Health Canada Santé Canada

Evaluation Report for Category B, Subcategory 4.1 Application

Application Number:	2007-6020
Application:	Conversion to full registration without consultation
Product:	Clothianidin Technical Insecticide
Registration Number(s):	27445
Active ingredient (a.i.):	Clothianidin
PMRA Document Number :	1867854

Background

The insecticide active ingredient, clothianidin, and the associated end-use product, Titan ST Insecticide (formerly known as Poncho 600 Seed Treatment Insecticide), were granted temporary registration under Section 17 of the Pest Control Products Regulations in 2004. Regulatory Note REG2004-06, *Clothianidin, Poncho 600 Seed Treatment Insecticide* provides a summary of data previously reviewed, the rationale for the regulatory decision, and the additional studies required as a condition of registration.

Purpose of Application

The purpose of this application was to convert the technical product, Clothianidin Technical Insecticide, to full registration. Conversion of the associated end-use product, Titan ST Insecticide, was reviewed in a separate application (Application Number 2007-6051).

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Chemistry Assessment

Common Name: Clothianidin Technical Insecticide
Chemical Name: (*E*)-1-(2-chloro-1,3-thiazol-5-thiazolyl)-3-methyl-2-nitroguanidine

Clothianidin Technical Insecticide Technical has the following properties:

Property	Result
Colour and physical state	Colourless powder
Nominal concentration	97.5%
Odour	Odourless
Density	1.61 g/mL at 20°C
Vapour pressure	1.3×10^{-10} Pa at 25°C 3.8×10^{-11} Pa at 20°C (extrapolated)
Solubility in water	0.327 g/L at 20°C
n-Octanol/water partition coefficient (K_{ow})	Kow = 5

The chemistry requirements for Clothianidin Technical Insecticide have been completed.

Health Assessments

Clothianidin is a neonicotinoid insecticide that is structurally and functionally related to nicotine. The mode of action for neonicotinoids is believed to involve binding or partial binding with the nicotinic acetylcholine receptors of the insect's nervous system.

A detailed review of the toxicological database for clothianidin was conducted previously in 2003 and is summarized in Regulatory Note REG2004-06, *Clothianidin, Poncho 600 Seed Treatment Insecticide*. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to clothianidin. The 2003 review of the toxicological database revealed that clothianidin elicited effects in the liver, kidneys, reproductive organs, gastrointestinal tract and immune system; however, there was little consistency in the identified target organs among studies or between species. Long-term studies in rats revealed an increased incidence of thyroid C-cell adenomas in females. Genotoxicity was noted in several in vitro assays.

A cancer risk assessment was performed on the basis of the observed thyroid tumors. However, there was a possibility that the tumorigenic response of clothianidin could have been due to a chemical batch which contained several contaminants of tumour causing potential, based on chemical structural analysis. Consequently, the PMRA requested a new battery of genotoxicity tests to investigate the possibility of contaminants mediating the tumorigenic response using the same chemical batch as the one used in the long-term rat study.

The neurotoxic potential of clothianidin was examined in acute, subchronic and developmental neurotoxicity (DNT) studies. No neuropathological findings were noted in any of these studies. However, signs of neurotoxicity were evident in the acute (clinical signs) and DNT (decreased motor activity and acoustic startle response) studies. In several toxicity studies, there were indications of effects on the immune system (i.e., changes in thymus and spleen weights, decreased white blood cell counts, hypocellularity of bone marrow, thymic involution and depletion of lymphoid cells in thymus, spleen and mesenteric lymph nodes). Increased susceptibility of the young was seen in both the two-generation reproductive toxicity study (delayed sexual maturation and increased stillbirths) and the DNT study (decreased acoustic startle response and motor activity). In the developmental toxicity studies, an increased incidence of missing lung lobe was identified in the fetuses of treated pregnant rabbits.

The potential effects on the immune system, as well as the indication of susceptibility of the young resulted in the requirement for additional testing to assess potential effects on the functionality of the developing immune system. An additional 3-fold factor was applied to the clothianidin risk assessment in 2003 to account for the increased susceptibility of the young and the requirement for a developmental immunotoxicity (DIT) study.

