

**Thiamethoxam (CAS# 153719-23-4) GreenScreen® for Safer Chemicals (GreenScreen®)
Assessment**

Prepared for:

Natural Resources Defense Council

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TABLE OF CONTENTS

GreenScreen® Executive Summary for Thiamethoxam (CAS# 153719-23-4).....	i
Chemical Name.....	1
GreenScreen® Summary Rating for Thiamethoxam.....	2
Transformation Products and Ratings.....	2
Introduction.....	3
GreenScreen® List Translator Screening Results.....	4
Physicochemical Properties of Thiamethoxam.....	4
Group I Human Health Effects (Group I Human)	6
Carcinogenicity (C) Score	6
Mutagenicity/Genotoxicity (M) Score	12
Reproductive Toxicity (R) Score.....	13
Developmental Toxicity incl. Developmental Neurotoxicity (D) Score	15
Endocrine Activity (E) Score	18
Group II and II* Human Health Effects (Group II and II* Human).....	19
Acute Mammalian Toxicity (AT) Group II Score.....	19
Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)	20
Group II Score (single dose)	20
Group II* Score (repeated dose)	21
Neurotoxicity (N)	27
Group II Score (single dose)	27
Group II* Score (repeated dose)	28
Skin Sensitization (SnS) Group II* Score	30
Respiratory Sensitization (SnR) Group II* Score	30
Skin Irritation/Corrosivity (IrS) Group II Score.....	31
Eye Irritation/Corrosivity (IrE) Group II Score.....	31
Ecotoxicity (Ecotox)	32
Acute Aquatic Toxicity (AA) Score.....	32
Chronic Aquatic Toxicity (CA) Score.....	33
Acute Terrestrial Vertebrates Toxicity Score (ATV) Score	33
Chronic Terrestrial Vertebrates (CTV) Toxicity Score	34
Acute Foliar Invertebrates and Pollinators (AFI) Toxicity Score.....	34
Chronic Foliar Invertebrates and Pollinators (CFI) Toxicity Score	35
Environmental Fate (Fate)	39
Persistence (P) Score	39
Bioaccumulation (B) Score	40
Physical Hazards (Physical).....	41
Reactivity (Rx) Score	41
Flammability (F) Score.....	42

References.....	43
APPENDIX A: Hazard Benchmark Acronyms	47
APPENDIX B: Results of Automated GreenScreen® Score Calculation for Thiamethoxam (CAS# 153719-23-4).....	48
APPENDIX C: Pharos Output for Thiamethoxam (CAS# 153719-23-4)	49
APPENDIX D: EPISuite Modeling Results for Thiamethoxam (CAS# 153719-23-4)	50
APPENDIX E: Known Structural Alerts for Reactivity	53
Licensed GreenScreen® Profilers.....	57

TABLE OF FIGURES

Figure 1: GreenScreen® Hazard Ratings for Thiamethoxam.....	2
Figure 2: Chemical Structures for Major Metabolites of Thiamethoxam.....	6

TABLE OF TABLES

Table 1: Transformation Product Summary Table	3
Table 2: Physical and Chemical Properties of Thiamethoxam (CAS# 153719-23-4).....	4

GreenScreen® Executive Summary for Thiamethoxam (CAS# 153719-23-4)

Thiamethoxam is a chemical that primarily functions as a neonicotinoid insecticide.

Thiamethoxam 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) and acute foliar invertebrates toxicity (AFI¹))

Data gaps (DG) exist 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), thiamethoxam meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gaps. In a worst-case scenario, if thiamethoxam were assigned a High score for any of the data gaps, 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 Thiamethoxam

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*												
L	L	<i>M</i>	<i>M</i>	DG	M	L	M	H	L	L	DG	L	L	vH	<i>L</i>	L	H	vH	vL	<i>L</i>	<i>L</i>

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 Thiamethoxam (CAS# 153719-23-4)

Method Version: GreenScreen[®] Version 1.2²
Assessment Type³: Certified

Chemical Name: Thiamethoxam

CAS Number: 153719-23-4

GreenScreen[®] Assessment Prepared By:

Name: Mouna Zachary, Ph.D.

Title: Toxicologist

Organization: ToxServices LLC

Date: October 11, 2015 (updated December 10, 2015, January 7, 2016)

Assessor Type: Licensed GreenScreen[®] Profiler

Quality Control Performed By:

Name: Bingxuan Wang, Ph.D., D.A.B.T.

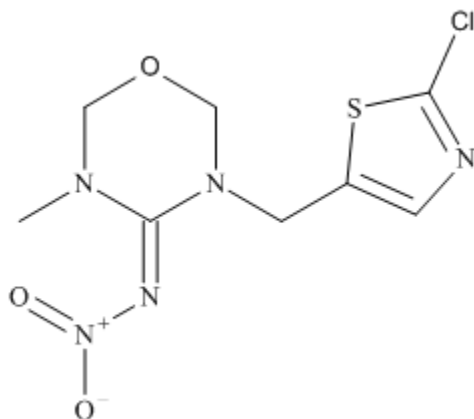
Title: Toxicologist

Organization: ToxServices LLC

Date: October 14, 2015 (updated December 10, 2015, January 7, 2016)

Confirm application of the *de minimus* rule⁴: N/A

Chemical Structure(s):



Thiamethoxam (CAS# 153719-23-4)

Also called: 3-((2-Chloro-5-thiazolyl)methyl)tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazin-4-imine, Actara, Actara 25WG, Actara 2GR, Adage, Adage 5FS, CGA 293343, Cruiser, Diaclofen, (ChemIDplus 2016).

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

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:

No surrogates were used as thiamethoxam has a relatively complete toxicological dataset.

Identify Applications/Functional Uses: (SCBP 2012)

1. Insecticide
2. Seed treatment/protectant
3. Wood Preservative

GreenScreen® Summary Rating for Thiamethoxam⁵: Thiamethoxam 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 Eco Toxicity (acute aquatic toxicity (AA), and acute foliar invertebrates toxicity (AFI⁶))

Data gaps (DG) exist 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), thiamethoxam meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gaps. In a worst-case scenario, if thiamethoxam were assigned a High score for any of the data gaps, it would still be categorized as a Benchmark 1 Chemical

Figure 1: GreenScreen® Hazard Ratings for Thiamethoxam

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*													
<i>L</i>	<i>L</i>	<i>M</i>	<i>M</i>	DG	<i>M</i>	<i>L</i>	<i>M</i>	H	<i>L</i>	<i>L</i>	DG	<i>L</i>	<i>L</i>	vH	<i>L</i>	<i>L</i>	H	vH	vL	<i>L</i>	<i>L</i>	

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

Thiamethoxam is not expected to be readily biodegradable; however, it is expected to hydrolyze in water under alkaline conditions and to degrade in soil under both aerobic and anaerobic conditions. It is also expected to photodegrade in water with a half-life of less than 3 days. Volatilization from

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.

water surfaces does not occur. Expected degradation products from these reactions are shown below in Table 1 along with their Pharos listings (SCBP 2012). As thiamethoxam is already assigned a GreenScreen Benchmark™ Score of 1, the hazards of the transformation products do not modify its Benchmark Score.

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}
Insecticide	In use and disposal	Hydrolysis	CGA 309335 [(2-chlorothiazol-5-yl)-methylamine]	120740-08-1	Y	Not in the Pharos database
Insecticide	In use and disposal	Hydrolysis, Photolysis and Anaerobic Degradation	NOA 407475 [3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-ylideneamine]	NA	Y	Not in the Pharos database
Insecticide	In use and disposal	Hydrolysis	NOA 404617 [1-(2-chlorothiazol-5-ylmethyl)-3-nitrourea]	NA	Y	Not in the Pharos database
Insecticide	In use and disposal	Hydrolysis, Photolysis and Aerobic Degradation in Soil	CGA 322704 [N-(2-chlorothiazol-5-ylmethyl)-N'-methyl-N"-nitroguanidine]	210880-92-5	Y	LT-P1
Insecticide	In use and disposal	Photolysis	CGA 353042 [3,6-dihydro-3-methyl-2H-1,3,5-oxadiazin-4-amine]	NA	Y	Not in the Pharos database
Insecticide	In use and disposal	Hydrolysis and Photolysis	CGA 355190 [3-(2-chlorothiazol-5-ylmethyl)-5-methyl-[1,3,5]oxadiazinan-4-one]	902493-06-5	Y	Not in the Pharos database

Introduction

Thiamethoxam is a systemic insecticide that belongs to the class of compounds called neonicotinoids. It has a broad spectrum of activity against many types of insects (JMPR 2010a,b).

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

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).

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 thiamethoxam can be found in Appendix C and a summary of the results can be found below:

- Mammalian Toxicity
 - CLP/GHS Hazard Statement H302 – Harmful if swallowed
 - EU Risk Phrase R22 – Harmful if swallowed
- Acute Aquatic Toxicity
 - EU Risk Phrase R50/53 – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
 - CLP/GHS Hazard Statement H400 – Very toxic to aquatic life
- Chronic Aquatic Toxicity
 - EU Risk Phrase R50/53 – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Thiamethoxam is not listed by DOT.

Physicochemical Properties of Thiamethoxam

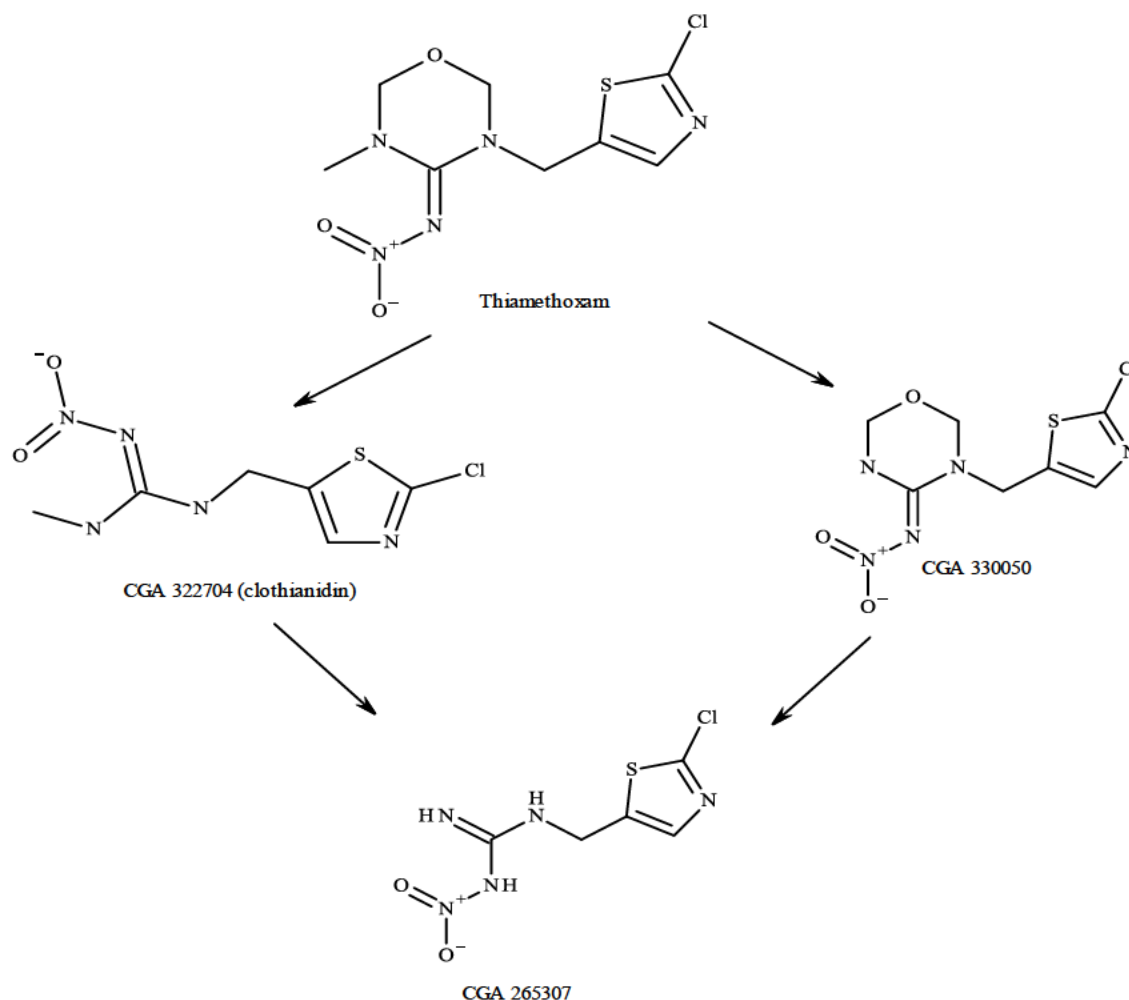
Thiamethoxam is a cream-colored, fine crystalline powder at room temperature and is soluble in water. Its vapor pressure indicates that it will exist mostly in the solid phase at room temperature and its measured partition coefficient of -0.13 indicates it has low potential to bioaccumulate.

