table 12. Summary of Residential Post-Application Exposures and Risks

Activity	Exposure (Dose) mg a.i./kg bw/day	MOE
Toddler oral hand to mouth from contacting treated turf	0.0059	1700
Toddler incidental oral ingestion of treated soil	0.00002	490000
Adult dermal post applic turf contact	0.00108	9100
Adult **combined** dermal exposure = application + postapplication	application 0.000026 post-application + 0.00108	8900
Toddler dermal post applic turf contact	0.00155	6300
Toddler **combined** oral (except granules) and dermal exposures	treated turf + treated soil + dermal 0.00747	1300
Adult golfer post app turf contact	0.000075	130000
Child golfer post app turf contact	0.000128	77000

MOE values greater than 1000 are considered adequate to protect adults and children from residential non-dietary post-application exposures to clothianidin. The estimated MOE's are based upon conservative assumptions and are >1000; therefore, the estimated risks from residential non-dietary post-application exposures do not exceed HED's level of concern.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

Aggregate exposure risk assessments were performed for acute and chronic aggregate exposure (food + drinking water). Since HED does not have ground and surface water monitoring data to calculate a quantitative aggregate exposure, drinking water levels of comparison (DWLOCs) were calculated. A DWLOC is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, drinking water consumption, body weights, and pesticide uses. Different populations will have different DWLOCs. HED uses DWLOCs as tools in the risk assessment process to assess potential concern for aggregate exposure to pesticides. DWLOC values are not regulatory standards for drinking water.

To calculate acute and chronic DWLOCs, the dietary food estimates (from DEEM-FCID and Lifeline) were subtracted from the acute /chronic PAD value to obtain the maximum water exposure level. DWLOCs were then calculated using the standard body weights and drinking water consumption figures: 70 kg/2L (adult male and US Population), 60 kg/2L (adult female), and 10 kg/1L (infant & children).

5.1 Acute Risk

The acute aggregate risk assessment takes into account exposure estimates from dietary consumption of clothianidin (food and drinking water). The Tier 1 acute dietary exposure estimates are below HED's level of concern (<100% aPAD) at the 95th exposure percentile for the general U.S. population and all other population subgroups. The most highly exposed population subgroup is infants <1 yr old, at 80% and 81% of the aPAD, as reported by DEEM-FCID and Lifeline, respectively. The calculated DWLOCs for acute exposure to clothianidin in drinking water range from 48 to 1500 µg/L (ppb). EECs generated by EFED are less than HED's calculated DWLOCs (Table 13). Therefore, the acute aggregate risks associated with the proposed use of clothianidin do not exceed HED's level of concern for the general U.S. population or any population subgroups (Table 13).

Table 13. Acute Aggregate Exposures to Clothianidin Residues.							
Population Subgroup	aPAD (mg/kg/day)	Acute Food Exposure (mg/kg/day)	% aPAD	Maximum Acute Water Exposure [1] (mg/kg/day)	Ground Water EEC [2] (µg/L)	Surface Water EEC [2] (µg/L)	Acute DWLOC [3] (µg/L)
General U.S. Population	0.025	0.004608	18	0.020392	5.84	7.29	710
All Infants (< 1 year old)	0.025	0.020197	81	0.004803	5.84	7.29	48
Children 1-2 years old	0.025	0.015766	63	0.009234	5.84	7.29	92
Females 13-49 years old	0.025	0.003661	15	0.021339	5.84	7.29	640
Adults 50+ years old	0.025	0.003567	14	0.021433	5.84	7.29	1500

[1] maximum water exposure (mg/kg/day) = aPAD (mg/kg/day) - food exposure (mg/kg/day)
[2]The crop producing the highest level was used.
[3] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximium water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu g / mg)}{\text{water consumption (liter / day)}}$$

