Clothianidin (CAS# 210880-92-5) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Natural Resources Defense Council

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GreenScreen® Executive Summary for Clothianidin (CAS# 210880-92-5)

Clothianidin is a chemical that functions as a neonicotinoid insecticide.

Clothianidin was assigned a **GreenScreen Benchmark™ Score of 1** ("Avoid – Chemicals of High Concern"). This score is based on the following hazard score:

- Benchmark **1c**
  - vPT = Very High Persistence (P) + Very High Ecotoxicity (acute aquatic toxicity (AA), chronic aquatic toxicity (CA) and acute foliar invertebrates toxicity (AFI[1]))

A data gap (DG) exists for respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), clothianidin meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gap. In a worst-case scenario, if clothianidin were assigned a High score for the data gap SnR*, it would still be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
As a standard approach for GreenScreen® evaluations, all exposure routes (oral, dermal and inhalation) were evaluated together, so the GreenScreen® Benchmark Score of 1 ("Avoid-Chemical of High Concern") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Clothianidin

Group I Human					Group II and II* Human									Ecotox				Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	ATV	AFI	P	B	Rx	F
						single	repeated*	single	repeated*												
M	**L**	**M**	**M**	*M*	**M**	**H**	**M**	**vH**	*H*	**L**	DG	**L**	**L**	**vH**	**vH**	**M**	**H**	*vH*	**vL**	*L*	*L*

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

[1] Because the maximum score for acute foliar invertebrates and pollinators toxicity per DfE criteria is a High, a score of High was considered equivalent to a Very High for this endpoint for benchmarking purposes

GreenScreen® Assessment for Clothianidin (CAS# 210880-92-5)

Method Version: GreenScreen® Version 1.2[2]
Assessment Type[3]: Certified

Chemical Name: Clothianidin

CAS Number: 210880-92-5

GreenScreen® Assessment Prepared By:
Name: Mouna Zachary, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: September 27 , 2015 (revised December 7, 2015, January 5, 2016)
Assessor Type: Licensed GreenScreen® Profiler

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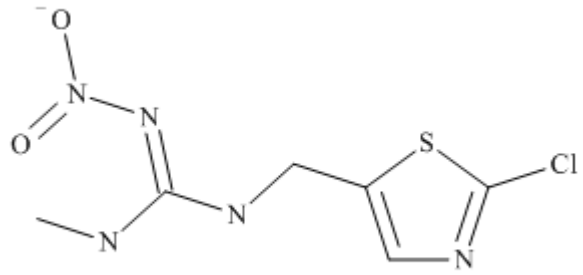
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 13, 2015 (revised December 11, 2015, January 7, 2016)

Confirm application of the *de minimus* rule[4]: N/A

Chemical Structure(s):



Clothianidin (CAS# 210880-92-5)

Also called: CCRIS 9264; Celero; Clothianidin; Pancho; Poncho 600;TI 435, UNII-V9906ABKQ

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
No surrogates were used as clothianidin has a relatively complete toxicological dataset.

Identify Applications/Functional Uses: (U.S. EPA 2003, SCP 2007)
1. Insecticide
2. Wood preservative

[2] Use GreenScreen® Assessment Procedure (Guidance) V1.2
[3] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent) or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen® Verification Program)
[4] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

GreenScreen® Summary Rating for Clothianidin[5]: Clothianidin was assigned a **GreenScreen Benchmark™ Score of 1** ("Avoid – Chemicals of High Concern") (CPA 2014). This score is based on the following hazard score:

- Benchmark **1c**
  - vPT = Very High Persistence (P) + Very High Ecotoxicity (acute aquatic toxicity (AA), chronic aquatic toxicity (CA) and acute foliar invertebrates toxicity (AFI[6]))

A data gap (DG) exists for endocrine activity (E) and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), clothianidin meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gap. In a worst-case scenario, if clothianidin were assigned a High score for the data gap SnR*, it would still be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Clothianidin

Group I Human					Group II and II* Human									Ecotox				Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	ATV	AFI	P	B	Rx	F
						single	repeated*	single	repeated*												
M	**L**	**M**	**M**	*M*	**M**	**H**	**M**	**vH**	*H*	**L**	DG	**L**	**L**	**vH**	**vH**	**M**	**H**	*vH*	**vL**	*L*	*L*

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[7]

Clothianidin is not expected to be readily biodegradable and it is considered highly persistent in the environment. Degradation is relatively rapid under anaerobic conditions; however, metabolic degradation occurs very slowly in aerobic soil. Clothianidin is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups. Photolysis is the major route of dissipation if sunlight occurs. It is expected to photodegrade in water with a half-life of less than 1 day. Volatilization from water surfaces is not expected. Expected degradation products are N-methyl-N'-nitroguanidine (MNG), nitroguanidine (NTG); N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine (TZNG); N-(2-chlorothiazole-5-ylmethyl)-N'-methylurea (TZMU) and N-(2-chlorothiazole-5-ylmethyl)-N'-methylguanidine (TMG) (U.S. EPA 2005). The Pharos listings for transformation products are shown in Table 1 below. As none of the transformation products are LT-

[5] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[6] Because the maximum score for acute foliar invertebrates and pollinators toxicity per DfE criteria is a High, a score of High was considered equivalent to a Very High for this endpoint for benchmarking purposes
[7] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

1 chemicals, and the parent chemical clothianidin is a Benchmark 1 chemical, the hazards of the transformation products do not change the score of the parent compound.

Table 1: Transformation Product Summary Table

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS#	Feasible and Relevant?	GreenScreen® List Translator Score or Benchmark Score[8,9]
Intermediate for Agrochemicals	End of Life	Aerobic degradation	N-methyl-N'-nitroguanidine	4245-76-5	Y	Not listed in Pharos
intermediate in the manufacturing of chemicals	End of Life	Aerobic degradation	Nitroguanidine	556-88-7	Y	LT-UNK
Insecticide	End of Life	Aerobic degradation	N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine	NA	Y	Not listed in Pharos
Insecticide	End of Life	Degradation	N-(2-chlorothiazole-5-ylmethyl)-N'-methylurea	NA	Y	Not listed in Pharos
Insecticide	End of Life	Anaerobic degradation	N-(2-chlorothiazole-5-ylmethyl)-N'-methylguanidine	NA	Y	Not listed in Pharos

Introduction

Clothianidin is one of the newest neonicotinoids and a systemic insecticide available as water-soluble powders, wettable powders, granules, and dusts. It is registered for agricultural use on various fruits, vegetables, forage, and grain crops (JMPR 2010, U.S. EPA 2005).

ToxServices assessed clothianidin against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.37 (GreenScreen® Hazard Assessment) (ToxServices 2013).

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012a). Pharos (Pharos 2016) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. It checks all of the lists in the List Translator with the exception of the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b) and these should be checked separately in conjunction with running the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for clothianidin can be found in Appendix C and a summary of the results can be found below:

- Acute Aquatic
    - EC - CLP/GHS Hazard Statements - H400 - Aquatic Acute 1 - Very toxic to aquatic life / M-Factor of 10
    - EC - Risk Phrases - R50: Very toxic to aquatic organisms.

[8] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2016) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[9] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

- Chronic Aquatic
    - EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects
    - EC - Risk Phrases - R53: May cause long-term adverse effects in the aquatic environment.
- Mammalian
    - EC - Risk Phrases - R22: Harmful if swallowed.
    - EC - CLP/GHS Hazard Statements - H302 Harmful if swallowed

Clothianidin is not listed by DOT.

Physicochemical Properties of Clothianidin

Clothianidin is a clear, colorless powder at room temperature and is moderately soluble in water. Its vapor pressure indicates that it will exist mostly in the solid phase at room temperature and its measured partition coefficient of 1.12 indicates a low potential for bioaccumulation.

Table 2: Physical and Chemical Properties of Clothianidin (CAS# 210880-92-5)

Property	Value	Reference
Molecular formula	$C_6H_8ClN_5O_2S$	ChemIDplus 2016
SMILES Notation	CN/C(=N\N(=O)[O-])/NCc1cnc(s1)Cl	ChemIDplus 2016
Molecular weight	249.7	U.S. EPA 2005
Physical state	Solid	U.S. EPA 2005
Appearance	Clear, colorless powder	U.S. EPA 2005
Melting point	176.8°C	U.S. EPA 2005
Vapor pressure	3.8×10^{-11} Pa (at 20°C)	U.S. EPA 2005
Water solubility	0.327g/L (at 20°C)	U.S. EPA 2005
Dissociation constant	pKa = 11.09 (at 20°C)	HSDB 2005
Density/specific gravity	1.61 g/mL (at 20°C), 1.59 g/cm^3	U.S. EPA 2005
Partition coefficient	K_{ow} = 1.12 (at pH 7) K_{ow} = 0.7 (at 25°C)	U.S. EPA 2005

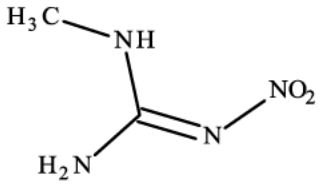
Toxicokinetics

- JMPR 2010
    - The toxicokinetic behavior of clothianidin was examined in a study conducted according the test method B.36 of European Commission directive 87/302/EEC using rats. Clothianidin was rapidly and almost completely absorbed (89-95%) from the gastrointestinal tract within 24 hours after an oral dose in the rats. The rate and extent of absorption were not influenced by sex, dose or dose rate. Clothianidin was widely distributed up to 72 hours with tissue residues slightly higher in liver and kidney. There was no potential for accumulation. Clothianidin and its metabolites were rapidly excreted with 89–95% of the compound found in urine after 24h and less than 7% was excreted in feces. Clothianidin is poorly metabolized in rats with 56–74% of the dose being excreted unchanged over 72 hours. The main metabolic pathways were oxidative demethylation and cleavage of the nitrogen–carbon bond between the thiazolyl-methyl position and the nitroimino moiety. The main metabolites identified in the urine were N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine (TZNG) (7-11%), N-methyl-N'-nitroguanidine (MNG) (8-13%), and nitroguanidine (NTG) (1-4%). The main fecal metabolites were N-(2-chlorothiazole-5-ylmethyl)-N'-methylguanidine (TMG) (2%) and 2-(methylthio)-thiazole-5-carboxylic acid (MTCA) (9%). Other metabolites such

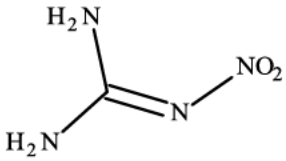
as N-(2-chlorothiazole-5-ylmethyl)-N'-methylurea (TZMU), 2-chlorothiazole-5-ylmethelurea (TZU), and methylguanidine (MG) were detected in the urine at less than 2% of administered dose. The structures of the urinary and fecal metabolites are shown below.

- The toxicokinetic behavior of clothianidin was also examined in plants and in farm animals such as goat and hen. These studies showed that similar degradation pathways to those found in the rat were seen in farm animals with absorption rate being somewhat lower and that plant metabolism was less extensive. Similarly, the major metabolites identified in farm animals and plants (> 5% of the TRR), were structurally related to rat metabolites and were of lower toxicity.

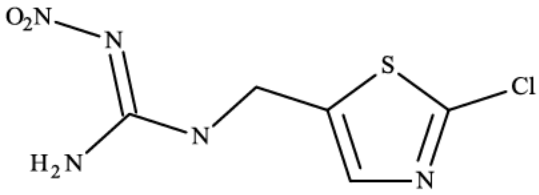
Chemical structures for major metabolites of clothianidin



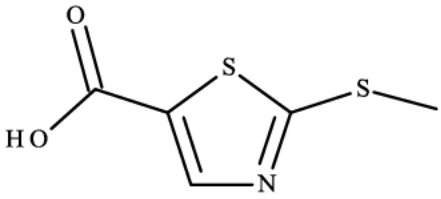
MNG



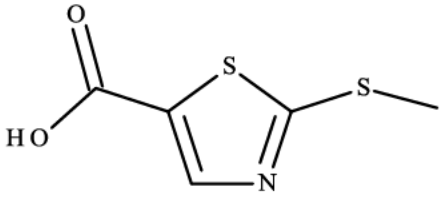
NTG



TZNG



MTCA



TMG

Hazard Classification Summary Section:

<u>Group I Human Health Effects (Group I Human)</u>

Carcinogenicity (C) Score (H, M, or L): M

Clothianidin was assigned a score of Moderate for carcinogenicity based on ToxServices classifying it as a GHS Category 2 carcinogen supported by long term carcinogenicity studies in rats and mice. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited or marginal evidence of carcinogenicity in animals and when they are classified to GHS

Category 2 (CPA 2012b). The confidence in the score was high as it was based on data from well-conducted studies.

- Authoritative and Screening Lists
    - *Authoritative:* not listed on any authoritative lists
    - *Screening:* not listed on any screening lists
- JMPR 2010
    - In a GLP-compliant combined chronic toxicity/carcinogenicity study conducted according to OECD Guideline 453, Sprague-Dawley rats (80/sex/group) were fed a diet containing clothianidin (purity 95.2-95.5%) at concentrations of 0, 150, 500,1,500 and 3,000 ppm for 103 weeks (equivalent to 0, 8.1, 27.4, 82.0 and 157 mg/kg/day for males and 0, 9.7, 32.5, 97.8 and 193 mg/kg/day for females as calculated by study authors). The survival rate of top-dose animals was better than that of controls. The most common unscheduled causes of death were pituitary neoplasms and mammary gland carcinoma, though these were not related to dosage. Decreases in feed consumption were seen in males at 1,500 ppm and in females at 500 ppm. Similarly, decreases in body weight, and body weight gain were observed primarily in weeks 1-53 in both sexes at 1,500 ppm and above. At the highest dose, there was clear histological evidence of local effects in the glandular stomach. Hepatocellular carcinomas in males were found at 500 ppm (one at termination, two in unscheduled deaths) and at 3,000 ppm (four in unscheduled deaths), though the low incidence rate and absence of a dose-effect relationship led study authors to conclude that the tumors were unlikely to be related to test substance administration. There was a slight increase in the incidence of thymus hyperplasia in females but it was likely not biologically significant because the increase could be attributed to the increased survivability of treated animals. An increase in thyroid C-cell adenoma was observed in females at 1,500 and 3,000 ppm when compared with controls. Combined adenoma and carcinoma incidence showed an increase in females at 1,500 ppm but not at the top dose. Since the top dose was not statistically significant when compared with the controls and since there was not a linear dose-effect relationship, study authors concluded that these neoplasms were not considered to be related to treatment. Statistically significant increases in interstitial hyperplasia of the ovaries were found in females at 500 ppm and above, though these incidences were attributed to the normal aging process. Study authors concluded that clothianidin was not carcinogenic in these experimental conditions. A NOAEL for chronic toxicity of 150 ppm (equivalent to 9.7 and 8.1 mg/kg/day in females and males, respectively) and a LOAEL of 500 pm (32.5 and 27.4 mg/kg/day in females and males, respectively), were established based on decreased feed consumption and body weight effects.
    - In a GLP-compliant chronic toxicity study conducted similar to OECD Guideline 451, Crl: CD-1 mice (50/sex/group) were fed a diet containing clothianidin (purity 95.2-95.5%) at concentrations of 0, 100, 350, 1,250, 2,000 ppm (males) and 1800 ppm (females) for 18 months. The doses are equivalent to 0, 13.5, 47.2, 171.4 and 251.9 mg/kg/day for males and 0, 17.0, 65.1, 215.9 and 281.1 mg/kg/day for females as calculated by study authors. The 2,000 ppm dose started as a 700 ppm dose but was increased to 2,000 ppm during week 5 in order to ensure exposure to an MTD. Treatment-related mortalities were seen in males and females at 1,250 ppm. The main cause of death was malignant lymphoma and amyloidosis. Body weights and body weight gains also significantly decreased at 1,250 ppm and above in both sexes. Organ weight reductions were seen in the heart of males at 350 ppm and above and in the kidneys of males at 100 ppm and above. However, in the kidney, no related histological

findings were observed. In the heart, myocardial degeneration was observed. An increase in fibromuscular hyperplasia of the cervix was seen in females at 1,250 and 1,800 ppm groups. Although these cervical lesions are common in nulliparous ageing females, study authors considered these effects as related to clothianidin treatment. No evidence of any treatment-related tumors was reported under the test condition. Study authors concluded that clothianidin was not carcinogenic under those experimental conditions. A NOAEL for systemic toxicity of 350 ppm (equivalent to 47.2 mg/kg day for females), and the LOAEL of 1,250 ppm, (equivalent to 171.4 mg/kg/day for females) were established by study authors based on body weight effects, clinical signs, and heart and cervical lesions. However, ToxServices noted that heart lesions were also seen in males at 350 ppm, therefore ToxServices assigned a NOAEL of 100 ppm and a LOAEL of 350 ppm instead for males based on the heart lesions (equivalent to 13.5 and 47.2 mg/kg/day, respectively).