Property	Value	Reference
Molecular formula	C ₈ H ₁₀ ClN ₅ O ₃ S	ChemIDplus 2016
SMILES Notation	C1OCN(\C(N1C)=N\([N+])([O-])=O)Cc1cnc(s1)Cl	ChemIDplus 2016
Molecular weight	291.718	ChemIDplus 2016
Physical state	Solid	JMPR 2010a, SCBP 2012
Appearance	Cream-colored, fine crystalline powder.	JMPR 2010a, SCBP 2012
Melting point	139.1°C	JMPR 2010a, SCBP 2012
Vapor pressure	2.7 x 10 ⁻⁹ Pa at 20°C 6.6 x 10 ⁻⁹ Pa at 20°C Measurements at 90.5-121°C	JMPR 2010a
Water solubility	4.1 g/L at 25°C	JMPR 2010a, SCBP 2012
Dissociation constant	No dissociation within pH range of 2-12	JMPR 2010a, SCBP 2012
Density/specific gravity	1.57 at 20°C	HSDB 2012, SCBP 2012
Partition coefficient	log P _{ow} = -0.13 at 25°C	JMPR 2010a, SCBP 2012

Toxicokinetics

- JMPR 2010b, Cal EPA 2008
 - The toxicokinetic behavior of thiamethoxam was examined in several studies using rats and mice. In rats, thiamethoxam was rapidly and almost completely absorbed from the gastrointestinal tract and readily distributed from the plasma into the body irrespective of dose level, site of the label or sex of the rat. Thiamethoxam was readily eliminated within 24 hours in the urine (84-95%) and feces (3-6%). Ultimately, 12 metabolites were isolated from the urine. The major fraction of the urine was unchanged thiamethoxam (70-80%), CGA 322704 clothianidin (12%) and CGA 265307 [N-(2-chlorothiazol-5-ylmethyl)-N'-nitroguanidine] (1.9%); all other metabolites represented less than 0.9% of the dose. The major metabolic pathway proposed is the cleavage of the oxadiazine ring to the corresponding nitroguanidine compound (See Figure 2). Other minor metabolic pathways include reduction of the nitroguanidine group to a hydrazine followed by either acylation or further reduction to a guanidine derivative, hydrolysis of the guanidine group to the corresponding urea, demethylation of the guanidine group, or substitution of the chlorine of the thiazole ring by glutathione.
 - In mice, metabolic degradation of thiamethoxam is similar to that seen in rats with 30–60% of the dose was biotransformed and eliminated mainly in urine, and only 19% was accounted for fecal elimination. Similarly, all major and almost all minor metabolites found in rat excreta were also detected in mouse excreta with plasma concentrations of two of the minor metabolites, CGA 330050 and CGA 265307, 5- to 140-fold higher in mouse than in rat.
 - *In vitro* studies of thiamethoxam metabolism in mouse, rat and human liver microsomal, however, showed that higher generation of the metabolites CGA 330050 and CGA 265307 were seen in mice compared with rats. In addition, human liver microsomes were shown to metabolize thiamethoxam in a manner quantitatively similar to and not exceeding that of rats. The structures of the urinary and fecal metabolites are shown below.
 - Dermal absorption of thiamethoxam was studied in two assays. One investigated dermal penetration in rats was and conducted according to OECD Guideline 427. The other study was a comparative *in vitro* assay conducted according to OECD Guideline 428 using rat and human skin. Very low dermal absorption of thiamethoxam was reported in these assays. Human dermal absorption was 4.8-5.8 times lower than rat dermal absorption.

Figure 2: Chemical Structures for Major Metabolites of Thiamethoxam



Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

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

Thiamethoxam was assigned a score of Low for carcinogenicity based on the weight of evidence supported by mechanistic data and on the recent U.S. EPA cancer classification for thiamethoxam as “unlikely to be carcinogenic in humans”. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when the weight of evidence indicates that the chemical is not classified per GHS (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
- Cal EPA 2008, JMPR 2010b
 - In a 2-year combined carcinogenicity and toxicity study, 4 groups of Sprague-Dawley rats (70/sex/group) were administered thiamethoxam in the diet at a concentration of 0 (control), 10, 30, 500, or 1,500 ppm (males) and 0, 10, 30, 1,000, or 3,000 (females);

- equivalent to 0, 0.41, 1.29, 21.0, and 63.0 mg/kg/day in males and to 0, 0.48, 1.56, 50.3, and 155 mg/kg/day, in females. Twenty rats/sex/group were designated for clinical laboratory investigations and 50 rats/sex/group for the carcinogenicity study. Additional groups of 10 rats/sex/group were similarly treated and then killed at 52 weeks for interim evaluation. Animals were evaluated for clinical signs, body weights, feed consumption, and water consumption, clinical chemistry, urinalysis, gross pathology, and histopathology. Survival incidence was not affected by treatment and there were no clinical signs of adverse effects due to treatment. The incidences of single and multiple palpable masses were unaffected by treatment at any dose level. Postmortem examination of rats after 52 weeks revealed no treatment-related lesions and most gross lesions occurred at comparable frequencies between control and treated groups. No treatment-related neoplastic lesions occurred in rats that were killed at 52 weeks or that died during the first 52 weeks. Some malignant and benign neoplasms were identified, though all were identified as types that occur spontaneously in this strain of rat. At 52 weeks, there were increased incidences of renal tubular regenerative changes, chronic tubular lesions, and tubular basophilic proliferation in males at 500 and 1,500 ppm. In females, a minimal increase in the severity of splenic hemisiderosis was seen at 3,000 ppm. Treatment-related, non-neoplastic changes were seen in the kidneys and liver of animals sacrificed at 104 weeks. These included a slight increase in the incidence of chronic nephropathy (slight/moderate) in males at 1,500ppm accompanied by a minimal increase in incidence of lymphocytic infiltration of the renal cortex and increase in the incidence of focal cellular alteration (slight/moderate) in females at 3,000 ppm. All neoplastic findings occurring at 104 weeks were considered incidental to treatment with thiamethoxam as incidences in treated and control groups were similar, no dose-response relationship was evident, or the incidences were within historical control ranges. Study authors identified a systemic toxicity NOAEL of 30 ppm based on increased incidences of renal chronic tubular lesions and basophilic proliferation in males at 500 ppm. However this renal lesion was considered to be α -2 microglobulin mediated nephropathy and therefore has no human relevance. Accordingly the relevant NOAEL of 1,000 ppm was established instead (equivalent to 50.3 mg/kg/day in females) based on foci of cellular alteration in the liver and increased severity of splenic hemisiderosis in females at 3,000 ppm (equivalent to 155 mg/kg/day).
- In a 78-week combined oncogenicity and long-term toxicity study, 5 groups of Tif:MAGf, SPF mice (60/sex/group) were administered thiamethoxam (purity 98.6%) in the diet at concentrations of 0, 5, 20, 500, 1,250, or 2,500 ppm (equivalent to 0 (control), 0.65, 2.63, 63.8, 162, and 354 mg/kg/day in males and 0, 0.89, 3.68, 87.6, 215, and 479 mg/kg/day in females as calculated by study authors). 10 mice/sex/group were designated for clinical laboratory investigation and 50 mice/sex/group for the oncogenicity study. Additional groups of 10 mice/sex/group were killed at 35 weeks for interim evaluation. Mice were observed for clinical signs, body weight/feed consumption, hematological, gross pathology, and histopathology. Survival incidence and incidence of palpable masses were not affected by treatment in either sex. Clinical signs were limited to increased incidence of abdominal distension in both sexes at 2,500 ppm and in females at 1,250 ppm. This finding correlated histologically with benign or malignant liver tumors, in most cases. Absolute and relative liver weights were increased in males at 1,250 ppm and above and in females at 500 ppm and above. No treatment-related gross lesions were detected at autopsy in week 35. Gross examinations at week 79 revealed an increased incidence of masses and nodules in the liver at doses of 500

- ppm and above, particularly in males. Liver histopathology performed at week 35 revealed non-neoplastic lesions only. At terminal sacrifice, treatment-related increases in the incidences of inflammatory cell infiltration, necrosis of single hepatocytes, Kupffer cell pigmentation, and hepatocyte hypertrophy were observed in both sexes at 500 ppm. Treatment-related non-neoplastic lesions in the liver occurred at 500 ppm and above. Lesions ranged in severity from minimal to marked and their incidences generally showed a positive dose-response relationship. The incidence of hepatocellular adenoma at 79 weeks was significantly greater than concurrent and historical control levels in both sexes at 500 ppm and above and the incidence of hepatocellular adenocarcinoma was significantly greater than concurrent and historical control level in females at 1,250 ppm and in both sexes at 2,500 ppm. Based on this, study authors concluded that thiamethoxam was tumorigenic in mice. A systemic toxicity NOAEL of 20 ppm, (equivalent to 2.63 mg/kg/day in males and 3.68 mg/kg/day in females) was established, based on increased liver weights, hepatocellular hypertrophy, pigment deposition, inflammatory cell infiltration, and single-cell necrosis at 500 ppm (equivalent to 63.8 mg/kg/day in males and 87.6 mg/kg/day in females).
- In a risk assessment on the carcinogenicity study in mice described above, Novartis Crop Protection argued that the mechanisms involved in liver tumors caused by thiamethoxam in mice are species-specific and threshold in nature. The authors proposed a margin of exposure approach rather than the conventional linear low dose extrapolation should be taken in the cancer risk assessment. The key arguments included the lack of mutagenicity, the lack of consistence across species (tumors only observed in mice, but not rats or dogs), and the proposed mechanism of action involving hepatocellular apoptosis and necrosis followed by regenerative hepatocyte proliferation that are unlikely to occur in humans.
 - An industry-sponsored mechanistic study was conducted to compare the liver toxicity of Tif:MAGf and CD-1 mice in their response to thiamethoxam and its two major metabolites. Mice (17/strain/interval) received 2,500 ppm thiamethoxam, 2,000 ppm CGA 322704, or 500 ppm CGA 265307 in the diet for 1, 10, or 20 weeks. Vocalizations and chirruping were commonly observed with CD-1 mice, and 10/17 were killed *in extremis* shortly after 10 weeks. Slight, and occasionally statistically significant decrease in body weight and approximately 10% decrease in food consumption were found for Tif:MAGf mice exposed to CGA 322704, while CD-1 mice showed more severe body weight effects and 20% reduction in feed consumption. Definitive liver pathology was only seen after thiamethoxam treatment, including hepatocyte apoptosis, hypertrophy and necrosis in $\geq 50\%$ of either strain. Tif:MAGf mice (20-week thiamethoxam) as well as CD-1 mice (10- and 20-week thiamethoxam) were frequently found with inflammatory infiltration and pigmentation of centrilobular hepatocytes. Statistically significant increase in BrdU labeling indices were found after thiamethoxam treatment in Tif:MAGf mice (20-week) and CD-1 mice (10- and 20-week), indicating increased DNA synthesis. No apoptosis was found in any group as measured by TUNEL-histochemistry. The authors concluded that thiamethoxam, rather than its major metabolites, is responsible for hepatotoxicity in mice.
 - An industry-sponsored mechanistic study was conducted to determine the level of oxidative stress in mice after thiamethoxam treatment. Male Tif:MAG(SPF) mice (10/group/interval) were exposed to the pesticide (purity 98.6%) in the diet at 0, 2,500 or 5,000 ppm for 7, 14, 28 or 60 days, which were estimated by the study authors to be 0, 448 and 976 mg/kg/day, respectively. Reduced body weight was found at the high dose only. No clinical signs were observed. No indication of oxidative stress was found, as

