(05/01/03)

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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 05/01/03

SUBJECT: PP# 1F06315 -- **Human Health Risk Assessment for Clothianidin (TI-435) --** Proposal for Tolerance of Residues in/on Canola and Corn.

DP Barcode:	D288841	PRAT Case:	294223
Submission No.:	S607124	Caswell No.:	none
Chemical#:	044309	Class:	Insecticide
Trade Name:	Poncho 600 FS	EPA Reg#:	3125-XXX
40 CFR:	§180.XXX		

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Registration Division (7505C)

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1.0 EXECUTIVE SUMMARY

General Background:

Bayer Corporation has proposed a Section 3 registration for TI-435 [clothianidin; *(E)*-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine] in/on corn and canola. TI-435 is a systemic insecticide belonging to the nitroguanidine subgroup of nicotinoid insecticides. It may also be referred to as a chloronicotinyl or neonicotinoid. TI-435 is intended for use as a seed treatment for corn and canola. A separate petition for foliar application to apples and pears has also been submitted. In addition, the petitioner has indicated that use of TI-435 on sugar beet, oil seed rape, and sunflower has been applied for in Europe.

Poncho™ 600 FS contains 48% active ingredient clothianidin (5 lbs active ingredient per U.S. gallon or 600 grams clothianidin per liter @ 20°C). The following general use directions are specified for the 5 lb/gal FlC formulation. For use by commercial treaters only. Not for use in agricultural establishments in hopper-box, slurry-box, or similar on farm seed treatment applicators used at planting. Any tank mixes are to be pre-tested to determine physical compatibility between formulations, and all cautions and limitations on labeling for products used in mixtures are to be observed. For **canola**, the proposed use rate would be 150 g to 400 g a.i./100 kg seed. The application rate would be approximately **0.01 to 0.024 lb ai/acre** based on a seeding rate of 6 lb. seeds/acre. For **corn**, the treatment rate is 0.25 or 1.25 mg ai/kernel. Based on a maximum planting rate of 35,000 seeds (kernels)/acre, the application rate would be 8.8 or 44 g ai/acre **(approximately 0.02 or 0.1 lb ai/acre)**.

Clothianidin (TI-435) is a major metabolite of the insecticide, thiamethoxam, which is a broad spectrum insecticide possessing activity against sucking and chewing insects. Tolerance for thiamethoxam include residues of clothianidin in both plant and livestock commodities.

Hazard Assessment

Clothianidin (TI-435) does not appear to have a consistent specific target organ toxicity. 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 at a dose level of 50 mg/kg with a NOAEL of 25 mg/kg. Rats exhibited decreased arousal and decreased motor and locomotor activity at 100 mg/kg, the lowest dose tested. In acute toxicity studies, the study in mice was classified in Category II, whereas the study in rats was classified in Category IV. In longer term studies, dogs appear to be the most sensitive species, exhibiting clinical signs of anemia. Rats appear to be the second most sensitive species in the chronic feeding studies, manifesting effects on the ovaries, liver and kidney. Chronic administration to mice only induced vocalization and decreases in body weight and body weight gain. Administration via the oral route is more toxic in the rat than via the dermal route. In the rat, although the NOAELs were similar for the subchronic and chronic feeding studies, 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; however, no indications of neurotoxicity were observed 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 these studies is low because the observed effects are well characterized and there are clear NOAELs/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 in 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/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity; conservative residue assumptions are used in the dietary risk assessments; there are no uses that will result in residential exposure; 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). In the reproduction study, these effects appeared in juvenile rats at a lower dose than the adults. Therefore, the HIARC recommended that testing be conducted to assess immune system function in adults and in young animals following developmental exposures. A 10x database factor is to be applied to all dietary and residential exposure endpoints for the lack of a developmental immunotoxicity study.

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. The acute dietary endpoint for the general population is based on an acute neurotoxicity/pharmacology study in mice (acute PAD (general population) = 0.025 mg/kg) and the acute dietary endpoint for the population subgroup females 13-50 is based on a developmental endpoint from a rabbit developmental toxicity study (acute PAD (females 13-50) = 0.025 mg/kg). The chronic dietary endpoint is based on offspring effects in a 2-generation reproduction study in rats (chronic PAD = 0.0098 mg/kg/day). The short- and intermediate-term incidental oral endpoints and the dermal and inhalation endpoints (all durations) are also based on offspring effects in a 2-generation reproduction study in rats (NOAEL = 9.8 mg/kg/day with target margins of exposure (MOEs) of 1000 for residential exposure and 100 for occupational exposure). The dermal and inhalation endpoints are based on oral studies and thus, route-to-route extrapolations were used. Although a 28-day dermal study was conducted, the protocol does not test for pre- and postnatal effects on pups; therefore, the 2-generation reproduction study was selected for the dermal endpoints. With respect to inhalation, only an acute inhalation study on the technical material is available. Therefore, an oral study was selected for the inhalation endpoints. A dermal absorption factor of 1% was determined from a dermal penetration study conducted in monkeys. Absorption via inhalation is assumed to be

equivalent to absorption via the oral route. 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, extrapolation from the oral to the dermal and inhalation routes is not likely to grossly underestimate anticipated adverse effects.

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

Residential Exposure Estimates

Currently there are no registered or proposed residential uses of clothianidin. Clothianidin is a major metabolite of the insecticide thiamethoxam in plants and animals. Since there are also no residential uses of thiamethoxam, possible residential exposure to clothianidin due to thiamethoxam uses is not expected.

Dietary Exposure Estimates

Residue Chemistry

Based on the available plant and animal metabolism studies, HED's Metabolism Assessment Review Committee (MARC) concluded that, for the current proposed uses, the nature of the residue in plants has been adequately delineated. Parent only is the residue of toxicological concern to be used in risk assessment and the tolerance expression. For ruminants, parent, TZNG, TZU, TZG, and ATMG-Pyr are the residues of concern to be included in the risk assessment, while parent only is the residue of concern for tolerance expression. For poultry, with future new uses where quantifiable 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 be included in the risk assessment, while parent only is needed for 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, and parent only is needed for the tolerance expression. For drinking water assessment, parent only is the residue of concern. (See Table 4. For names and structures of the above metabolites, see Attachment 3).

Enforcement methods (also as data collection methods) for plant (detects parent only) and animal commodities (detects parent, TZG, TZU, ATMG-Pyr) have been submitted. Although not all residues of concern are measured by the data collection methods, such residues can be estimated using ratios from the radiolabeled studies (See Table 4) . HED concludes that these methods are considered acceptable for purposes of data collection given the currently understood residues of concern for plants and livestock. The LOQ for parent was 0.01 ppm for corn grain and canola seed. The LOQ was 0.01 ppm for each analyte in milk and 0.02 ppm for each analyte in animal tissues. A successful independent lab validation (ILV) has been completed. These analytical methods have been sent to the Agency's Analytical Chemistry Branch for tolerance method validation (TMV). Clothianidin and five of its metabolites were not recovered by the FDA multiresidue methods.

Currently there are no tolerances established for only TI-435 on any commodity. However, TI-435 is a major metabolite of thiamethoxam, and tolerances for the combined residues of thiamethoxam and its metabolite TI-435 have been established under 40 CFR § 180.565. Tolerances range from 1.5 ppm on cotton gin byproducts to 0.02 ppm on corn grain.

Adequate field trial studies on corn and canola have been submitted. The results from the field trials support the proposed tolerances of clothianidin on corn grain and canola seed at 0.01 ppm, and on corn forage and stover at 0.10 ppm. HED also recommends a 0.01 ppm (LOQ) tolerance be set for the parent on milk. Tolerances are not required for livestock tissues or processed commodities. Tolerances of 0.02 ppm are needed for those rotational crops which will have a 30 day plantback interval.

No Codex, Canadian, or Mexican maximum residue levels (MRLs) have been established for residues of TI-435.