5.2 Short- and Intermediate-Term Risk

The HIARC has determined that, for clothianidin, the toxicological effects are the same across oral, dermal, and inhalation routes of exposure and has selected the same endpoint and dose for short- and intermediate-term exposure scenarios. Therefore, the exposures are simply summed (combined/aggregated) for use in risk calculations. Combined residential exposure estimates range from an MOE of 1,300 for combined oral and dermal exposure to toddlers (treated turf + treated soil + dermal) to 8,900 for dermal exposure to adults (application + postapplication) adults. The calculated short- and intermediate-term DWLOCs for short- and intermediate-term exposure to clothianidin in drinking water range from 8.7 to 320 ug/L. EDWCs generated by EFED for both surface and ground water were less than 5.84 ug/L, less than HED's calculated short- and intermediate-term DWLOCs. Therefore, the short- and intermediate-term aggregate risk associated with the proposed use of clothianidin does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Table 14. Short-and Intermediate-Term Aggregate Exposures to Clothianidin Residues.										
Population	NOAEL mg/kg/day	Target MOE[1]	Max Exposure[2] mg/kg/day	Average Food Exposure[3] mg/kg/day	Residential Exposure[4] mg/kg/day	Aggregate MOE (food and residential)[5]	Max Water Exposure[6] mg/kg/day	Ground Water EDWC[7] (µg/L)	Surface Water EDWC[7] (µg/L)	DWLOC[8] (µg/L)
Toddler	9.8	1000	0.0098	0.001457	0.007470	1100	0.000873	5.84	1.35	8.7
Females 13-49	9.8	1000	0.0098	0.000486	0.001106	6200	0.008208	5.84	1.35	250
Adult (male)	9.8	1000	0.0098	0.000552	0.001106	5900	0.008142	5.84	1.35	280

Adult golfer	9.8	1000	0.0098	0.000552	0.000075	16000	0.009173	5.84	1.35	320
Youth golfer	9.8	1000	0.0098	0.000404	0.000128	18000	0.009268	5.84	1.35	280

[1] Includes the conventional 100 UF and an additional 10x database UF
[2] Maximum Exposure (mg/kg/day) = NOAEL/Target MOE
[3] Higher chronic food exposure from either DEEM-FCID or Lifeline analysis
[4] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]
[5] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Residential Exposure)]
[6] Maximum Water Exposure (mg/kg/day) = Maximum Exposure - (Food Exposure + Residential Exposure)
[7] The crop producing the highest level was used.
[8] DWLOC(µg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

Body weight = 70 kg for adult males, 60 kg for adult females and youth, 10 kg for toddlers
Water consumption = 2 L/day for adults/youth, 1 L/day for toddlers

5.3 Chronic Risk

Chronic aggregate risk estimates do not exceed HED's level of concern. Using the Tier 2 approach, the DEEM-FCID and Lifeline chronic dietary risk estimates indicated that the chronic exposures to clothianidin from food for the general U.S. population will utilize 6% and 5% of the cPAD, respectively. The most highly exposed population subgroup is children 1-2 years old, which utilizes 15% of the cPAD, as reported by DEEM-FCID. The calculated DWLOCs for chronic exposure to clothianidin in drinking water range from 83 to 330 ug/L. Both surface and ground water EDWCs were less than 5.84 ug/L, substantially less than the DWLOCs. Therefore, the chronic aggregate risk associated with the proposed use of clothianidin does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Table 15. Chronic Aggregate Exposures to Clothianidin Residues.

Population Subgroup	cPAD (mg/ kg/day)	Chronic Food Exposure (mg/kg/day)	% cPAD	Max. Chronic Water Exposure [1] (mg/kg/day)	Ground Water EDWC [2] (µg/L)	Surface Water EDWC [2] (µg/L)	Chronic DWLOC [3] (µg/L)
General U.S. Population	0.0098	0.000552	6	0.009248	5.84	1.35	320
All Infants (< 1 year old)	0.0098	0.001304	13	0.008496	5.84	1.35	85
Children 1-2 years old	0.0098	0.001457	15	0.008343	5.84	1.35	83
Females 13-49 years old	0.0098	0.000486	5	0.009314	5.84	1.35	280
Adults 50+ years old	0.0098	0.000485	5	0.009315	5.84	1.35	330

[1] maximum water exposure (mg/kg/day) = cPAD (mg/kg/day) - chronic food exposure (mg/kg/day)
[2] The crop producing the highest level was used.
[3] DWLOC calculated as follows:

$$\text{DWLOC} = \frac{(\text{maximum water exposure (mg / kg / day)}) * (\text{body weight (kg)}) * (1000\ \mu\text{g / mg})}{\text{water consumption (liter / day)}}$$

Body weight = 70 kg for adult males and general US population, 60 kg for females 13-49, and 10 kg for infants/children
Water consumption = 2 L/day for adults, 1 L/day for infants/children

5.4 Cancer Risk

Clothianidin has been classified by HED HIARC as a "not likely human carcinogen." A cancer aggregate risk assessment **is not required**.