Subsequent to the issuance of the temporary registration, the applicant submitted a new battery of genotoxicity studies conducted with the same batch of clothianidin as that used in the long-term rat study. These studies demonstrated a negative genotoxic response in all assays. In addition, the applicant provided a re-evaluation of the thyroid tumor data consisting of an independent review by a new pathologist, as well as a consensus diagnosis by the new and the original pathologists. The results of this independent re-examination did not suggest an increase in thyroid tumors as a result of clothiandin treatment. The PMRA concurred with the results of this re-examination of the thyroid tumor data.

In the DIT study, maternal animals were dosed from gestation day six through to lactation day 13. A Sheep Red Blood Cell (SRBC) antibody-forming cell response assay to assess humoral immunity and a delayed-type hypersensitivity (DTH) assay to assess cell-mediated immunity were conducted in F_1 weanling rats (post-natal day 22 through post-natal day 41). No mortality, reproductive performance or gross pathology effects were noted in the maternal animals. Treatment-related findings in maternal animals of the high-dose group included an increased incidence of ptosis, decreased body weight and/or body weight gains at lactation and gestation, as well as reduced food consumption during gestation and lactation. No treatment-related effects were observed on pup viability, litter size, or in clinical signs of toxicity in pups. Decreased body weights, body weight gains, and food consumption were observed in offspring at the mid- and high-dose levels.

The antibody-forming cell response assay did not suggest a concern with respect to the developing immune system. In the DTH assay, no effect on cell-mediated immunity was observed in treated group animals of either sex at 24 and 48 hours after challenge relative to control.

Under the conditions of the DIT study, there were no immunologically adverse effects on humoral or cell-mediated immunity in male and female rats exposed to clothianidin during the prenatal, postnatal and post-weaning periods.

As a consequence of the submission and review of the supplemental information on the cancer assessment as well as the genotoxicity studies and required DIT study, a re-examination of the endpoints selected for dietary and occupational risk assessments was undertaken.

The re-examination of the toxicological database resulted in amending the reviews for the short- and long-term dog, rabbit developmental toxicity and DNT study. The dose-related decrease in alanine aminotransferase (ALT) levels noted in all dog studies was considered to be treatment-related and adverse. In the 4-week range-finding study, decreased ALT was observed in females at all dose levels tested and in males at the mid- and high-dose levels. The findings that previously defined the lowest-observed-adverse-effect level (LOAEL) of 40.9 mg/kg bw/day in males for the 13-week dog dietary study now includes decreased ALT in females (LOAEL 42.1 mg/kg bw/day). The male/female no-observed-adverse-effect level (NOAEL) remains unchanged at 19.3/21.2 mg/kg bw/day. The LOAEL for the 1-year dog study has been amended to 36.3/40.1 mg/kg bw/day based on decreased ALT in males and females, respectively. The NOAEL was established at 16.6/15.0 mg/kg bw/day (male/female).

In the developmental toxicity studies, an increased incidence of missing lung lobe was identified in the fetuses of treated pregnant rabbits, and has now been characterized as a malformation. The established LOAEL at 75 mg/kg bw/day and NOAEL at 25 mg/kg bw/day remain unchanged.

In the DNT study, there were additional brain morphometric changes that were considered to be treatment-related in high-dose female pups. The established offspring LOAEL at 42.9 mg/kg bw/day includes the additional brain morphometric changes and the NOAEL remains unchanged at 12.9 mg/kg bw/day.

Results of the amended and newly submitted studies conducted on laboratory animals as well as the toxicological endpoints selected for the human health risk assessment are summarized in Appendix I, Tables 1 and 2.

PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of and toxicity to infants and children, as well as potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the data as it pertains to the toxicity to infants and children, extensive data were available for clothianidin. The database contained a full complement of required studies including developmental toxicity studies in rats and rabbits, a rat reproductive toxicity study, a rat DNT study, and a rat DIT study.