Dietary Exposure Analysis

The acute and chronic analysis are conservative, Tier 1 assessments which are based on tolerance level residues and the assumption of 100% crop treated. Although the only proposed uses for TI- 435 are on canola and corn, TI-435 is a major metabolite of thiamethoxam which has many registered and several pending uses. As a result, residues of TI-435 which would theoretically result from the metabolism of thiamethoxam were included in the analysis. In thiamethoxam crop field trials and animal feeding studies, residue levels of both TI-435 and thiamethoxam were reported. Based on these field trial data, ratios of TI-435 to thiamethoxam were calculated for each commodity. These ratios range from 0.09 to 0.63 . By multiplying these ratios times the respective thiamethoxam tolerance level, maximum theoretical TI-435 residues from thiamethoxam uses can be obtained. These maximum TI-435 residues were then used in the acute and chronic analyses. For the commodities which have both thiamethoxam tolerances and proposed TI-435 tolerances (i.e., sweet corn, field corn, pop corn, canola, and milk), although it is unlikely that concurrent exposure to TI-435 will be from both sources, there are no label restrictions for simultaneous use of these chemicals. Therefore, for conservative purposes, the proposed TI-435 tolerances were added to the residues which result from use of thiamethoxam. Processing studies were waived for TI-435 based on exaggerated rate data, and so, processing factors were DEEM (Version 7.76) default processing factors. The DEEM-FCID program, which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII, 1994-1996 and 1998 data), was used.

For acute dietary exposure, at the 95th percentile exposure, the General U.S. Population and the most highly exposed population subgroup (children 1-2 years) utilize **7%** and **16%** of the aPAD, respectively. For chronic dietary exposure, the General U.S. Population and the most highly exposed population subgroup (children 1-2 years) utilize **6%** and **18%** of the cPAD, respectively.

Drinking Water Exposure Estimates

EFED provided Tier I estimated environmental concentrations (EECs) 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 EECs and the SCI-GROW model was used to calculate the groundwater EECs. It is assumed that maximum application rates were at 0.05 and 0.10 lb ai/A for canola and corn, respectively. These rates are higher than the proposed use rates for corn and canola and therefore, cover the subject petition. The EECs for surface water are 3.97 ug/L for acute and 2.14 ug/L for chronic exposure. For ground water, the EEC is 1.46 ug/L for both acute and chronic exposure. Clothianidin is a new chemical, therefore monitoring data were not available. Although clothianidin (TI-435) 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 of TI-435 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 most conservative Tier I approach, the Dietary Exposure Evaluation Model (DEEM) for acute dietary risk estimates concluded that the acute exposures to TI-435 from food for the general US population, infants and children will utilize **#16%** of the **aPAD**. The calculated DWLOCs for acute exposure to TI-435 in drinking water range from **210 to 810 ppb.** Both surface and ground water EECs were less than 4 ppb, substantially less than the DWLOCs. Therefore, the acute aggregate risk associated with the proposed use of TI-435 does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Chronic Aggregate Risk (Food + Water + Residential)
Chronic aggregate risk includes exposures from food and water (residential exposure is not expected). Using the most conservative Tier I analysis, it is estimated that the chronic exposures to TI-435 from food for general US population, infants and children will utilize **#18%** of the cPAD. The calculated chronic DWLOCs for chronic exposure to TI-435 in drinking water range from **80** to **320 ppb**. EECs generated by EFED for both surface and ground water were less than 3 ppb, substantially less than HED's calculated chronic DWLOCs. Therefore, the chronic aggregate risk associated with the proposed use of TI-435 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)
Since there no registered/proposed residential uses on either TI-435 or thiamethoxam, exposures from residential uses are not expected. Therefore, a short- and intermediate- term aggregate risk assessment for TI-435 is **not required.**

Cancer

TI-435 has been classified by HED HIARC as a "not likely human carcinogen." A cancer risk assessment **is not required**.

Occupational Exposure Estimates

Data submitted by the seed treatment registrant (Bayer) were jointly reviewed by the HED and the Pest Management Regulatory Agency (PMRA) of Canada. The registrant provided HED with estimates of the typical quantities of corn and canola seed treated per day for different types of facilities and equipment. Based on information provided by BEAD, PMRA, and other sources, seed treater exposure durations are anticipated to be short- (30 days or less) to intermediate-term (1 to 6 months). The assessment found that seed treater and planter risk estimates did not exceed the HED's level of concern.

There are currently no registered or proposed residential uses associated with clothianidin. Clothianidin is a major metabolite of the insecticide thiamethoxam in plants and animals. Since there are also no residential uses of thiamethoxam, possible residential exposure to clothianidin due to thiamethoxam uses is not expected.

Chemical specific data for assessing human exposure during seed treatment activities were not submitted to the Agency in support of this new chemical use (Section 3) application. However, the registrant, Bayer, submitted three studies in support of the registration of clothianidin for seed treatment: two seed treatment exposure studies, for isofenphos (Oftanol) and triadimenol (Baytan); and one planter exposure study, using isofenphos treated seed.

These studies were jointly reviewed by Pesticide Management and Registration Agency (PMRA) Canada and the U.S. EPA Office of Pesticides. The studies are neither chemical specific nor are they unique for this type of activity. However, the data were compared to other similar studies and found to be representative of median to higher exposures for the same work. Also, the type of work performed was deemed typical for seed treatment and planting. Because the submitted isofenphos seed treatment study more closely resembled the labeled use of clothianidin for commercial seed treatment, and the unit exposures were consistent with values obtained from other studies used by the Agency to assess large seed treatment operations, those data were generally preferred over the triadimenol study data. However, the triadimenol bagger task exposure data were considered applicable and comparable for small to medium sized facilities, and were averaged with the isofenphos data for the same task. The study data submitted resulted in higher exposure estimates (more conservative) than the default Pesticide Handler Exposure Database (PHED) values for mixer/loaders, which are used by HED when there are no chemical-specific data. The isofenphos planter exposure study data were used and were higher (more conservative) than PHED surrogate data historically used for estimating exposure from planting treated seeds.

There is one formulated product associated with this action; Clothianidin 600 FS (liquid) for seed treatment. The difficulty in assessing seed treatment exposure is that there are multiple, often overlapping duties performed by personnel in different sized operations. Two major job categories exist in most seed treatment facilities: the actual seed treating process and the bagging and handling of treated seed. Mixer/loaders may also operate or monitor the treatment equipment (treating, calibrating), and baggers may also sew the bags closed and stack them

manually or mechanically. However, the major tasks were analyzed separately to characterize the range of exposure for separate tasks, and to allow risk managers the greatest flexibility in mitigating task- specific exposures. The loader/applicators have the highest exposures in most seed treatment studies, and the bagger/sewers generally have lower exposures; together they are used to represent a range of exposure.

The small/medium facility estimates reflect the addition of bagger exposure data from the Baytan study, which was from a medium sized facility. The studies submitted to HED for estimating seed treatment were not specific to large, modern, commercial facilities. The registrants (Bayer/Gustafson) state most corn and canola are treated in large facilities, and that most equipment is more efficient than what was used in these older studies.

None of the single layer with gloves seed treater estimates exceed the HED level of concern. Because the Oftanol and Baytan study replicates were wearing long sleeved shirts, long pants, and chemical resistant gloves, the risk estimates assume the same level of protection. Much of the exposure for the loader/applicators was to the head and neck, so wearing head and neck covering while doing that operation could significantly reduce exposure and risk. The target margin of exposure (MOE) for occupational non-cancer risk assessments was 100. The single layer with gloves total dermal and inhalation MOEs ranged from 380 to 960 for loader/applicators in large commercial facilities. The small/medium facility estimates reflect the addition of bagger exposure data from the Baytan study, which was from a medium sized facility. The lowest handler MOE was 110 for seed baggers in small/medium sized facilities. This exposure estimate is driven principally by the inhalation exposure. Analysis of available seed treatment studies has shown that some workers perform multiple activities; the tasks have been divided into the two general job categories which consistently have the highest exposures: "loader/applicators" and "baggers" (the latter may include bag sewing and stacking, which do not contribute significantly to overall exposure).