- measured by total 8-isoprostane $F_{2\alpha}$ in liver and free 8-isoprostane $F_{2\alpha}$ in plasma, malondialdehyde, α -tocopherol and oxidized glutathione (GSH) in liver. Highly significant and dose-related increase in reduced liver GSH was observed in both treatment groups, which was interpreted by the study authors as indications of liver induction (i.e., increased synthesis of GSH). The study authors concluded that no evidence of oxidative stress was found.
- An industry-sponsored mechanistic study was conducted to determine the level of oxidative stress in mice after thiamethoxam treatment. Male Tif:MAG(SPF) mice (10/group/interval) were exposed to the pesticide (purity 98.6%) in the diet at 0, 2,500 or 5,000 ppm for 10, 20, 30, 40 or 50 weeks, which were estimated by the study authors to be 0, 318 and 693 mg/kg/day, respectively. Reduced body weight was found at both doses. No clinical signs were observed. Livers commonly showed “accentuated lobular pattern” at both doses, and non-neoplastic liver pathology findings at 50 weeks include hypertrophy (incidence: 0, 6, 8), necrosis (0, 9, 9), apoptosis (0, 4, 5), inflammatory cell infiltration (4, 8, 8), and pigmentation (0, 6, 7). Liver neoplasia (hepatocellular adenoma and carcinoma) incidences were 1, 1, and 4. Free plasma 8-isoprostane $F_{2\alpha}$ was unaffected, whereas total liver 8-isoprostane $F_{2\alpha}$ was statistically significantly reduced at the high dose only. Liver α -tocopherol was unaffected. Oxidized GSH in the liver was unaffected, while reduced liver GSH was statistically significantly, and dose relatedly increased in both treatment groups. Significantly elevated liver γ -glutamylcystein synthetase (the enzyme responsible for GSH synthesis) activity was found in both groups. The study authors concluded that there was no indication of oxidative stress and strong indication of liver metabolic induction.
 - An industry-sponsored mechanistic study was conducted to assess hepatic cell proliferation and apoptosis in mice in response to thiamethoxam. Male Tif:MAGf(SPF) mice (15/dose/interval) were exposed to the pesticide (purity 98.6%) at 0, 50, 200, 500, 1,250, or 5,000 ppm for 10, 20, 30, 40 or 50 weeks in the diet (equivalent to 6.3, 25, 62, 151, 314 and 684 mg/kg/day, respectively, according to the study authors). Significant reduction of body weight was found at the two highest doses (5% and 17%, respectively, at 30 weeks). Statistically significantly increased relative, but not absolute, liver weight was found at the two highest doses. A dose-related and time-dependent increase in plasma alanine aminotransferase was found at doses of 1,250 ppm and above. A lesser, but also statistically significant increase was observed for aspartate aminotransferase, but not alkaline phosphatase, in this dose range. Gross liver pathology revealed a dose-related “accentuated lobular pattern” at 500 ppm and above, but not at the highest dose. Consistent pattern of fatty change, hepatocellular apoptosis and necrosis, and inflammatory cell infiltration were observed at 500 ppm and above. A strong dose-dependent increase of hepatocellular hypertrophy was found at the two highest doses, and of hepatocellular pigmentation was found at the three highest doses. BrdU labeling indices indicated cell proliferation at 1,250 ppm and above without time-dependence (a later re-evaluation found statistically significant increases in BrdU labeling indices at 500 and 1,250 ppm). TUNEL assay indicated increased (and time-dependent) apoptosis at 500 ppm and above. The authors concluded that male mice showed a consistent pattern of liver pathology including altered functional behavior, cell losses through necrosis and apoptosis, and heightened compensatory or repair activity at 500 ppm and higher doses. The authors also hypothesized that these observations pre-dispose conditions to hepatocellular tumors.
 - An industry-sponsored mechanistic study was conducted to assess hepatic apoptosis in response to thiamethoxam. Liver sections from the previously described mouse

- carcinogenicity study (control and 2,500 ppm males only) and a study on hepatic cell proliferation and apoptosis in mice (dose levels of 0, 100, 500 and 2,500 ppm at 3, 7, 13, 27 and 59 days, details not available) were evaluated for apoptosis with TUNEL histochemistry as well as Eosin staining to obtain a measurement of hepatic tissue area. In the carcinogenicity study, apoptosis was highly significant. In the other study, apoptosis was increased only after 59 days and was dose-related.
- In industry-sponsored mechanistic study was performed to determine enzymes involved in the biosynthesis and modulation of GSH in mice liver following subchronic exposure to thiamethoxam. Male Tif:MAGf(SPF) mice (10/duration/dose) were exposed to thiamethoxam (purity 98.6%) in the diet at 0, 2,500 or 5,000 ppm for 7, 14, 28 or 60 days. Increased γ -glutamylcysteine synthetase activity at all treatment intervals was found in both treatment groups, which is an inducible enzyme and rate-limiting for GSH biosynthesis. Highly significant increase in glutathione S-transferase activity was found at both doses at all time intervals with a modest dose-response. No or little influence was observed on treatment response after 14-28 weeks.
 - An industry-sponsored mechanistic study was performed to examine the role of nitric oxide in the development of liver toxicity in mice. Tumor necrosis factor α (TNF- α) enhances tumorigenesis, and nitric oxide inhibits TNF- α . Nitric oxide is produced by the enzyme inducible nitric oxide synthase (iNOS) from arginine. The thiamethoxam metabolite CGA265307 is structurally similar to a known iNOS inhibitor. In this study, the investigators evaluated the iNOS-dependent inhibition of nitric oxide release *in vitro* in the presence of thiamethoxam and its metabolites CGA265307, CGA332704, CGA330050, NOA421276, NOA412275, and NOA404617. CGA265307 inhibited iNOS by 39%, whereas the positive control L-NAME reduced its activity by 11%. NOA421276 showed a marginal inhibition. No other tested compounds showed any effects. In a subsequent *in vivo* study, male mice (5/group) received an i.p. injection of the known hepatotoxicant carbon tetrachloride 16 hours before sacrifice, or 7 days with 2,000 ppm of CGA265307 (yielding plasma concentration similar to that following 2,500 ppm dietary thiamethoxam), or a combination of CGA265307 and carbon tetrachloride. The combined treatment enhanced liver histopathology, including microvesicular vacuolation, subcapsular necrosis, and possibly hepatocyte necrosis and hydropic degeneration over either treatment alone. The authors concluded that thiamethoxam might elicit liver toxicity including tumors by its metabolite CGA265307 inhibiting iNOS.
 - An industry-sponsored mechanistic study was conducted to examine the changes in plasma cholesterol levels during dietary feeding studies. Data were submitted from multiple animal experiments. Statistically significant reduction in cholesterol was found in Tif:MAG mice and CD-1 after treatment with thiamethoxam in the diet for various durations (as short as one day, although not statistically significant). Thiamethoxam metabolites CGA330050, but not CGA322704 or CGA265307, also decreased cholesterol levels in mice. A recovery study found a return to normal cholesterol after 2 and 4 weeks of recovery in Tif:MAG mice after exposure to 2,500 ppm thiamethoxam for 4 weeks. However, Tif:RAIF rats exposed to thiamethoxam for 1 to 50 weeks in the diet at 1,000 or 3,000 ppm did not have altered plasma cholesterol levels. Thiamethoxam or its metabolites did not alter HMGCoA reductase activity in liver microsomes *in vivo* or *in vitro* (species not specified), which is a rate-limiting enzyme in cholesterol biosynthesis and a target for statin pharmaceuticals. The authors concluded that thiamethoxam does not have a mechanism similar to statins.

- An industry-sponsored mechanistic study was conducted to compare the hepatotoxicity of weanling and adult mice in response to dietary exposure to thiamethoxam (up to 2,500 ppm for 7 days). Adults had reduced cholesterol at a lower dose than weanling rats, while plasma concentrations of thiamethoxam and its metabolites are higher in weanlings than in adults. Neither adults nor weanlings had altered liver weights, or plasma ALT or AST activities. The only histopathological finding was a slight increase in reduced eosinophilic staining of centrilobular hepatocytes in adults at 1,250 ppm and higher, and possibly in weanlings at 2,500 ppm. The authors found that adults were more sensitive than weanlings to hepatotoxicity.
- Three industry-sponsored mechanistic studies were reported on the hepatotoxicity of thiamethoxam metabolites. In the first study, male TifLMAGf mice (17/group/interval) were exposed to thiamethoxam (2,500 ppm), CGA322704 (2,000 ppm) and CGA265307 (500 ppm) in the diet for 1, 10 or 20 weeks. Only thiamethoxam showed liver toxicity: hepatocyte apoptosis, hypertrophy and necrosis, reduced cholesterol, increased plasma ALT activity, and increased BrdU indices suggesting increased DNA synthesis. No effects were seen in TUNEL-histochemistry tests for apoptosis. In the second study (previously described as the mechanistic study on plasma cholesterol), reduced plasma cholesterol was found after 1, 4, and 10-week exposure to CGA330050 at 500 ppm and 1,000 ppm in mice. Hepatocellular hypertrophy (minimal) was also observed at 1,000 ppm. Significant increase in BrdU was found at 1,000 ppm at 10 weeks. Significant increase in apoptosis was report at 500 ppm, but not at 1,000 ppm, which weakly suggests a treatment response. In the third study, Tif:Ralf rats were exposed to CGA330050 at 0, 500 or 1,000 ppm for 1 week. Plasma cholesterol was marginally reduced, and plasma ALT and AST activities were modestly but statistically significantly reduced, indicative of altered liver function but not losses in cellular viability. Summarizing the three studies, the authors concluded that thiamethoxam and CGA330050 may share a common mode of action, which may be associated with CGA330050 alone. Hepatotoxicity was less evidence in rats, as the metabolite CGA330050 is a very minor metabolite in rats. The authors suggested that CGA330050 as the key metabolite responsible for changes leading to the development of liver tumors in mice treated with thiamethoxam.
- An industry-sponsored mechanistic data was conducted to examine the effects of 1 and 10-week dietary exposure to thiamethoxam on biochemical parameters in rat livers (females only). Of the 30 metabolizing enzymes assayed, 10 had slightly elevated activities (up to 51% increase), five had slightly reduced activities (up to 34% reduction), and 15 were unaffected. The investigators concluded that none of the observations indicate remarkable changes, in contrast to responses in a comparable study in mice.
- Syngenta provided a summary report on the mode of action for thiamethoxam-related mouse liver tumors. In this report, the authors noted that mouse liver tumors arise from perturbed cholesterol synthesis, hepatotoxicity, cell death, and tumors associated with increased cell proliferation. Species-specific metabolic pattern predisposes mouse to liver tumors while rats do not acquire liver tumors and have a different metabolic pattern. The authors also suggested that these effects were expected to be limited to comparably high dose levels.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Low was assigned. Thiamethoxam was not carcinogenic to the rat. However, liver tumors were observed in both male and female mice receiving thiamethoxam in the diet at concentrations of 500 ppm or more for 78 weeks. These tumors were observed at doses exceeding the MTD and/or causing organ toxicity and induction of liver enzymes. Due to the lack of mutagenicity (detailed in mutagenicity section below), it was concluded that the mechanism of liver cancers in mice was not via genotoxic effects. As a result of this, the mode of action of thiamethoxam on the carcinogenic response observed in mice was investigated by the pesticide sponsor Syngenta in several mechanistic animal experiments (Green et al. 2005a, Green et al. 2005b, Pastoor et al. 2005 and others). These study authors indicated that the mechanism of action is species-specific and involves hepatocellular apoptosis and necrosis followed by regenerative hepatocyte proliferation (Green 2005a). These key events were shown not to occur in rats and are unlikely to occur in humans. In addition, the studies identified that certain major metabolites of thiamethoxam (CGA330050 and CGA265307 see Figure 2) were responsible for the hepatic changes in mice that are formed at a much lower rate (at least 54-fold lower) in rats than in mice, leading to rats not developing hepatic tumors in the chronic study described above. In humans, the rate of this conversion was even lower than in rats. Based on this, the U.S. EPA's Office of Pesticide Program changed its original cancer classification for thiamethoxam from "likely to be carcinogenic in humans" to "not likely to be carcinogenic in humans" (U.S. EPA 2014). In addition, thiamethoxam is not proposed to be classified as carcinogenic under the EU regulation for classification, labelling and packaging of chemical substances, as the response was unique to the mouse liver with a non-genotoxic mode of action (SCBP 2012).