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Moderate was assigned. Long term carcinogenicity studies of clothianidin were conducted in mice and rats. In rats, several types of tumors (pituitary neoplasms and mammary gland carcinoma at unspecified doses, hepatocellular carcinomas seen at 500 and 3,000 ppm, thymus hyperplasia at unspecified doses, thyroid C-cell adenoma in females at 1,500 and 3,000 ppm and interstitial hyperplasia of the ovaries at 500 ppm and high doses) were seen. However, these incidences were considered by the study authors as not related to the clothianidin treatment due to lack of dose-response relationship or due to normal ageing. Of these tumors, only hepatocellular carcinomas are malignant neoplasms. It is not clear if the other lesions would progress to malignant neoplasms. The combined incidences of adenomas and carcinomas for all neoplasms reached statistical significance only at 1,500 ppm in females. In the 18-month carcinogenicity study in mice with dietary concentrations of up to 2,000 ppm, death occurred in males and females at 1,250 ppm. The main cause of death was malignant lymphoma and amyloidosis. In addition, increased incidences of fibromuscular hyperplasia of the cervix were seen in treated females at 1,250 and 1,800 ppm. Although these cervical lesions are common in nulliparous ageing females, study authors could not rule out these effects to be related to clothianidin treatment as there was a dose-response relationship. Based on limited evidence of carcinogenicity (non-dose related increased incidences of mostly non-malignant tumors), ToxServices conservatively classified clothianidin to GHS Category 2. GHS Category 2 carcinogens are defined as having limited or marginal evidence of carcinogenicity in animals (UN 2013).

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

Clothianidin was assigned a score of Low for mutagenicity/genotoxicity based on negative *in vitro* and *in vivo* genotoxicity/mutagenicity tests. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012b). Confidence in the score is high because it is based on experimental data from well-conducted studies.

- Authoritative and Screening Lists
    - *Authoritative:* not listed on any authoritative lists
    - *Screening:* not listed on any screening lists

- JMRP 2010
    - *In vitro*: Negative results for mutagenicity were obtained in several gene mutation assays conducted according to European Commission directive 2000/32/EEC or OECD Guideline 471. In these tests, *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* tester strain *WP2 uvr A* were exposed to clothianidin (purity >95%) in dimethyl sulfoxide (DMSO) at concentrations up to 5,000 µg/plate for 48 hours, with and without metabolic activation. No increase in the mutation frequency was observed in the presence or absence of metabolic activation. In one study, clothianidin was weakly positive at the limit dose of 5,000 µg/plate in *S. typhimurium* strain TA1535 with metabolic activation
    - *In vitro*: Negative results for mutagenicity were obtained in a mammalian cell mutation assays conducted according to OECD Guideline 476. Mouse lymphoma L5178Y cells were exposed to the test material (90% purity) in DMSO at 1,600-2,000 µg/ml, with and without metabolic activation. No increase in the mutation frequency was observed in the presence or absence of metabolic activation at concertation below cytotoxicity.
    - *In vitro*: Negative results for mutagenicity were obtained in another three mammalian cell mutation assays conducted according to OECD Guideline 476. In these assays, Chinese hamster V79 cell lines were exposed to the test material (purity > 95%) %) in DMSO at concentrations up to 2,500 µg/plate, with and without metabolic activation. No increase in the mutation frequency was observed in the presence or absence of metabolic activation.
    - *In vitro*: Negative results for clastogenicity were obtained in a chromosome aberration test conducted according to OECD Guideline 473. Chinese hamster lung cells were exposed to the test material (90% purity) in DMSO at concentrations up to 1,875 µg/ml, with and without metabolic activation. No increase in the incidence of polyploidy was observed at any dose level in any of the exposure groups. However, an increase of cells with aberrations was seen in cells treated at near-cytotoxic or cytotoxic doses, for both short and long treatment periods.
    - *In vitro*: In another chromosome aberration test conducted according to OECD Guideline 473 using Chinese hamster V79 cell lines, clothianidin was clastogenic in the absence of metabolic activation .
    - In a third chromosome aberration test conducted according to OECD Guideline 473 using Chinese hamster V79 cell lines, clothianidin was not clastogenic in the absence and presence of metabolic activation at concertation up to 1,500 µg/ml.
    - *In vivo*: Clothianidin was tested in an *in vivo* micronucleus test conducted according to OECD Guideline 474. CD-1 mice (5/sex/dose) were administered the test material in in arachis oil by oral gavage at the concentration of 0, 25, 50 and 100 mg/kg. There were no increases in the frequencies of micronucleated normochromatic erythrocytes reported from the bone marrow smears. No significant changes in the percentages of polychromatic erythrocytes were observed.
    - *In vivo*: In another two *in vivo* micronucleus tests conducted according to OECD Guideline 474. NMRI mice (12/sex/high dose or 6/sex/other doses) were administered clothianidin dissolved in 0.5% w/v Cremophor at a dose level of 75, 150 or 300 mg/kg by intraperitoneal injection. There were no increases in the frequencies of micronucleated normochromatic erythrocytes reported from the bone marrow smears. No significant changes in the percentages of polychromatic erythrocytes were observed. Clothianidin was not clastogenic under these experimental conditions.

- *In vivo*: In a DNA damage and repair test conducted according to OECD Guideline 486, a single oral dose of clothianidin (purity 99.8%) at 2,000 mg/kg was given to male Wistar rats via gavage. No unscheduled DNA synthesis was found in the liver.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Low was assigned. Although an increase in frequencies of chromosomal aberrations was observed in two *in vitro* chromosomal aberration tests using CHL/V79 cells at cytotoxic concentrations, clothianidin did not show evidence of clastogenicity in other two *in vivo* mouse micronucleus assays or in an *in vivo* UDS assay. In addition, clothianidin was not mutagenic in several bacteria and mammalian tests with Chinese hamster V79 cells. Based on this, clothianidin is not likely to be genotoxic.

Reproductive Toxicity (R) Score (H, M, or L): M

Clothianidin was assigned a score of Moderate for reproductive toxicity based on ToxServices classifying it as a GHS Category 2 reproductive toxicant supported by a two-generation toxicity study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when they having limited or marginal evidence of reproductive toxicity in animals and when they are classified to GHS Category 2 (CPA 2012b). The confidence in the score is high because it is based on well conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- JMPR 2010
  - In a one-generation dose range-finding study conducted similar to OECD Guideline 416, Sprague-Dawley rats (20/sex/dose) were administered clothianidin in the diet at concentrations of 50, 100, 500, or 1,000 ppm (equivalent to 0, 2.9, 5.8, 29.1 and 58.9 mg/kg/day for males and 0, 3.4, 6.6, 34.2 and 68.6 mg/kg/day (premating period) and 0, 3.4, 6.4, 34.4 and 69.1 mg/kg/day (gestation period) for females as calculated by study authors) for 8 weeks before mating, during gestation, and through day 21 of lactation. No indications of toxicity other than minimal decreases in body weight were detected in parental animals. No abnormalities were detected in the litters. Based on this, the study authors identified a NOAEL of 1,000 ppm, which was the highest dose tested.
  - In a two-generation reproduction study conducted similar to test method B.35 of the European Commission directive 92/69/EEC, Sprague-Dawley rats (30/sex/group) were exposed to clothianidin (purity 95.2-96.0%) in the diet at concentrations of 150, 500, or 2,500 ppm (equivalent to 0, 10.2, 32.7 and 179.6 mg/kg/day for males and 0, 11.8, 37.9 and 212.9 mg/kg/day for females as calculated by study authors). Parental animals were treated 10 weeks prior to mating, then throughout mating, gestation and lactation, for a total of about 16/20 weeks. Dams were continuously exposed through gestation and lactation, treatment continued in F1 offspring for a total of about 20/24 weeks. Significant body weight decreases were observed in both adult males and females of the F_0 and F_1 generations at the 2,500 ppm dose. Similarly, absolute and relative organ weights were decreased in animals at this dose group. There were no necropsy or histological findings and no difference in number or duration of estrous cycles between treated and control animal in both F_0 and F_1 generations. A statistically significant increase in number of early stillborn deaths was seen in 2,500 ppm in F1 pups and in F2 pups at 500 and 2,500 ppm. However this apparent increase in stillbirths was not

considered by study authors to be toxicologically significant. In F_1 pups, preputial separation was delayed at 500 ppm and above in a dose-dependent trend and vaginal opening was delayed at the 2,500 ppm dose, in parallel with a body weight decrease of 13%. Total sperm count was slightly affected at the top dose compared with controls, but the differences were not statistically significant. At 2,500 ppm, the proportion of motile sperm in F_2 males and the progressive motility of sperm in both F_1 and F_2 generations were decreased. No effects were seen at lower doses. Study authors concluded that clothianidin showed no toxicity to reproduction under the experimental conditions. A NOAEL for parental and offspring toxicity was 150 ppm (equivalent to 32.7 mg/kg/day) based on decreased body weight in parental and offspring animals and on subsequent effect on preputial separation at 500 ppm in offspring. The NOAEL for reproductive toxicity was 2,500 ppm (equivalent to 179.6 mg/kg/day), which was the highest dose tested. However in the U.S EPA report, a NOAEL of 500 ppm for reproductive toxicity was established for the same study based on decreased sperm motility and increased number of sperm with detached head.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Moderate was assigned. In a two-generation reproduction study performed with rats, decreased sperm motility, and increased number of sperm with detached heads were seen in both generations (F1 and F2 litters). These changes were considered by study authors as not statistically significant and it was concluded that clothianidin is not a reproductive toxicant under the experimental conditions. However, the U.S. EPA stated that although these effects did not reduce rat fertility, they do raise an uncertainty as to possible reproductive effects to other species that may have a less frequent reproductive capability as small mammals may feed on fruit and thus, be subject to repeated or continuous exposure to the pesticide. In addition, although the study authors did not consider the increased incidences of early stillborn deaths at 2,500 ppm in F1 pups and at 500 and 2,500 ppm in F2 pups toxicologically significant, ToxServices found insufficient evidence to rule out as toxicologically insignificant. Therefore, based on effects on sperm parameters and early stillbirth rates, ToxServices classified clothianidin as a GHS Category 2 reproductive toxicant. GHS Category 2 reproductive toxicants are defined as having limited or marginal evidence of reproductive toxicity in animals (UN 2013).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): M
Clothianidin was assigned a score of Moderate for developmental toxicity based on the effects on the development of coordinated movement, swimming and olfactory orientation, sense equilibrium, and/or muscular power in several developmental neurotoxicity studies using rats and mice. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity (CPA 2012b). Confidence in the score is high because it is based on experimental data from well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- JMPR 2010
  - In a developmental toxicity study, mated female Sprague-Dawley rats (8/group) were administered clothianidin (purity 96%) by gavage at concentrations of 0, 125, 250, 500, or 1,000 mg/kg/day. At 1,000 mg/kg/day, all animals were found dead or killed

moribund. Clinical signs of toxicity were seen at 250 mg/kg and above, and included localized alopecia, scant feces, and red perivaginal substance. At 500 mg/kg and above, piloerection, tremors, hypoactivity, emaciation, ptosis, coldness to touch, and dehydration were also observed. At all doses, body weight, body weight gain, and feed consumption were decreased compared to control animals. Adverse effects in fetuses occurred at 250 mg/kg and above. Fetal external abnormalities at that dose included short snout, bilateral flexed fore- and hind limbs, exencephaly, gastroschisis, bilateral eye bulge depression, and short trunk. At 500 mg/kg, findings included anasarca, short trunk, and short tail. The maximum tolerated dose (MTD) was considered to be 125 mg/kg as no NOAEL was observed.