Although the risk estimates herein are based on relatively few data points from one or two studies, the HED considers these exposure estimates to be typical to higher end for medium-to-large facilities, and adequately conservative to protect most workers under similar conditions. However, the evaluation is based on the proposed label, which specifically *prohibits* use in hopper-box, slurry-box or similar on-farm seed treatment equipment, which would likely be less efficient than commercial equipment and result in higher exposures per lb ai handled.

The risk estimates for loading and planting corn or canola seed do not exceed the HED level of concern. Although it is assumed that exposure to treated seed, which has been stored for an indefinite time before use, represents minimal exposure hazard to the handler, an estimate of the inherent risk from treated seed was conducted using the only available study data. The exposure scenario consists of the farmer purchasing bags of treated seed, placing the seed in hopper, and planting seed in the fields using a "drill." Bayer submitted a surrogate study of seed handling and planting using the chemical Oftanol (isofenphos). The HED found this study acceptable, and has estimated planter exposure using these study data. The study data provided higher unit exposure values than the default PHED mixer/loader scenario for granular formulations and PHED applicator scenario for solid broadcast spreader. The MOEs for loading and driving the planter were greater than 100 for corn and canola planting using both data sets (range 15,000-26,000) and therefore, did not exceed HED's level of concern. HED has determined that following soil- incorporated treatments (planting seed), postapplication agricultural exposure is

considered to be negligible as long as the soil is not directly contacted.

Recommendations:

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 TI-435 residues. Contingent on successful Agency analytical method validation, and 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 TI-435, expressed as parent, in or on **the following:**

Canola, seed 0.01 ppm
Corn, field, grain 0.01 ppm
Corn, pop, grain 0.01 ppm
Corn, sweet, kernel plus cob with husk removed 0.01 ppm
Corn, field, forage 0.10 ppm
Corn, sweet, forage 0.10 ppm
Corn, field, stover 0.10 ppm
Corn, pop, stover 0.10 ppm
Corn, sweet, stover 0.10 ppm
Milk 0.01 ppm

For rotational crops:

Grain, cereal, forage,fodder and straw, Group16 0.02 ppm
Grass, forage, fodder and hay, Group 17 0.02 ppm
Animal feed, nongrass, Group 18 0.02 ppm
Soybean, forage 0.02 ppm
Soybean, hay 0.02 ppm

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Common Name: Clothianidin

Chemical Name (CAS): [C(E)]-N-[2-chloro-5-thiazolyl)methyl]-N'-methyl-N''-nitroguanidine

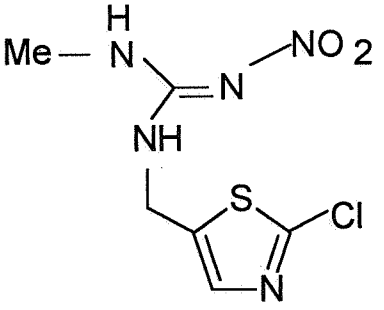
(IUPAC): (E)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine

CAS No.: 210880-92-5(formerly 205510-53-8) CAS number 131748-59-9 refers generally to clothianidin and its tautomers. This number had been used for clothianidin until the above number was assigned specifically to clothianidin

PC Code No.: 044309

Empirical formula: $C_6 H_8 Cl N_5 O_2 S$

Molecular Weight: 249.68 g/mol
Structural formula:



Melting point/Melting range	176.8 ^{0}C
Density/relative density/bulk density	1.61 g/ml @ 20 ^{0}C
Dissociation constants in water	pKa = 11.09 at 20 ^{0}C
Partition coefficient (n-octanol/water), shake flask method	log P o/w = 0.7; P o/w = 5 @ 25 ^{0}C
Vapor pressure	1.3 x 10 $^{-10}$ Pa at 25 ^{0}C

3.0 HAZARD CHARACTERIZATION (Attachment 1, HED HIARC report of 03/31/03, TXR No. 0051713)

3.1 Hazard Profile

Table 1. Acute Toxicity Profile - Clothianidin (TI-435) 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
TI-435-CCMT-**Adduct Intermediate**	870.1100	Acute Oral - rat	45422630	Oral LD_{50} > 2000 mg/kg (%+&)	III
TI-435-Hexahydropyrimidine **Intermediate**	870.1100	Acute Oral - rat	45422631	Oral LD_{50} > 2000 mg/kg (%+&)	III
TI-435- 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
Technical	870.1100	Acute Oral - mouse	45422622	LD_{50} (M): 389 mg/kg bw (95% c.i. = 380-475) LD_{50} (F): 465 mg/kg bw (95% c.i. = 384-561) LD_{50} Combined: 425 mg/kg bw (95% c.i. = 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
TI-435-CCMT-**Adduct Intermediate**	870.2400	Primary Eye Irritation	45422814	Not irritating to the eye	IV
TI-435- 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
TI-435-CCMT-**Adduct Intermediate**	870.2500	Primary Dermal Irritation	45422813	Not irritating to the skin.	IV
TI-435- 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
TI-435-CCMT-**Adduct Intermediate**	870.2600	Dermal Sensitization	45422815	Is not a sensitizer under conditions of study.	N/A
TI-435- Triazan **Intermediate**	870.2600	Dermal Sensitization	45422821	Is a sensitizer under the conditions of the study	N/A

Table 2. 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).
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 bod 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 Fg/plate +/-S9; still present but weaker in it absence. The positive response was only reproducible at 5000 Fg/plate +/-S9. TI-435 considered mutagenic under conditions of this test.
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.
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**	TI-435 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 and body weight gains)
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 TI-435, 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

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 hour post-dose was considerably less than 1% of the administered dose. Therefore, neither TI-435 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 (TI-435) and TZNG [N-(2-chlorothiazol-5-ylmethyl)-NN-nitroguanidine] which resulted from N-demethylation of TI-435. 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]-TI-435 the metabolism pathway proposed by the investigators was supported.

870.7600	Dermal Penetration - monkey	Dermal absorption as the sum of urinary and fecal excretion and Cage/Pan/Chair Wash, Debris was 0.2 (± 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 (TI-435) is a member of the relatively new neonicotinoid class of chemicals and is a metabolite of the insecticide, thiamethoxam. The Agency currently has data on three chemicals in the neonicotinoid class: imidacloprid, acetamiprid and a yet unregistered new active ingredient. The database on thiamethoxam indicates 4 primary targets for this chemical: the liver, kidney, hematopoietic system, and testes. The nervous system is the primary target organ of imidacloprid. Acetamiprid does not appear to have specific target organ toxicity; it induces decreases in body weight, body weight gain, food consumption and food efficiency. The new unregistered active ingredient has also been shown to affect the liver and thyroid, including follicular cell tumors and also induces uterine and ovarian tumors. There was also some indications neurotoxicity in the acute and subchronic neurotoxicity studies.

Clothianidin induces some effects that are similar to the other neonicotinoids, particularly effects on the liver, hematopoietic system and kidneys. In subchronic studies in rats and dogs, decreases in body weight and body weight gain were observed in both species. Dogs also displayed some anemia and decreased white blood cells, albumin, and total protein and appear to be more sensitive to the effects of clothianidin. In the dog study, males are more sensitive than females. No effects were observed up to the limit dose in the 29-day dermal study in rats. Thus, the oral route of administration appears to be more toxic in the rat than the dermal route.

In the chronic feeding studies in the dog, rat and mouse, again the dog appears to be the most sensitive species followed by the rat and females appear to be more sensitive than males in all three species. 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 focus of the liver were observed in females; and 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 males. 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.

In the rat, although the NOAELs and LOAELs for the subchronic and chronic feeding studies were similar, a wider spectrum of effects were observed in the chronic study. Therefore, it appears that there may be more toxicity when exposure is over a longer period of time. In the dog, administration of clothianidin for a longer period of time does not appear to have any additional

effects or effects at lower dose levels.

In an acute neurotoxicity study in rats via gavage, FOB effects were observed, which included decreased arousal and decreased motor and locomotor activity on Day 0 in males. Effects at dose levels above the LOAEL included tremors, slightly uncoordinated gait, effects on pupil response and righting reflex, decrease in body temperature and ataxia. Mice appear to be more sensitive to the acute neurotoxic effects of clothianidin when administered by gavage. Effects were also observed on day 0 in males (no female mice were tested) at lower dose levels than in rats which 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. The acute dietary endpoint for the general population is based on this mouse study because mice appear to be the most susceptible species and the effects observed in this study are observed following a single dose.

