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MEMORANDUM

Date: September 28, 2007

Subject: Clothianidin: Occupational Exposure Assessment for the Use of Poncho Beta containing Clothianidin and *beta*-Cyfluthrin on Sugar Beet.

A. I.: Clothianidin	D.P. No.: D340131
PC Code: 044309	Other D.P. No. D339445
MRID: 47007811	EPA File Symbol: 264-RNLA
Pesticide Type: Insecticide	Petition No. 6F7159

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Bayer CropScience, has submitted a tolerance petition for registering a new use for clothianidin insecticide on sugar beet. Also, the petitioner is proposing to register a new formulation, Poncho Beta (EPA File Symbol: 264-RNLA) containing a mixture of clothianidin and *beta*-cyfluthrin as active ingredients (AI/ai) for the seed treatment of sugar beet. This document deals with an occupational risk assessment performed to evaluate the potential exposures and risks to the handlers and post-treatment workers from clothianidin. A separate document (S. Oonnithan, D339445, 9/28/2007) addresses the occupational exposures and risks to *beta*-cyfluthrin, the second AI found in the Poncho Beta formulation.

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1. EXECUTIVE SUMMARY

Use Pattern: Bayer CropScience is proposing to add a new use, sugar beet to the uses of clothianidin insecticide, as a seed treatment. For this purpose, a new seed treatment formulation, Poncho Beta is being registered. The sugar beet seeds may be treated with Poncho Beta (a ready-to-use liquid concentrate) at a maximum rate of 0.032 lb of clothianidin per lb of seed, in a commercial treatment facility using liquid or slurry coating equipment. The treated seeds are stored until planted.

Hazard Characterization: Clothianidin insecticide works as a nicotine acetylcholine receptor antagonist in insects. Technical clothianidin has low to moderate acute oral, dermal, and inhalation toxicities (Toxicity Categories II to IV). It is not a dermal or eye irritant (Toxicity Category IV) and is not a dermal sensitizer.

HED has concluded that the toxicological database is adequate to assess clothianidin's hazard potential for dietary and occupational exposures. The dermal and inhalation end points selected are no observed adverse effect levels (NOAELs) of 9.8 mg/kg/day, based on the decreased mean body weight gain, and decreased absolute thymus weights in F₁ pups, and increased stillbirths in both generations. Since the basis for dermal and inhalation endpoints are the same, the daily dermal and inhalation doses were combined to calculate a total occupation MOE to the seed treatment workers. Health effects Division (HED) has also determined that the NOAELs for both short- and intermediate-term exposure durations are the same.

Even though there is quantitative evidence of increased susceptibility of the young following exposures to clothianidin in the 2-generation reproduction and developmental neurotoxicity studies in rats, because of low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity, the Food Quality Protection Act (FQPA) Safety Factor was set at 1. There was a concern for immunotoxicity following exposure of test animals to clothianidin during the period of organogenesis and was assigned an additional uncertainty factor (UF) 10x when assessing exposure (for children only) under residential conditions. Thus the level of concern (LOC) for the margin of exposure (MOE) for occupational risks becomes 100 (10x each to account for intra- and inter-species variations) and that for the residential risks becomes 1000. The cancer classification "not likely to be carcinogenic to humans" was assigned to clothianidin.

Non-Occupational and Residential Exposures: Clothianidin is registered for insect control in residential areas such as turf, landscapes, and ornamental plants. These uses may result in exposures to children and adults in residential settings, which have been estimated previously (Dow, M., D296176, 2/24/2006). There are no new residential and/or non-occupational uses for clothianidin being proposed at this time.

Occupational Exposures: Based on the proposed use pattern of Poncho Beta formulation, it was determined that the proposed treatment of sugar beet seeds could result in worker exposures of both short- and intermediate-term durations. The likely scenarios include exposures to loaders/applicators, baggers of treated seeds, and sewers of bags.