- In a prenatal developmental toxicity study conducted according to the OECD Guideline 414, pregnant female Sprague-Dawley rats (25/dose) were administered clothianidin (purity 95.2%) by gavage at concentrations of 0, 10, 40, or 125 mg/kg/day on gestation days 6-19. No deaths or relevant clinical signs occurred. A decrease in body weight was observed in the 40 and 125 mg/kg group during days 6-9. Caesarean section observation revealed no remarkable differences in treated and control animals. Fetal alterations and abnormalities occurred at similar incidences in litters of all dose groups, were comparable with recent historical controls, or showed no dose-dependent relationship. Study authors concluded that clothianidin was not a developmental toxicant under the conditions of the experiment. A maternal NOAEL was 10 mg/kg/day based on decreased feed consumption and body weight effects at 40 mg/kg/day. The developmental and fetal NOAEL was identified as 125 mg/kg/day; which was the highest dose tested.
- In another prenatal developmental toxicity study conducted according to the OECD Guideline 414, pregnant female New Zealand White rabbits (23/dose) were administered clothianidin (purity 95.2%) by gavage at concentrations of 0, 10, 25, 75, or 100 mg/kg/day on days 6-28 after mating. Three animals in the higher two doses died before scheduled sacrifice. Decreased fecal output and orange/red urine were observed at 25 mg/kg/day and above. There were no relevant necropsy findings. Feed consumption was significantly decreased at 75 mg/kg/day and above. Reductions in uterine weight at 75 mg/kg/day and above were considered biologically significant. Increased post-implantation loss, reduced fetal body weight, and retarded sternal ossification were observed at the 100 mg/kg/day level and considered related to treatment. Other alterations, such as fused caudal vertebrae and absent hind paw phalanges, were present but considered unrelated to treatment and not statistically significant. The maternal NOAEL was 10 mg/kg/day based on the clinical signs seen at 25 mg/kg/day. The developmental NOAEL was 75 mg/kg/day based on increased resorption, reduced fetal body weight, and retarded sternal ossification at 100 mg/kg/day.
- In a developmental neurotoxicity study conducted according to OECD Guideline 426, clothianidin (purity 95.5–95.9 %) was administered to female Crl:CD®(SD)IGS BR VAF/Plus® rats (25/dose) via corn oil in the diet at concentrations of 0, 150, 500 or 1,750 ppm from gestation day 0 through postnatal day 21, when pups were weaned. Average daily intake of clothianidin was 0, 12.9, 42.9 and 142.0 mg/kg/day during gestation and 0, 27.3, 90.0 and 299.0 mg/kg/day during lactation period. Maternal animals were checked daily for changes in clinical signs and mortality. On postnatal day 4, offspring were culled to yield four females and four males and were observed for clinical observations, assessment of motor activity, auditory startle response, habituation, learning and memory, and ophthalmology. Pup physical development was assessed by bodyweight, surface righting auditory startle, eye opening, pupillary constriction, vaginal patency in females, and balanopreputial separation in males. The FOB tests were

conducted between days 4 and 60. Neural tissues were collected from 10/sex/dose of offspring on postnatal day 11 and termination of the study (75 days of age) for evaluation. No maternal deaths or treatment-related clinical signs were observed for the duration of the study. The only treatment-related effects noted was changes in body weight of the dams and pups at the high dose (1,750 ppm). Food consumption decreased for dams in the high dose group (1,750 ppm) during the third week of gestation and first week of lactation. There were no treatment-related effects on the number of litters, liver litter size, number of stillborn pups, live birth index, or viability index. Study authors identified a NOAEL for fetal and maternal toxicity of 500 ppm (equivalent to 42.9 mg/kg/day), based on changes in body weight at higher doses. With regard to the neurobehavioral effects, subtle modification of acoustic startle habituation and motor activity were observed in the pups at the high dose immediately after weaning. However these were considered as secondary to nonspecific toxicity. No biologically significant effects on the central nervous system were observed histomorphometrically or histologically. Based on this the study authors identified the developmental neurotoxicity NOAEL of 1,750 ppm (equivalent to 142 mg/kg/day), the highest dose tested.

- Tanaka 2012a
    - In a developmental neurotoxicity study conducted according to OECD Guideline 426, mated female Crlj: CD1 mice (10/dose) were administered 0.002%, 0.006% and 0.018% clothianidin (purity >99%) in diet during gestation and lactation periods. Animals were evaluated for body weight and food intake. Offspring were evaluated for survival, number and sex of pups and body weight. There were no treatment-related effects on any of the fertility or reproductive indices measured. The average body weight and food intake of dams showed no significant differences between treatments. The average body weight of male and female offspring was increased significantly in a dose related manner during the lactation period. Functional and behavioral developmental parameters were measured and scored for all individual offspring during the lactation period (postnatal days, PNDs) in the F_1 generation and analyzed on score frequencies. Offspring were evaluated for surface righting (PNDs 4 and 7), negative geotaxis (PNDs 4 and 7), cliff avoidance (PND 7), swimming behavior (PNDs 7 and 14), olfactory orientation (PND 14) and exploratory behavior and spontaneous behavior was measured in the animal movement analysis system SCANET CV-40 on distance mode at 3 and 8 weeks of age and 9 and 10 weeks of age. Authors observed significantly accelerated surface righting on PND 7 in low dose (0.002%) females, development of swimming direction on PND 7 in middle dose (0.006%) females, and olfactory orientation on PND 14 in middle dose (0.006%) females. Other variables showed no difference related to treatment in either sex. Movement activity of exploratory behavior at 3 weeks of age showed a significant increase in average speed in males in a dose related manner; at 8 weeks of age a significant decrease in average rearing time was observed in middle dose (0.006%) females. Movement activity of spontaneous behavior in each sex was parallel. No difference in multiple-T water maze performance related to treatment was observed. Authors concluded clothianidin treatment influences development of coordinated movement, swimming development and olfactory orientation. Additionally, clothianidin may affect the central nervous system as the middle dose of clothianidin (0.006%) produced more activities for exploratory and spontaneous behavior. Authors also concluded sensitivity to clothianidin may be sex-dependent in mice. A LOAEL of 0.006 % (equivalent to 9–33 mg/kg/day as calculated by study authors) was established based

on significant adverse effects on exploratory and spontaneous behavior in F1 generation mice.

- Tanaka 2012b
    - In another developmental neurotoxicity study conducted according to OECD Guideline 426, male and female Crlj: CD1 mice (10/sex/dose) were administered 0.003%, 0.006% and 0.012% clothianidin (purity >99%) in the diet from 5 weeks of age of the F_0 generation to through mating, gestation and lactation. There was no adverse effect of clothianidin on litter size, litter weight, or sex ratio at birth. Exploratory behavior was measured in the F_0 generation at 8 weeks of age. At 9 weeks of age, males and females from the same treatment group were paired for 5 days. After birth, one male and one female offspring from each litter were selected to continue treatment. Offspring were weighed every week from 4 weeks to 11 weeks of age after weaning. Functional and behavioral developmental parameters were measured and scored for all individual offspring during the lactation period (postnatal days, PNDs) in the F_1 generation and analyzed on score frequencies. Offspring were evaluated for surface righting (PNDs 4 and 7), negative geotaxis (PNDs 4 and 7), cliff avoidance (PND 7), swimming behavior (PNDs 7 and 14), olfactory orientation (PND 14) and exploratory behavior and spontaneous behavior was measured in the animal movement analysis system SCANET CV-40 on distance mode at 3 and 8 weeks of age and 9 and 10 weeks of age. Additionally, each mouse underwent 3 trials in a Biel-type multiple-T water maze at 7 weeks of age. Movement activity of exploratory behavior (movement time, number of rearing, and rearing time) in F_0 males significantly increased in a dose related manner. Authors observed a delay in the development of swimming head angle at PND 7 in middle dose (0.006%) males and olfactory orientation at PND 14 in middle dose (0.006%) females. Additionally, authors observed significantly accelerated olfactory orientation at PND 14 in middle dose (0.006%) males, surface righting at PND 4 of low dose (0.003%) females, development of swimming head angle at PND 7 in low and middle dose (0.003% and 0.006%) females, and negative geotaxis in low dose (0.003%) females. Other variables showed no difference related to treatment in either sex. Movement activity of exploratory behavior at three weeks of age showed significant increase in the number of rearing in a dose dependent manner in females. Movement activity of exploratory behavior at 8 weeks of age showed significant increase in movement time in a dose dependent manner in males and significant decrease in average rearing time in middle dose (0.006%) males. Movement activity of spontaneous behavior in each sex was parallel, except for movement time of females. No difference in multiple-T water maze performance related to treatment was observed. Authors concluded clothianidin treatment influences development of the sense equilibrium, development of coordinated movement, and muscular power. Additionally, clothianidin treatment slightly accelerated behavioral development of offspring during the early lactation period, and may affect the central nervous system as the middle dose of clothianidin (0.006%) produced more activities for exploratory and spontaneous behavior. Authors also concluded sensitivity to clothianidin may be sex dependent in mice. No NOAEL or LOAEL was established in this study.
- Ozdemir et al. 2014
    - In a developmental neurotoxicity study, the effects of clothianidin on learning and memory in infant and adult male rats and the expression of related genes in the hippocampus was investigated. To study effects on juvenile rat models pregnant albino Wistar female rats were divided into four groups and their male offspring (4/dose) were

administered 0, 2, 8, and 24 mg/kg of clothianidin (purity not reported; water vehicle) by gavage starting on the seventh day, for 90 days. Rats were evaluated for learning performance in a Morris water maze with a probe trail, and visual acuity and motor function test. Rats were sacrificed after tests and the brain was immediately removed for evaluation of the hippocampus and cortex. Authors studied gene expressions of GRIN1, M1, SYP and GAP-43 using real time PCR. Authors observed similar cognitive performance in treated infants compared to controls, and inconsistent results were obtained in latency times. In the probe trial, authors observed a significant difference in performance between infants treated with 24 mg/kg and controls. No changes in GRIN1, SYP, GAP-43 or M1 expression were observed between treated animals and controls. Authors concluded clothianidin it causes a small decrease in infant rats under the conditions of this study.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Moderate was assigned. Clothianidin showed no teratogenicity after administration on days 6 to 19 of gestation in rats and the NOAELs were 10 mg/kg/day for maternal toxicity and 125 mg/kg/day for developmental toxicity, which was the highest dose tested. In a rabbit developmental toxicity study, fetal and developmental toxicity (increased post implantation loss, reduced fetal body weight and retarded sternal ossification) occurred only at maternally toxic doses. The maternal and developmental NOAELs were 10 and 75 mg/kg/day respectively. However, clothianidin influenced the development of coordinated movement, swimming and olfactory orientation, sense equilibrium, and/or muscular power in several developmental neurotoxicity studies using rats and mice. The significance of these effects was not clear. Therefore, ToxServices considered these results as limited evidence of developmental toxicity, and assigned a Moderate score.

Endocrine Activity (E) Score (H, M, or L): *M*
Clothianidin was assigned a score of Moderate for endocrine activity based on limited, but plausible evidence of endocrine activity in animal studies. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when there is evidence of endocrine activity (CPA 2012b). The confidence in the score is reduced due to limited evidence available.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- WRc 2013
  - The endocrine disruption activity of clothianidin was evaluated. Increased ovary/uterus weight was observed in a 90-day oral toxicity study in rats but not in other studies. Interstitial ovarian gland hyperplasia was reported in a 2-year oral study in rats, and cervix hyperplasia was observed in a 2-year oral study in mice. Delayed preputial separation/vaginal opening, decreased sperm motility, morphological effects on sperm, and increased number of stillborns were observed in a 2-generation reproduction study in rats via oral exposure. These suggest endocrine disruption, but the effects were only observed at high doses with other systemic toxicities. Some authors suggested that the

observed adverse effects were secondary to generalized toxicity that could be attributed to induction of aromatase activity. However, this could not be proven. It was concluded that there is insufficient information to conclude that clothianidin is more or less likely to be an endocrine disruptor, while this possibility cannot be ruled out, either.

- Based on the plausible, but limited evidence of an endocrine disruption mechanism of action, ToxServices assigned a score of Moderate for this endpoint. The confidence in the score was reduced due to the limited data available.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M, or L): M

Clothianidin was assigned a score of Moderate for acute toxicity based on its measured oral LD_{50} values of 389-465 in mice and on being associated with EU Hazard statement of H302. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when oral LD_{50} values are between 300 and 2,000 mg/kg and when they are associated with EU hazard statement of H302 (CPA 2012b). Confidence in the score is high because it is based on experimental data from well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* EC - Risk Phrases - R22: Harmful if swallowed.
  - *Authoritative:* EC - CLP/GHS Hazard Statements - H302 Harmful if swallowed
  - *Screening:* not listed on any screening lists
- Cal EPA 2005, JMPR 2010
  - *Oral*: LD_{50} = 5,000 mg/kg (rats)
  - *Oral*: LD_{50} = 389-465 mg/kg (mice)
- U.S. EPA 2003, JMPR 2010
  - *Inhalation*: LC_{50} > 6.14 mg/L (rats)
  - *Dermal*: LD_{50} >5,000 mg/kg (rats)
- JMPR 2010
  - *Inhalation*: LC_{50} > 5.58 mg/L (rats)
  - *Dermal*: LD_{50} >2,000 mg/kg (rats)

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

***Group II Score (single dose)* (vH, H, M, or L): H**

Clothianidin was assigned a score of High for systemic toxicity (single dose) based on its acute oral LOAELs in mice and rats being between 300-2,000 mg/kg. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (single dose) when evidence of systemic toxicity is seen between the guidance values of 300-2,000 mg/kg in an acute oral toxicity study and when they are classified to GHS Category 2 (CPA 2012b). Confidence in the score is high because it is based on experimental data from well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists

- Marfo et al. 2015
    - A prevalence case-control study was performed to examine the relationship between urinary neonicotinoid pesticides (and their metabolites) levels and typical symptoms of neonicotinoid pesticides poisoning. Spot urine samples were obtained from 35 symptomatic patients (unknown causes) and 50 non-symptomatic volunteers. The study authors considered typical symptoms of neonicotinoid pesticides as recent memory loss, finger tremor, and at least five of the six symptoms below: headache, general fatigue, palpitation/chest pain, abdominal pain, muscle pain/weakness/spasm, and cough (TSG, n = 19, age 5 - 69). Symptoms other than these were considered atypical symptoms (ASG, n = 16, age 5 – 78). Urine samples were analyzed using liquid chromatography-tandem mass spectrometry. Urine clothianidin was among the chemicals examined, and it was detected in none of the patients in TSG, 6.3% of the patients in ASG (1 of 16, not quantified), and in 2.0% of the volunteers in the NSG (1 of 50, 1.6 ppb). There was no statistical significance regarding the frequency of detection among three groups.
- JMPR 2010
    - *Oral*
        - In an acute oral toxicity study conducted according to OECD Guideline 401, (CRL:CD®1(ICR)BR) rats (5/sex/dose) were administered clothianidin in aqueous gum arabic at single doses of 1,758, 2,283, 2,965, 3,850 or 5,000 mg/kg by oral gavage followed by a 14-day observation period. A single female rat treated with a dose of 2,965, 3,850 and 5,000 mg/kg and one male at a dose of 5,000 mg/kg died. Clinical signs of toxicity, including palpebral closure, decreased activity, tremor, hunched posture, and hair loss were observed at all doses. After 2 weeks, recovery from all clinical signs except hair loss was considered to have occurred at lower dose levels. Males and females at all doses had also reduced body weight or body weight gain with effects being more pronounced in the females. An oral LD_{50} of 5,000 mg/kg was identified in this study. ToxServices identified the LOAEL at 1,758 mg/kg for this study based on clinical signs of toxicity and a decrease in body weight. *The LOAEL of 1,758 mg/kg is within the GHS guidance values for Category 2 of 300-2,000 mg/kg for systemic toxicity (single exposure). Therefore clothianidin is classified to GHS Category 2.*
        - In another acute oral toxicity study conducted according to test method B.1 of European Commission directive 92/69/EEC, Fischer 344 rats (5/sex/dose) were administered clothianidin in aqueous methylcellulose at single doses of 290, 523 and 1,216 mg/kg by oral gavage followed by a 14-day observation period. Treatment-related clinical signs of toxicity were seen at dose level of 523 mg/kg and above. These included tremors, locomotor incoordination, hypoactivity, oral clear/red/brown stain and lacrimation. Animals continued to exhibit these signs 24 hours after treatment, with incomplete recovery at 72 hours. Decreases in body weights and body weight gains were seen in males and females at 500 mg/kg and above. The acute oral LD_{50} of 1,216 – 2,000 mg/kg for males and between 523 and 1216 mg/kg for females were identified in this study. ToxServices identified the NOAEL at 290 mg/kg for this study based on clinical signs of toxicity and a decrease in body weight. *The LOAEL of 523 mg/kg is within the GHS guidance values for Category 2 of 300-2,000 mg/kg for systemic toxicity (single exposure). Therefore clothianidin is classified to GHS Category 2.*