In the subchronic feeding neurotoxicity study in rats, no indications of neurotoxicity were observed. Slightly decreased food consumption, body weights, and body weight gains were the only observed effects. The LOAEL was similar to the subchronic feeding study in rats. The NOAEL was higher because the selected dose levels were different between the two studies.

In the developmental neurotoxicity study, there was evidence of quantitative susceptibility in pups. The NOAEL for offspring toxicity is based on decreased body weight gains, motor activity and acoustic startle response at the same dose level as the NOAEL for the parents. The parental LOAEL is based on decreased body weights, body weight gains and food consumption.

No quantitative or qualitative susceptibility was observed in either of 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 are not considered to be qualitatively more severe than the maternal effects; however, the acute dietary endpoint for females 13-50 is based on the increased litter incidence of a missing lobe of the lung, which is considered to be a possible single dose effect. The developmental NOAEL for this study is the same as the NOAEL for the acute neurotoxicity study. Thus, all populations are protected.

Quantitative susceptibility was observed in the reproduction study. At 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. All of the remaining dietary, residential and occupational endpoints are based on the effects on pups in this study because it is protective of effects observed in all of the other available studies and because the observed effects may be a result of either short- and/or longer-term exposure.

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 in 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.

The mutagenicity 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.

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. Without full functioning of these two organs, the developing immune system would be severely compromised. Therefore, the HIARC recommends that testing be conducted to assess immune system function in adults and in young animals following developmental exposures. An additional 10x database uncertainty factor has been added to the dietary and residential endpoints for the lack of 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 TI-435 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 (TI-435) and TZNG [N-(2-chlorothiazol-5-ylmethyl)-NN-nitroguanidine] which resulted from N-demethylation of TI-435.

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.
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 TI-435-Triazan Intermediate tested as a dermal sensitizer under the conditions of the study whereas the parent was not a dermal sensitizer. In mutagenicity studies, none of the intermediates or metabolites appeared to have genotoxic potential under the conditions of the studies.

3.2 FQPA Considersations

The HIARC met on November 14, 2002 to evaluate clothianidin according to the February 2002 OPP 10X Guidance Document. The HIARC concluded that the toxicology database for clothianidin is not complete for FQPA purposes. A complete complement of acceptable developmental, reproduction, developmental neurotoxicity, mammalian neurotoxicity and special neurotoxicity studies are available; however, 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, the HIARC recommended that testing be conducted to assess immune system function in adults and in young animals following developmental exposures.

A number of neurotoxicity studies are available. In a combination of two acute neurotoxicity studies in rats, decreased arousal and decreased motor and locomotor activity were observed on Day 0 in males. In a special acute neurotoxicity study in mice, transient signs of decreased spontaneous motor activity, tremors, and deep respirations were observed. In a subchronic neurotoxicity study in rats, no neurotoxic effects were observed at dose levels up to 200 mg/kg/day. Decreases in food consumption, body weights and body weight gains were the only observed effects. In the developmental neurotoxicity study, again, only body weight, body weight gain and food consumption were affected in the dams. In pups, decreased body weights and body weight gains were observed; however, motor activity, and acoustic startle response were also affected in the females.

As stated previously, no quantitative or qualitative susceptibility was observed in either of the developmental rat or rabbit studies; however, quantitative susceptibility was observed in both the reproduction and developmental neurotoxicity studies. In the 2-generation reproduction study, the NOAEL for offspring toxicity is 9.8/11.5 mg/kg/day (M/F) 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 at the LOAEL of 31.2/36.8 mg/kg bw/day (M/F). The parental systemic NOAEL is 31.2/36.9 mg/kg/day (M/F) based on decreased absolute body weights and body weight gains with decreased absolute and relative thymus weights in both sexes at the

LOAEL of 163.4/188.8 mg/kg bw/day (M/F).

In the developmental neurotoxicity study, the NOAEL for offspring toxicity is 12.9 mg/kg/day based on decreased body weight gains, motor activity and acoustic startle response at the LOAEL of 42.9 mg/kg/day. The parental NOAEL is 42.9 mg/kg/day based on decreased body weights, body weight gains and food consumption at the LOAEL of 142 mg/kg bw/day.

The degree of concern for the 2-generation reproduction study is low because the observed effects are well characterized and there are clear NOAELs/LOAELs. In addition, the endpoint of concern is the one that is being used for short, intermediate and long term dietary and non-dietary exposure risk assessments. The degree of concern for the developmental neurotoxicity study is also low because the observed effects are well characterized and there are clear NOAELs/LOAELs. There are no residual uncertainties.

Based on the hazard data, the HIARC recommended the special FQPA SF be reduced to 1x because there are no/low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity. The TI-435 risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the special FQPA SF be reduced to 1x. The recommendation is based on the following:

- No quantitative or qualitative susceptibility was observed in either of the developmental rat or rabbit studies.

- Quantitative susceptibility was observed in both the reproduction and developmental neurotoxicity studies. However, the degree of concern for the 2-generation reproduction study is low because the observed effects are well characterized and there are clear NOAELs/LOAELs. In addition, the endpoint of concern is the one that is being used for short, intermediate and long term dietary and non-dietary exposure risk assessments. The degree of concern for the developmental neurotoxicity study is also low because the observed effects are well characterized and there are clear NOAELs/LOAELs. There are no residual uncertainties.

- The *acute* and *chronic* dietary food exposure assessment utilizes existing and proposed tolerance level residues and 100% CT information for all commodities. By using these screening-level assessments, actual and chronic exposures/risks will not be underestimated.

- The dietary drinking water assessment (Tier1 estimates) utilizes values generated by model and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

- There are no residential uses for either TI-435 or thiamethoxam.

Again, as stated previously, the HIARC concluded that there is a concern for immunotoxicity following exposure of clothianidin during the period of organogenesis and they are recommending that testing be conducted to assess immune system function in adults and young animals following exposure during the period of organogenesis. In accordance with the Feburary 2002 OPP 10X Guidance Policy, HIARC recommended a 10X database uncertainty factor be applied for

dietary/residential risk assessments.

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 the this population subgroup because the observed developmental effects may occur following a single dose. In addition, the route of administration is oral, which is appropriate for dietary considerations. With a NOAEL of 25 mg/kg/day and a LOAEL of 75 mg/kg/day, the dose spread is not considered to be large; therefore, the endpoint is not considered to be overly conservative. Other effects observed at the same dose level were premature deliveries, decreased gravid uterine weights and decreased litter average for ossified sternal centra per fetus. These are not considered to be single dose effects.

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 dose. This endpoint is considered appropriate for the general population because the effects were observed following a single dose and the route of administration (oral) is appropriate for dietary considerations. Again, with a NOAEL of 25 mg/kg and a LOAEL of 50 mg/kg, the dose spread is not considered to be large; therefore, the endpoint is not considered to be overly conservative.

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. This endpoint is considered appropriate for chronic dietary exposure because the route of administration (oral) is appropriate for dietary considerations. The study and endpoint were selected because it is protective of effects observed in all the other available studies. With an offspring NOAEL of 9.8 mg/kg/day and a LOAEL of 31.2 mg/kg/day, the dose spread is not wide; however, the endpoint is considered to be conservative because the observed effects, although present, were only slightly different when compared to the control values. The body weight gains of F_1 mid-dose pups (31.2 mg/kg/day) of both sexes were slightly decreased during LD 7-14 (90% of controls for both sexes and 89% of controls for combined sexes; $p<0.05$). Although there were statistically significant increases in the incidences of pups born dead in the F_1 mid-dose group, the number of litters affected were not statistically significant. The same is true in the F_2 generation. The provided historical control data did not include sufficient detail to fully evaluate the significance of these increases. The statistically significant increase in the mid-dose group's time to balanopreputial separation was considered to be within the normal range according to the study report, which stated that results within "5% of concurrent controls were considered normal for the particular rodent strain at the testing facility. Finally, at the mid-dose, the absolute thymus weights were statistically significantly lower than the control weights in the F_1 male pups. Neither in female pups nor in any other generation were either the absolute or relative thymus weights significantly lower than the control values at this dose level.