As stated earlier, the dermal and inhalation exposures were combined to estimate a total MOE for short- and intermediate-term exposure durations, because of the same NOAELs. The MOEs for the seed treatment workers were estimated using surrogate values from HED's SOP Nos. 14 and 15. The estimated MOEs indicate that the short- and intermediate-term total risks to loaders/treaters, and baggers, from exposure to Poncho Beta containing clothianidin, are not of concern when the workers are wearing the basic personal protective equipment (PPE). However, the PPEs on the label recommended long sleeved shirt, long pants, shoes plus socks, chemical resistant gloves, and a dust/mist respirator for all workers.

Post-Treatment Exposure: The post-treatment exposure of planters to clothianidin is likely when the farmers are transferring the treated sugar beet seeds from bags to planter-hopper and while planting and/or drilling seeds. HED has determined that the handling and planting of treated sugar beet seeds involve both short- and intermediate-term exposures even if the treated seeds are not contacted directly. The estimated risks to planters of Poncho Beta treated sugar beet seeds were found to be not of concern.

2. BACKGROUND

Clothianidin is a nitroguanidine type of insecticide. It is registered for the control of insect pests of cereal grains, canola, and sunflower, and ornamentals. Clothianidin is formulated into flowables, soluble concentrates, and granules and also as a seed treatment to control early season pests like aphids, leaf minors, leaf hoppers and soil pests like wire worms, grubs, and root maggots of canola, cereals, and corn. The proposed Poncho Beta formulation is for the treatment of sugar beet seeds only.

3. USE PATTERN

Bayer CropScience has submitted an application for registering a new formulation, Poncho Beta (EPA File Symbol: 264-RNLA) for the seed treatment of sugar beet. It is a liquid formulation containing clothianidin (34.3% or 3.33 lb ai/gal) and *beta*-cyfluthrin (4.6% or 0.44 lb ai/gal) and is used without dilution. The sugar beet seeds are to be treated in a commercial facility using a liquid or slurry coating equipment at the rate of 5.07 fl. oz of product per 1 unit seed (1 unit = 100,000 seeds) which amounts to a maximum application rate amounts 0.032 lb clothianidin and 0.0043 lb *beta*-cyfluthrin per lb of seed. The proposed use directions for Poncho Beta are summarized in Table 1.

Table 1. Use Directions for Poncho Beta (EPA File Symbol: 264-RNLA) for Treatment of Sugar Beet Seeds		
Use Site	Equipment	Maximum Application Rate
Sugar beet	Commercial seed treaters (liquid or slurry type).	5.07 fl. oz. of product per 1 Unit seed = 0.132 lb clothianidin per 1Unit seed = 0.032 lb of clothianidin/lb of seed ¹

1. The conversion factor used is 1 unit of seed sugar beet seeds weighs 4.085 lbs; or 24,480 sugar beet seeds/lb (ExpoSAC Policy No. 15)

The proposed use of Poncho Beta on sugar beet seed is expected to result in occupational exposures that are of short- and intermediate-term term durations, the rationale of which is discussed under the occupational exposure section.

4. HAZARD CHARACTERIZATION

Clothianidin insecticide works as a nicotine acetylcholine receptor antagonist in insects. Technical clothianidin has low to moderate acute oral, dermal, and inhalation toxicities (Toxicity Categories II to IV). It is not a dermal or eye irritant (Toxicity Category IV) and is not a dermal sensitizer (Table 2).

Table 2. Acute Toxicity Profile of Technical Clothianidin ¹			
G.L. No.	Study Type	Results	Toxicity Category
870.1100	Acute Oral Toxicity	LD ₅₀ = >5000 mg/kg (rat)	IV
870.1100	Acute Oral Toxicity	LD ₅₀ = 425 mg/kg (mouse)	II
870.1200	Acute Dermal Toxicity	LD ₅₀ = >2000 mg/kg (rat)	III
870.1300	Acute Inhalation	LC ₅₀ (M/F) > 5.538 mg/L	IV
870.2400	Primary Eye Irritation	Slightly irritating	IV
870.2500	Primary Dermal Irritation	Non-irritating	IV
870.2600	Skin Sensitization	Not a sensitizer	N/A