6.0 CUMULATIVE RISK

FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

HED did not perform a cumulative risk assessment as part of this tolerance action for clothianidin because HED has not yet initiated a review to determine if there are any other chemical substances that have a mechanism of toxicity common with that of clothianidin. For purposes of this tolerance action, EPA has assumed that clothianidin does not have a common mechanism of toxicity with other substances.

On this basis, the Registrant must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether clothianidin shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for clothianidin need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with clothianidin, HED will perform aggregate exposure assessments on each chemical and will begin to conduct a cumulative risk assessment.

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This guidance was issued for public comment on January 16, 2002 (67 FR 2210-2214) and is available from the OPP Website at: http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf. In the guidance, it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed.

Before undertaking a cumulative risk assessment, HED will follow procedures for identifying chemicals that have a common mechanism of toxicity as set forth in the "*Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity*" (64 FR 5795-5796, February 5, 1999).

As previously noted, clothianidin is a metabolite of the active ingredient thiamethoxam. As part of this aggregate risk assessment, HED has considered uses of the active ingredient thiamethoxam.

7.0 OCCUPATIONAL EXPOSURE AND RISK

The requested uses of clothianidin include uses on pome fruit, turfgrass, landscape ornamental plantings, and tobacco. Proposed labels for all new uses specify applicators and other handlers to wear long-sleeved shirts, long pants, shoes plus socks, and waterproof gloves.

CLUTCH™ 50 WDG (a 50 % water dispersible granule) is currently proposed for FIFRA Section 3 registered use on apple and pear. The proposed new uses are for tobacco, turfgrass, and landscape ornamentals. HED has presumed that applications are made by ground equipment. Aerial applications are not prohibited on the label, but there are no specific label directions for aerial applications. At the maximum rate, three applications are permitted per season. Clothianidin should be applied in rotation with a different class of pesticide with a different mode of action, i.e., not applied consecutively. The rate of application for foliar applications to tobacco ranges from 0.05-0.06 lb a.i./A. There is a maximum of 0.2 lb a.i./A/season. There is a 7 day application interval and a 14 day preharvest interval (PHI). It may not be applied through any type of irrigation system.

On the proposed labels, the term "ornamentals" is not described further except to say for use in commercial and residential landscapes and interior plantscapes. For "ornamentals", applications can be foliar as well as soil injections, drenches, and broadcast sprays. The rate of application ranges from 0.2-0.4 lb a.i./A with a maximum of 0.4 lb a.i./A/season. Again, ground application is assumed. Aerial application is not prohibited, but there are no directions for the use of aerial applications. There is a 12 hour restricted entry interval (REI) for CLUTCH™.

BELAY™ 16 WSG (a 16 % water soluble granule) is proposed for use only on tobacco. It is intended to be applied as a soil application in transplant water as a drench to trays or flats prior to transplanting. If it is applied as a foliar spray to plants in trays or flats, the plants should be watered from overhead sprinklers to wash the clothianidin into the soil. The rate of application ranges from 0.05-0.1 lb a.i./A. There is a 14 day PHI. There is a maximum of 0.2 lb a.i./A/season and a 12 hour REI.

ARENA® 0.5 G (a 0.5 % granule) is proposed for use only on turfgrass. It is to be applied through drop-type or rotary-type spreaders. Application rates range from 0.2-0.4 lb a.i./A with a maximum of 0.4 lb a.i./A/season. There is a 12 hour REI.

7.1 Occupational Handler

Based upon the proposed use patterns, the most highly exposed occupational pesticide handlers are: 1) mixer/loader using open pour loading of granules in support of broadcast operations to commercial turf, 2) applicator using open cab ground boom spray equipment, 3) applicator using open-cab, granular, broadcast ground equipment, and 4) mixer/loader/applicator using walk behind push-type granular spreader. Repeat applications of clothianidin should not be applied consecutively. Typically, the acreage blocks to be treated are expected to be relatively small, not requiring the volume of material or amount of time as might be required for large block crops such as corn, soybeans, cotton, or wheat. At the high rates of application, the number of repeat applications is low. Therefore, for these proposed uses, occupational pesticide handler exposures will typically be short-term (1 - 30 days).