Occupational/Residential endpoints: All of the incidental oral, dermal and inhalation endpoints are based on the offspring effects in the 2-generation reproduction study. Again, the study and endpoint were selected because it is protective of effects observed in all the other available studies. In

addition, the endpoint is appropriate for all durations as the effect may be a result of either short- and/or longer-term exposure.

For the dermal endpoints, a dermal study is available; however, the selected endpoint addresses potential effects on offspring, which are not normally examined in the dermal study. This endpoint is likely to be conservative because no systemic effects were observed in the dermal study up to the limit dose of 1000 mg/kg/day. In the reproduction study, the parental NOAEL is 31.2/36.8 mg/kg/day based on decreases in body weight and body weight gain and decreased absolute and relative thymus weights in both sexes at the LOAEL of 163.4/188.8 mg/kg bw/day in males/females, respectively. No such effects were observed in the 28-day dermal study.

No inhalation studies are available for selection of inhalation endpoints. Therefore, an oral study was selected to estimate risk using a route-to-route extrapolation. Many chemicals are more toxic via inhalation than via oral administration. A comparison of the acute oral study with the acute inhalation study indicates that TI-435 is not very **acutely** toxic via either route (both in Toxicity Category IV). Nevertheless, the selected endpoint for assessment of risk via inhalation exposure is not considered to be conservative because the endpoint is extrapolated from an oral study and may possibly underestimate the risk.

Table 3. 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.
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**		

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, MOE = margin of exposure, 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 bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA 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, TI-435 may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

For TI-435, 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

Bayer Corporation has proposed the establishment of permanent tolerances for residues of TI-435 [clothianidin; (E)-N-[(2-chloro-5-thiazolyl)methyl]-N'-methyl-N''-nitroguanidine, in or on the following raw agricultural commodities:

Crop	Proposed Tolerance (PPM)
Canola, seed	0.01
Corn, field, grain	0.01
Corn, pop, grain	0.01
Corn, sweet, kernal plus cob with husk removed	0.01
Corn, field, forage	0.10
Corn, sweet, forage	0.10
Corn, field, stover	0.10
Corn, pop, stover	0.10
Corn, sweet, stover	0.10
Milk	0.01
Grain, cereal, forage, fodder and straw, Group 16	0.02
Grass, forage, fodder and hay, Group 17	0.02
Animal feed, nongrass, Group 18	0.02
Soybean, forage	0.02
Soybean, hay	0.02

TI-435 is a systemic insecticide belonging to the chloronicotinyl class of chemicals and is intended for use as a seed treatment for corn and canola. In addition, the petitioner has indicated that use of TI-435 on sugar beet, oil seed rape, and sunflower has been applied for in Europe, and separate petitions for foliar application to apples and pears have also been submitted.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile (Attachment 2, HED memo of 05/01/03 ,Y. Donovan, D282446)

Residue chemistry data for the proposed use of TI-435 on corn and canola have been previously reviewed by HED. Below are summaries from that review.

Poncho™ 600 FS contains 48% active ingredient clothianidin (5 lbs active ingredient per U.S. gallon or 600 grams clothianidin per liter @ 20°C), U.S. EPA Reg. No. 3125-xxx . The following general use directions are specified for this 5 lb/gal FlC formulation. Application using hopper-box, slurry-box, or similar seed treatment applications used at planting is prohibited. Any tank mixes are to be pre-tested to determine physical compatibility between formulations, and all cautions and limitations on labeling for products used in mixtures are to be observed. For **canola**, the proposed use rate would be 150 g to 400 g a.i./100 kg seed. The application rate would be 0.009 or 0.024 lb ai/acre based on a seeding rate of 6 lb. seeds/acre. For **corn**, the treatment rate is 0.25 or 1.25 mg ai/kernel. Based on a maximum planting rate of 35,000 seeds (kernels)/acre, the application rate would be 8.8 or 44 g ai/acre (0.0193 or 0.0965 lb ai/acre).

Based on the available plant metabolism studies, HED's Metabolism Assessment Review Committee (MARC) concluded that, for the current 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 TMG and parent in field trials (see attachment 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 TI-435, 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 that 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. (For detailed information, see Attachment 3, HED MARC decision memo of 04/25/03, Y. Donovan, D282449)

Method 00552, used for data gathering and proposed as an enforcement method, determines residues of TI-435 in plant commodities. The validated limit of quantitation (LOQ) 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. A modification of the method has been submitted (M001) which adds the use of an internal standard, d_3-TI-435, for quantitation. 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) which adequately covers the proposed tolerance for canola seed and corn grain]. A successful independent lab validation (ILV) has been completed with corn grain along with adequate radiovalidation data for apple, corn forage, stover, and grain. LC-MS/MS Method 00624, proposed as an enforcement method, determines residues of TI-435 and its metabolites, TZG [(2- chloro-5-thiazolyl)methyl guanidine], TZU [2-chloro-5-thiazolyl)methyl urea], and ATMG-pyruvate [N'-[(2-chlorothiazol-5-ylmethylamino) (methylamino)methylene]-2-oxopropano

hydrazide] in ruminant commodities. The validated LOQ was 0.01 ppm for each analyte in milk and 0.02 ppm for each analyte in animal tissues. A successful ILV has been completed. These methods are considered acceptable for purposes of data collection given the currently understood residues of concern for plants and livestock. These analytical methods have been sent to the Agency's Analytical Chemistry Branch for tolerance method validation (TMV). Prior to acceptance by the U.S. EPA for enforcement purposes, the methods are required to pass the Agency validation.

Table 4. Summary of MARC Decisions and Analytical Method Detections for *TI-435*

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

Although not all residues of concern are measured by the data collection methods, such residues can be estimated using ratios from the radiolabeled studies.

Adequate field trial studies on corn and canola have been submitted. Other than the processing study, the highest application rate used in the corn field trials was 2.0 mg a.i./seed, which is 1.6 X the proposed use rate. No quantifiable residues (<0.01 ppm) of TI-435 were found in field corn grain and sweet corn ears. HED concludes that the proposed tolerances of 0.01 ppm on corn grain are adequate, and the proposed tolerances of 0.10 ppm on corn forage and corn stover are also adequate. The highest application rate used in the canola field trials was 600 g a.i./100 kg seed, which is 1.5X of the proposed maximum rate on the label. The results from the field trials indicated that residues of clothianidin on canola seed are less than 0.01 ppm. HED concludes that the proposed tolerance of 0.01 ppm on canola seed is adequate.

For processing studies, the field trials were conducted at 8x and 6x of the proposed rates for corn and canola, respectively. No quantifiable residues were found in the RAC's, and so no processing study is needed.

The cattle feeding study indicated that at the highest dose level, 2.56 mg/kg feed (about 6.9X of the dairy cattle dietary burden and about 9.8X for beef cattle), residues of parent and all metabolites were below the LOQ of 0.02 ppm for tissues. HED concludes no tolerance is needed for meat and meat by-products. For milk, the highest residue level of parent TI-435 is 0.012 ppm, while each metabolite was below the LOQ of 0.01 ppm. HED concludes that the proposed 0.01 ppm tolerance for milk is adequate. Based on the goat metabolism study, parent TI-435 accounts

for about 50% of the TRR in milk. Therefore, HED recommends using 0.02 ppm for milk in a Tier 1 dietary risk assessment.

A request for waiver of poultry feeding study was submitted based on the results from the corn metabolism studies and the nature of the residue in hen. HED calculated the maximum theoretical dietary burden (MTDB) for poultry and swine (included thiamethoxam uses), and the MTDB are # 0.013 ppm. The submitted hen metabolism study (DER. 45422535) using [nitroimino-2-^{14}C] clothianidin dosing at 140 ppm (10,800X the MTDB) resulted in the highest residue of 7.9 : g/g (ppm) in kidney. Dividing 7.9 ppm by 10,800X, the expected residue in kidney (TRR) would be 0.0007 ppm, which is well below the LOQ of 0.02 ppm. Therefore, the waiver request for a poultry feeding study is classified as scientifically acceptable. No feeding study/tolerance is needed. However, additional feed items in the future will require the re-evaluation of the dietary burden and may trigger a poultry feeding study.