With respect to identified concerns relevant to the assessment of risk to infants and children, the prenatal developmental toxicity study in rats did not demonstrate fetotoxicity at the dose levels tested. An increased incidence of absent intermediate lung lobe (considered a malformation) and decreased ossification of sternal centers were noted in rabbit fetuses in a developmental toxicity study at a dose level that also resulted in pronounced toxicity to maternal animals. Decreased body weight, body weight gain and food consumption were seen in offspring at a maternally non-toxic dose in the DIT study. In the reproductive toxicity study, decreased body weight gain, delayed sexual maturation and decreased thymus weight in offspring, as well as an increased incidence of stillbirth was observed at a maternally non-toxic dose. The level of concern for the increase in stillbirths was lowered by the fact that there were no changes in the live birth index, live litter size or number of implantations, as well as the fact that the increase in stillbirths was not observed in the DNT study. In the DNT study, decreased body weight and body weight gain, as well as effects on auditory startle response and decreased motor activity were noted in offspring at a dose that did not cause adverse effects in maternal animals. The NOAELs for offspring in the reproductive toxicity, DNT and DIT studies were comparable (9.8-12.9 mg/kg bw/day) and lower than that established in the rabbit developmental toxicity study for the missing lung lobe (25 mg/kg bw/day).

As previously mentioned, clothianidin is a neonicotinoid that is structurally related to nicotine. Studies in the published literature suggest that exposure to cigarette smoke causes developmental toxicity, including functional deficits, in humans that are exposed prenatally (e.g., Butler and Goldstein, 1973; Indredavik et al. 2007; Lefkowitz 1981; Naeye and Peters, 1984; Orlebeke et al. 1999; Wakschlag et al. 2002; Weitzman et al. 2002; all as reported in Slotkin, 2008). Although nicotine is not the only constituent of cigarette smoke, there is ample evidence linking nicotine exposure to effects on the developing nervous system (Dwyer et al. 2008). The published literature contains numerous studies demonstrating neurotoxicity in developing animals following direct dosing of nicotine *in utero* (e.g., Ajarem and Ahmad, 1998; Vaglenova et al. 2004; Thomas et al. 2000; Shacka et al. 1997; Levin et al. 1993; Slotkin, 1998). The postulated mode of action for nicotine involves disruption of the processes of cell development and cell signaling, which results in alterations to the developing cholinergic, catecholaminergic and serotoninergic neurotransmitter systems. This mode of action is believed to be plausible in humans because the nicotine receptor is present in the developing human brain (Slikker et al. 2005).

These data should be considered when assessing the effects of clothianidin on the developing young, in view of the fact that clothianidin is a neonicotinoid that is structurally related to nicotine. Effects on auditory startle response and motor activity were observed in offspring in the DNT study at doses that were not toxic to the dams. Although auditory startle response is known to represent a reflex involving sensory and muscular systems, there is a cognitive component as well. Motor activity assesses motor and sensory function, and also can be used to test behavioural ontogeny (habituation). These neurobehavioural effects may be indicative of potential functional deficits in the nervous system. The neurological implications of these findings in humans, i.e., seriousness of the manifested effects, are unknown. For these reasons, there is concern regarding the potential human neurotoxicity resulting from exposure to clothianidin.

Overall, the toxicology database is complete and all required studies for assessing risk to infants and children were available. Sensitivity of the young was identified in the reproductive toxicity, DNT and DIT studies. As previously mentioned, there is concern regarding potential human neurotoxicity resulting from exposure to clothianidin. Based on the strength of all the available information, the PCPA factor was reduced to 3-fold when the DNT study was used for risk assessment. Additionally, there was concern regarding the serious endpoint (stillbirths) observed in the absence of maternal toxicity in the reproductive toxicity study; however, this particular concern was tempered by the absence of effect on live birth index, live litter size and number of implantations, and no increase in stillbirth was seen in the DNT study. For these reasons, the PCPA factor was reduced to 3-fold when the two-generation reproductive toxicity study was used for risk assessment.

Determination of Acute Reference Dose

The recommended acute reference dose (ARfD) for clothianidin has been updated to 0.043 mg/kg bw (previously 0.25 mg/kg bw in REG2004-06). The most appropriate study for selection of a toxicity endpoint for acute dietary exposure was the DNT study, in which a NOAEL of 12.9 mg/kg bw/day was determined in female offspring based on decreased body weight and body weight gain, reduced motor activity and reduced auditory startle response at the LOAEL of 42.9 mg/kg bw/day. The neurological effects noted in offspring in this study may occur following a single exposure; therefore these effects are relevant to the selection of the ARfD.