- In an acute oral toxicity study conducted according to OECD Guideline 401, (CRL:CD®1(ICR)BR) mice (5/sex/dose) were administered clothianidin in aqueous gum Arabic at single doses of 304, 380, 475, 594 or 742 mg/kg by oral gavage followed by a 14-day observation period. Death occurred in treated animals form both sexes at dose of 380 mg/kg and above. Clinical signs of toxicity were seen in these animals and included palpebral closure, decreased activity, ataxia and tremor. Lethargy and respiratory impairment were seen in mice at 594 mg/kg and above. No noticeable macroscopic abnormality was noted during necropsy. The oral LD_{50} of 389 mg/kg in males and 465 mg/kg in females were identified in this study. ToxServices identified the NOAEL at 304 mg/kg for this study based on clinical signs of toxicity. *Both the NOAEL of 304mg/kg and the LOAEL of 380 mg/kg are within the GHS guidance values for Category 2 of 300-2,000 mg/kg for systemic toxicity (single exposure). Therefore clothianidin is classified to GHS Category 2.*

- *Dermal*
  - CRL:CD®BR rats (5/sex) received clothianidin moistened with water on the skin at 2,000 mg/kg according to OECD Guideline 402. No mortality or behavioral abnormality was noted during the test period (up to 14 days post dosing). No erythema or edema was observed. Body weight was not affected by the treatment and no noticeable macroscopic abnormality was noted during necropsy. A dermal LD_{50} of > 2,000 mg/kg in males and females were identified in this study.
- *Inhalation*:
  - In an acute inhalation toxicity study conducted according to the OECD Guideline 436, CRL:CD®BR rats (3/sex/dose) were exposed by head only inhalation to clothianidin dust aerosol with particles size <4 μm at concentration of 5.538 ± 1.954 mg/L (by gravimetry) for 4.5 hours. Animals were then observed for 14 consecutive days. No mortalities were observed. Clinical signs of toxicity were seen in animals between Days 1 and 4 and included hypothermia during exposure; ataxia, ptosis, hunched posture, stained body/eyes/nose and lethargy. By day 5, all animals were entirely free from clinical signs. No abnormalities were found at macroscopic examination of the animals. An inhalation LC_{50} of > 5.538 mg/L air was identified in this study. ToxServices identified the NOAEC at 5.538 mg/L/4.5h for this study based on the lack of significant systemic toxicity or respiratory irritation observed.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of High was assigned. The majority of acute oral and inhalation studies reported evidence of neurological effects, which will be discussed under neurotoxicity (single dose), below. No systemic toxicity was reported upon acute exposure to clothianidin via the dermal and inhalation routes of exposure. However, in acute oral toxicity studies in mice and rats, decreases in body weight along with clinical signs of toxicity were seen in animals exposed to clothianidin. The LOAELs identified for clothianidin in these studies were between the guidance values for Category 2 (300-2,000 mg/kg) as shown above. Therefore clothianidin is classified to GHS Category 2, which corresponds to a score of High.

Group II* Score (repeated dose) **(H, M, or L): M**

Clothianidin was assigned a score of Moderate for systemic toxicity (repeated dose) based on several subchronic and chronic toxicity studies demonstrating effects between 10 and 100 mg/kg/day. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when the oral LOAEL is between 10 and 100 mg/kg/day for studies lasting at least 90 days and when they are classified to GHS Category 2 (CPA 2012b). Confidence in the score is high because it is based on experimental data from well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- JMPR 2010
  - *Oral:*
    - In the previously described combined chronic toxicity/carcinogenicity study conducted according to OECD Guideline 453, Sprague-Dawley rats (80/sex/group) were fed a diet containing clothianidin (purity 95.2-95.5%) at concentrations of 0, 150, 500,1,500 and 3,000 ppm for 103 weeks (equivalent to 0, 8.1, 27.4, 82.0 and 157 mg/kg/day for males and 0, 9.7, 32.5, 97.8 and 193 mg/kg/day for females as calculated by study authors). The survival rate of top-dose animals was better than that of controls. The most common unscheduled causes of death were pituitary neoplasms and mammary gland carcinoma, though these were not related to dosage. Decreases in feed consumption were seen in males at 1,500 ppm and in females at 500 ppm. Similarly, decreases in body weight, and body weight gain were observed primarily in weeks 1-53 in both sexes at 1,500 ppm and above. At the highest dose, there was clear histological evidence of local effects in the glandular stomach. Hepatocellular carcinomas in males were found at 500 ppm (one at termination, two in unscheduled deaths) and at 3,000 ppm (four in unscheduled deaths), though the low incidence rate and absence of a dose-effect relationship led study authors to conclude that the tumors were unlikely to be related to test substance administration. There was a slight increase in the incidence of thymus hyperplasia in females but it was likely not biologically significant because the increase could be attributed to the increased survivability of treated animals. An increase in thyroid C-cell adenoma was observed in females at 1,500 and 3,000 ppm when compared with controls. Combined adenoma and carcinoma incidence showed an increase in females at 1,500 ppm but not at the top dose. Since the top dose was not statistically significant when compared with the controls and since there was not a linear dose-effect relationship, study authors concluded that these neoplasms were not considered to be related to treatment. Statistically significant increases in interstitial hyperplasia of the ovaries in females at 500 ppm and above, though these incidences were attributed to the normal aging process. Study authors concluded that clothianidin was not carcinogenic in these experimental conditions. A NOAEL for chronic toxicity of 150 ppm (equivalent to 9.7 and 8.1 mg/kg/day in females and males) and a LOAEL of 500 pm (32.5 and 27.4 mg/kg/day in females and males), were established based on decreased feed consumption and body weight effects. *The LOAEL of 27.4 mg/kg/day is above the duration-adjusted GHS guideline values for Category 2 of 1.26-12.6 mg/kg/day[10] for 103-week studies. The NOAEL of 8.1 mg/kg/day is below the*

[10] 10 mg/kg/day x 13 weeks/103 weeks = 1.26 mg/kg/day

cutoff of 12.6 mg/kg/day. Therefore, it is impossible to determine if adverse effect would occur at 12.6 mg/kg/day with high confidence. However, clothianidin is at most classified to GHS Category 2.

- In the previously described chronic toxicity study conducted similar to OECD Guideline 451, Crl: CD-1 mice (50/sex/group) were fed a diet containing clothianidin (purity 95.2-95.5%) at concentrations of 0, 100, 350, 1,250, 2,000 ppm (males) and 1800 ppm (females) for 18 months. The doses are equivalent to 0, 13.5, 47.2, 171.4 and 251.9 mg/kg/day for males and 0, 17.0, 65.1, 215.9 and 281.1 mg/kg/day for females as calculated by study authors. The 2,000 ppm dose started as a 700 ppm dose but was increased to 2,000 ppm during week 5 in order to ensure exposure to an MTD. Treatment-related mortalities were seen in males and females at 1,250 ppm. The main cause of death was malignant lymphoma and amyloidosis. Body weights and body weight gains also significantly decreased at 1,250 ppm and above in both sexes. Organ weight reductions were seen in the heart of males at 350 ppm and above and in the kidneys of males at 100 ppm and above. However, in the kidney, no related histological findings were observed. In the heart, myocardial degeneration was observed. An increase in fibromuscular hyperplasia of the cervix was seen in females at 1,250 and 1,800 ppm groups. Although these cervical lesions are common in nulliparous ageing females, study authors considered these effects as related to clothianidin treatment. No evidence of any treatment-related tumors was reported under the test condition. Study authors concluded that clothianidin was not carcinogenic under those experimental conditions. A NOAEL for systemic toxicity of 350 ppm and the LOAEL of 1,250 ppm were established by study authors based on body weight effects, clinical signs, and heart and cervical lesions. However, ToxServices noted that heart lesions were also seen in males at 350 ppm, therefore ToxServices assigned a NOAEL of 100 ppm and a LOAEL of 350 ppm instead for males based on the heart lesions (equivalent to 13.5 and 47.2 mg/kg/day, respectively). *The LOAEL of 47.2 mg/kg/day is above the duration-adjusted GHS guideline values for Category 2 of 1.66-16.6 mg/kg/day[11] for 78-week studies. The NOAEL of 13.5 mg/kg/day is below the cutoff of 16.6 mg/kg/day. Therefore, it is impossible to determine with confidence if adverse effect would occur at 16.6 mg/kg/day. However, clothianidin is at most classified to GHS Category 2.*
- In a repeated dose toxicity study conducted similar to OECD Guideline 407, clothianidin was administered in the diet to four groups of Sprague-Dawley rats (five/sex/group) at concentrations of 1,250, 2,500, 5,000, or 7,500 ppm for 4 weeks (equivalent to 0, 120, 249, 475 and 602 mg/kg/day for males and 0, 137, 228, 454 and 689 mg/kg/day for females as calculated by study authors). No deaths occurred. Clinical signs of toxicity were seen at 5,000 and 7,500 ppm and these included half-closed eyes and occasional hair loss. Body weights, weight gains, feed consumption, and feed efficiency were reduced at 2,500 ppm and above in both males and females. Hematocrit, hemoglobin, and red blood cell counts were increased at 2,500 ppm and above while reticulocytes were decreased at 5,000 ppm and above. White blood cell count in males at 5,000 ppm and above was decreased. Fluctuations in absolute and relative organ weight were detected for multiple organs at doses of 2,500 ppm and above. No

[11] 10 mg/kg/day x 13 weeks/78 weeks = 1.6 mg/kg/day

treatment-related effects on hematology, gross pathology, and histopathology were seen. Study authors identified a NOAEL of 1,250 ppm (equivalent to 120 mg/kg/day) and a LOAEL of 2,500 ppm (equivalent to 249 mg/kg/day) based on effects on feed consumption, body weight, and body weight gain. *Both the LOAEL of 249 mg/kg/day and the NOAEL of 120 mg/kg/day are within the tripled GHS guideline values for Category 2 of 30-300 mg/kg/day for 4-week studies. Therefore clothianidin is classified to GHS Category 2.*

- In another repeated dose toxicity study conducted similar to OECD Guideline 407, clothianidin was administered in the diet to CRL:CD-1®(ICR)BR mice (5/sex/group) at concentrations of 0, 500, 1,000, 2,000 and 4,000 ppm for 4 weeks (equivalent to 0, 90, 190, 383 and 683 mg/kg/day for males and 0, 122, 248, 491 and 619 mg/kg/day for females as calculated by study authors). A treatment-related mortality occurred in four males and all females at 4,000 ppm. Clinical signs of toxicity were seen at 2,000 and 4,000ppm. These included lethargy, tremors, hunched posture, piloerection, emaciation, half-closed eyes, unsteady gait, hypothermia and extremity pallor. Body weights, weight gains, and feed consumption were significantly reduced at 2,000 ppm and above in both males and females. Atrophic changes in ovaries and uterus were seen in females at 2,000 ppm. In males the incidence of atrophic change (testicular atrophy, reduced colloid in prostate or seminal vesicle) was increased at 4,000 ppm. These changes in the reproductive system were considered by study authors to reflect the markedly reduced body weight gain. Study authors identified a NOAEL of 1000 ppm (190 mg/kg/day) and a LOAEL of 2,000 ppm (383 mg/kg/day) based on effects on body weight gain, clinical signs and clinical chemistry changes. *The LOAEL of 383 mg/kg/day is above the tripled GHS guideline values for Category 2 of 30-300 mg/kg/day for 4-week studies. The NOAEL of 190 mg/kg/day is below the cutoff of 300 mg/kg/day. Therefore, it is impossible to determine with confidence if adverse effect would occur at 300 mg/kg/day. However, clothianidin is at most classified to GHS Category 2.*
- Clothianidin was also evaluated for potential systemic repeated-dose toxicity in three 90-days studies conducted according to the OECD Guidelines 408 and 409 using rats, and dogs. In these studies, clothianidin was administered in diet at a dose level of 0, 100, 250, 1,250 or 2,500 ppm to Sprague-Dawley rats (10/sex/dose) or at 0**,** 325, 650, 1,500 and 2,250 ppm to Beagle dogs (4/sex/dose). In rats a NOAEL of 250 ppm (equivalent to 19.7 mg/kg/day as calculated by study authors) was established based on reduced body weight and body weight gain at 1,250ppm (equivalent to 96.0 mg/kg/day). In dogs, clinical signs of toxicity, decreases in red blood cell and white blood cell parameters and lymphoid hyperplasia were seen in at 1,500 ppm (equivalent to 40.9 mg/kg/day). Based on this, a NOAEL of 650 ppm, (equivalent to 19.3 mg/kg/day) was established by study authors. *The LOAELs of 1,250 ppm (equivalent to 96.0 mg/kg/day) in rats and 1,500 ppm (equivalent to 40.9 mg/kg/day) in dogs are within the GHS guideline values for Category 2 of 10-100 mg/kg/day for 90-day studies. Therefore clothianidin is classified to GHS Category 2.*
- In an immunotoxicity study conducted according to the U.S. EPA OPPTS guideline 870.7800, clothianidin (purity not specified) was administered in the diet to 3 groups of rats (numbers and sexes not specified) at concentrations of 150, 500, or 3,000 ppm for 28 days. The doses are equivalent to 0, 13.8, 45.8 and

252.8 mg/kg/ day for males and 0, 14.0, 46.2 and 253.0 mg/kg/day for females, as calculated by study authors. All rats survived to scheduled termination and no clinical observations related to treatment occurred. Body weights and absolute feed consumption values were significantly reduced in both sexes in the 3,000 ppm group for the entire study. No changes were observed at necropsy. No effects on immunoglobulin M antibody-forming cell response to the T cell-dependent antigen in both sexes when evaluated as specific activity and total spleen activity. A NOAEL for systemic toxicity was 500 ppm (equivalent to 45.8 mg/kg/day (males) or 46.2 mg/kg/day (females)) based on reduced body weights and feed consumption. A NOAEL for immunotoxicity was 3,000 ppm (equivalent to 252.8 mg/kg/day), the highest dose tested. *Both the systemic toxicity LOAEL of 252.8mg/kg/day and NOAEL of 45.8 mg/kg/day are within the tripled GHS guideline values for Category 2 of 30-300 mg/kg/day for 4-week studies. Therefore clothianidin is classified to GHS Category 2.*