In rotational crop field studies, quantifiable residues of parent clothianidin were found in mustard greens, turnip tops, and wheat foliage at plantback intervals (PBI's) out through 8 months. Therefore, plantback intervals of one year are required for all crops (except corn and canola) unless rotational crop tolerances are established. The petitioner has submitted a revised Section F to establish such tolerances on cereal grains, forage, fodder and straw (Group16), grass forage, fodder and hay (Group 17), animal feed, nongrass (Group 18), and soybean forage and hay, all at 0.02 ppm. HED concluded that based on rotational crop field data, the requested 30 day plantback restrictions for those crops are adequate.

Current status sheets available to HED indicate that no Codex, Canadian, or Mexican maximum residue levels (MRLs) have been established for residues of TI-435.

4.2.2 Acute Dietary (Attachment 4, HED DEEM memo of 03/11/03, D. Dotson, D288075)

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

The acute analysis was a conservative, Tier 1 assessment which was based on tolerance level residues and the assumption of 100% crop treated. Although the only proposed uses for TI-435 are on canola and corn, TI-435 is a major metabolite of thiamethoxam which has many registered uses and several pending uses. As a result, residues of TI-435 which would theoretically result from the metabolism of thiamethoxam were included in the analysis. In crop field trials and in animal feeding studies, the quantities of both TI-435 and thiamethoxam were measured. The ratio of TI-435 to thiamethoxam in each commodity was multiplied by the respective thiamethoxam tolerance level to arrive at the theoretical maximum TI-435 residue level which would be present. These maximum TI-435 residues were used in the acute analysis. For the commodities which have both thiamethoxam tolerances and proposed TI-435 tolerances (i.e., sweet corn, field corn, pop corn, canola, and milk), the proposed TI-435 tolerances were added to the residues which result from use of thiamethoxam. Processing factors were DEEM (Version 7.76) default processing factors. The DEEM-FCID program, which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII, 1994-1996 and 1998 data), was used.

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 acute population adjusted doses (aPADs) are all below 100%). The most highly exposed population subgroup is children 1-2 years of age, which utilizes 16% of the aPAD.

Table 5. Results of Acute Dietary Exposure Analysis at the 95th Percentile of Exposure			
Population Subgroup	aPAD (mg/kg/day)	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.025	0.001825	7.3
All Infants (< 1 year old)	0.025	0.002855	11
Children 1-2 years old	0.025	0.004001	16
Children 3-5 years old	0.025	0.003126	13
Children 6-12 years old	0.025	0.001976	7.9
Youth 13-19 years old	0.025	0.001351	5.4
Adults 20-49 years old	0.025	0.001349	5.4
Females 13-49 years old	0.025	0.001347	5.4
Adults 50+ years old	0.025	0.001491	6.0

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

4.2.3 Chronic Dietary (Attachment 4, HED DEEM memo of 03/11/03, D. Dotson, D288075)
Chronic Dietary Exposure and Risk. **cPAD = chronic RfD = 0.0098 mg/kg bwt/day**.

The chronic analysis was a conservative, Tier 1 assessment which was based on tolerance level residues and the assumption of 100% crop treated. Although the only proposed uses for TI-435 are on canola and corn, TI-435 is a major metabolite of thiamethoxam which has many registered uses and several pending uses. As a result, residues of TI-435 which would theoretically result from the metabolism of thiamethoxam were included in the analysis. In crop field trials and in animal feeding studies, the quantities of both TI-435 and thiamethoxam were measured. The ratio of TI-435 to thiamethoxam in each commodity was multiplied by the respective thiamethoxam tolerance level to arrive at the theoretical maximum TI-435 residue level which would be present. These maximum TI-435 residues were used in the chronic analysis. For the commodities which have both thiamethoxam tolerances and proposed TI-435 tolerances (i.e., sweet corn, field corn, pop corn, canola, and milk), the proposed TI-435 tolerances were added to the residues which result from use of thiamethoxam. Processing factors were DEEM (Version 7.76) default processing factors. The DEEM-FCID program, which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII, 1994-1996 and 1998 data), was used.

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 chronic population adjusted doses (cPADs) are all below 100%). The most highly exposed population subgroup is children 1-2 years of age, which utilizes 18% of the cPAD.

Table 6. Results of Chronic Dietary Exposure Analysis			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**% cPAD**

General U.S. Population	0.0098	0.000580	5.9
All Infants (< 1 year old)	0.0098	0.000962	9.8
Children 1-2 years old	0.0098	0.001754	18
Children 3-5 years old	0.0098	0.001285	13
Children 6-12 years old	0.0098	0.000799	8.2
Youth 13-19 years old	0.0098	0.000465	4.7
Adults 20-49 years old	0.0098	0.000446	4.6
Females 13-49 years old	0.0098	0.000449	4.6
Adults 50+ years old	0.0098	0.000475	4.9

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

4.2.4 Cancer Dietary

The Hazard Identification Assessment Review Committee (HIARC) determined that TI-435 is not likely to be a human carcinogen. As a result, a cancer dietary exposure analysis was not performed.

4.3 Water Exposure/Risk Pathway (Attachment 5, EFED memo of 02/10/03, M. Barrett, D278110.)

EFED provided Tier I estimated environmental concentrations (EECs) for clothianidin in surface water and in ground water for use in human health risk assessments. The EECs are summarized in Table 7. The simulation model FIRST was used to calculate the surface water EECs and the SCI-GROW model was used to calculate the groundwater EEC. Clothianidin is a new chemical, therefore monitoring data were not available. Although clothianidin (TI-435) is a major metabolite of thiamethoxam in plants and in animals, it was not found in environmental fate studies. Therefore, exposure of TI-435 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 surface water and ground water assessments, the application rates for the seed treatments to both canola and corn were modeled, with the canola use providing the highest EECs for surface water and the corn use providing the highest EECs for ground water. Since seed treatment uses are not expressed on the registration labels as lbs ai per acre, assumptions had to be made regarding the total pounds of seeds applied per acre in order to calculate the pesticide application rates used for model input; the effective maximum application rates were determined to be 0.05 and 0.10 lb ai/A for canola and corn, respectively. Exposure would be expected to be higher should additional uses involving direct field application of clothianidin be registered, since such uses typically involve application of significantly more active ingredient per acre.

Table 7. Estimated Tier 1 concentrations of clothianidin in drinking water.

Chemical	Surface Water (ug/L)		Groundwater (ug/L)
	Acute	Chronic	Acute and Chronic
Clothianidin	**3.97**	**1.06 - 2.14**	**1.46**

4.4 Residential Exposure/Risk Pathway

Currently there are no registered or proposed residential uses of clothianidin. Clothianidin is a major metabolite of the insecticide thiamethoxam in plants and animals. Since there are also no residential uses of thiamethoxam, possible residential exposure to clothianidin due to thiamethoxam uses is not expected. Assessments addressing residential risks are not warranted at this time.

4.5 Other (Spray Drift, Farm Worker Kids, etc.)

No spray drift associated with seed treatment.

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 in the risk assessment process to assess potential concern for exposure associated with pesticides in drinking water. DWLOC values are not regulatory standards for drinking water.

To calculate acute and chronic DWLOCs, the dietary food estimates (from DEEM^{TM}) 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: 70kg/2L (adult male and US Population), 60 kg/2L (adult female), and 10kg/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 children 1-2 years old, at 16 % of the aPAD. The calculated DWLOCs for acute exposure to TI-435 in drinking water range from 210 to 820 Fg/L (ppb). EECs generated by EFED are less than HED's calculated DWLOCs (Table 8). Therefore, the acute aggregate risk associated with the proposed use of TI-435 does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Table 8. Acute Aggregate Exposures to TI-435 Residues.