1. S.-C. Wang, D309473, 10/20/2006.

HED has concluded that the toxicological database is adequate to assess clothianidin's hazard potential for dietary and occupational exposures. The endpoints selected for the dermal and inhalation exposures were based on the offspring toxicity seen in the two generation reproduction study. A NOAEL of 9.8 mg/kg/day was selected for assessing both dermal and inhalation exposures based on the decreased mean body weight gain, and decreased absolute thymus weights in F₁ pups and, increased stillbirths in both generations. The dermal and inhalation absorption rates selected for this assessment are 1% and 100%, respectively. Since the basis for endpoint selection for dermal and inhalation exposures are the same, the daily dermal and inhalation doses were combined to calculate a combined risk to workers.

There is quantitative evidence of increased susceptibility of the young following exposures to clothianidin in the 2-generation reproduction and developmental neurotoxicity studies in rats. The follow-up analysis indicated that the observed effects in the two studies are well characterized and have a low degree of concern. Because of low concerns but having no residual uncertainties with regard to pre- and/or postnatal toxicity, the FQPA safety factor was set at 1x. There was a concern for immunotoxicity following exposure of clothianidin during the period of organogenesis. This concern was based on the decreases in absolute and adjusted thymus and spleen weights observed in other studies. In addition, the available data indicated that the juvenile rats appeared to be more sensitive to these effects than adults in the two-generation reproduction study. Therefore, a 10x UF was added to account for the lack of a developmental immunotoxicity study when assessing acute and repeated exposure scenarios for children in residential settings. Thus the LOC for residential MOE becomes 1000 (10x each to account for inter- and intra-species variations with an additional 10x UF) while the occupational MOE remains at 100. The cancer classification "not likely to be carcinogenic to humans" was assigned for clothianidin. The doses and endpoints selected for the occupational risk assessment are summarized in Table 3.

Table 3. Summary of Toxicological Doses Selected for Assessing the Occupational Risks of Clothianidin.		
Exposure Scenario	Toxicological Doses	Study and Toxicological End Points
Dermal and Inhalation (All durations)	NOAEL = 9.8 mg/kg/day DAF = 1% IAF = 100% FQPA SF = 1x MOE = 100 is LOC (occupational) MOE = 1000 is LOC (residential) ²	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 still births in both generations.
Cancer	Classified as "Not likely to be a carcinogen"	

1. DAF = Dermal absorption factor, IAF = Inhalation absorption factor, LOAEL = lowest observed adverse effect level, LOC = Level of concern, NOAEL = no observed adverse effect level, FQPA SF = food quality protection act safety factor, UF = Uncertainty factor.

2. An additional 10x uncertainty factor (UF) was added to the default 100x to account for the lack of a developmental immunotoxicity study when assessing acute and repeated exposure scenarios in residential settings.

5. NON-OCCUPATIONAL AND RESIDENTIAL EXPOSURES

Clothianidin is registered for insect control in residential areas such as turf, landscapes, and ornamental plants. These uses may result in exposures to children and adults in residential settings, which have been estimated previously (M. Dow, D296176, 2/24/2006). There are no new residential and/or non-occupational uses for clothianidin being proposed at this time.

6. OCCUPATIONAL EXPOSURE

Exposure Characterization: A previous assessment on clothianidin reviewed the occupational risks from its use as an agricultural insecticide (S-C. Wang, D309473, 10/20/2006). The petitioner has submitted an occupational risk assessment summary (MRID 47007811) with this application. But, it was not reviewed because it did not contain any original occupational exposure data.

The proposed use pattern for Poncho Beta on sugar beet indicates that the seed treatment process may last a month or more, resulting in short- (1-30 days) and intermediate-term (1-6 months) exposures of workers. The Poncho Beta is a ready-to-use (RTU) formulation; therefore, no mixing with a diluent is required prior to pouring it in the seed treatment equipment. The likely occupational exposure scenarios during treatment of sugar beet seeds are the following:

1. loader/applicator who transfers the formulation and treats the seeds
2. bagger of treated seeds
3. sewer of bags after filling with the treated seeds
4. workers doing multiple activities (in a small seed treatment setup, all the operations may be performed by the same worker).