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

Thiamethoxam 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
- JMPR 2010b, SCBP 2012
 - *In vitro*: Negative results for mutagenicity were obtained in two gene mutation assays. *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* tester strain WP2 *uvr A* were exposed to thiamethoxam at concentrations up to 5,000 ug/plate, with and without metabolic activation. No increase in the mutation frequency was observed in the presence or absence of metabolic activation
 - *In vitro*: In a mammalian cell mutation assay using Chinese hamster V79 cell lines, thiamethoxam was not mutagenic in the presence and absence of metabolic activation at concentration up to 3,330 µg/mL.
 - *In vitro*: In a chromosome aberration test using Chinese hamster ovary cells, thiamethoxam was not clastogenic in the presence and absence of metabolic activation at concentrations up to 4,540 µg/ml.

- *In vitro*: Negative results were obtained in two unscheduled DNA synthesis activity assays conducted using primary cultures of hepatocytes from rats and mice at concentration up to 1,665µg/ml and 235µg/ml, respectively.
- *In vivo*: Thiamethoxam was tested in an *in vivo* micronucleus test using mice. Male and female Tif:MAGf mice (5/sex) were administered the test material by oral gavage at concentration of 1,000 mg/kg (males) and 1,250 mg/kg (females). There were no increases in the frequencies of micronucleated normochromatic erythrocytes reported from the bone marrow smears.

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

Thiamethoxam was assigned a score of Moderate for reproductive toxicity based on reduced testis weights and/or abnormal sperm parameters in animal studies at doses causing generalized systemic toxicities. GreenScreen[®] criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity (CPA 2012b). Confidence in the score is reduced because it is unclear if the male reproductive toxicity is secondary to systemic toxicity.

- Authoritative and Screening Lists
 - *Authoritative*: not listed on any authoritative lists
 - *Screening*: not listed on any screening lists
- JMPR 2010b, Cal EPA 2008
 - In a two-generation reproduction study in rats, 4 groups of male and female Tif:RAIf, SPF rats (30/sex/dose) were administered thiamethoxam (purity 98.6%) in the diet at doses of 0 (control), 10, 30, 1,000, or 2,500 ppm throughout both generations. Dietary concentrations were equivalent to 0, 0.4-1.5, 1.4-4.3, 45.6-144.0, and 117.6-362.9 mg/kg/day for males and 0, 0.6-2.1, 1.8-6.4, 59.3-219.6, and 14.8-541.3 mg/kg/day for females as calculated by the study authors. Parental animals were treated 10 weeks prior to mating, then throughout mating, gestation and lactation, for two litters per generation. Dams were continuously exposed through gestation and lactation. The parental animals were evaluated for clinical signs of toxicity, body weight, food consumption, testes and epididymis weights, gross pathology, and histopathology. Reproductive parameters (mating, gestation, and parturition parameters) along with pup survival and development, and behavioral landmarks were recorded. Sperm analysis (motility, morphology, spermatid counts, weights) was performed on 15 males/group in the F₀ and F₁ generations and 30 unmated male Tif:RAIf, SPF rats. Male and female mating and fertility indices, female gestation and parturition indices, and litter live birth, viability, and lactation indices were calculated. No treatment-related deaths or clinical signs were seen. Body weight gain was significantly reduced by 10.4% throughout the study in males at 2,500 ppm. There were no effects on the microscopic appearance of the reproductive organs of F₀ males and females at 2,500 ppm or in any non-pregnant females or males that failed to mate. An increased incidence of minimal to marked hyaline change in renal tubule cells in males at 1,000 and 2,500 ppm and a slightly increased incidence of renal tubular casts in males at 2,500 ppm were attributed to treatment. Further re-examination showed a similarity between the incidence and severity of minute focal tubular changes and diffuse tubular atrophy. An increase in incidence and severity of diffuse tubular atrophy in the 1,000 ppm group was unlikely to be treatment-related. No effects were seen on spermatid concentration or sperm morphology at any dose. Sperm motility in all thiamethoxam-treated groups was reduced significantly, though variation was high which suggests technical flaws. There was also no dose-response relationship. There were no

- treatment-related effects on any of the reproductive parameters measured. Similarly, no treatment-related effects in litter size, mean birth weight, sex ratio, or viability/lactation indices were observed. A slight decrease in pup weight gain was observed in both F1a and F1b at 2,500 ppm during the last 2 weeks of lactation and for F2a and F2b pups at 1000 and 2,500 ppm. Study authors identified a parental toxicity NOAEL of 30 ppm, equal to 1.4 mg/kg/day for male rats, based on hyaline change and casts in renal tubules in males at 1,000 ppm, equal to 45.6 mg/kg/day. Since this observation has no human relevance, the relevant parental toxicity was 1,000 ppm based on significantly reduced body weight gain at 2,500 ppm, equal to 117.6 mg/kg/day, in F₀ generation males. A reproductive toxicity NOAEL was identified as 2,500 ppm, the highest dose tested. A NOAEL for pups and developing offspring was 30 ppm based on reduced pup weight at 1,000 ppm.
- In a two-generation reproduction study in rats, 4 groups of male and female Tif:RAIf, SPF (Sprague-Dawley-derived) rats (26/sex/group) were administered thiamethoxam (purity 98.6%) in the diet at doses of 0 (control), 20, 50, 1,000, or 2,500 ppm throughout the two generations. Parents (both F₀ and F₁) were exposed to thiamethoxam for 10 weeks before pairing. Study authors monitored parental growth, reproductive function, mating behavior, conception, gestation, parturition, lactation and weaning, and the growth and development of pups. No effects of thiamethoxam on the clinical condition of F₀ or F₁ parents or F₁ satellite males were observed. Body weights were statistically significantly reduced in F₀ males given 2,500 ppm. This was accompanied by a reduction in feed consumption and feed utilization during weeks 1–4. No effects were seen on reproductive function in either F₀ or F₁ females, including mean cycle length, number of cycles, the precoital interval, gestation period length, or mating success. Proportions of successful matings were lower in the 20 and 2,500 ppm groups compared to the control group, but these results were not statistically significant. Up to five whole-litter losses occurred in each group of the F₀ and F₁ generations, but the incidence of litters affected was not related to dose and study authors considered it unrelated to treatment. Thiamethoxam did not affect the sex ratio or clinical condition of F_{1A} or F_{2A} pups. Total litter weight of the F_{1A} pups was statistically significantly lower in the 2,500 ppm group in comparison with the control. Relative (to body weight) adrenal and kidney weights were statistically significantly increased in F₀ males at 2,500ppm. Similarly, liver weights were significantly increased in F₀ males at 1,000 ppm, and relative liver weights were significantly increased in F₁ male and F₁ female rats of the 2,500 ppm group. Microscopic examination of the kidneys revealed increased tubule cell hyaline droplet formation in F₀ and F₁ males given 1,000 ppm and above with the incidence in F₁ males being much higher than in the F₀ generation. Absolute weight of the combined epididymides in the F₁ generation were statistically significantly greater in the 2,500 ppm group than in the control group and relative weights of the combined epididymides were statistically significantly greater in both the 1,000 and 2,500 ppm groups compared to the control. Testis weights in the F₁ 20, 1,000, and 2,500 ppm groups were significantly increased compared to the control weight, though study authors suggested that this is due to a particularly low control group testis weight as weights were unaffected by treatment in the F₀ generation. Sperm analysis showed a statistically significant decrease in the total number of sperm and the number of sperm per gram of right testis in F₁ males given 50, 1,000, or 2,500 ppm, despite no effect being seen in the F₀ males. Also in F₁ males, total sperm number in the right cauda epididymis was statistically significantly higher at 2,500 ppm than in the control group, despite no effect being seen in F₀ males. An increased incidence (14/26) of minimal germ cell loss/disorganization with or without

- Sertoli cell vacuolation was observed in the testis of F1 males given 2,500 ppm compared with the control and lower dose groups (1/26 – 3/26). No other statistically significant or dose-related observations were made. Study authors identified a parental toxicity NOAEL of 50 ppm (equivalent to 3.0 mg/kg/day for males), based on hyaline change and casts in renal tubules in males at 1,000 ppm (equivalent to 61.7 mg/kg/day). Since this observation has no human relevance, a relevant NOAEL for parental toxicity was identified as 1,000 ppm based on significantly reduced body weight gain at 2,500 ppm (equivalent to 155.6 mg/kg/day in F₀ generation males). The NOAEL for reproductive toxicity was 1,000 ppm (equivalent to 74.8 mg/kg/day for F₁ males), based on minimal testicular germ cell loss at 2,500 ppm, equal to 191.5 mg/kg/day. The NOAEL for pups and developing offspring was 1,000 ppm, equal to 74.8 mg/kg/day for males and 110.1 mg/kg/day for females, based on reduced body weight gains of pups during F₁ lactation at 2,500 ppm, equal to 191.5 mg/kg/day for males and 276.6 mg/kg/day for females. Study authors concluded that thiamethoxam was not a selective reproductive toxicant.
- Cal EPA 2008
 - In a range-finding reproductive toxicity study, male and female Tif:RAIf (SPF) rats (15/sex/dose) were administered thiamethoxam (purity 98%) in diet at doses of 0, 1,000, 2,000 and 4,000 ppm beginning two weeks before mating and continuing through two weeks postpartum. No treatment-related mortalities or clinical signs were observed. High dose males (4,000 ppm) had reduced body weight and body weight gain during pre-mating, females in all dose groups had reduced body weight gain during pre-mating. High dose females (4,000 ppm) had reduced body weights during lactation. Food consumption was reduced in high dose males (4,000 ppm) and in mid and high dose females (2,000 and 4,000 ppm) during pre-mating. No effects were reported on male and female mating and fertility indices or gestation and parturition indices. Litters from the high dose parents (4,000 ppm) had decreased litter weights and litter weight gain.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Moderate was assigned. Reduced sperm motility was observed in the first reproductive toxicity study in rats at all treated doses, although the authors disregarded this effect based on the high variations in this finding. A statistically significant decrease in total sperm and the number of sperm per gram of testis was also reported in F₁ males in the second reproduction study. In the second two-generation reproduction study performed with rats that was described above, an effect on testicular histopathology (germ cell loss/disorganization and Sertoli cell vacuolation) was seen in F1 males. These changes were unaccompanied by any reduction in epididymal sperm numbers and they were not observed in the first two-generation rat study. Therefore, the study authors did not consider these as signs of specific reproductive toxicity. However, as described in repeated dose toxicity section below, testis toxicity and/or reduced spermatogenesis was also observed in repeated dose toxicity studies in rats and dogs. These effects usually occurred at doses with other generalized systemic toxicity. As testis toxicity has been consistently observed across studies, ToxServices considered these effects limited evidence of the reproductive toxicity of thiamethoxam and assigned a Moderate score for this endpoint.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): M

Thiamethoxam was assigned a score of Moderate for developmental toxicity based on delayed skeletal development, body weight reduction and post-implantation loss in the presence of mild to

severe maternal toxicity (i.e. reduced body weight to mortality). GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity (CPA 2012b). The confidence in the score is reduced as the possibility could not be ruled out that the effects occurring in the presence of maternal toxicity were not secondary to maternal toxicity.