Population Subgroup	aPAD (mg/ kg/day)	Acute Food Exposure (mg/kg/day)	Maximum Acute Water Exposure [1] (mg/kg/day)	Ground Water EEC [2] (Fg/L)	Surface Water EEC [2] (Fg/L)	Acute DWLOC [3] (Fg/L)
General U.S. Population	0.025	0.001825	0.023175	1.46	3.97	810
All Infants (< 1 year old)	0.025	0.002855	0.022145	1.46	3.97	220
Children 1-2 years old	0.025	0.004001	0.020999	1.46	3.97	210
Females 13-49 years old	0.025	0.001347	0.023653	1.46	3.97	710
Adults 50+ years old	0.025	0.001491	0.023509	1.46	3.97	820

[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:

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

5.2 Short- and Intermediate-Term Risk

Since there no registered/proposed residential uses of either TI-435 or thiamethoxam, exposures from residential uses are not expected. Therefore, short- and intermediate- term aggregate risk assessments for TI-435 are **not required.**

5.3 Chronic Risk

The chronic aggregate risk assessment takes into account average exposures estimates from dietary consumption of TI-435 (food and drinking water) and residential uses. Since there are no registered/proposed residential uses of either TI-435 or thiamethoxam, exposures from residential uses are not expected.

The Tier 1 chronic dietary exposure estimates are below HED's level of concern for the general U.S. population and all population subgroups. The most highly exposed population subgroup is children 1-2 years old, at 18 % of the cPAD. The calculated chronic DWLOCs for chronic exposure to TI-435 in drinking water range from 80 to 320 Fg/L (ppb). EECs generated by EFED are less than HED's calculated chronic DWLOCs (Table 9) . Therefore, the chronic aggregate risk associated with the proposed use of TI-435 does not exceed HED's level of concern for the general U.S. population or any population subgroups.

Table 9. Chronic Aggregate Exposures to TI-435 Residues.						
Scenario/ Population Subgroup	cPAD, (mg/kg/day)	Chronic Food Exposure, (mg/kg/day)	Maximum Chronic Water Exposure[1], (mg/kg/day)	Ground Water EEC [2], (ppb)	Surface Water EEC [2], (ppb)	Chronic DWLOC[3] (ppb)
General U.S. Population	0.0098	0.000580	0.00922	1.46	2.14	320
All Infants (< 1 year old)	0.0098	0.000962	0.008838	1.46	2.14	88
Children 1-2 years old	0.0098	0.001754	0.008046	1.46	2.14	80
Females 13-49 years old	0.0098	0.000449	0.009351	1.46	2.14	280
Adults 50+ years old	0.0098	0.000475	0.009325	1.46	2.14	320

1 Maximum chronic water exposure (mg/kg/day) = cPAD (mg/kg/day) - chronic food exposure from DEEM (mg/kg/day).

2 EECs from EFED studies.

3 Chronic DWLOCs were calculated as follows:

5.4 Cancer Risk

TI-435 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 TI-435 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 TI-435. For purposes of this tolerance action, EPA has assumed that TI-435 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 TI-435 shares a common mechanism of toxicity with any other substance and, if so, whether any tolerances for TI-435 need to be modified or revoked. If HED identifies other substances that share a common mechanism of toxicity with TI-435, 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).

7.0 OCCUPATIONAL EXPOSURE AND RISK (Attachment 6, HED ORE memo of 04/15/03, G. Bangs, D289014)

The maximum application rate for Clothianidin 600 FS is 0.4 lbs ai per 100 lbs of canola seed (0.004 lbs ai/lb seed) or 1.25 mg/kernel for corn. The registrant (Bayer) correspondence provided HED with information on the estimated quantities of seed treated per day at different types of establishments, using different size treatment systems. The registrant has suggested a typical daily treatment/processing range of 50,000 lbs seed/day in small facilities to 250,000 lbs seed in large commercial establishments.

7.1 Occupational Handler

Data submitted by the seed treatment registrant (Bayer) were jointly reviewed by the HED and the Pest Management Regulatory Agency (PMRA) of Canada. The registrant provided HED with estimates of the typical quantities of corn and canola seed treated per day for different types of facilities and equipment. Based on information provided by BEAD, PMRA, and other sources, seed treater exposure durations are anticipated to be short- (30 days or less) to intermediate-term (1 to 6 months).

Handler Exposure and Risk Estimates

Data Sources and Assumptions

Chemical specific data for assessing human exposure during seed treatment activities were not submitted to the Agency in support of this new chemical use (Section 3) application. It is the policy of the HED to use surrogate chemical data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 to assess handler exposures for regulatory actions when chemical-specific monitoring

data are not available. However, there are no studies within the PHED that are close surrogates for seed treatment. The liquid mixer/loader scenario data in PHED is the most similar to and may be used to estimate loader exposure, while the granular spreader scenario data may be used to estimate planter exposure from treated seed. The submitted study data for both the seed treatment tasks and the planter tasks resulted in higher unit exposures than the most nearly similar PHED unit exposures. Analysis of available seed treatment studies has shown that some workers perform multiple activities; the tasks have been divided into the two general job categories which consistently have the highest exposures: "loader/applicators" and "baggers" (the latter may include bag sewing and stacking, which do not contribute significantly to overall exposure).

The registrant, Bayer, submitted three studies in support of the registration of clothianidin for seed treatment: two seed treatment exposure studies, for isofenphos (Oftanol), MRID 422519-02 and triadimenol (Baytan), MRID 455874-03.; and one planter exposure study, using isofenphos treated seed, MRID 422519-01. These studies were jointly reviewed by Pesticide Management and Registration Agency (PMRA) Canada and the U.S. EPA Office of Pesticides. The studies are neither chemical specific nor are they unique for this type of activity. However, the data were compared to other similar studies and found to be representative of median to higher exposures for the same work. Also, the type of work performed was deemed typical for seed treatment and planting. Because the submitted isofenphos seed treatment study more closely resembled the labeled use of clothianidin for commercial seed treatment, and the unit exposures were consistent with values obtained from other studies used by the Agency to assess large seed treatment operations, those data were generally preferred over the triadimenol study data. However, the triadimenol bagger task exposure data were considered applicable and comparable for small to medium sized facilities, and were averaged with the isofenphos data for the same task. The study data submitted resulted in higher exposure estimates (more conservative) than the default Pesticide Handler Exposure Database (PHED) values for mixer/loaders.

There is one formulated product associated with this action; Clothianidin 600 FS (liquid) for seed treatment. The difficulty in assessing seed treatment exposure is that there are multiple, often overlapping duties performed by personnel in different sized operations. Two major job categories exist in most seed treatment facilities: the actual seed treating process and the bagging and handling of treated seed. Mixer/loaders may also operate or monitor the treatment equipment (treating, calibrating), and baggers may also sew the bags closed and stack them manually or mechanically. However, the major tasks were analyzed separately to characterize the range of exposure for separate tasks, and to allow risk managers the greatest flexibility in mitigating task-specific exposures. The loader/applicators have the highest exposures in most seed treatment studies, and the bagger/sewers generally have lower exposures; together they are used to represent a range of exposure.

The small/medium facility estimates reflect the addition of bagger exposure data from the Baytan study, which was from a medium sized facility. The studies submitted to HED for estimating seed treatment were not specific to large, modern, commercial facilities. The registrants (Bayer/Gustafson) state most corn and canola are treated in large facilities, and that most equipment is more efficient than what was used in these older studies.

See **Table 10** for detailed inputs, calculations and exposure estimates.

Exposure and Risk Estimates

None of the single layer with gloves seed treater estimates exceed the HED level of concern (**Table 10**). Because the Oftanol and Baytan study replicates were wearing long sleeved shirts, long pants, and chemical resistant gloves, the risk estimates assume the same level of protection. Much of the exposure for the loader/applicators was to the head and neck, so wearing head and neck covering while doing that operation could significantly reduce exposure and risk. The target margin of exposure (MOE) for occupational non-cancer risk assessments was 100. The single layer with gloves total dermal and inhalation MOEs ranged from 380 to 960 for loader/applicators in large commercial facilities. The small/medium facility estimates reflect the addition of bagger exposure data from the Baytan study, which was from a medium sized facility. The lowest handler MOE was 110 for seed baggers in small/medium sized facilities. This exposure estimate is driven principally by the inhalation exposure. Analysis of available seed treatment studies has shown that some workers perform multiple activities; the tasks have been divided into the two general job categories which consistently have the highest exposures: "loader/applicators" and "baggers" (the latter may include bag sewing and stacking, which do not contribute significantly to overall exposure).