Handler Exposure and Risk Estimates

Data Sources and Assumptions

It is expected that some private (i.e., grower) applications may perform all tasks, that is, mix, load, and apply the material. However, HED Science Advisory Council for Exposure (ExpoSac) draft Standard Operating Procedure (SOP) (29 March 2000) directs that although the same individual may perform all tasks, in some cases 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. Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand-held operations, all handling activities are assumed to be conducted by the same individual. The available monitoring data support this, and HED presents them in this way. Conversely, for equipment types such as fixed-wing aircraft, groundboom 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 (Table 16) are based upon surrogate study data available in the Pesticide Handler's Exposure Database (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 "baseline" **plus the use of protective gloves** or other Personal Protective Equipment (PPE) as might be

necessary. The proposed product labels involved in this assessment direct applicators and other handlers to wear long-sleeved shirt, long pants, waterproof gloves, and shoes and socks.

Table 16. Estimated Handler Exposure and Risk from the Use of Clothianidin on Turfgrass, Landscape Ornamentals and Tobacco

Unit Exposure[1] mg a.i./lb handled	Applic. Rate[2]	Units Treated[3] Per Day	Average Daily Dose[4] mg a.i./kg bw/day	NOAEL[5] mg a.i./kg bw/day	MOE[6]
Mixer/Loader - Granular - Open Pour					
Dermal: No Glove 0.0084 LC With Glove 0.0069 MC Inhal. 0.0017 HC	0.4 lb a.i./A	80 A	Dermal: No Glove 0.000045 W Glove 0.000037 Inhal 0.00009	9.8	Dermal: No Glove 73,000 W Glove 77,000
Applicator - Open Cab - Ground-boom					
Dermal: No Glove 0.014 HC With Glove 0.014 MC Inhal 0.00074 HC	0.4 lb a.i./A	80 A	Dermal: No Glove 0.000075 W Glove 0.000075 Inhal 0.00039	9.8	Dermal: No Glove 21,000 W Glove 21,000
Applicator - Open Cab - Granule Broadcast					
Dermal: No Glove 0.0099 LC With Glove 0.0069 LC Inhal 0.0012 LC	0.4 lb a.i./A	80 A	Dermal: No Glove 0.000053 W Glove 0.000037 Inhal 0.00064	9.8	Dermal: No Glove 14,000 W Glove 14,000
Mixer/Loader/Applicator - Push-type Spreader					
Dermal: No Glove 2.9 LC With Glove no data Inhal 0.0063 HC	0.4 lb a.i./A	0.20833	Dermal: No Glove 0.00097 W Glove no data Inhal 0.00021	9.8	Dermal: No Glove 8,300 W Glove no data

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 = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. Data Confidence: LC = Low Confidence, MC = Medium Confidence, HC = High Confidence
2. Applic. Rate. = Taken from proposed CLUTCH and ARENA label for turfgrass.
3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; SOP No. 9.1. Science Advisory Council for Exposure; Revised 5 July 2000.
4. Average Daily Dose = Unit Exposure * Applic. Rate * Units Treated * % absorption (1 % dermal absorption; 100 % inhalation absorption) ÷ Body Weight (60 kg).
5. No Observed Adverse Effect Level (NOAEL) short-term dermal NOAEL = 9.8 mg a.i./kg bw/day; short-term inhalation NOAEL 9.8 mg a.i./kg bw/day. The NOAEL is based upon a 2-generation rat reproduction study where the effects seen were decreased body weight gains, delayed sexual maturation, decreased absolute thymus weights in F_1 pups and an increase in still births in both generations at the Lowest Observed Adverse Effect Level (LOAEL) of 31.2 mg a.i./kg bw/day.
6. MOE = Margin of Exposure = No Observable Adverse Effect Level (NOAEL) ÷ ADD. ADD = dermal + inhalation.

Exposure and Risk Estimates

MOE values greater than 100 are considered adequate to protect occupational pesticide handlers. All estimated MOE's are > 100; therefore, the proposed uses do not exceed HED's

level of concern. The same endpoint and dose were selected for the short- and intermediate-term assessments. In addition, short- and intermediate-term exposures are equivalent; therefore, the estimated risks are the same.

7.2 Postapplication Exposure and Risk Estimates

Data and Assumptions

There is a potential for agricultural workers to experience post-application exposure to pesticides 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. HED has also identified Transfer Coefficients (TC) (as cm^2/hr) relative to the various activities, which express the amount of foliar contact over time during each of the activities. For the proposed use sites, the post-application activities with the highest TCs are summarized in Table 17.