- Authoritative and Screening Lists
 - *Authoritative*: not listed on any authoritative lists
 - *Screening*: not listed on any screening lists
- JMPR 2010b, Cal EPA 2008
 - In a developmental toxicity study, time-mated female Sprague-Dawley (Tif:RAIf, SPF) rats (24 /group) were exposed to thiamethoxam (purity 98.6%) orally by gavage at dose levels of 0, 5, 30, 200, or 750 mg/kg/day from day 6 through 15 of gestation. Mortality, clinical signs, body weight, and feed consumption were measured throughout gestation. After delivery, the uterine tract and contents were removed and weighed. Ovaries, uteri, and placentae were examined macroscopically. Fetuses were examined for soft tissue and skeletal malformations, anomalies, and variations. No treatment-related deaths occurred and clinical findings were limited to transient hypoactivity, piloerection, and regurgitation of dosing material (2 dams). Maternal body weight gain was moderately depressed during the treatment period at 750 mg/kg/day and to a lesser extent at 200 mg/kg/day. Feed consumption was decreased during treatment at 750 mg/kg/day. There were no effects on pregnancy incidence, mean number of corpora lutea, preimplantation loss, number of implantation sites, number of post-implantation losses, mean numbers of live fetuses, and sex ratios at all dose levels. A significant reduction in mean body weight of fetuses at 750 mg/kg/day was attributed to the maternal toxicity (reduced body weight gain) seen at this dose level. There were no skeletal malformations at any dose level. However, increased incidences of skeletal anomalies and variants occurred at 750 mg/kg/day. Anomalies included asymmetric sternbrae and irregular, poor, or absent ossification of the occipital bone. These findings are considered to represent a treatment-related delay of ossification, secondary to reduced pup weight which reflects maternal toxicity. No other dose level had treatment-related skeletal effects. Study authors identified a NOAEL for maternal toxicity of 30 mg/kg/day, based on slightly decreased body weight gain in dams at 200 mg/kg/day (LOAEL). The NOAEL for fetotoxicity was established as 200 mg/kg/day based on mild reduction in mean fetal body weight and increased incidences of skeletal anomalies at 750 mg/kg/day. Study authors concluded that thiamethoxam was not teratogenic in this study.
 - In another developmental toxicity study, time-mated female Russian Chbb:HM rabbits (19 /group) were administered thiamethoxam (purity 98.6%) orally by gavage from day 7 through day 19 of gestation at a daily dose level of 0, 5, 15, 50, or 150 mg/kg/day. Females were observed twice daily for mortality and once daily for clinical signs and body weights. Feed consumption was also recorded. Reproductive tract contents were removed and weighed. The main organs of the thoracic and abdominal cavities and the ovaries, uteri, and placentae were examined. Numbers of corpora lutea were counted. Number and location of implantation/abortion sites in the uterus were counted in dams that died or were killed before scheduled autopsy. In dams killed at scheduled autopsy, the number and location of live and dead fetuses or early and late losses were recorded. Fetuses were numbered, tagged, weighed, sexed, and examined for external malformations and variations, including those in the tissue and skeleton. Treatment-related clinical signs were seen at 150 mg/kg/day and included a bloody discharge in the

- perineal area of 13 rabbits, including three rabbits, which died or were killed for humane reasons at the end of the treatment period. These clinical signs and deaths were not apparent at lower doses. Mean body weight was markedly reduced by treatment at 150 mg/kg/day with weight gain reduction in animals at 50 mg/kg/day being minimal and non-significant. Weight gain recovery at 150 mg/kg/day was rapid in post-treatment. Feed consumption was significantly and dose-dependently reduced in the 50 and 150 mg/kg/day groups during treatment but a significant increase in consumption was recorded in the 150 mg/kg/day group post-treatment. At autopsy, the uteri of the 3 rabbits that died or were killed before schedule were hemorrhagic. One rabbit showed a hemorrhagic vagina. There was a treatment-related reduction in the number of rabbits with live fetuses as total resorption occurred in 3 rabbits at 150 mg/kg/day and 1 rabbit at 50 mg/kg/day. Mean pup weights of both sexes were reduced due to treatment at 150 mg/kg/day. No external or skeletal fetal malformations or treatment-related visceral malformations were evident. No skeletal or physical anomalies were determined to be treatment-related other than the incidence of fused sternbrae which was increased at 150 mg/kg/day. However, this was considered to be a consequence of reduced birth weight, which in turns reflects maternal toxicity. Study authors identified a NOAEL for maternal toxicity in rabbits of 15 mg/kg/day based on reduction in body weight gain and feed consumption during the treatment period in dams at 50 mg/kg/day. A NOAEL for fetotoxicity in rabbits was 50 mg/kg/day based on increased post-implantation loss and reduction in fetal body weights at 150 mg/kg/day.
- In a developmental neurotoxicity study conducted according to OECD Guideline 426, pregnant female Alpk:APfSD rats (30/group) were administered thiamethoxam (purity 98.8%) in the diet at a concentration of 0(control), 50, 400, or 4,000 ppm from gestation day 7 through postnatal day 22. These concentrations were equal to 0, 4.3, 34.5, and 298.7 mg/kg/day during gestation and 0, 8.0, 64.0, and 593.5 mg/kg/day postpartum as calculated by study authors. Both maternal rats and F₁ pups were observed for clinical signs, body weights, and feed consumption and were subject to a FOB. F₁ pups were only examined for specific developmental landmarks, including vaginal opening in females and preputial separation in males, motor activity testing, and auditory startle reflex. No treatment-related clinical signs were seen in any females during general observations or during FOBs. Body weights and feed consumption of dams fed 4,000 ppm thiamethoxam were statistically significantly lower than those of controls. No clinical observations were made on pups in the F₁ generation. Body weights of F₁ pups were statistically significantly lower than controls at 4,000 ppm but no other treatment-related effects on pup weights. No treatment-related effects were observed during clinical observations or FOB evaluation in selected F₁ rats. Body weights at 4,000 ppm remained lower than controls for the rest of the study. Preputial separation in 4,000 ppm males was delayed by an average of 1.5 days compared to controls, though no treatment-related effect was observed on the days of vaginal opening in females. Locomotor activity, startle amplitude, ability to learn, and memory were all unaffected by treatment. Absolute brain weight was lower than that of controls at 4,000 ppm, though there were no differences from the control following adjustments for terminal body weight. Upon examination of the brain, a number of statistically significant differences were observed in both males and females at 4,000 ppm in several parameters at levels 3-5 after adjustment for body weight. Also at 4,000 ppm in males, there were decreases at level 5 in thalamus and hippocampus width. At 4,000 ppm in females, there were decreases at level 4 in thalamus and total brain width and at level 5 in thalamus width. No statistically significant differences were noted in these regions at lower dose groups. In both sexes at

day 12, a small number of brain morphometry parameters were statistically significantly different from controls at 4,000 ppm. Any other statistically significant findings were considered unrelated to treatment due to the test values being within historical control ranges, unusually high/low control values, adjustment for body weight, or an absence of a dose-response relationship. A NOAEL for maternal toxicity was identified as 400 ppm by study authors, equal to 34.5 mg/kg/day, based on decreased body weight gain and feed consumption in dams throughout gestation and postpartum at 4,000 ppm, equal to 298.7 mg/kg/day. The NOAEL for fetotoxicity was 400 ppm, equal to 64.0 mg/kg/day, based on reduced birth weight, reduced pup body weight gain, and some evidence of delayed preputial separation at 4,000 ppm, equal to 298.7 mg/kg/day. The NOAEL for developmental neurotoxicity was 4,000 ppm based on an absence of any quantitative histological or behavioral changes.

- Cal EPA 2008
 - In a dose range-finding developmental neurotoxicity study, time-mated female Alpk:AP_iSD (Wistar-derived) rats (10/dose) were administered 0, 1,000, 2,500 or 5,000 ppm thiamethoxam (purity 98.8%) from day 7 of gestation through day 22 post-partum (equivalent to 0, 92.3, 212.5 or 362.1 mg/kg/day during gestation, and 0, 156.5, 395.8 or 740.6 mg/kg/day during lactation). Middle and high dose groups (2,500 and 5,000 ppm) had decreased mean body weights during gestation, and the high dose group (5,000 ppm) had a decreased mean body weight during lactation. Additionally, the high dose group (5,000 ppm) had decreased mean food consumption throughout the duration of the study. Male pups from the 2,500 ppm dose group and male and female pups from the 5,000 ppm dose had a decreased mean body weight during lactation.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Moderate was assigned. In teratology studies described above, oral administration of thiamethoxam to pregnant female rats and rabbits caused developmental toxicity (reduced fetal weight, an increase in minor skeletal anomalies or variations indicative of delayed development, increased post-implantation loss and decreased mean body weight during lactation), which occurred in the presence of, and were attributed to, maternal toxicity by the study authors. In rabbits, the NOAEL for maternal toxicity was 15 mg/kg/day and for developmental toxicity was 50 mg/kg/day. In rats, 200 and 750 mg/kg/day caused maternal toxicity, but developmental toxicity secondary to maternal toxicity was observed only at 750 mg/kg/day. The NOAEL for maternal toxicity was 30 mg/kg/day and for developmental toxicity was 200 mg/kg/day. Fetotoxicity and skeletal anomalies (malformations and variants) were only seen at maternally toxic doses. Minor body weight reduction and delayed skeletal development are most often attributed to maternal toxicity. The increased post-implantation loss is a more serious effect that occurred in the presence of severe maternal toxicity including death. However, reduced body weight during lactation may not be attributable to maternal toxicity. As a mechanism of direct developmental toxicity cannot be ruled out, ToxServices conservatively assigned a Moderate score for this endpoint. The confidence in the score was reduced as the effects occurring in the presence of maternal toxicity could be secondary to maternal toxicity.

Endocrine Activity (E) Score (H, M, or L): DG

Thiamethoxam was assigned a score of Data Gap for endocrine activity 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
- 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.
- U.S. EPA 1999
 - Thiamethoxam does not belong to a class of chemicals known or suspected of having adverse effects on the endocrine system. In addition, no evidence of any effect on endocrine function was seen in developmental or reproduction studies with thiamethoxam. Furthermore, histological investigation of endocrine organs in chronic toxicity studies using dogs, rats and mice did not indicate that the endocrine system is targeted by thiamethoxam. However, ToxServices considered this information insufficient to conclude that thiamethoxam is not an endocrine disruptor, as the GreenScreen® criteria require data that demonstrate lack of activity for all endocrine pathways to assign a Low score, and thiamethoxam is not adequately tested for pathways other than estrogen, androgen and thyroid pathways as required by the EPA Office of Pesticides. Therefore, a score of DG was assigned.

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

Thiamethoxam was assigned a score of Moderate for acute toxicity based on its measured oral LD₅₀ values of 783-964 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 LD₅₀ 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. The EU Risk phrase of R22 corresponds to a score of High or Moderate.