Table 10: Handler Exposure to Clothianidin While Treating Corn or Canola Using Commercial System with Single Layer Clothing and Chemical Resistant Gloves										
Seed Treatment System (Data Source)(1)	Scenario	Dermal unit exposure (mg/lb ai handled)	Inhalation unit exposure (mg/lb ai handled)	Treatment throughput: lbs seed/day	Absorbed dermal dose (mg/kg/day)(2)	Dermal MOE (3)	Inhalation dose (mg/kg/day) (2)	Inhalation MOE (3)	Total Absorbed Dose (mg/kg/day)(4)	Total MOE (5)
Canola: Typical Large Commercial Volume (Using Bayer Submitted Oftanol Data)	Loader/ Applicator: Open Loading	0.085	0.00068	100,000	0.0057	1,700	4.53E-03	2,200	0.010	960
	Bagger	0.0093	0.000051	100,000	0.00062	16,000	3.40E-04	28,800	9.6E-04	10,200
Corn: Typical Commercial Volume (Using Bayer Submitted Oftanol Data)	Loader/ Applicator: Open Loading	0.085	0.00068	250,000	0.014	690	0.011	865	0.026	380
	Bagger	0.0093	0.000051	250,000	0.00155	6,300	8.50E-04	11500	0.0024	4,100
Small/ Medium Size Treater (Using Bayer Submitted Oftanol Data)	Loader/ Applicator: Open Loading	0.085	0.00068	50,000	0.0028	3,500	2.27E-03	4300	0.0051	1,900
Small/ Medium Size Treater (Using Mean of Oftanol and Baytan Bagger Replicates)	Bagger	0.042	0.026	50,000	0.0014	7,000	0.087	110	0.088	110

Notes:

1. Dermal and inhalation unit exposures are derived from "Exposure to Treatment Workers [sic] to Isofenphos during Application of Oftanol-Containing Seed Coating to Canola Seed, MRID 422519-02; and "Exposure of Workers to Triadimenol During Treatment of Grain Seeds with BAYTAN 312 FS", MRID 455874-03.
2. Dose (mg/kg/day) = Unit Exposure (mg/lb ai) x Application Rate (0.004 lb ai/lb seed) x Amount Handled (lb seed/day) x Absorption Factor / 60 kg BW; Dermal Absorption = 1%
3. MOE = NOAEL (9.8mg/kg/day) / Absorbed Dose (mg/kg/day)
4. Total Absorbed Dose = Absorbed Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day)
5. Total MOE = NOAEL (9.8 mg/kg/day) / Total Dose (mg/kg/day)

Risk Characterization

Although the risk estimates herein are based on relatively few data points from one or two studies, the HED considers these exposure estimates to be typical to higher end for medium-to-large facilities, and adequately conservative to protect most workers under similar conditions. However, the evaluation is based on the proposed label, which specifically *prohibits* use in hopper-box, slurry-box or similar on-farm seed treatment equipment, which would likely be less efficient than commercial equipment and result in higher exposures per lb ai handled.

7.2 Postapplication (Planter) Exposure and Risk Estimates

Data and Assumptions

The exposure scenario consists of the farmer purchasing bags of treated seed, placing the seed in hopper, and planting seed in fields. The isofenphos planter exposure study data were higher (more conservative) than PHED surrogate data historically used for estimating exposure from planting treated seeds. Both the isofenphos study data-based estimates and the PHED granular loader/applicator data-based estimates were calculated using the formula:

See **Table 11** for detailed inputs, calculations, and exposure estimates.

Exposure and Risk Estimates

The risk estimates for loading and planting corn or canola seed do not exceed the HED level of concern **(Table 11)**. Although it is assumed that exposure to treated seed, which has been stored for an indefinite time before use, represents minimal exposure hazard to the handler, an estimate of the inherent risk from treated seed was conducted using the only available study data. The exposure scenario consists of the farmer purchasing bags of treated seed, placing the seed in hopper, and planting seed in the fields using a " drill." Bayer submitted a surrogate study of seed handling and planting using the chemical Oftanol (isofenphos). The HED found this study acceptable, and has estimated planter exposure using these study data. The study data provided higher unit exposure values than the default PHED mixer/loader scenario for granular formulations and PHED applicator scenario for solid broadcast spreader. The MOEs for loading and driving the planter were greater than 100 for corn and canola planting using both data sets (range 15,000-26,000) and therefore, did not exceed HED's level of concern. HED has determined that following soil-incorporated treatments (planting seed), postapplication agricultural exposure is considered to be negligible as long as the soil is not directly contacted.

Table 11: Estimation of Seed Loader / Planter Exposure to Clothianidin from Treated Seed Comparing Oftanol Study Data to PHED Granular Open Loading and Broadcast Spreading										
Activity	Data Source (1)	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (mg/lb ai)	Seed Planting Rate (lbs / A)	Acres/Day	Absorbed Dermal Dose with 1% DA (mg/kg/day) (2)	Dermal MOE (3)	Inhalation Dose (mg/kg/day) (2)	Inhalation MOE (3)	Total MOE (4)
Corn	(a) Oftanol Study	0.169	0.00022	15	200	3.4E-04	2.9E+04	4.4E-05	2.2E+05	2.6E+04
	(b) PHED Granular	0.0168	0.0029	15	200	3.4E-05	2.9E+05	5.8E-04	1.7E+04	1.6E+04
Canola	(a) Oftanol Study	0.169	0.00022	8	400	3.6E-04	2.7E+04	4.7E-05	2.1E+05	2.4E+04
	(b) PHED Granular	0.0168	0.0029	8	400	3.6E-05	2.7E+05	6.2E-04	1.6E+04	1.5E+04

1 a. Dermal and inhalation unit exposures from Oftanol (isofenphos) planter exposure study: MRID 42251901. Exposures of Workers to Isofenphos During Planting of Oftanol-Treated Canola Seeds, V.C. Dean, January 20, 1990, Mobay Corporation. Workers monitored for single-layer equivalent (dosimeters were just under coveralls) clothing and gloves.

1 b. Dermal and inhalation unit exposures are derived from PHED Version 1.1. Granular loading and spreading unit exposures were added together. Loaders wore gloves and work clothing. Planters wore only normal work clothing.

2. Dose (mg/kg/day) = Unit Exposure (mg/lb ai) x Application Rate (0.004 lb ai/lb seed) x Amount Handled (seed planting rate x acres planted = lb seed/day) x Absorption Factor / 60 kg BW; Dermal absorption = 1%

3. MOE = NOAEL (9.8mg/kg/day) / Absorbed Dose (mg/kg/day)

4. Total MOE = NOAEL (9.8 mg/kg/day) / Total Dose (mg/kg/day); Total Dose = Absorbed Dermal Dose (mg/kg/day) + Inhalation Dose (mg/kg/day)

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.

A developmental immunotoxicity study with comparative measures between the pups and the parents

The above data requirements can be conditions of registration.

8.2 Residue Chemistry

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.

860.1340: Analytical Methods- Agency validation of the enforcement methods for plants and livestock commodities is needed.

Attachments:
1. HED HIARC report of 03/31/03, TXR No. 0051713;
2. HED Residue Summary memo of 05/01/03, Y. Donovan, D282446;
3. HED MARC decision memo of 04/25/03, Y. Donovan, D282449;
4. HED DEEM memo of 03/11/03, D. Dotson, D288075;
5. EFED memo of 02/10/03, M. Barrett, D278110;
6. HED ORE memo of 04/15/03, G. Bangs, D289014.

cc with Attachments: Y.W. Donovan.cc without Attachments: Gary Bangs, Pam Hurley, RAB2 reading file, PP#1F06315.