- In a the previously described developmental immunotoxicity study, clothianidin (purity not specified) was administered to 3 groups of pregnant rats (25/group) in the diet at concentrations of 150, 500, or 2,000 ppm daily from day 6 of gestation through 21 or 24 of presumed gestation. After weaning, 190 male and 190 female rats (1 pup per litter per assay, when possible) were selected for immunological evaluation. The rats were separated into two assays: Assay 1(180) and Assay 2 (200 rats). Clothianidin was administered to these rats in the diet daily beginning on PND21 through termination at concentrations 150, 500, or 2,000 ppm. Terminal body weights in both sexes were significantly reduced in the 2,000 ppm exposure group. Absolute spleen and thymus weights for both sexes in the 2,000 ppm exposure group were also significantly reduced, but ratios of spleen and thymus weights to the terminal body weight did not differ significantly among the groups. A significant increase in terminal body weight occurred in male rats in the 150 ppm group. Statistically significant decreases in spleen cell number were seen in the 2,000 ppm group for both sexes. Statistically significant increases in specific activity and total spleen activity were seen in low dose males and high dose females. However, these differences were attributed to the variability found in the Crl:CD (SD) rat strain. No effects on delayed-type hypersensitivity response were seen at any dose levels in either sex. No deaths related to treatment occurred. Absolute and relative feed consumption values were significantly reduced during the gestation and lactation periods at 2,000 ppm and during the lactation period at 500 ppm. Average pup weights per litter were significantly reduced in the 2,000 ppm group. There were no other treatment-related effects on litter observations. In the F_1 generation rats no mortalities or treatment-related effects on clinical signs of toxicity were seen. Body weights, body weight gains and absolute feed consumption were significantly reduced for both male and female F1 rats in the 500 ppm exposure group and above. Absolute thymus and spleen weights were significantly reduced in both sexes in the 2,000 ppm group, though this finding is considered a result of significant overall body weight reductions as relative thymus and spleen weights were not significant. No immunologically relevant adverse effects on humoral immunity or cell-mediated immunity were seen in male and female F1 generation rats following exposure to clothianidin in the uterus during gestation, via maternal milk and maternal feed during the postpartum period or via the diet

during the post-weaning period. The study authors identified a maternal NOAEL for systemic toxicity of 500 ppm (equivalent to 35 mg/kg/day during gestation and 68.3 mg/kg/day during lactation), based on reductions in body weight and feed consumption and increased incidence of ptosis at 2,000 ppm. In the F1 generation, the NOAEL for systemic toxicity of 150 ppm (equivalent to 27.5 and 28.2 mg/kg/day for males in Assays 1 and 2 and 26.4 and 26.8 mg/kg/day for females in Assays 1 and 2, respectively), was established based on reductions in body weight in males at weaning at 500 ppm. *As the duration of the exposure was not clearly reported, it is impossible to apply the Haber's rule* [12] *to compare the NOAEL/LOAELs with GHS guidance values.*

- *Dermal*
  - In a repeated dose dermal toxicity study conducted according to OECD Guideline 410, (Crl:CD→(SD)IGS BR) rats (10/sex/dose) were exposed to clothianidin (purity 95.2%) at a dose level of 0, 100, 300 or 1,000 mg/kg/day for 29 days (6 hours per day, 7 days per week). No treatment-related mortalities or clinical signs of toxicity were seen. There was also no evidence of irritancy or other changes at the application site. A statistically significant reduction in weight gain was seen in males at the high dose during week 1 (−61%), but thereafter weight gains were comparable to those of all other groups. At the end of treatment, there was a slight decrease in body weight gain, by −21%, reflecting the change in week 1. Based on this study authors considered the initial lower weight gain as incidental to treatment. Slight increases in red blood cells, hemoglobin, hematocrit and prothrombin time were observed in both sexes at 300 mg/kg/day, but not at the top dose, and are considered not treatment-related. There were no effects on clinical chemistry, necropsy, organ weights or histopathology. Study authors identified a systemic NOAEL of 1,000 mg/kg/day, which was the highest dose tested.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Moderate was assigned. In repeated-dose oral toxicity studies in mice, rats and dogs, main effects of oral administration of clothianidin were a reduction in body weight gain and frequently reduced food consumption compared to the control. The majority of subchronic and chronic studies reported oral LOAEL values between the GHS guidance values for Category 2 of 10 and 100 mg/kg/day as described above. Accordingly, clothianidin is classified to GHS Category 2 for systemic toxicity (repeated exposure), which corresponds to a score of Moderate.

Neurotoxicity (N)
***Group II Score (single dose)* (vH, H, M, or L): vH**
Clothianidin was assigned a score of Very High for neurotoxicity (single dose) based on ToxServices classifying it as a GHS Category 1 for neurotoxicity (single dose). GreenScreen® criteria classify

[12] According to GHS criteria, the guidance values proposed refer basically to effects seen in a standard 90-day toxicity study conducted in rats. For studies of greater or lesser duration, the guidance values are adjusted using Haber's Rule, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. For example, for a 28-day study the guidance values would be increased by a factor of three.

chemicals as a Very High hazard for neurotoxicity (single dose) when they are classified to GHS Category 1 (CPA 2012b). Confidence in the score is high because it is based on experimental data from well-conducted acute neurotoxicity studies.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- JMPR 2010
  - In a preliminary range-finding study, three groups of Fischer 344 rats (5/sex/dose) were administered clothianidin (purity 95.2-96%) by gavage at concentrations of 250, 500, or 1,000 mg/kg/day. Treatment-related mortalities were seen at dose level of 500 mg/kg and above. Mortality rate at 1,000 mg/kg was 40% in males and 100% in females. Clinical signs of neurotoxicity were seen at 500 mg/kg and included tremors and decreased activity. These signs began 3 hours post-treatment and persisted for up to 3 days after exposure. Based on this, ToxServices identified an acute neurotoxicity LOAEL at 500 mg/kg for this study. *The LOAEL of 500 mg/kg is within the GHS guidance values for Category 2 of 300-2,000 mg/kg for systemic toxicity (single exposure). Therefore clothianidin is classified to GHS Category 2 for neurotoxicity toxicity (single exposure).*
  - In an acute neurotoxicity study conducted according to U.S. EPA test method OPPTS 870.6200, Fischer 344 rats (12/sex/group) were administered clothianidin (purity 95.2-96%) by gavage at single doses of 100, 200 or 400 mg/kg. No mortality occurred. Clinical signs of neurotoxicity were seen at the top dose and included tremors, decreased activity, and ataxia. No relevant effects on body weight were observed. All functional observational battery (FOB) and figure-eight maze findings were restricted to the day of treatment. Substantial effects occurred at the top dose in both sexes, including tremors, hypoactivity, decreased arousal, miosis from light stimulation, and hypothermia. The decreased arousal effect was biologically significant at 100 mg/kg and above in males and at 200 mg/kg and above in females. There were no compound-related histopathological effects on neuronal tissue. A neurotoxicity LOAEL of 100 mg/kg was identified based on reduced locomotor activity in males at this dose. *The LOAEL of 100 mg/kg is below the GHS guidance value for Category 1 of 300 mg/kg for systemic toxicity (single exposure). Therefore clothianidin is classified to GHS Category 1.*
  - In a follow-up acute neurotoxicity study, clothianidin was administered to 2 groups of male rats (10/dose) at single doses of 60 or 80 mg/kg. Figure-eight maze activity was conducted on the day of dosing but no statistically significant observations were made. No mortality or relevant clinical signs occurred.
  - In a second follow-up study conducted similar to U.S. EPA test method OPPTS 870.6200, 3 groups of male Fischer 344 rats (12/group) received clothianidin (purity 95.3-95.5%) by gavage in concentrations of 20, 40, or 60 mg/kg. No statistically or biologically significant changes in any neurotoxicity parameter were detected in treated animals compared to the control group in the FOB or figure-eight maze. A neurotoxicity NOAEL of 60 mg/kg and a LOAEL of greater than 60 mg/kg were identified.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Very High was assigned. Neurobehavioral effects consisting of decreased arousal and decreased motor activity were observed in acute neurotoxicity studies of clothianidin in rats as described above. The lowest NOAEL identified

for acute neurotoxicity was 60 mg/kg, on the basis of reduced locomotor activity in males at 100 mg/kg. The lowest identified LOAEL of 100 mg/kg is below the GHS guidance value for Category 1 (300 mg/kg) and therefore a score of Very High was assigned.

Group II* Score (repeated dose) **(H, M, or L):** *H*

Clothianidin was assigned a score of High for neurotoxicity (repeated dose) based on oral developmental neurotoxicity studies in mice demonstrating several adverse effects in the neurobehavioral parameters at dose of 9 mg/kg/day. GreenScreen® criteria classify chemicals as a High hazard for neurotoxicity (repeated dose) when neurological effects are seen below the guidance values of 10 mg/kg/day for studies lasting 90-days and when they are classified to GHS Category 1 (CPA 2012b). The confidence in the score is reduced because a range of LOAEL was reported, which corresponds to the scores of Moderate to High.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- Marfo et al. 2015
  - A prevalence case-control study was performed to examine the relationship between urinary neonicotinoid pesticides (and their metabolites) levels and typical symptoms of neonicotinoid pesticides poisoning. Spot urine samples were obtained from 35 symptomatic patients (unknown causes) and 50 non-symptomatic volunteers. The study authors considered typical symptoms of neonicotinoid pesticides as recent memory loss, finger tremor, and at least five of the six symptoms below: headache, general fatigue, palpitation/chest pain, abdominal pain, muscle pain/weakness/spasm, and cough (TSG, n = 19, age 5 - 69). Symptoms other than these were considered atypical symptoms (ASG, n = 16, age 5 – 78). Urine samples were analyzed using liquid chromatography-tandem mass spectrometry. Urine clothianidin was among the chemicals examined, and it was detected in none of the patients in TSG, 6.3% of the patients in ASG (1 of 16, not quantified), and in 2.0% of the volunteers in the NSG (1 of 50, 1.6 ppb). There was no statistical significance regarding the frequency of detection among three groups.
- JMPR 2010
  - In a subchronic neurotoxicity study conducted according to the U.S. EPA test method OPPTS 870.6200, clothianidin (purity 95.3–96%) was administered to Fischer 344 rats (12/sex/dose) in the diet at dose levels of 0, 150, 1,000 or 3,000 ppm (equivalent to 0, 0, 9.2, 60.0 and 177.0 mg/kg/day for males and 0, 10.6, 71.0 and 200.1 mg/kg/day for females.as calculated by study authors) for 90-days. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed on week-1, 4, 8 and 13. The animals were also evaluated for clinical signs of toxicity, body weight, gross pathology, and histopathology. There were no mortalities or treatment-related effects on clinical signs of toxicity. A slight body weight decrease (−5%) was observed in males (weeks 11–13) and females (weeks 9–13) at the high dose group. Similarly, feed consumption was decreased in both males and females from high dose group. There were no relevant findings in the FOB, figure-eight maze, gross necropsy or histopathology. Study authors identified a NOAEL for systemic toxicity of 1,000 ppm (equivalent to 60 mg/kg/day), based on decreased feed consumption and decreased body weight. The neurotoxicity NOAEL was 3,000 ppm (equivalent to 177 mg/kg/ day), which was the highest dose tested.

  - In the previously described developmental neurotoxicity study conducted according to OECD Guideline 426, clothianidin (purity 95.5–95.9 %) was administered to female Crl:CD®(SD)IGS BR VAF/Plus® rats (25/dose) via corn oil in the diet at concentrations of 0, 150, 500 or 1,750 ppm from gestation day 0 through postnatal day 21, when pups were weaned. Average daily intake of clothianidin was 0, 12.9, 42.9 and 142.0 mg/kg/day during gestation and 0, 27.3, 90.0 and 299.0 mg/kg/day during lactation period. No maternal deaths or treatment-related clinical signs were observed for the duration of the study. The only treatment-related effects noted was changes in body weight of the dams and pups at the high dose (1,750 ppm). Food consumption decreased for dams in the high dose group (1,750 ppm) during the third week of gestation and first week of lactation. There were no treatment-related effects on the number of litters, liver litter size, number of stillborn pups, live birth index, or viability index. Study authors identified a NOAEL for fetal and maternal toxicity of 500 ppm (equivalent to 42.9 mg/kg/day), based on changes in body weight at higher doses. With regard to the neurobehavioral effects, subtle modification of acoustic startle habituation and motor activity were observed in the pups at the high dose immediately after weaning. However these were considered as secondary to nonspecific toxicity. No biologically significant effects on the central nervous system were observed histomorphometrically or histologically. Based on this the study authors concluded that clothianidin is not a developmental neurotoxicant and a developmental neurotoxicity NOAEL of 1,750 ppm (equivalent to 142 mg/kg/day) was established, which is the highest dose tested.

- Ozdemir et al. 2014
  - In the previously described developmental neurotoxicity study, the effects of clothianidin on learning and memory in infant and adult male rats and the expression of related genes in the hippocampus was investigated. To study potential neurotoxic effects on adult rat models albino Wistar rats (6/dose) were administered 0, 2, 8 and 24 mg/kg of clothianidin (purity not reported; corn oil or DMSO vehicle) by gavage, daily for three months. Rats were evaluated for learning performance in a Morris water maze with a probe trail, and visual acuity and motor function test. Rats were sacrificed after tests and the brain was immediately removed for evaluation of the hippocampus and cortex. Authors studied gene expressions of GRIN1, M1, SYP and GAP-43 using real time PCR. Authors observed similar cognitive performance in treated adults compared to controls; inconsistent results were obtained in latency times. In the probe trial, no difference in performance between treated adults and controls were observed. No changes in GRIN1, SYP, GAP-43 or M1 expression were observed between treated animals and controls. Authors concluded clothianidin did not have an impact on learning or memory or the related genes for adult rats under the conditions of this study.
- Tanaka 2012a,b
  - In the previously described two developmental neurotoxicity studies conducted according to OECD Guideline 426, mated female Crlj: CD1 mice (10/dose) were administered 0.002%, 0.006% and 0.018% clothianidin (purity >99%) in diet during gestation and lactation periods in one study or male and female Crlj: CD1 mice (10/sex/dose) were administered 0.003%, 0.006% and 0.012% clothianidin (purity >99%) in the diet from 5 weeks of age of the F_0 generation to through mating, gestation and lactation in the second study. Developmental neurobehavioral effects characterized by reduced motor activity and surface righting reflex in offspring were reported in these studies at doses causing general toxicity to offspring and dams. A LOAEL for neurotoxicity of 0.006 % (equivalent to 9–33 mg/kg/day as calculated by study authors) was established based on

significant adverse effects on exploratory and spontaneous behavior in F1 generation mice. *As the critical effects occurred during the sensitive life stage, the Guidance values were not adjusted based on Haber's Rule. The LOAEL of 9 mg/kg/day is below the GHS guidance value for Category 1 of 10 mg/kg/day; while the LOAEL of 33 mg/kg/day is within the duration adjusted GHS guidance values for Category 2 of 10-100 mg/kg/day. As a most conservative approach, clothianidin is classified to GHS Category 1 with reduced confidence.*

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of High was assigned. Although available neurotoxicity studies in rats indicate that clothianidin is not a neurotoxicant, several adverse effects in the neurobehavioral parameters were seen in mice studies, especially in developmental studies. The lowest identified LOAEL was 9 mg/kg/day, which is below the GHS guidance value for Category 1 (as explained above) and therefore a score of High was assigned. The confidence level is reduced because a range of LOAEL was reported, which corresponds to the scores of Moderate to High.