Uncertainty factors of 10-fold for interspecies extrapolation as well as 10-fold for intraspecies variability were applied in the setting of the ARfD. For the reasons outlined in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold. This results in a Composite Assessment Factor (CAF) of 300. The ARfD is considered to be protective of all sensitive sub-populations.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{12.9 \text{ mg/kg bw}}{300} = 0.043 \text{ mg/kg bw of clothianidin}$$

Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for clothianidin remains 0.0327 mg/kg bw/day. The most appropriate study for selection of a toxicity endpoint for chronic dietary exposure was the two-generation reproduction study, in which a NOAEL of 9.8 mg/kg bw/day was determined in offspring based on decreased body weight gain, increased stillbirth, delayed sexual maturation in males and decreased thymus weight at the LOAEL of 10 mg/kg bw/day. This is the lowest NOAEL in the toxicology database and is considered to be protective of the most sensitive subpopulations.

Uncertainty factors of 10-fold for interspecies extrapolation as well as 10-fold for intraspecies variability were applied in the setting of the ADI. For the reasons outlined in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold. This results in a CAF of 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{9.8 \text{ mg/kg bw/day}}{300} = 0.0327 \text{ mg/kg bw/day of clothianidin}$$

Environmental Assessment

The following environmental data were submitted to support conversion to full registration: long-term hydrolysis, acute oral toxicity to leaf-cutter bees, acute oral toxicity to bumble bees, acute oral toxicity to mallard duck, acute oral toxicity to house sparrow, and acute oral toxicity to red-winged blackbird.

Review of the data submitted on long-term hydrolysis of clothianidin confirmed the previous conclusions on the fate and behaviour of clothianidin as outlined in Regulatory Note REG2004-06, *Clothianidin, Poncho 600 Seed Treatment Insecticide*.

The additional data on avian species indicate that the acute oral toxicity in the mallard duck (LD_{50} 503 mg a.i./kg bw) and house sparrow (LD_{50} 530 mg a.i./kg bw) is similar to that of the Japanese quail (LD_{50} 423 mg a.i./kg bw). The study submitted on the oral toxicity of clothianidin to red-winged blackbird was not acceptable due to high variability in response and insufficient replication; however, no further data are required.

Although a qualitative assessment of the acute oral toxicity to bumble bees indicated that clothianidin-treated pollen resulted in worker bee mortality, an acute toxicity endpoint (i.e. LC_{50}) could not be determined. Although the study was of limited value, no further data is required on the toxicity of clothianidin to bumble bees. A waiver for the requirement of a study on the acute oral toxicity to leaf-cutter bees was also granted considering a validated test protocol is not available and additional data on other bee species have since been generated.

No further environmental data are required for the full registration of clothianidin technical as a seed treatment.

Value Assessment

A value assessment was not required for this application.

Conclusion

The PMRA conducted an evaluation of the subject application and found all conditions of registration have been satisfied for Clothianidin Technical Insecticide. However, the PMRA determined that there was insufficient information to support full registration of Titan ST Insecticide (formerly known as Poncho 600 Seed Treatment Insecticide) in the associated application (Application Number 2007-6051). Therefore, Clothianidin Technical Insecticide will remain conditionally registered contingent on the conversion to full registration of at least one of its associated end-use products.

References

List of studies/information submitted by registrant

PMRA Document Number: 846340
Reference: 2004, 104-Week dietary combined chronic toxicity and carcinogenicity study with TI-435 in rats, Data Numbering Code: 4.4.4

PMRA Document Number: 846341
Reference: 2003, TI-435 *Salmonella typhimurium* reverse mutation assay, Data Numbering Code: 4.5.4

PMRA Document Number: 846342
Reference: 2003, Gene mutation assay in Chinese hamster V79 cells *in vitro* (V79/HPRT) with TI-435, Data Numbering Code: 4.5.5

PMRA Document Number: 846343
Reference: 2003, TI-435 gene mutation assay in Chinese hamster V79 cells *in vitro* (V79/HPRT), Data Numbering Code: 4.5.5

PMRA Document Number: 846344
Reference: 2003, *In vitro* chromosome aberration test in Chinese hamster V79 cells with TI-435, Data Numbering Code: 4.5.6

PMRA Document Number: 846345
Reference: 2003, TI-435 *in vitro* chromosome aberration test in Chinese hamster V79 cells, Data Numbering Code: 4.5.6