- Authoritative and Screening Lists
 - *Authoritative*: EU Risk Phrase R22 – Harmful if swallowed
 - *Authoritative*: CLP/GHS Hazard Statement H302 – Harmful if swallowed
 - *Screening*: not listed on any screening lists
- JMPR 2010b, SCBP 2012
 - *Oral*: LD₅₀ = 1,563 mg/kg (rats)
 - *Oral*: LD₅₀ = 783 mg/kg (male mice)
 - *Oral*: LD₅₀ = 964 mg/kg (female mice)
 - *Dermal*: LD₅₀ > 2,000 mg/kg (rats)
 - *Inhalation*: LC₅₀ > 3.72 mg/L (rats, 4h)

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

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

Thiamethoxam was assigned a score of Low for systemic toxicity (single dose) based on lack of significant systemic toxicity observed in acute oral, dermal and inhalation toxicity studies.

GreenScreen[®] criteria classify chemicals as a Low hazard for systemic toxicity (single dose) 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
- 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 thiamethoxam was among the chemicals examined, and it was detected in 31.6% of the patients in TSG (6 of 19, 1.4 ppb), 6.3% of the patients in ASG (1 of 16, 1.9 ppb), and none of the volunteers in the NSG. The difference of prevalence between TSG and NSG reached statistical significance ($p < 0.0001$). The symptoms persistent mostly for days to months after cessation of consumption of locally grown produce.
- JMPR 2010b, SCBP 2012
 - *Oral*
 - In an acute oral toxicity study conducted according to OECD Guideline 401, Sprague-Dawley (Crj:CD SD) rats (5/sex/dose) were administered thiamethoxam (purity 98.6%) in aqueous methylcellulose at single doses of 0, 900, 1,500, 2,300, 3,800, or 6,000 mg/kg by oral gavage followed by a 14-day observation period. Treatment-related mortalities were seen in both sexes at dose of 1,500 mg/kg and above. Surviving animals from these dose groups showed reduced locomotor activity. Ptosis was seen in all treated groups 1 hour after dosing. There were no effects on gross pathology or body weight. An oral LD₅₀ of 1,563 mg/kg was identified in this study. ToxServices identified the systemic toxicity (single exposure) NOAEL at 6,000 mg/kg for this study based on the lack of significant systemic toxicity observed.
 - In an acute oral toxicity study conducted according to OECD Guideline 401, SPF (Crj:CD1(ICR)) mice (5/sex/dose) were administered thiamethoxam (purity 98.6%) in aqueous methylcellulose at single doses of 0, 500, 700, 1,000, 1,400 or 2,000 mg/kg by oral gavage followed by a 14-day observation period. Death occurred in treated animals from both sexes at dose of 700 mg/kg and above. Reduced locomotor activity or prostration was seen in all treated animals within 5–15 minutes of treatment, and clonic convulsions were seen 15 minutes to 4 hours after treatment. By day 2, all animals were entirely free from clinical signs. There were no effects on body weight. No noticeable macroscopic abnormality

was noted during necropsy. The oral LD₅₀ of 783 mg/kg in males and 964 mg/kg in females were identified in this study. ToxServices identified the NOAEL at 2,000 mg/kg for this study based on the lack of significant systemic toxicity observed.

- *Dermal*
 - Sprague-Dawley (Crj:CD) rats were (5/sex) received thiamethoxam (purity 98.6%) on the skin at 2,000 mg/kg under occlusive condition for 24 hours 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 LD₅₀ of > 2,000 mg/kg in males and females were identified in this study. ToxServices identified the NOAEL at 2,000 mg/kg for this study based on the lack of significant systemic toxicity observed.
- *Inhalation:*
 - In an acute inhalation toxicity study conducted according to the OECD Guideline 403, Sprague-Dawley (Crj:CD) rats (5/sex/dose) were exposed by nose only inhalation to thiamethoxam (purity 98.6%) dust aerosol with particles size <7.07 µm at a concentration of 1.02 ± 0.05 and 3.72 ± 0.73 mg/L for 4 hours. Animals were then observed for 14 consecutive days. No mortalities or clinical signs of toxicity were observed. No abnormalities were found at macroscopic examination of the animals. An inhalation LC₅₀ of > 3.72 mg/L air was identified in this study. ToxServices identified the NOAEC at 3.72 mg/L/4h 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 Low was assigned. The acute oral studies reported evidence of neurological effects, which will be discussed under neurotoxicity (single dose), below. However, no systemic toxicity was reported upon acute exposure to thiamethoxam via oral, dermal and inhalation routes of exposure. Therefore thiamethoxam is considered to have a low systemic toxicity via single exposure.

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

Thiamethoxam was assigned a score of Moderate for systemic toxicity (repeated dose) based on several subchronic and chronic oral toxicity studies demonstrating effects between 10 and 100 mg/kg/day and on a dermal LOAEL of 250 mg/kg/day in a 28-day study in rat. 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 and dermal LOAEL is between 20-200 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 2010b, Cal EPA 2008

- Oral

- In a 90-day dietary toxicity study, 5 groups of Tif:RAIf rats (10/sex/group) were administered thiamethoxam (purity 98.4%) in the diet at a concentration of 0 (control), 25, 250, 1,250, 2,500, or 5,000 ppm, equal to 0, 1.74, 17.6, 84.9, 169, and 329 mg/kg/day in males and 0, 1.88, 19.2, 92.5, 182, and 359 mg/kg/day in females, as calculated by study authors. Animals were evaluated for clinical signs, body weight, food consumption, hematology, blood chemistry, urinalysis, gross pathology, and histopathology. No treatment-related deaths or clinical signs of toxicity were observed. There was no evidence of ocular toxicity. Body weight gains were statistically significantly decreased at 1,250, 2,500, and 5,000 ppm in males but were unaffected in females at all dose groups and in males up to 250 ppm. Males at 5,000 ppm exhibited an increase in the number of circulating platelets. Other hematological differences were attributed to physiological variation as they were within reference ranges. In males, relative weights of the adrenals, heart, and spleen were increased at 5,000 ppm and relative weights of the liver and kidney were increased at both 2,500 and 5,000 ppm. Microscopic examination of the liver showed treatment-related incidences of Kupffer cell pigmentation in females at 5,000 ppm and hepatocyte hypertrophy in males at 2,500 ppm and in females at 5,000 ppm. In the kidney, changes occurred at 250 ppm and above in males and 2,500 ppm and above in females. These included acute tubular lesions (males), hyaline change in the renal tubular epithelium (males) and chronic tubular lesions (both sexes) and nephrocalcinosis (females only). The pattern of effects seen in male rat kidneys at 250 ppm and above was considered by study authors to be indicative of alpha-2microglobulin mediated nephropathy that is generally unique to male rats and therefore has no human relevance. Upon examination of the spleen, increases in severity of hemosiderosis were seen in males at 5,000 ppm and in females at 2,500 ppm and above. Treatment-related cortical fatty change in the adrenal glands and hepatocyte necrosis were also noted in males at 1,250 ppm and above and in females at 2,500 ppm and above. Based on this, study authors identified the liver, kidney, spleen, and adrenal glands as target organs for thiamethoxam and a NOAEL of 250 ppm (equivalent to 17.6 mg/kg/day) was established, based on reduced body weight gain and increased incidence of fatty change in the adrenals in males at 1,250 ppm, equal to 84.9 mg/kg/day. *The LOAEL of 84.9 mg/kg/day and the NOAEL of 17.6 mg/kg/day are within the GHS guideline values for Category 2 of 10-100 mg/kg/day for 90-days studies. Therefore thiamethoxam is classified to GHS Category 2.*
 - In a 90-day dietary toxicity study conducted according to OECD Guideline 408, Tif:MAGf, SPF mice (10/sex/group) were administered thiamethoxam (purity 98.4%) in the diet at concentrations of 0 (control), 10, 100, 1,250, 3,500, or 7,000 ppm. These were equivalent to 0, 1.41, 14.3, 176, 543, and 1,335 mg/kg/day for males and 0, 2.01, 19.2, 231, 626, and 1,163 mg/kg/day for females as calculated by study authors. No treatment-related deaths occurred and clinical signs were limited to transient respiratory sounds at 3,500 and 7,000 ppm. Body weight gain was markedly reduced in males and to a lesser extent in females at 7,000 ppm. Feed consumption was reduced in females at 7,000 and to a lesser extent at 3,500 ppm. Hematological data indicated anemia, hyperchromasia, and macrocytosis,

which manifested as significant reduction in erythrocyte count, hemoglobin concentration, and hematocrit in males and females at 7,000 ppm. In females at 1,250 ppm and higher, there were minimal but statistically significant elevations in platelet numbers. Female mice at 3,500 and 7,000 ppm showed statistically significant increases in absolute and relative liver weight but statistically significant decreases in ovary, spleen, and carcass weights. Male mice at 7,000 ppm showed increases in relative liver weight and marked decreases in carcass weight. The decreased carcass weights were associated with changes in the absolute or relative weights of organs, including the heart, liver, and kidneys. In the livers of males and females at 3,500 and 7,000 ppm, minimal to marked hypertrophy of centrilobular hepatocytes, minimal pigmentation of Kupffer cells, and an increased incidence of minimal lymphocytic infiltration of the parenchyma were present. At 7,000 ppm, minimal to moderate necrosis of single hepatocytes was also present. Minimal centrilobular hypertrophy was also seen in both sexes at 1,250 ppm and in males at 100 ppm as an isolated change. These were considered an adaptive response or an early sign of mouse-specific hepatotoxicity by study authors due to the absence of any other hepatic changes. Females at 3,500 and 7,000 ppm had minimal to moderate atrophy in the ovaries in the form of reduced numbers of corpora lutea. Study authors attributed these effects to the growth retardation seen at those dose levels. Study authors identified a NOAEL of 100 ppm (equivalent to 14.3 mg/kg/day), based on raised platelet counts in females at 1,250 ppm. *The LOAEL of 1,250 ppm (equivalent to 176 mg/kg/day (F)) is above the GHS guideline values for Category 2 of 10-100 mg/kg/day for 90-days studies. The NOAEL of 14.3 mg/kg/day is below the cutoff of 100 mg/kg/day. Therefore, it is impossible to determine with confidence if adverse effect would occur at 100 mg/kg/day. However, thiamethoxam is at most classified to GHS Category 2.*

- In a 90-day oral toxicity study in dogs, purebred Beagle dogs (4/sex/group) were administered thiamethoxam (purity 98.6%) in the diet at a concentration of 0 (control), 50, 250, 1,000, or 2,500/2,000 ppm, equal to 0, 1.58, 8.23, 32.0, and 54.8 mg/kg/day in males and 0, 1.80, 9.27, 33.9, and 50.5 mg/kg/day in females as calculated by study authors. Dogs were observed for clinical signs of toxicity, body weight, eye irritation, hematology, blood chemistry, and organ weight. Major organs were also examined microscopically. All dogs survived the treatment period and no clinical signs due to treatment were observed. Seven dogs in the highest dose group (2,500 ppm) lost weight during the first two weeks, so the dose was reduced to 2,000 ppm. Weight gains in groups up to 1,000 ppm were not affected at any time. Feed consumption at 2,500 ppm and later at 2,000 ppm was decreased, though to a lesser extent at 2,000 ppm. No evidence of ocular toxicity was seen. Treatment-related hematology and blood chemistry effects occurred at 1,000 and 2,000 ppm in both sexes, including slight anemia associated with hypochromasia, anisochromasia, and microcytosis in females at 2,000 ppm. Reduced white blood cell counts were also seen in females. Prolonged thromboplastin (prothrombin) times were seen in some dogs at 1,000 ppm and above. Testis and ovary weights were reduced and heart, liver, and kidney weights in females were slightly reduced at 2,000 ppm. Minimal to marked reductions in spermatogenesis and increased incidence of spermatic giant cells occurred in the testis of all males at 2,000 ppm. Immature ovaries were observed in females at 2,000 ppm, though these females all had decreased weight

gains throughout the 13 week period. Study authors attributed the delays in sex organ development to the general delay in growth and development. A NOAEL of 250 ppm was established by study authors, equal to 8.23 mg/kg/day, based on prolonged thromboplastin times at 1,000 ppm, equal to 32.0 mg/kg/day. *The LOAEL of 32.0 mg/kg/day is within the GHS guideline values for Category 2 of 10-100 mg/kg/day for 90-days studies. The NOAEL of 8.23 mg/kg/day is just below the GHS guideline values of 10 mg/kg/day. Therefore thiamethoxam is most likely classified to GHS Category 2.*