Lacking product-specific exposure data for estimating the occupational exposures to the workers, surrogate exposure values from HED's SOP Nos. 14 and 15 were used. The inputs used to estimate the worker exposures are presented in Table 4.

Table 4. Application Rates and Other Parameters Used for Estimating the Worker Exposures to Clothianidin	
Details	Values
AIs in Poncho Beta formulation	Clothianidin and <i>beta</i> cyfluthrin
Conc. of Clothianidin in Poncho Beta	3.33 lb ai/gal (per label)
Proposed appl. rate of Poncho Beta	5.07 fl. oz./1 Unit seed (per label)
1 Unit seed of sugar beets =	100,000 seeds (per label)
Conc. of clothianidin in 5.07 fl. oz	0.132 lb ai [(3.33/128)*5.07] /1 Unit seed
No. of sugar beet seeds per lb	24,480 ¹
Weight of 1 Unit sugar beet seeds	4.085 lbs (100,000)/24,480)
Proposed seed treatment method	commercial
Conc. of AI / lb of seed	0.032 lb ai (0.132/4.085)
Treating and Planting	--
Quantity of seeds treated per day	52,000 lbs ¹ (ranges 13,200 to 105,600) lbs
Area planted	80 Acres/day ¹
Quantity of seed planted	640 lbs/day
Average work	8 Hours / day
Expected frequency of exposures	short-term (1-30 days) and intermediate term (1-6 months)/year
Body weight of workers	60 kg ²
Dermal and Inhalation Unit exposures	from ExpoSAC Policy # 14 ³

1. ExpoSAC Policy No. 15, dated March 4, 2004

2. Body weight of workers = 60 kg was used because the NOAELs were based on female test animals.

3. ExpoSAC Policy No. 14, dated May 1, 2003.

The equations used to calculate the exposures and risk to the seed treatment workers are presented in Table 5.

Table 5. Equations Used to Estimate the Exposures to Workers Applying the Poncho Beta Formulation Containing Clothianidin	
Equation No.1	$DD = [AR * AT * DUE * DAF * CF2] / BW$
Equation No. 2	$ID = [AR * AT * IUE * CF1 * IAF * CF2] / BW$
Equation No. 3.	Total MOE = Dermal/Inhalation NOAEL / (DD+ID)
Where,	
AR	maximum single application rate
AT	quantity of seeds treated and/or planted/day
BW	body weight of workers
CF1	conversion factor 0.001 for µg/lb ai to mg/lb ai
CF2	conversion factor 0.01 for %
DAF	dermal absorption factor (%)
DUE	dermal unit exposure (mg/lb ai handled)
DD	dermal dose (mg/kg/day)
DMOE	dermal MOE (short- or intermediate-term)
DNOAEL	dermal NOAEL (short- or intermediate-term)
IAF	inhalation absorption factor (%)
ID	inhalation dose (mg/kg/day)
IUE	inhalation unit exposure (µg/lb ai handled)
IMOE	inhalation MOE (short- or intermediate-term)
INOAEL	inhalation NOAEL (short- or intermediate-term)

Table 6. Short- and Intermediate-Term Risks to Workers and Planters Resulting From the Seed Treatment of Sugar Beet with Poncho Beta Containing Clothianidin¹

Exposure Scenarios	PPE ²	Qty Treated or Planted/day (lbs)	Unit Exp. Dermal/day (mg/lb ai)	Unit Exp. Inhal/day (µg/lb ai)	Dermal Dose (mg/kg/day) ³	Inhal. Dose (mg/kg/day) ³	Total MOE ⁴
Treatment:							
Loading/Treating	S, G	52,000	0.023	0.34	0.00644	0.00952	610
Bagging, treated seed	S	52,000	0.0091	0.16	0.00255	0.00448	1,400
Sowing, bagged seed	S	52,000	0.0062	0.23	0.00174	0.00644	1,200
Doing multiple jobs	S, G	52,000	0.0420	1.6	0.01176	0.04479	170
Post-treatment:							
Planting of treated seeds	S #	640	0.25	3.4	0.00086	0.00117	4,800

1. Application rate and other values and assumptions are from Tables 1, 3, 4, and 5

2. S = Single layer (long sleeve shirt and long pants) and no gloves, G = chemical resistant gloves.

3. Dermal dose = Equation No. 1 and Inhalation dose = Equation No. 2

4. Total MOE (combined dermal and inhalation, Equation No. 3) for the short- and Intermediate-term. The Total MOE for both exposure durations are the same because of the same NOAEL.