PMRA Document Number: 846346
Reference: 2003, TI-435 micronucleus assay in bone marrow cells of the mouse, Data Numbering Code: 4.5.7

PMRA Document Number: 846347
Reference: 2003, TI-435 micronucleus assay in bone marrow cells of the mouse, Data Numbering Code: 4.5.7

PMRA Document Number: 846348
Reference: 2003, *In vivo/ in vitro* unscheduled DNA synthesis in rat hepatocytes with TI-435, Data Numbering Code: 4.5.8

PMRA Document Number: 846349
Reference: 2003, TI-435 *in vivo/ in vitro* unscheduled DNA synthesis in rat hepatocytes, Data Numbering Code: 4.5.8

PMRA Document Number: 941750
Reference: Franklin MT, Winston ML, Morandin LA, 2004, Effects of clothianidin on *Bombus impatiens* (Hymenoptera: Apidae) colony health and foraging ability, J Econ Entomol 97(2): 369-373, Data Numbering Code: 9.2.4

PMRA Document Number: 941753
Reference: 2004, Clothianidin: An acute oral toxicity study with the mallard, Data Numbering Code: 9.6.2.3

PMRA Document Number: 1140672
Reference: 2004, Chemistry requirements for the registration of clothianidin technical, Data Numbering Code: 2.1, 2.10, 2.11.1, 2.11.2, 2.11.3, 2.11.4, 2.12.1, 2.13.1, 2.13.2, 2.13.3, 2.13.4, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.9 Confidential Business Information

PMRA Document Number: 1194574
Reference: 1998, Palatability pilot study for dietary concentrations of TI 435 in dogs, Data Numbering Code: 4.3.3

PMRA Document Number: 1194575
Reference: 2000, 4-Week dietary toxicity study with TI 435 in dogs, Data Numbering Code: 4.3.3

PMRA Document Number: 1194584
Reference: 2000, 13-Week dietary toxicity study with TI 435 in dogs, Data Numbering Code: 4.3.8

PMRA Document Number: 1194585
Reference: 2000, 52-Week dietary chronic toxicity study with TI 435 in dogs, Data Numbering Code: 4.3.8

PMRA Document Number: 1194586
Reference: 2001, 52-Week dietary chronic toxicity study with TI 435 in dogs, Data Numbering Code: 4.3.8

PMRA Document Number: 1194615, 1194624
Reference: 2000, Developmental neurotoxicity study of TI 435 administered orally via diet to CRL:CD® presumed pregnant rats, Data Numbering Code: 4.5.12

PMRA Document Number: 1194620
Reference: 1998, Oral (stomach tube) developmental toxicity study of TI-435 in rabbits, Data Numbering Code: 4.5.3

PMRA Document Number: 1256056
Reference: 2001, Product chemistry of clothianidin technical, Data Numbering Code: 2 Confidential Business Information

PMRA Document Number: 1256058
Reference: 2001, Product chemistry of clothianidin technical, Data Numbering Code: 2 Confidential Business Information

PMRA Document Number: 1463984
Reference: 2004, Five lot analysis of TI-435 technical, Data Numbering Code: 2.13.3 Confidential Business Information

PMRA Document Number: 1463985
Reference: 2004, Nitrosamine analysis of five lots of TI-435 technical, Data Numbering Code: 2.13.3 Confidential Business Information

PMRA Document Number: 1463987
Reference: 2007, Waiver request for acute oral toxicity study for leafcutter bee, Data Numbering Code: 9.2.7

PMRA Document Number: 1463988
Reference: 2005, Clothianidin (TI 435) - Acute oral toxicity test (LD50) with the red-winged blackbird (*Agelaius phoeniceus*), Data Numbering Code: 9.6.2.3

PMRA Document Number: 1463989
Reference: 2005, Clothianidin (TI 435) - Acute oral toxicity test (LD_{50}) with the house sparrow (*Passer domesticus*), Data Numbering Code: 9.6.2.3

PMRA Document Number: 1464605
Reference: 2006, Clothianidin: Long-term hydrolytic degradation, Data Numbering Code: 8.5