- In the previously described long-term toxicity and carcinogenicity studies, mice and rats were administered thiamethoxam in the diet at a concentration up to 3000 ppm (rats, 2 years) or 2,000 ppm (mice, 78 weeks). The main target organs identified in these studies were the liver in mice and female rats and the kidneys in male rats. Minor and morphologically different changes occurred in the spleen of both rats and mice. In rats increased incidences of renal chronic tubular lesions and basophilic proliferation were seen in males at 500 ppm but these were considered to be indicative of α -2microglobulin mediated nephropathy and therefore have no human relevance.
 - Accordingly the NOAEL in the 2-year dietary study in rats was 1,000 ppm (equivalent to 50.3 mg/kg/day in females) based on foci of cellular alteration in the liver and increased severity of splenic hemosiderosis in females at 3,000 ppm (equivalent to 155 mg/kg/day). *Both the LOAEL and NOAEL of 155 and 50.3 mg/kg/day, respectively, are above the duration-adjusted GHS guideline value for Category 2 of 1.25-12.5 mg/kg/day¹⁰ for 104-week studies.*
 - The NOAEL in the 78-week dietary study in mice was 20 ppm (equal to 2.63 mg/kg/day), based on hepatotoxic effects (i.e. increased liver weights, hepatocellular hypertrophy, pigment deposition, inflammatory cell infiltration and single-cell necrosis) at 500 ppm (equal to 63.8 mg/kg/day). *The LOAEL of 63.8 mg/kg/day is above the duration-adjusted GHS guideline value for Category 2 of 1.6-16.6 mg/kg/day¹¹ for 78-week studies. The NOALE of 2.63 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, thiamethoxam is at most classified to GHS Category 2.*
- In a 52-week oral toxicity study, purebred Beagle dogs (4/sex/group) were administered thiamethoxam (purity 98.6%) in the diet at concentrations of 0 (control), 25, 150, 750, or 1,500 ppm, equal to 0, 0.70, 4.05, 21.0, and 42.0 mg/kg/day in males and 0, 0.79, 4.49, 24.6, and 45.1 mg/kg/day in females as calculated by study authors. Dogs were observed for mortality, clinical signs of toxicity, feed consumption, and body weight. Eye examinations, hematology, blood chemistry analysis, urinalysis, organ weight recording, and microscopic organ examinations were also performed. No deaths or treatment-related clinical signs occurred during the study. There was a minimal decrease in absolute and relative testis weights in 1,500 ppm males. Prothrombin times were lower in both sexes at 1,500 ppm compared to controls. Study authors identified a NOAEL of 750 ppm, equal to 21.0 mg/kg/day, based on prolonged thromboplastin times and

¹⁰ 10 mg/kg/day x 13 weeks/104 weeks = 1.25 mg/kg/day

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

reduced testis weights at 1,500 ppm, equal to 42.0 mg/kg/day. *The LOAEL of 42 mg/kg/day is above the duration-adjusted GHS guideline value for Category 2 of 2.5-25 mg/kg/day¹² for 52-week studies. The NOAEL of 21 mg/kg/day is below the cutoff of 25 mg/kg/day. Therefore, it is impossible to determine with confidence if adverse effect would occur at 25 mg/kg/day. However, thiamethoxam is at most classified to GHS Category 2.*

- In a 28-day oral toxicity study, 4 groups of Tif:RAIf (SPF) rats (5/sex/group) were administered thiamethoxam (purity 95.0%) in the diet at dose levels of 0 (control), 100, 1,000, 2,500, or 10,000 ppm, equal to 0, 8.0, 81.7, 198.6, and 710.6 mg/kg/day in males and 0, 8.7, 89.3, 210.6, and 762.6 mg/kg/day in females. No deaths or clinical signs related to treatment were evident during the administration period. At 10,000 ppm, males experienced reduced body weight gain and marked feed consumption reduction but females were not affected beyond slightly reduced feed consumption during the first week. No treatment-related effects on hematological profiles at any dose level were observed. Isolated statistically significant differences from controls were seen but were considered incidental to treatment as they did not have a dose-response relationship. Treatment-related effects on organ weights occurred in both sexes at 1,000 ppm and above, including increased absolute liver weights in females and relative liver weights in both sexes at 10,000 ppm. Relative kidney weights were increased in males at 2,500 ppm but not females, despite increased absolute and relative kidney weights in females at 1,000 ppm. Minimal to marked hypertrophy of centrilobular hepatocytes occurred in both sexes at 2,500 and 10,000 ppm. Glycogen depletion was observed in males at 10,000 ppm. In the kidneys, minimal to moderate hyaline change to the tubule epithelium occurred in males at 1,000 and 2,500 ppm but not any other dose level. Minimal to moderate fatty change of the zona fasciculata was observed in both sexes at 10,000 ppm but in no other group. In the thyroid gland, the incidence of follicular cell hypertrophy was increased in males at 10,000 ppm. Study authors identified a NOAEL of 100 ppm, equal to 8.0 mg/kg/day based on increased kidney weights in both sexes and renal tube epithelium changes in males at 1,000 ppm, equal to 81.7 mg/kg/day.
- In a 28 day oral toxicity study, male PRT GAV 01M rats (5/dose) were administered thiamethoxam (purity >95%) daily by gavage at dose levels of 0, 100, 300 and 1,000 mg/kg/day. One rat in the 100 mg/kg/day group died accidentally on day 29. High dose animals (1,000 mg/kg/day) displayed a treatment-related decrease in mean body weight, as well as treatment-related increases in alkaline phosphatase, aspartate aminotransferase and gamma-glutamyl transpeptidase levels. Animals in the 300 and 1,000 mg/kg/day dose groups had treatment-related increases in relative liver and kidney weights. Treatment-related increases in incidences of large livers and renal pelvis dilation were evident in microscopic examination of high dose rats (1,000 mg/kg/day). Additionally, microscopic examination revealed increased incidences of hepatocyte hypertrophy at 300 and 1,000 mg/kg/day, hyaline change in the renal tubule at 100 and 300 mg/kg/day and renal pelvis dilation and adrenal cortex fatty change at 1,000 mg/kg. Authors established a NOEL < 100 mg/kg/day for males based on treatment-related increased incidence of renal tubular hyaline change.

¹² 10 mg/kg/day x 13 weeks/52 weeks = 2.5 mg/kg/day

- In a 28-day oral repeated dose toxicity study male and female Beagle dogs (2/sex/dose) were administered thiamethoxam (purity 98.4%) at dose levels of 0, 300, 1,000 or 3,000 ppm (equivalent to 0, 10, 31.6 and 47.7 mg/kg/day, respectively, for males and 0, 10.7, 32.6 and 43 mg/kg/day, respectively, for females) mixed to pelleted food. One male in the high dose group (3,000 ppm) was found dead on day 15; no treatment-related clinical signs were observed. High dose male and females (3,000 ppm) displayed treatment-related decreases in body weight and food consumption, as well as a decrease in relative thymus weight. Microscopic examination revealed treatment-related pigmentation in the Kupffer cells and atrophy of the thymus and of the marginal zone of splenic white pulp. Authors established a NOEL of 1,000 ppm (31.8 mg/kg/day) for males and a NOEL of 1,000 ppm (32.6 mg/kg/day) for female based on decreased body weight and food consumption and microscopic findings.
- *Dermal*
 - In a 28-day dermal toxicity study, Tif:RAIf, SPF rats (5/sex/group) were administered thiamethoxam (purity 98.6%) to intact shaved dorsal skin at doses of 0 (control), 20, 60, 250, or 1,000 mg/kg/day for 6 hours/day, 5 days/week for 4 weeks. Rats were observed for mortality, clinical signs, body weights, and feed and water consumption. Hematology and blood chemistry investigations were performed towards the end of treatment. Postmortem examination, organ weighing, and microscopic examination of tissues were also performed. No deaths or clinical signs of toxicity occurred during the study. Any statistically significant values showed no dose-response relationship or values were within historical ranges. All absolute organ weights and body weight gains were unaffected by treatment other than the body weights of males at 1,000 mg/kg/day, which were decreased for the first two weeks of treatment only. No anomalies were observed at autopsy. Increased incidence of minimal inflammatory cell infiltration and necrosis of single hepatocytes occurred in females at 250 and 1,000 mg/kg/day. Females at 250 and 1,000 mg/kg/day had slightly raised plasma glucose concentrations and minimally raised alkaline phosphatase activities. Study authors identified a NOAEL of 60 mg/kg/day (equivalent to 42 mg/kg/6h/day¹³) based on blood chemistry changes (increased glucose and alkaline phosphatase level) in females at 250 mg/kg/day group had reduced body weights and reduced body weight gain compared to controls. *The LOAEL of 250 mg/kg/day (equivalent to 178 mg/kg/6h/day¹⁴) is within the tripled GHS guideline value for Category 2 of 60-600 mg/kg/day for 28-week studies Therefore thiamethoxam is classified to GHS Category 2.*

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, liver, kidneys and spleen were identified as target organs. 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. Similarly the dermal LOAEL for systemic toxicity in rats was within the GHS guidance values for Category 2

¹³ Converting exposure period 5days/week to daily = 60 mg/kg x 5 / 7(days) = 42 mg/kg/day

¹⁴ Converting exposure period 5days/week to daily = 250 mg/kg x 5 / 7(days) = 178 mg/kg/day

of 20-200. Accordingly, thiamethoxam is classified to GHS Category 2 for systemic toxicity (repeated exposure oral and dermal route), which corresponds to a score of Moderate.

Neurotoxicity (N)

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

Thiamethoxam was assigned a score of High for neurotoxicity (single dose) based on decreased locomotor activity and convulsions observed at doses as low as 500 mg/kg/day after oral exposure. GreenScreen® criteria classify chemicals as a High hazard for neurotoxicity (single dose) when the LOAELs are between 300 and 2,000 mg/kg/day (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
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- JMPR 2010b
 - In a single-dose neurotoxicity study, Sprague-Dawley rats (CrI:CD BR) (10/sex/group) were administered thiamethoxam (purity 98.7%) at single doses of 0 (control), 100, 500, or 1,500 mg/kg by oral gavage. Animals were evaluated for morbidity, mortality, clinical observations, physical examinations, body weights, functional observational battery (FOB) tests, and assessment of locomotor activity prior to treatment. Treatment-related clinical signs were observed at 1,500 mg/kg on the day of dosing only, including partial closure of eyes in both sexes, and tremors, hypoactivity, and coldness to the touch in females only. Body weight gain was significantly reduced in males at 1,500 mg/kg during the first week after dosing. Treatment effects in the FOB were limited to the evaluation performed 2-3 hours after dosing as no effects were observed at any dose level during the week 1 or week 2 evaluations. At 2-3 hours post-dose, there was an increased incidence of active or rigid handling/body tone, tremors, and ptosis at 1,500 mg/kg. There was also a slightly drooped palpebral closure at 500 and 1,500 mg/kg. Slight lacrimation occurred in females at 1,500 mg/kg. Open-field observation in the 1,500 mg/kg group revealed a mild to moderate impairment of gait, tremors, hypoarousal, and reduced rearing behavior in females. An increased incidence of uncoordinated landing, lower mean rectal temperatures, and significantly higher mean forelimb grip strength values were recorded for males at 500 and 1,500 mg/kg. The auditory startle response test required a significantly higher mean input stimulus value for males at 1,500 mg/kg. Rats at 500 and 1,500 mg/kg also showed significantly lower activity during the first 15-20 minutes of testing. Pathological findings in the three females that died prior to scheduled sacrifice revealed that all had dark-brown lobes of the liver and one had mottled dark-red lobes of the lung. In rats that survived to the end of the study, there were no treatment-related postmortem findings at any dose level. Due to the absence of treatment-related neurohistological changes and persistent functional changes, the observed effects were considered to be signs of overt toxicity or pharmacological overstimulation. Study authors identified a neurotoxicity NOAEL of 100 mg/kg based on transient behavioral changes at 500 mg/kg.
 - In the previously described acute oral toxicity study conducted according to OECD Guideline 401, Sprague-Dawley (Crj:CD SD) rats (5/sex/dose) were administered thiamethoxam (purity 98.6%) in aqueous methylcellulose at single doses of 0, 900, 1,500, 2,300, 3,800, or 6,000 mg/kg by oral gavage followed by a 14-day observation period. Signs of acute neurotoxicity were seen in treated animals. These included ptosis in all

dose groups and reduced locomotor activity at dose of 1,500 mg/kg and above. There were no effects on gross pathology or body weight. An oral LD₅₀ of 1,563 mg/kg was identified in this study.