Table 17. Summary of Highest Transfer Coefficients (cm^2/hr) For Post-application Activities in the Proposed New Use Sites

Use Site	Post-application Activity	Transfer Coefficient cm^2/hr
Turf - Sod Farm	harvest	6800
Turf - Golf Course	maintenance	3400
Tobacco	hand harvest, stripping, thinning, topping, weeding	2000

The transfer coefficients used in this assessment are from an interim transfer coefficient Standard Operating Procedure (SOP) developed by HED's Science Advisory Council for Exposure using proprietary data from the Agricultural Re-Entry Task Force (ARTF) database (SOP # 3.1). It is the intention of HED's Science Advisory Council for Exposure 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.

The transfer coefficients for turf - golf course maintenance and turf - sod harvesting were determined from studies conducted by the Agricultural Reentry Task Force, MRID NOs 45530101 and 45432303 respectively. As such, use of the transfer coefficient information in this risk assessment is compensable. If the registrant of these proposed products is not a member of the ARTF, then compensation must be made to the ARTF for the use of these data. If the registrant is not a member and compensation is not made, these data must remain confidential and may not be used in this risk assessment in support of the proposed registrations.

Lacking compound-specific dissipation data, HED assumes 20% of the application rate is available as foliar dislodgeable residue on the day of application. This is adapted from the Science Advisory Council For Exposure SOP No. 003 (7 May 1998 - Revised 7 August 2000). Foliar dislodgeable residues are assumed to decline 10% each day following application.

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

Average Daily Dose (ADD) (mg a.i./kg bw/day) = DFR $\mu g/cm^2$ * TC cm^2/hr * hr/day * 0.001 mg/μg * 1/60 kg bw

where:

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

D = Post-application day on which exposure is being assessed
t = fraction of residue that dissipates daily

Turf Hand Harvest

0.4 lb a.i./A * 0.20 * $(1-0)^0$ * 4.54 x 10^8 $\mu g/lb$ * 2.47 x 10^{-8} A/cm^2 = 0.897 $\mu g/cm^2$ ∴

0.897 $\mu g/cm^2$ * 6,800 cm^2/hr * 8 hr/day * 0.001 mg/μg * 1 % dermal absorption * 1/60 kg bw = 0.00813 mg/kg bw/day

MOE = NOAEL ÷ ADD ∴ 9.8 mg a.i./kg bw/day ÷ 0.00813 mg a.i./kg bw/day = **1,205.**

Golf Course Maintenance

0.4 lb a.i./A * 0.20 * $(1-0)^0$ * 4.54 x 10^8 $\mu g/lb$ * 2.47 x 10^{-8} A/cm^2 = 0.897 $\mu g/cm^2$ ∴

0.897 $\mu g/cm^2$ * 3,400 cm^2/hr * 8 hr/day * 0.001 mg/μg * 1 % dermal absorption * 1/60 kg bw = 0.0041 mg/kg bw/day

MOE = NOAEL ÷ ADD ∴ 9.8 mg a.i./kg bw/day ÷ 0.0041 mg a.i./kg bw/day = **2,390.**

Tobacco Harvest

0.2 lb a.i./A * 0.20 * $(1-0)^0$ * 4.54 x 10^8 $\mu g/lb$ * 2.47 x 10^{-8} A/cm^2 = 0.449 $\mu g/cm^2$ ∴

0.449 $\mu g/cm^2$ * 2,000 cm^2/hr * 8 hr/day * 0.001 mg/μg * 1 % dermal absorption * 1/60 kg bw = 0.0012 mg/kg bw/day

MOE = NOAEL ÷ ADD ∴ 9.8 mg a.i./kg bw/day ÷ 0.0012 mg a.i./kg bw/day = **8,166.**

Exposure and Risk Estimates

MOE values greater than 100 are considered to be adequate to protect agricultural workers from post-application exposures to clothianidin. The estimated MOE's are based upon

conservative assumptions and are > 100; therefore, the estimated risks from post-application exposures do not exceed HED's level of concern.

7.3 Restricted Entry Interval

Clothianidin is classified in Toxicity Category III for acute dermal toxicity and Category IV for acute inhalation, primary eye irritation, and primary skin irritation. It is not a dermal sensitizer. Therefore, the Worker Protection Standard (WPS) interim restricted entry interval of 12 hours is adequate to protect agricultural workers.