PMRA Document Number: 1628836
Reference: 2008, Oral (diet) developmental immunotoxicity study of TI 435 (clothianidin) in Crl:CD (SD) rats, Data Numbering Code: 4.8

Additional information considered

PMRA Document Number: 1938742
Reference: Ajarem JS, Ahmad M, 1998, Prenatal nicotine exposure modifies behavior of mice through early development, Pharmacology Biochemistry and Behavior 59:313-318

PMRA Document Number: 1938743
Reference: Butler NR, Goldstein H, 1973, Smoking in pregnancy and subsequent child development, Br. Med. J. 4:573-574

PMRA Document Number: 1938746
Reference: Dwyer JB, Broide RS, Leslie FM, 2008, Nicotine and brain development, Birth Defects Res. C. Embryo Today 84:30-44

PMRA Document Number: 1938747
Reference: Indredavik MS, Brubakk AM, Romundstad P, Vik T, 2007, Prenatal smoking exposure and psychiatric symptoms in adolescence, Acta Paediatr. 96:377-382

PMRA Document Number: 1938748
Reference: Lefkowitz MM, 1981, Smoking during pregnancy: long-term effects on the offspring, Dev. Psychol. 17:192-194

PMRA Document Number: 1938749
Reference: Levin ED, Briggs SJ, Christopher NC, Rose JE, 1993, Prenatal nicotine exposure and cognitive performance in rats, Neurotoxicology and Teratology 15:251-260

PMRA Document Number: 1938750
Reference: Naeye RL, Peters EC, 1984, Mental development of children whose mothers smoked during pregnancy, Obstet. Gynecol. 64:601-607.

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Reference: Orlebeke JF, Knol DL, Verhulst FC, 1999, Child behavior problems increased by maternal smoking during pregnancy, Arch. Environ. Health 54:15-19

PMRA Document Number: 1938752
Reference: Shacka JJ, Fennell OB, Robinson SE, 1997, Prenatal nicotine sex-dependently alters agonist-induced locomotion and stereotypy, Neurotoxicology and Teratology 19:167-176

PMRA Document Number: 1938753
Reference: Slikker W Jr, Xu ZA, Levin ED, Slotkin TA, 2005, Mode of action: Disruption of brain cell replication, second messenger, and neurotransmitter systems during development leading to cognitive dysfunction – developmental neurotoxicity of nicotine, Critical Reviews in Toxicology 35:703-711

PMRA Document Number: 1938754
Reference: Slotkin TA, 1998, Fetal nicotine or cocaine exposure: which one is worse? J. Pharmacol. Exp. Ter. 285:931-945

PMRA Document Number: 1938759
Reference: Thomas JD, Garrison ME, Slawecki CJ, Ehlers CL, Riley EP, 2000, Nicotine exposure during the neonatal brain growth spurt produces hyperactivity in preweanling rats, Neurotoxicology and Teratology 22:695-701

PMRA Document Number: 1938761
Reference: Vaglenova J, Birru S, Pandiella NM, Breese CR, 2004, An assessment of the long-term developmental and behavioral teratogenicity of prenatal nicotine exposure, Behavioural Brain Research 150: 159-170

PMRA Document Number: 1938763
Reference: Wakschlag LS, Pickett KE, Cook E, Benowitz NL, Leventhal BL. 2002, Maternal smoking during pregnancy and severe antisocial behavior in offspring: a review, Am. J. Public Health 92:966-974

PMRA Document Number: 1938764
Reference: Weitzman M, Byrd RS, Aligne CA, Moss M, 2002, The effects of tobacco exposure on children's behavioral and cognitive functioning: implications for clinical and public health policy and future research, Neurotoxicol. Teratol. 24:397-40