Skin Sensitization (SnS) Group II* Score (H, M, or L): L
Clothianidin was assigned a score of Low for skin sensitization based on negative results in an OECD 406 skin sensitization study. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when negative data, no structural alerts, and no GHS classification are available (CPA 2012b). Confidence in the score is high because it is based on experimental data from a well-conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- JMPR 2010
  - Clothianidin was not sensitizing in a maximization test conducted according to OECD Guideline 406 performed with Dunkin-Hartley-guinea pigs (20 females/group). Animals were induced with 1 and 55% (intradermally) of clothianidin (purity not specified) dissolved in coconut oil in and topically challenged with 10 and 20%. Varying levels of erythema was observed at day 1 after intradermal injection in both control and test animals. On the next day, erythema was observed only in control animals. 24 hours after challenge, 10-15% of test animals showed slight erythema. Since none of the dermal reactions in the test animals were clearly more severe than those of the control group, clothianidin was concluded not to be sensitizing in this study.

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): DG
Clothianidin was assigned a score of Data Gap for respiratory sensitization based on a lack of adequate data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- Hernandez et al. 2008
  - A cross sectional study was conducted to evaluate potential respiratory function abnormalities following long term pesticide exposure by means of complete pulmonary function testing. The study population was comprised of workers from a prominent

agriculture area of southern Spain. A questionnaire was used to determine sociodemographic factors, occupational exposure and clinical symptoms. Multiple regression analysis showed a relationship of short term exposures to pesticides with reduced forced expired volume, and a long term exposure relationship with reduced forced expiratory flow rate. A relationship was found between neonicotinoid insecticides and lower pulmonary volumes, suggestive of restrictive lung disease, and with an increased risk of reporting irritative symptoms.

- Hernandez et al. 2011
    - Several clinical and epidemiological studies have reported an association between exposure to pesticides, and bronchial hyper-reactivity and asthma symptoms. Hernandez et al. summarized that pesticide aerosols can lead to asthma by interaction with functional irritant receptors in the airway and promoting neurogenic inflammation. Some pesticides (organophosphorus) can disrupt negative feedback control of cholinergic regulation in the lungs, acting synergistically with allergen sensitization leaving individuals more susceptible for developing asthma. Overall, many pesticides were found to be sensitizers or irritants capable of directly damaging the airway, increasing the risk of developing asthma.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a Data Gap was assigned. There have been reports of effects on respiratory function due to exposure to pesticides in general, but it is unclear whether effects represent an allergic asthmatic response rather than an irritant response or other respiratory effect. Furthermore, no studies have specifically investigated the relationship between clothianidin exposure and respiratory sensitization. In the absence of sufficient data, a Data Gap was assigned.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): L

Clothianidin was assigned a score of Low for skin irritation/corrosivity based on negative results in skin irritation studies in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when negative data, no structural alerts, and no GHS classification are available (CPA 2012b). Confidence in the score is high because it is based on experimental data from a well-conducted study.

- Authoritative and Screening Lists
    - *Authoritative:* not listed on any authoritative lists
    - *Screening:* not listed on any screening lists
- JMPR 2010
    - In a skin irritation study conducted according to OECD Guideline 404, six New Zealand White rabbits (one female, five males) were administered dermal applications of 0.5 g clothianidin (purity not specified) moistened with water to back skin under semi-occlusive dressing for 4 hours. No skin irritation or dermal reaction was observed through 3 days post-application. Study authors concluded that clothianidin was not irritating to the skin in this test.
- HSDB 2005
    - No skin irritation was observed on the shaved skin of albino rats in a repeated application short-term dermal toxicity study. Male rats showed reduced body weight gains at the limit dose of 1,000 mg/kg/day. No other details of the study were provided.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): L
Clothianidin was assigned a score of Low for eye irritation/corrosivity based on negative results in an OECD 405 ocular irritation study. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when negative data, no structural alerts, and no GHS classification are available (CPA 2012b). Confidence in the score is high because it is based on experimental data from a well-conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- JMPR 2010
  - In an ocular irritation study conducted according to OECD Guideline 405, six male New Zealand White rabbits were administered ocular instillations of 0.1 mL of undiluted clothianidin for 24 hours. Minor conjunctival reactions were observed on treatment day in all rabbits but these reactions had resolved by 24 hours post-treatment. No ocular effects were observed at any of the post-treatment evaluations. Study authors concluded that clothianidin was practically non-irritating to the eye in this test.

Ecotoxicity (Ecotox)[13]

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): vH
Clothianidin was assigned a score of Very High for acute aquatic toxicity based on being associated with EU hazard statement of H400 and EU risk phrase of R50 and on its measured LC_{50}/ EC_{50} values in fish and daphnia being less than 1 mg/L. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when acute aquatic toxicity values are ≤ 1 mg/L when they are associated with EU H400 and R50 and when classified to GHS Category 1 (CPA 2012b).
Confidence in the score is high because it is based on experimental data from well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative*: EC - CLP/GHS Hazard Statements - H400 - Aquatic Acute 1 - Very toxic to aquatic life
  - *Authoritative*: EU Risk Phrase R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment[14]
  - *Screening:* EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects[15].
- U.S. EPA 2005
  - 96-hour LC_{50} (*Lepomis macrochiru,* fish) ≥ 117 ppm
  - 96-hour LC_{50} (*Oncorhynchus mykiss,* fish) ≥ 105.8 ppm
  - 48-hour EC_{50} (*Daphnia magna,* invertebrate) ≥ 119 ppm
  - 48-hour EC_{50} (*Chironomus riparius,* invertebrate) = 0.022 ppm
  - 96-hour LC_{50} (*Cyprinodon variegatus,* fish) ≥ 93.6 ppm
  - 96-hour EC_{50} (*Crassostrea virginica*, invertebrate) ≥ 129.1 ppm
  - 96-hour LC_{50} (*Americamysis bahia,* crustacea) = 0.051 ppm
  - *Metabolite—TMG*: 96-hour LC_{50} (*Oncorhynchus mykiss*) ≥ 110 ppm

[13] Per GreenScreen® guidance, terrestrial toxicity was evaluated according to U.S. EPA's Design for the Environment (DfE) Alternatives Assessment Criteria for Hazard Evaluation (DfE 2011).
[14] This is an authoritative EU R-phrase that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation
[15] This is a screening EU H-Statement that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation

  - *Metabolite—MNG*: 96-hour LC_{50} (*Oncorhynchus mykiss*) ≥ 105 ppm
  - *Metabolite—TZNG*: 96-hour LC_{50} (*Oncorhynchus mykiss*) ≥ 116 ppm
- ABC 2015
  - 48h EC_{50} (*Daphnia magna*) = 109,523 µg/L
  - 96h LC_{50} (*Americamysis bahia*)= 51 µg/L
- Goulson 2013
  - 96h LC_{50} (*Oncorhynchus mykiss,* fish) = 106 ppm
  - 96h LC_{50} (*Lepomis macrochirus,* fish) = 117 ppm
  - 96h LC_{50} (*Cyprinodon variegatus,* fish) = 93.6 ppm
  - 96h LC_{50} (*Leptocheirus plumulosus,* crustacea) = 20.4 ppb
  - 96h LC_{50} (*Mysidopsis bahia,* crustacea) = 51 ppb

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): vH
Clothianidin was assigned a score of Very High for chronic aquatic toxicity based on its measured NOEC values in aquatic organisms being less than 0.1 mg/L. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when chronic NOECs ≤ 0.1 mg/L (CPA 2012b). Confidence in the score is high because it is based on experimental data from well-conducted studies.

- Authoritative and Screening Lists
  - *Authoritative:* EU Risk Phrase R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment[16].
  - *Screening:* EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects[17].
- U.S. EPA 2005
  - Chronic early life stage NOAEC of 9.7 ppm and a LOAEC of 20 ppm (equivalent to 9.7 and 20 mg/L, respectively) for length and dry weight of freshwater fish (*Pimephales promelas*, fish)
  - 21-day NOAEC of 0.042 ppm and LOAEC of 0.12 ppm (equivalent to 0.042 and 0.12 mg/L, respectively) for reproduction (*Daphnia magna*).
  - 39-day NOAEC of 5.1 ppb and LOAEC of 9.7 ppb for reproduction in mysid shrimp (equivalent to 0.0051 and 0.0097 mg/L, respectively)

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Very High was assigned. The available measured aquatic chronic toxicity values for clothianidin are well below 0.1 mg/L, which correspond to a score of vH.

Acute Terrestrial Vertebrates[18] Toxicity Score (ATV) Score (vH, H, M, or L): M
Clothianidin was assigned a score of Moderate for acute terrestrial vertebrate toxicity based on its measured oral LD_{50} values in Japanese quail of 423 mg/kg. GreenScreen® criteria classify chemicals as a Moderate hazard for acute terrestrial vertebrate toxicity (oral exposure) when acute avian toxicity values are between 51 and 500 mg/kg as per the U.S. EPA DfE criteria (CPA 2012b, DfE

[16] This is an authoritative EU R-phrase that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation
[17] This is a screening EU H-Statement that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation
[18] Includes birds and mammals

2011). Confidence in the score is high because it is based on consistent results in several experimental studies.

- U.S. EPA 2005
  - *Oral*: LD_{50} (*Colinus virginianus*, bobwhite quail) > 2,000 mg/kg
  - *Oral*: LD_{50} (*Coturnix japonica*, Japanese quail) = 423 mg/kg
  - *Oral*: LC_{50} (*Colinus virginianus*, bird) > 5,230 ppm
  - *Oral*: LC_{50} (*Anas platyrhynchos*, mallard duck) > 5,040 ppm
- ABC 2015
  - *Oral:* LD_{50} > 2,000 mg/kg (Bobwhite quail)
  - *Oral:* LD_{50} = 430 mg/kg (Japanese quail)
  - *Oral:* LD_{50} > 752 mg/kg- (mallard duck)

ToxServices' summary and conclusion:

- Based on the weight of evidence a score of Moderate was assigned. The most conservative acute oral avian toxicity valu**e** for clothianidin was 423 mg/kg in Japanese quail, which corresponds to a score of Moderate according to U.S. EPA's Design for the Environment (DfE) Alternatives Assessment Criteria for Hazard Evaluation (DfE 2011).

Chronic Terrestrial Vertebrates (CTV) Toxicity Score: N/A

Clothianidin was not assigned a score for chronic terrestrial vertebrates toxicity as the U.S. EPA DfE (DfE 2011) guidance does not report criteria for chronic toxicity. Therefore the hazard scoring of this endpoint is not applicable due to lack of recognized criteria. Toxicity studies on the chronic exposure of clothianidin to birds were identified and are described below.

- ABC 2015, U.S. EPA 2005
  - In a reproductive toxicity study performed with *Colinus virginianus* (bobwhite quail) exposed to seeds treated with clothianidin, a NOAEL of 5.10 mg/kg/day and a LOAEL of 7.38 mg/kg/day were identified based on adverse effects on eggshell thickness
  - In another reproductive toxicity study performed with *Anas platyrhynchos* (mallard ducks) exposed to seeds treated with clothianidin, a NOAEC of 250 ppm and a LOAEC of 525 ppm were identified based on several small non-significant deficits in many parameters.

ToxServices' summary and conclusion:

- The available data indicate that chronic exposure to seeds treated with clothianidin may result in reproductive/developmental effects in small mammals and birds.

Acute Foliar Invertebrates and Pollinators[19] (AFI) Toxicity Score (H, M, or L): H

Clothianidin was assigned a score of High for acute foliar invertebrates and pollinators toxicity based on its measured oral and dermal LD_{50} values in bees being less than 2 ug/bee. GreenScreen® criteria classify chemicals as a High hazard for acute foliar invertebrates and pollinators toxicity when the oral and dermal LD_{50} values in bees are less than 2 µg/bee as per the U.S. EPA DfE criteria. Confidence in the score is high because it is based on consistent results in several experimental studies.

[19] Includes bees

- *Oral*
  - U.S. EPA 2005
    - 48-hour LD_{50} (*Apis mellifera,* honey bee) = 0.0439 µg ai/bee
    - 48-hour LD_{50} (*Apis mellifera,* honey bee) = 0.0037 µg ai/bee
    - Metabolite—TMG: 48-hour LD_{50} (*Apis mellifera*, honey bee) > 152 µg ai/bee
    - Metabolite—MNG: 48-hour LD_{50} (*Apis mellifera,* honey bee) > 153 µg ai/bee
    - Metabolite—TZMU: 48-hour LD_{50} (*Apis mellifera,* honey bee) > 113 µg ai/bee
    - Metabolite—TZNG: 48-hour LD_{50} (*Apis mellifera*, honey bee) = 3.95 µg ai/bee
  - Blacquiere et al. 2012
    - LD_{50} = 0.003 µg/bee (*Apis mellifera,* honey bee)
  - Goulson 2013
    - LD_{50} = 4 ng/bee (*Apis mellifera,* honey bee,)
  - Poquet et al. 2015
    - In an acute toxicity study honey bee workers (*Apis mellifera*) were exposed to clothianidin (99% purity) either on the thorax or on the wings at doses of 0, 0.5, 5, 10, 25, 40, 50, 75 and 100 ng/bee. Eight replicates of 30 bees per contact area and dose were performed. Bees were observed for mortality 24, 48, 72, 96 and 120 hours after exposure. Authors determined 120 hour LD_{50} values of 36.49 ng clothianidin for wing exposure and 25.84 ng clothianidin for the thorax exposure.
- *Contact*
  - Iwasa et al. 2004
    - LD_{50} = 21.8 ng/bee (*Apis mellifera,* honey bee)
  - Scott-Dupree et al. 2009
    - $LC_{50} = 0.39x10^{-3}$ % (percentage of solution wt:vol; equivalent to 3.9 mg/L) (48-hour) (bumblebee, *Bombus impatiens*)
    - $LC_{50} = 0.08x10^{-3}$ % (percentage of solution wt:vol; equivalent to 0.8 mg/L) (48-hour) (leafcutter bee, *Megachile rotundata*)
    - $LC_{50} = 0.1x10^{-3}$ % (percentage of solution wt:vol; equivalent to 1.0 mg/L) (48-hour) (hornfaced bee, *Osmia lignaria*)
  - Goulson 2013
    - LD_{50} = 27 ng clothianidin (*Leptinotarsa decemlineata*, insect)
  - Blacquiere et al. 2012
    - LD_{50} = 0.044 µg/bee clothianidin (honey bee, *Apis mellifera*)

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of High was assigned. The available data showed that *Osmia lignaria* and *M. rotundata* are more sensitive to clothianidin than bumble bees with acute oral and contact LD_{50}/LC_{50} values in honey bees are clearly below 2 µg/bee (2,000 ng/bee). Therefore clothianidin warrants a score of High based on acute toxicity to honey bees.