8.0 DATA NEEDS

8.1 Toxicology

The HIARC has requested that the composition of the test materials used in the mutagenicity studies be investigated to determine whether or not the differences in composition may have affected the results from the studies. These data have been submitted and are currently under review.

870.7800: Immunotoxicity - A developmental immunotoxicity study with comparative measures between pups and the parents is required. The protocol for this testing should be developed following discussion with OPP/HED scientists (for specific details, see HED memo, *Clothianidin - 3rd Report of the Hazard Identification Assessment Review Committee.* B. Tarplee. 09/15/03, TXR# 0052118).

HED is recommending that the above data requirements be conditions of registration.

8.2 Residue Chemistry

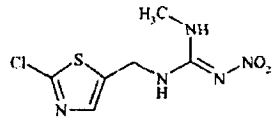
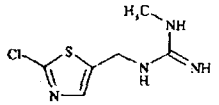
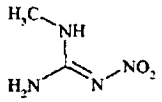
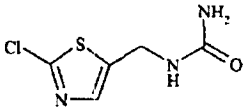
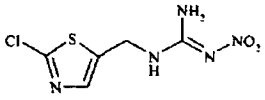
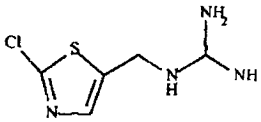
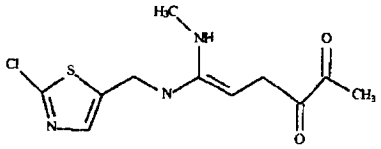
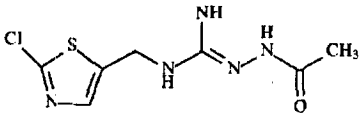
860.1200: Directions for Use - Although allowed in the proposed label, adjuvants were not utilized in the apple and pear field trials. There could be increased residues when adjuvants are included in the tank mix, and therefore, the use of adjuvants should be removed from the label.

860.1300: Nature of the Residue - Future new uses on root crops and/or leafy vegetables will require analysis of TMG and parent in field trials. Alternatively, the registrant may submit additional metabolism data, preferably side-by-side thiazol- and nitroimino radiolabeled studies. For future uses with significantly higher dietary burdens, ruminant and/or poultry metabolism studies with thiazolyl ring label will also be required. While this is not a condition of registration for the currently proposed new uses, it may be a requirement for new uses proposed in the future.

References:
1. Clothianidin and Metabolite Structures (attached)
2. HED HIARC Report, TXR No. 0052118, 09/15/03
3. HED Residue Chemistry, PP#1F6342, D287182, W. Cutchin, 7/12/04
4. HED MARC, D282449, Y. Donovan, 04/25/03
5. HED Dietary Exposure, D304498, W. Cutchin, 7/12/04
6. EFED Water D299401 and D301729, L. Liu, in process
7. HED ORE, D296176, M. Dow, 2/24/04.

cc with Attachments: RAB2 reading file, PP#1F6342.

Reference 1. Structures of Clothianidin and Metabolites

Common name/code	Chemical name	Chemical structure
Clothianidin(TI-435)	[*C(E)*]-*N*-[(2-Chloro-5-thiazolyl)methyl]-*N'*-methyl-*N''*-nitroguanidine	
TMG	*N*-(2-Chloro-5-thiazolylmethyl)-*N'*-methylguanidine	
MNG	*N*-Methyl-*N'*-nitroguanidine	
TZU	N-(2-Chlorothiazol-5-ylmethyl) urea	
TZNG	*N*-(2-Chloro-5-thiazolylmethyl)-*N'*-nitroguanidine	
TZG	N-(2-Chlorothiazol-5-ylmethyl) guanidine	
ATMG-Pyr	*N'*-[(2-chlorothiazol-5-ylmethylamino)(methylamino)methylene]-2-oxopropano hydrazide	
ATG-Ac	*N'*-[amino(2-chlorothiazol-5-ylmethylamino)methylene] acetohydrazide	

13544

R105895

Chemical:	**Clothianidin**
PC Code:	**044309**
HED File Code	**14000 Risk Reviews**
Memo Date:	**01/06/2005**
File ID:	**DPD304499**
Accession Number:	**412-05-0091**

HED Records Reference Center
03/17/2005