APPENDIX I

Table 1 Amended and Newly Submitted Toxicity Studies of Technical Clothianidin

Study Type	Species	Results[a] (M/F)	Reference
28-day dietary range-finding	Dog	Effect levels not established since study considered supplemental. Mortalities, clinical signs, ↓fc, ↓bwg, hematological effects, ↓ALT, bone marrow congestion, hypocellularity, and hemorrhage, depleted lymph of the spleen, ileum, thymus and mesenteric lymph nodes	1194574 1194575
90-day dietary	Dog	NOAEL: 19.3/21.2 mg/kg bw/day LOAEL: 40.9/42.1 mg/kg bw/day, based on thinness, ↓bw, ↓bwg, ↓RBC, ↓Hgb, and ↓hematocrit in M ↓ALT in F At higher doses, ↓lymphocytes and ↓WBC noted	1194584
1-year dietary	Dog	NOAEL: 16.6/15.0 mg/kg bw/day LOAEL: 36.3/40.1 mg/kg bw/day, based on ↓ALT in M/F At HDT, ↓RBC, ↓Hgb, and ↓hematocrit noted in F	1194585 1194586
Developmental toxicity	Rabbit	**Maternal:** NOAEL: 25 mg/kg bw/day LOAEL: 75 mg/kg bw/day, based on scant feces, orange urine, mortality, ↓bwg, ↓fc, early delivery, ↓gravid uterine wt and abortion **Developmental:** NOAEL: 25 mg/kg bw/day LOAEL: 75 mg/kg bw/day, based on absent intermediate lung lobe and ↓ossified sternal center	1194620

Study Type	Species	Results[a] (M/F)	Reference
Genotoxicity with Comparative TGAI Batches			
In vitro mammalian chromosomal aberration (96.4%)	Chinese hamster lung (V79) cells	Negative with activation Positive without activation (at precipitating concentrations)	846344
Gene mutations in mammalian cells in vitro (96.4%)	Chinese hamster lung (V79) cells	Negative	846342
In vitro unscheduled DNA synthesis (96.4%)	Primary rat hepatocytes	Negative	846348
In vivo mammalian cytogenetics (96.4%)	NMRI Mouse	Negative	846346
Reverse gene mutation assay (99.8%)	*Salmonella typhimurium* strains TA 98, TA 100, TA 102 TA 1535 and TA 1537	Negative	846341
In vitro mammalian chromosomal aberration (99.8%)	Chinese hamster lung (V79) cells	Negative	846345
Gene mutations in mammalian cells in vitro (99.8%)	Chinese hamster lung (V79) cells	Negative	846343
In vitro unscheduled DNA synthesis (99.8%)	Primary rat hepatocytes	Negative	846349
In vivo mammalian cytogenetics (99.8%)	NMRI Mouse	Negative	846347

Study Type	Species	Results[a] (M/F)	Reference
Special Studies			
Developmental neurotoxicity dietary	Rat	**Maternal:** NOAEL: 42.9 mg/kg bw/day LOAEL: 142 mg/kg bw/day, based on ↓bw, ↓bwg and ↓fc **Developmental:** NOAEL: 12.9 mg/kg bw/day LOAEL: 42.9 mg/kg bw/day, based on ↓bw, ↓bwg, ↓motor activity (F), ↓acoustic startle response (F)	1194615 1194624
Developmental immunotoxicity	Rat	**Maternal:** NOAEL: 35 mg/kg bw/day LOAEL: 121 mg/kg bw/day, based on ↑ptosis, ↓bw, ↓bwg, bw loss and ↓fc **Developmental:** NOAEL: 10 mg/kg bw/day LOAEL: 35 mg/kg bw/day, based on ↓bw, ↓bwg and ↓fc No immunologically adverse effects on humoral (anti-SRBC assay) or cell-mediated (DTH assay) immunity in M/F offspring during prenatal, postnatal and post-weaning periods	1628836

[a] Effects observed in males as well as females unless otherwise reported

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Clothianidin

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	CAF[1] or Target MOE
Acute dietary	NOAEL = 12.9	Developmental Neurotoxicity	Decreased body weight, decreased body weight gain, reduced motor activity and reduced auditory startle response	300
	ARfD = 0.043 mg/kg bw			
Chronic Dietary	NOAEL = 9.8	Two-Generation Reproductive	Decreased body weight gain, increased stillbirth, delayed sexual maturation in males and decreased thymus weight	300
	ADI = 0.0327 mg/kg bw/day			
Short-, Intermediate- and Long-term Dermal or Inhalation	NOAEL = 9.8	Two-Generation Reproductive	Decreased body weight gain, increased stillbirth, delayed sexual maturation in males and decreased thymus weight	300

[a] CAF (Composite assessment factor) refers to the total of uncertainty and PCPA factors for dietary and residential risk assessments, MOE refers to target MOE for occupational assessments

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