#. For handlers/planters, gloves are to be used for loading only.

The proposed label of Poncho Beta specifies the following PPEs: (i) loaders/treaters must wear long sleeved shirt and long pants, shoes with socks, chemical resistant gloves, and dust/mist respirator and (ii) baggers and sewers must wear long sleeved shirt and long pants, shoes with socks, and dust/mist respirator. Because the clothianidin NAOEL is the same (Table 3) for both exposure routes (dermal and inhalation) and both durations (short- and intermediate-term), the total MOEs were calculated for each exposure scenario.

Table 6 summarizes the total risk (dermal and inhalation) to loaders/treaters, baggers, and sewers who do individual jobs as well as to the worker who may do multiple jobs on a day. In all cases the estimated combined clothianidin MOEs are not of concern (MOEs >170 and LOC = 100) for all seed treatment scenarios, if the workers wear label-specified PPEs while using Poncho Beta.

7. POST-TREATMENT EXPOSURE

Exposure Characterization: The post-treatment exposure of planters to clothianidin is likely when the farmers are transferring the treated sugar beet seeds from bags to planter-hopper and while planting and/or drilling seeds. HED has determined that the handling and planting of treated sugar beet seeds involve both dermal and inhalation exposures even if the treated seeds are not contacted directly. It is assumed that the sugar beet planting season may last for >30 days/season resulting in short- and intermediate-term exposures to planters

The postapplication exposure to planters was estimated using surrogate values from HED's SOP Nos. 14 and 15, and the results are presented in Table 6. The estimated total short- and intermediate-term risks are not of concern (MOEs 4,800, LOC = 100) to planters of Poncho Beta treated sugar beet seeds. While the planters are seeding/planting, no direct contact with the treated seeds are expected because the planting machinery places/drills the seed and covers it with soil, doing both steps in one operation. The treated seeds once covered with soil are protective of workers who may reenter the field soon after planting for irrigation. No other postapplication activity is performed in a freshly seeded sugar beet field. There is no restricted entry interval (REI) for treating and planting of pre-treated seeds as REI is not applicable for seed treatment operations.

8. CONCLUSIONS AND RECOMMENDATIONS

1. The non-cancer total short- and intermediate-term clothianidin risk estimates for workers wearing label specified PPE and treating sugar beet seeds with clothianidin containing Poncho Beta formulation do not exceed HED's LOC. The second active ingredient, *beta*-cyfluthrin, present in the Poncho Beta formulation may require additional PPEs and/or mitigation measures for workers, depending upon its exposure potential while treating seeds.
2. The post-treatment risk to farmers who plant the treated sugar beet seeds is not of concern for clothianidin.

9. REFERENCES

Clothianidin: EPA Pesticide Fact Sheet. 5/30/2003.

Bangs, G., D289014, 4/15/2003. Clothianidin (TI-435): Occupational Exposure and Risk Estimates for Proposed Uses in Commercial Seed-Treatment of Corn and Canola Seed.

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Oonnithan, S., D339445, 9/28/2007. Cyfluthrin and *Clothianidin*: Occupational Risk Assessment to Support the Uses on Alfalfa and Grasses and the Use of *Clothianidin* on Sugar Beet. Petition Nos. 6E7058 (Grasses), 6F7160 (Sugar Beet) and 7F7226 (Alfalfa).

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Wang, S-C., D309473, 10/20/2006. Occupational and Residential Exposure/Risk Assessment of Clothianidin for Crop Protection Uses on Potato and Grape and for Seed Treatment Uses on Sorghum and Cotton.