Chronic Foliar Invertebrates and Pollinators (CFI) Toxicity Score: N/A
Clothianidin was not assigned a score for chronic foliar invertebrates toxicity as the U.S. EPA DfE (DfE 2011) guidance does not report criteria for chronic toxicity. Therefore the hazard scoring of this endpoint is not applicable due to lack of recognized criteria. Several toxicity studies on the chronic exposure of clothianidin to bees were identified and these are described below.

- Cutler et al. 2014
    - In a GLP compliant terrestrial toxicity study, the adverse impacts of clothianidin seed-treated canola on honey bees (*Apis mellifera*) was investigated in a large-scale field experiment. Clothianidin was applied to canola seed as Prosper FX ® formulation (20.4% clothianidin) at a target label rate of 1,400 mL Prosper per 100 kg of seed. Five fields in southwest Ontario, Canada were planted with clothianidin treated seeds of approximately 2 ha canola. 40 colonies were placed in the treated fields for 14 days, and then moved to an isolated apiary. Authors monitored colony weight gain, honey production, pest incidence, bee mortality, number of adults, and amount of sealed brood. There were no significant differences in any of the parameters measured between clothianidin treated canola and control. Authors concluded exposure to canola grown from seed treated with clothianidin poses low risk to honey bees.
- Di Prisco et al. 2013
    - In a terrestrial toxicity study, the ability of clothianidin to negatively modulate NK-κB immune signaling resulting in adverse effects on honey bee antiviral defenses controlled by this transcription factor was investigated. Honey bees (*Apis mellifera*) were exposed to clothianidin (purity not reported) at a concentration of 21 ng/bee on the thorax. One hour after treatment, bees were immune-challenged with *S. cerevisiae* at the base of the forewing and transcript levels of apidaecin were assessed with real-time PCR at 6 hours and transcript levels of the XP00325113.1 gene was assessed using qRT-PCR at 0.5, 1, 2, 4, 6, 8 and 24 hours. Authors observed a significantly lower apidaecin transcript level in response to infection, associated with up regulation of the XP00325113.1 gene. Authors concluded this upregulation of the XP00325113.1 gene interferes with NF-κB signaling resulting in a modulated immune response.
    - To investigate clothianidin's effects on deformed wing virus (DWV) infection and replication, authors performed three separate experiments. In experiment one, honey bees were exposed to clothianidin at doses of 0, 3, 10, 20 and 30 ng/bee on the thorax. The number of DWV genome copies was assessed at 24 hours. Authors observed a dose dependent positive response in number of DWV genome copies In experiment two, honey bees were exposed to clothianidin at concentrations of 0.02, 0.2 and 2 ng/bee on the thorax and the number of DWV genome copies was assessed at 24, 48 and 72 hours. Authors observed a significant enhancement of viral replication. In experiment three, honey bees were fed sugar syrup containing clothianidin at concentrations 0.1, 1 and 10 ppb. The number of DWV genome copies was assessed at 24, 48 and 72 hours. Authors observed clothianidin treatment promoted DWV proliferation. Overall, authors concluded clothianidin actively promote DWV replication due to altering of the innate immune response.
- Scholer and Krischik 2014
    - In a terrestrial toxicity study, the effects of clothianidin on individual behavior and colony health of the American bumble bee (*Bombus impatien*) was investigated. Authors monitored queen health (mortality and movement), worker behavior (movement, and consumption of sugar) and colony health (weight, number of wax pots, brood production, and bee weight). Colonies (8/dose) were exposed to clothianidin (purity not reported) in 50% sugar syrup at concentrations of 0, 10, 20, 50 and 100 ppb for eleven weeks. Authors recorded queen status weekly, and video recorded movement of queens and workers twice for 30 minutes in weeks 4 and 8. Colonies were sacrificed at the end of 11 weeks and dissected for evaluation. Authors observed significantly higher queen mortality at 6 weeks in doses 50 and 100 ppb and in 20, 50 and 100 ppb by eleven weeks.

A significant reduction in queen survival, worker movement, colony consumption, and colony weight was observed at doses 20, 50 and 100 ppb by eleven weeks. Authors concluded exposure to clothianidin causes behavior changes resulting in detrimental effects on colonies at exposure levels of 20 ppb and above.

- Rundlof et al. 2015
  - In a terrestrial toxicity study, the effect of clothianidin on wild bee density, solitary bee nesting (*Osmia* bicornis) and bumble bee (*Bombus* terrestris) and honey bee (*Apis mellifer*) colony growth and reproduction in field conditions was investigated. Eight fields were sown with clothianidin coated seeds that were treated with 25 mL Elado (400 g/L clothianidin) per kg of seed. Authors observed a decrease in wild bee density in clothianidin treated fields, a decrease in nesting of the solitary bee in clothianidin treated fields, and a negative relation of clothianidin seed coating to bumble bee colony growth and reproduction. However, treatment had no significant influence on honey bee colony strength. Authors concluded clothianidin seed coating has negative effects on wild bees, which differ according to species, and may lead to potential negative effects on populations.
- Pecenka and Lundgren 2015
  - In a terrestrial toxicity study, a dose response study investigated the lethal concentrations of clothianidin on monarch butterflies (*Danaus plexippus*) in a 36 hour exposure scenario. Neonate monarchs were fed clothianidin (purity not stated) for 36 hours at doses of 1, 5, 10, 25, 50, 100, 500 and 1,000 ppb (n=30, 30, 40, 40, 10, 40, 10 and 40, respectively) on a milkweed disc. Mortality was recorded daily and monarch fitness was evaluated. Authors observed an LC_{10}, LC_{20}, LC_{50}, and LC_{90} of 7.72, 9.89, 15.63 and 30.70 ppb, respectively. Significant differences were evident in development time, body length, and weight for newly enclosed second instars between treated monarchs and controls, as well as head capsule width of newly enclosed third instars. Specifically, authors observed significant reductions in body length at 5 ppb and head capsules at 1 ppb. Authors concluded clothianidin exposure could negatively affect larval monarch populations.
- Babendreier et al 2015
  - In a terrestrial toxicity study, the detrimental effects of clothianidin coated seeds used for control of the maize pest chrysomelid *Diabrotica virgifera* on non-target arthropods was investigated. Seeds were coated with 2.08 µL of Poncho FS 600 (dose 600 g/L clothianidin), equivalent to 0.19 L Poncho per 86,000 seeds per hectare, and were artificially infested with ready-to-hatch eggs of *D. v. virgifera*. Authors recorded the emergence of non-target arthropods weekly, 18 difference taxa were assessed. Authors observed a lower number of specimens emerging, particularly for non-target cleopterans and beneficial insects such as Coccinellidae, Hymenoptera, Araneae, Staphylinidae and Chrysopidae; however, no statistically significant effect on non-target community composition was evident from clothianidin treatment.

ToxServices' summary and conclusion:

- Based on the above data, clothianidin has the potential for toxic chronic exposure to honey bees, as well as other non-target pollinators, through the translocation of clothianidin residues in nectar and pollen. In honey bees, the effects of this toxic chronic exposure may include lethal and/or sub-lethal effects in the larvae and reproductive effects in the queen.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vH*
Clothianidin was assigned a score of Very High for persistence based on its measured half-lives in soil being between 148 to 1155 days. GreenScreen™ criteria classify chemicals as a Very High hazard for persistence when they are not biodegradable and when data indicate a half-life of > 180 days in soil or sediment (CPA 2012b). Confidence level is reduced as modeling was used to predict the predominant compartment of clothianidin.

- Authoritative and Screening Lists
  - *Authoritative:* EU Risk Phrase R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment[20].
  - *Screening:* EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects[21].
- U.S. EPA 2005
  - The degradation of clothianidin in the environment was evaluated in a number of studies. These studies showed that clothianidin is a persistent compound (no details on these studies were provided). Degradation is relatively rapid under anaerobic aquatic conditions with measured half-life of 14 days in water; 37 days in sediment; and 27 days overall. However, metabolic degradation occurs very slowly in aerobic soil. The measured aerobic half-lives in soils were 148 to 1155 days.
  - Clothianidin is extremely labile in light with aqueous photolysis half-life is less than one day. However, field studies showed a very slow rate of dissipation, suggesting that photolysis is likely not significant under most actual condition.
- U.S. EPA 2012
  - The BIOWIN model predicted that clothianidin is not readily biodegradable. Using a fugacity model, clothianidin is predicted to appear mainly in the soil compartment (87.5%), with 11.9% in water and minor amounts in sediment and air (< 0.1%). The predicted half-lives in soil and water are 75 days and 38 days, respectively (See Appendix D for modeling output).

ToxServices' summary and conclusion:

- Based on weight of evidence, a score of Very High was assigned. Available experimental data indicate that clothianidin is not readily biodegradable and persistent in the environment. EPISuite predicts that clothianidin is going to mainly partition to soil. In soil, clothianidin has a measured half-life between 128-1155 days at environmental temperature (25^{o}C), which corresponds to a score of Very High.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Clothianidin was assigned a score of Very Low for bioaccumulation based on its measured log K_{ow} and modeled BCF. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the BCF/BAF is ≤ 100 and when log K_{ow} is ≤ 4 (CPA 2012b). Confidence in the score is high because it is based on measured data from well-conducted studies.

[20] This is an authoritative EU R-phrase that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation
[21] This is a screening EU H-Statement that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation

- Authoritative and Screening Lists
  - *Authoritative:* EU Risk Phrase R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment[22].
  - *Screening:* EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects[23].
- U.S. EPA 2005
  - Clothianidin has a measured log K_{ow} of 1.12 at pH 7.
- HSDB 2005
  - Clothianidin has a measured log K_{ow} of 0.7 at 25^0C.
- U.S. EPA 2012
  - BCFBAF predicts a BCF of 3.162 based on a measured log K_{ow} of 0.7 (see Appendix D).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Clothianidin was assigned a score of Low for reactivity based on weight of evidence. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when they are not explosive or self-reactive and they are not classifiable under GHS (CPA 2012b). Confidence level was reduced due to a lack of measured data.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- No measured data were identified. Therefore screening procedures for explosivity were used here to estimate the reactivity property of clothianidin. These procedures are listed in the GHS (UN 2013).
  - Clothianidin contains nitro chemical group (NO_2) which is associated with explosive properties (Appendix E). In addition, its calculated oxygen balance (as shown below) is greater than -200. Based on this, clothianidin is considered a potential explosive and according to GHS criteria further testing is necessary to determine the explosive property of clothianidin
    - Oxygen balance equation:
      OB = -1600 x (2x+(y/2)-z)/MW Where CxHyOz
      Total number of carbons, hydrogens, and oxygens in clothianidin:
      X = C = 6 Y = H= 8 Z =O = 2
      OB= -1600 ×(2(6)+(8/2)-2)/ 249.7= - 89
  - Clothianidin is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible material (See Appendix E).
- Turf Alliance 2010
  - A material safety data sheet for clothianidin states that it has a reactivity rating of 0 from NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water").
- SCBP 2007
  - Clothianidin is not considered an explosive or an oxidizing substance.

[22] This is an authoritative EU R-phrase that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation
[23] This is a screening EU H-Statement that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Low was assigned. Clothianidin contains a structural alert for explosivity and its calculated oxygen balance indicated a potential for explosivity. However, it has received an NFPA rating of 0 for physical hazards which indicates that it is not explosive, and it was considered not explosive or an oxidizing substance when evaluated by ECHA (SCBP 2007). It does not contain alerts for self-reactivity, or substances that may produce flammable gases on contact with water. Therefore a score of Low was assigned, but the confidence in the score is reduced due to the lack of experimental data on the neat target chemical.

Flammability (F) Score (vH, H, M, or L): *L*
Clothianidin was assigned a score of Low for flammability based on its NFPA flammability rating. GreenScreen® criteria classify chemicals as a Low hazard for flammability when they are not flammable solids (CPA 2012b). Confidence in this endpoint was reduced due to the lack of measured data.

- Authoritative and Screening Lists
  - *Authoritative:* not listed on any authoritative lists
  - *Screening:* not listed on any screening lists
- Turf Alliance 2010
  - A material safety data sheet for clothianidin states that it has an NFPA flammability rating of 0. An NFPA flammability rating of 0 corresponds to "Materials that will not burn under typical fire conditions, including intrinsically noncombustible materials such as concrete, stone, and sand".
- SCBP 2007
  - Clothianidin is not considered flammable.

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Clothianidin (CAS# 210880-92-5)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
									S	R *	S	R *	*	*								
Table 2: Chemical Details																						
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	Clothianidin	210880-92-5	M	L	M	M	*M*	M	H	M	vH	*H*	L	DG	L	L	vH	vH	*vH*	vL	*L*	*L*

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	Yes	No	No		
2	STOP						
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Clothianidin	1

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Clothianidin	1

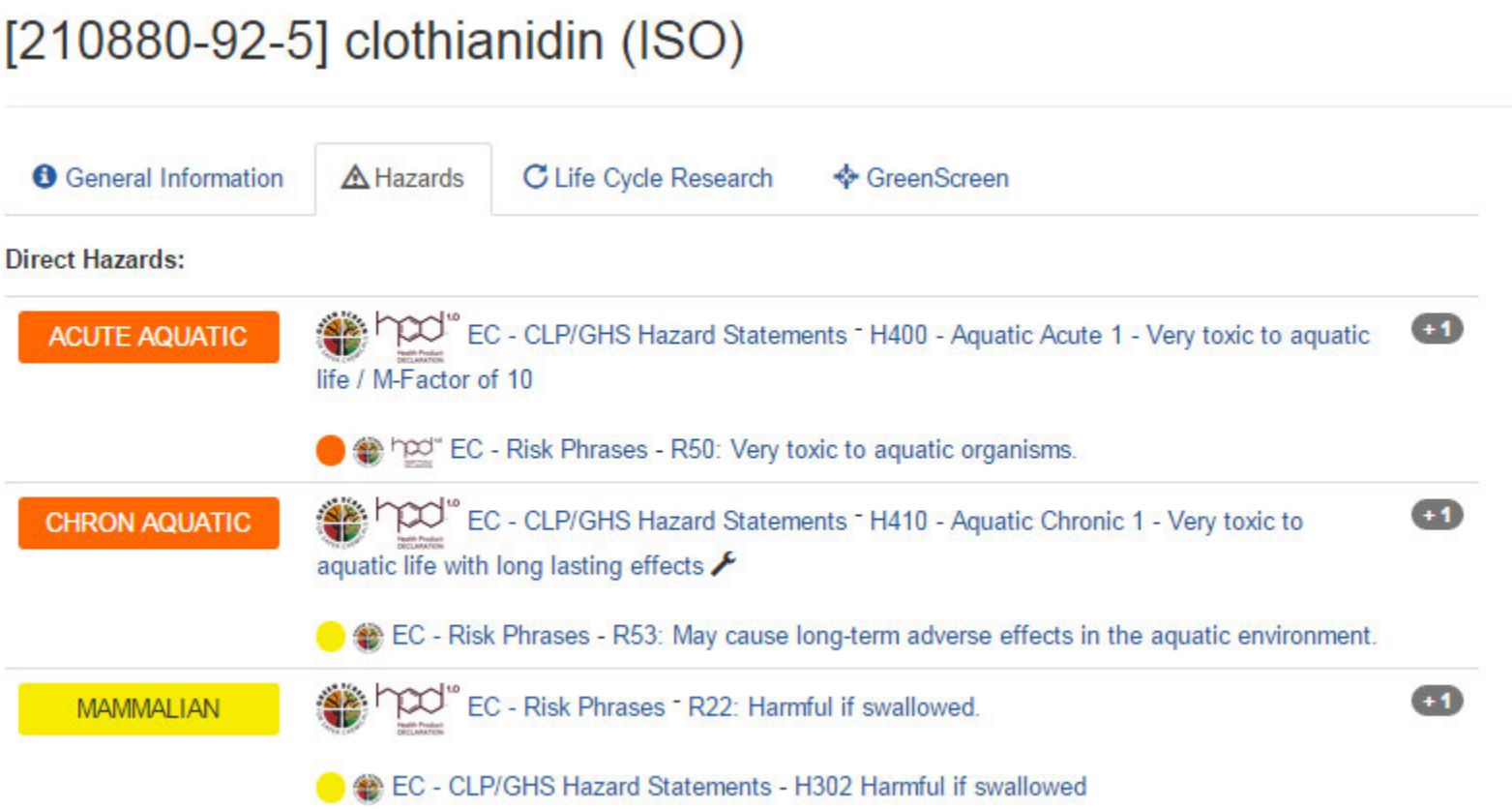
After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												1
2												
3												
4												

[1]The ecotoxicity scores presented in the table and used in the score calculation represent the most conservative score of the aquatic and terrestrial endpoints.

APPENDIX C: Pharos Output for Clothianidin (CAS# 210880-92-5)



APPENDIX D: EPISuite Modeling Results for Clothianidin (CAS# 210880-92-5)

CAS Number: 210880-92-5
SMILES: CNC(=NN(=O)(=O))NCc1cnc(s1)CL
CHEM: Clothianidin
MOL FOR: C6 H8 CL1 N5 O2 S1
MOL WT: 249.68
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log K_{ow} (octanol-water): ------
Boiling Point (deg C): ------
Melting Point (deg C): ------
Vapor Pressure (mm Hg): ------
Water Solubility (mg/L): ------
Henry LC (atm-m^3/mole): ------

Log Octanol-Water Partition Coef (SRC):
Log K_{ow} (K_{ow}WIN v1.68 estimate) = 0.64
Log K_{ow} (Exper. database match) = 0.70
Exper. Ref: TOMLIN, C. (2003)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 363.86 (Adapted Stein & Brown method)
Melting Pt (deg C): 146.49 (Mean or Weighted MP)
VP (mm Hg,25 deg C): 3.61E-006 (Modified Grain method)
VP (Pa, 25 deg C): 0.000482 (Modified Grain method)
Subcooled liquid VP: 6.18E-005 mm Hg (25 deg C, Mod-Grain method)
: 0.00823 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log K_{ow} (WSK_{ow} v1.42):
Water Solubility at 25 deg C (mg/L): 5997
log K_{ow} used: 0.70 ($expk_{ow}$ database)
no-melting pt equation used

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 6.4958e+005 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Aliphatic Amines
Neonicotinoids

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method: 9.21E-016 atm-m^3/mole (9.33E-011 Pa-m^3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:

HLC: 1.978E-010 atm-m^3/mole (2.004E-005 Pa-m^3/mole)
VP: 3.61E-006 mm Hg (source: MPBPVP)
WS: 6E+003 mg/L (source: $WSK_{ow}WIN$)

Log Octanol-Air Partition Coefficient (25 deg C) [K_{oa}WIN v1.10]:
Log K_{ow} used: 0.70 (exp database)
Log K_{aw} used: -13.424 (HenryWin est)
Log K_{oa} (K_{oa}WIN v1.10 estimate): 14.124
Log K_{oa} (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model): 0.4463
Biowin2 (Non-Linear Model): 0.0723
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.4408 (weeks-months)
Biowin4 (Primary Survey Model): 3.3222 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model): -0.0715
Biowin6 (MITI Non-Linear Model): 0.0075
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.2515
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 0.00824 Pa (6.18E-005 mm Hg)
Log K_{oa} (K_{oa}win est): 14.124
Kp (particle/gas partition coef. (m^3/ug)):
Mackay model: 0.000364
Octanol/air (K_{oa}) model: 32.7
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model: 0.013
Mackay model: 0.0283
Octanol/air (K_{oa}) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 136.9667 E-12 cm^3/molecule-sec
Half-Life = 0.078 Days (12-hr day; 1.5E6 OH/cm^3)
Half-Life = 0.937 Hrs.
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.0206 (Junge-Pankow, Mackay avg)
1 (K_{oa} method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (K_{oc}WIN v2.00):
K_{oc}: 929.4 L/kg (MCI method)
Log K_{oc}: 2.968 (MCI method)
K_{oc}: 27.81 L/kg (K_{ow} method)
Log $_{Koc}$: 1.444 (K_{ow} method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.8501 days (HL = 0.01412 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.034 (BCF = 1.081)
Log BAF Arnot-Gobas method (upper trophic) = 0.034 (BAF = 1.081)
log K_{ow} used: 0.70 (expkow database)

Volatilization from Water:
Henry LC: 9.21E-016 atm-m^3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 1.004E+012 hours (4.185E+010 days)
Half-Life from Model Lake: 1.096E+013 hours (4.566E+011 days)

Removal in Wastewater Treatment:
Total removal: 1.87 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.77 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

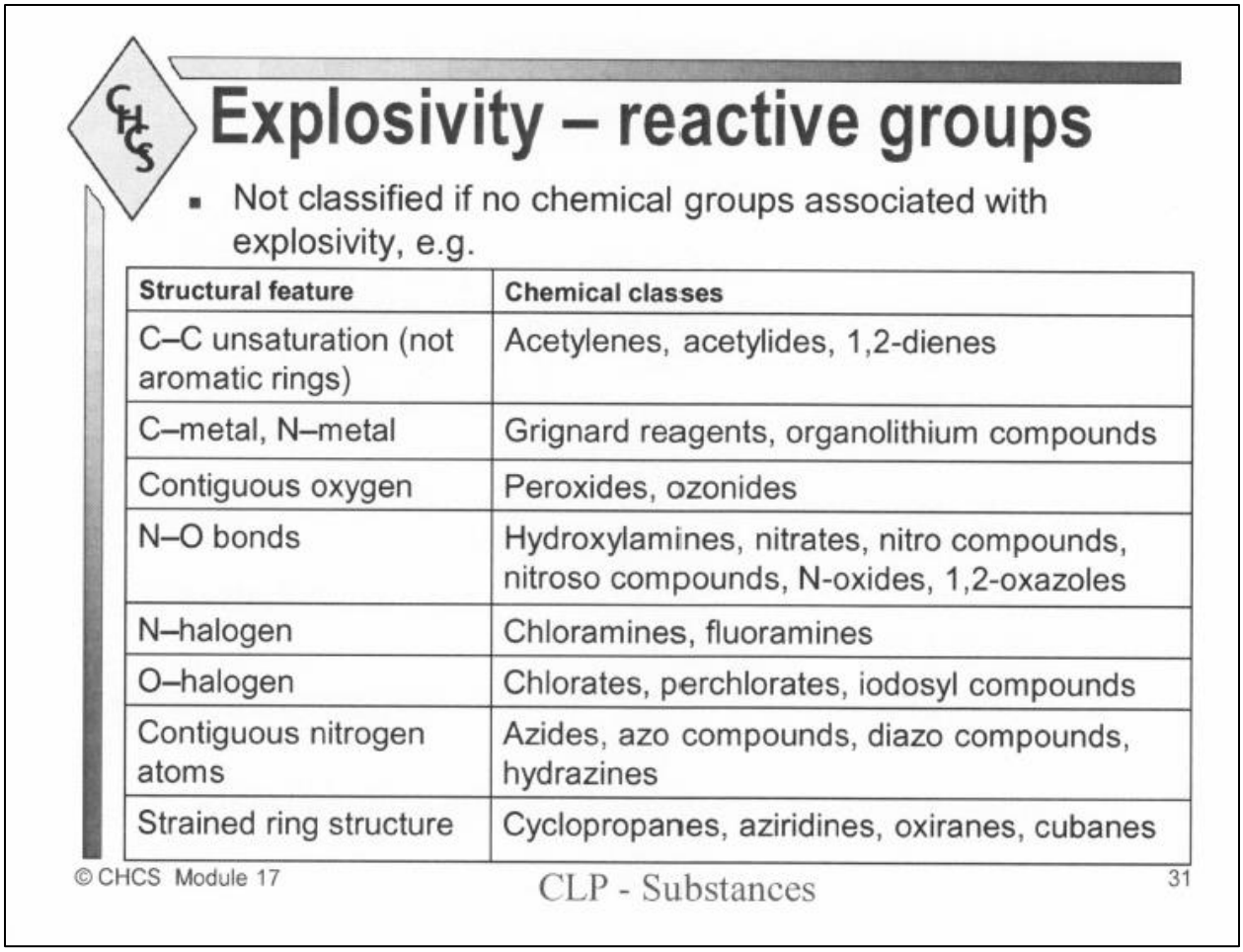
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr.)	Emissions (kg/hr.)
Air	6.99e-009	1.87	1000
Water	11.9	900	1000
Soil	87.5	1.8e+003	1000
Sediment	0.611	8.1e+003	0

Persistence Time: 1.83e+003 hr.

APPENDIX E: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



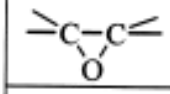
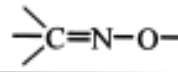
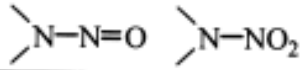
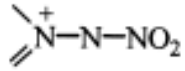
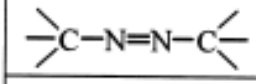
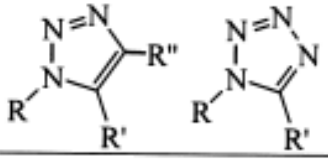
Explosivity – reactive groups

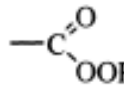
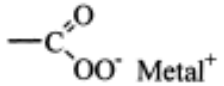
- Not classified if no chemical groups associated with explosivity, e.g.

Structural feature	Chemical classes
C–C unsaturation (not aromatic rings)	Acetylenes, acetylides, 1,2-dienes
C–metal, N–metal	Grignard reagents, organolithium compounds
Contiguous oxygen	Peroxides, ozonides
N–O bonds	Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles
N–halogen	Chloramines, fluoramines
O–halogen	Chlorates, perchlorates, iodosyl compounds
Contiguous nitrogen atoms	Azides, azo compounds, diazo compounds, hydrazines
Strained ring structure	Cyclopropanes, aziridines, oxiranes, cubanes

Explosivity – Full List

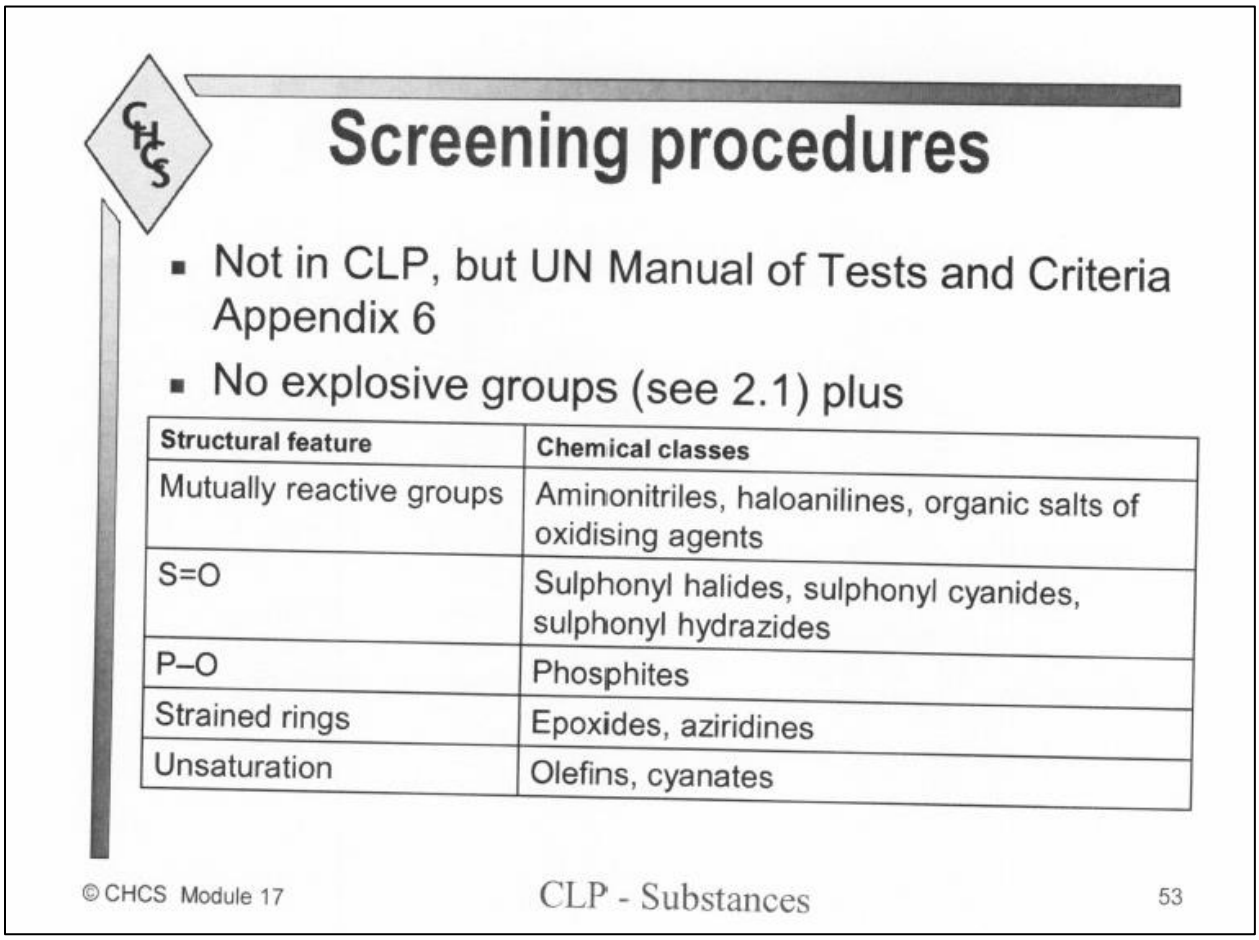
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or *aci*-Nitro Salts
	N-Metal Derivatives (especially heavy metals)
	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. $NC1_3$, $RNC1_2$	N-Halogen Compounds

Adapted from Bretherick (Bretherick's Handbook of Reactive Chemical Hazards 6th Ed., 1999, Butterworths, London)

Self-Reactive Substances



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