- In the previously described acute oral toxicity study conducted according to OECD Guideline 401, SPF (Crj:CD1(ICR)) mice (5/sex/dose) were administered thiamethoxam (purity 98.6%) in aqueous methylcellulose at single doses of 0, 500, 700, 1,000, 1,400 or 2,000 mg/kg by oral gavage followed by a 14-day observation period. Clinical signs of neurotoxicity such as reduced locomotor activity or prostration were seen in all treated animals within 5–15 minutes of treatment, and clonic convulsions were seen 15 minutes to 4 hours after treatment. By day 2, all animals were entirely free from clinical signs. The oral LD₅₀ of 783 mg/kg in males and 964 mg/kg in females were identified in this study.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of High was assigned. Acute exposure to thiamethoxam via the oral route showed reversible clinical signs of neurotoxicity such as ptosis, reduced locomotor activity and convulsions. One of the study authors considered these observations to be signs of overt toxicity or pharmacological overstimulation. The lowest LOAEL was 500 mg/kg/day, which corresponds to a score of High.

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

Thiamethoxam was assigned a score of Low for neurotoxicity (repeated dose) based on no neurotoxicity effects seen in a 13-week neurotoxicity study and a developmental neurotoxicity study in rats. GreenScreen[®] criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when negative data for neurotoxicity (repeated dose), 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
- 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 thiamethoxam was among the chemicals examined, and it was detected in 31.6% of the patients in TSG (6 of 19, 1.4 ppb), 6.3% of the patients in ASG (1 of 16, 1.9 ppb), and none of the volunteers in the NSG. The difference of prevalence between TSG and NSG reached statistical significance (p < 0.0001). The symptoms persistent mostly for days to months after cessation of consumption of locally grown produce. *ToxServices noted that multiple neonicotinoid pesticides were detected in urine*

samples, and N-desmethyl-acetamiprid, a metabolite of acetamiprid, was the most frequently detected species (47.4% in TSG up to 6.0 ppb, 12.5% in ASG at 4.4 ppb, and 6.0% in NSG at 2.2 ppb). Therefore, the increased neurological symptoms in thiamethoxam-exposed individuals may be confounded by co-exposure to other neonicotinoids pesticides. In addition, a statistically significant association does not necessarily demonstrate causality, which is an inherent limitation of prevalence case-control studies.

- JMPR 2010b
 - In a 13-week repeated-dose neurotoxicity study, Sprague-Dawley rats (CrI:CD BR) (10/sex/group) were administered thiamethoxam (purity 98.7%) in the diet at concentrations of 0 (control), 10, 30, 500, or 1,500 ppm (0, 0.7, 1.9, 31.8, and 95.4 mg/kg/day) for males and 0 (control), 10, 30, 1,000, or 3,000 ppm (0, 0.7, 2.1, 73.2, and 216.4 mg/kg/day) for females. Study authors recorded morbidity, mortality, clinical observations, physical examinations, body weights, feed consumption, ophthalmoscopic examinations, FOB, and locomotor activity assessment. After treatment, perfusion was performed on the first six rats of each sex per group in order to evaluate central and peripheral nervous system tissues. Remaining rats were subjected to autopsy. No deaths occurred and there were no treatment-related clinical signs of adverse effects of treatment. Body weight developments and feed consumption throughout the study were unaffected by treatment at all dose levels. There was no evidence of ocular toxicity at any dose level after 13 weeks. Neurobehavioral assessment of animals at all dose levels revealed no treatment-related effects on any observations or performance measures. There were also no treatment-related gross pathological findings. Study authors identified a NOAEL for systemic toxicity and neurotoxicity of 1,500 ppm in males (equivalent to 95.4 mg/kg/day) and 3,000 ppm in female (equivalent to 216.4 mg/kg/day), based on the absence of treatment-related effects at these doses. *The NOAEL of 216 mg/kg/day is above the GHS guideline values for Category 2 of 10-100 mg/kg/day for 90-days studies. Therefore thiamethoxam is not classified per GHS.*
- JMPR 2010b, Cal EPA 2008
 - In the previously described developmental neurotoxicity study conducted according to OECD Guideline 426, pregnant female Alpk:APfSD rats (30/group) were administered thiamethoxam (purity 98.8%) in the diet at a concentration of 0(control), 50, 400, or 4,000 ppm from gestation day 7 through postnatal day 22. There were no treatment-related effects on FOB evaluation in selected F₁ rats. Locomotor activity, startle amplitude, ability to learn, and memory were all also unaffected by treatment. However absolute brain weight was lower than that of controls at 4,000 ppm, though there were no differences from the control following adjustments for terminal body weight. Upon examination of the brain, a number of statistically significant differences were observed in both males and females at 4,000 ppm in several parameters at levels 3-5 after adjustment for body weight. Also at 4,000 ppm in males, there were decreases at level 5 in thalamus and hippocampus width. At 4,000 ppm in females, there were decreases at level 4 in thalamus and total brain width and at level 5 in thalamus width. No statistically significant differences were noted in these regions at lower dose groups. In both sexes at day 12, a small number of brain morphometry parameters were statistically significantly different from controls at 4,000 ppm. The study authors considered these variations in brain morphometry as a consequence of non-specific effects on the development of F₁ offspring rather than a direct neurological effect due to the lack of any histological or clinical neurological effects. Therefore, a NOAEL of 4,000 ppm (equivalent to 298.7

mg/kg/day) was established for developmental neurotoxicity, which was the highest dose tested, based on an absence of any quantitative histological or behavioral changes.

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Low was assigned. Although thiamethoxam is a member of the neonicotinoid chemical class, whose biological effects are mediated primarily by an interaction with nicotinic acetylcholine receptor sites, it did not cause neurotoxicity in a 13-week neurotoxicity study and a developmental neurotoxicity study in rats. A human prevalence case-control study found a statistically significant association between urine thiamethoxam levels and typical neurological effects caused by neotinoids pesticides exposure. However, due to confounding exposure to other neonicotinoids and inability for these types of study to demonstrate causality, ToxServices did not weight this study heavily in evaluating this endpoint. Therefore, based primarily on animal data, ToxServices did not classify thiamethoxam as a neurotoxicant under GHS criteria.

Skin Sensitization (SnS) Group II* Score (H, M, or L): L

Thiamethoxam 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 2010b
 - Thiamethoxam was not sensitizing in a maximization test conducted according to OECD Guideline 406 performed with Pirbright White guinea pigs (10/sex). Animals were induced with 1 and 30% (intradermally) of thiamethoxam (purity 98.6%) dissolved in peanut oil or petroleum jelly and topically challenged with 10%. A skin reaction occurred in one male in the test group (5% reaction rate). Positive and negative control groups produced expected results. Study authors determined that thiamethoxam is not a skin sensitizer based on the results seen in this study.

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): DG

Thiamethoxam 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 or reporting irritative symptoms.

- Hernandez et al. 2011
 - Several clinical and epidemiological studies have reported an association between exposure to pesticides, such as thiamethoxam, and bronchial hyper-reactivity and asthma symptoms. Hernandez et al. summarized pesticide aerosols can lead to asthma by interaction with allergen sensitization. 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 thiamethoxam 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

Thiamethoxam 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 well-conducted studies.

- Authoritative and Screening Lists
 - *Authoritative:* not listed on any authoritative lists
 - *Screening:* not listed on any screening lists
- JMPR 2010b
 - In a dermal irritation study conducted according to OECD Guideline 404, six female Japanese White rabbits were administered dermal applications of 0.5 thiamethoxam (purity 98.6%) to clipped dorsal skin under semiocclusive dressing for 4 hours. No skin irritation or dermal reaction was observed through 3 days post-application. Study authors concluded that thiamethoxam was not irritating to the skin in this test.
 - In the previously described 28-day dermal toxicity study, 4 groups of Tif:RAIf, SPF rats (5/sex/group) were administered thiamethoxam (purity 98.6%) to intact shaved dorsal skin at doses of 0 (control), 20, 60, 250, or 1,000 mg/kg/day for 6 hours/day, 5 days/week for 4 weeks. No evidence of skin irritation was observed during the study.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): L

Thiamethoxam 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 2010b
 - In an ocular irritation study conducted according to OECD Guideline 405, nine female Japanese White rabbits were administered ocular instillations of 0.1g thiamethoxam (purity 98.6%) for 24 hours and the animals were observed for 7 days. Minimal erythema and edema of the conjunctivae occurred and rabbits displayed transient eye closure and discharge immediately after application. No signs of eye irritation were present at any other reading time point (24, 48 and 72 hours). Study authors concluded that thiamethoxam was transiently minimally irritating to the eye in rabbits.

Ecotoxicity (Ecotox)¹⁵

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): vH

Thiamethoxam 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 LC₅₀ in crayfish of 0.967 mg/L and EC₅₀ in invertebrates of as low as 0.014 mg/L. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when acute aquatic toxicity values are ≤ 1 mg/L or, 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 and authoritative listings.

- 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 environment¹⁶.
 - *Screening*: EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects¹⁷.
- SCBP 2012
 - 96-hour LC₅₀ (*Oncorhynchus mykiss*, fish) > 100 mg/L
 - 96-hour LC₅₀ (*Lepomis macrochirus*, bluegill sunfish) > 114 mg/L
 - 48-hour EC₅₀ (*Ostracoda*, invertebrate) = 0.18 mg/L
 - 48-hour EC₅₀ (*Gammarus Sp*, invertebrate) = 2.8 mg/L
 - 48-hour EC₅₀ (*Daphnia magna*, invertebrate) > 100 mg/L
 - 48-hour EC₅₀ (*Daphnia pulex Leydig*, invertebrate) > 100 mg/L
 - 48-hour EC₅₀ (*Thamnocephalus platyurus*, invertebrate) > 100 mg/L
 - 48-hour EC₅₀ (*Lymnea stagnalis (mollusc)*, invertebrate) = 100 mg/L
 - 72-hour EC₅₀ (*Selenastrum capric*, green algae) > 81.8 mg/L
 - 96-hour EC₅₀ (*Selenastrum capric*, green algae) > 100 mg/L
- HSDB 2012
 - 96-hour LC₅₀ (*Americamysis bahia*, opossum shrimp) = 6.9 mg/L
 - 96-hour LC₅₀ (*Cypirinodon variegatus*, sheepshead minnow) > 111 mg/L
 - 96-hour LC₅₀ (*Procambarus clarkia*, red swamp crayfish) = 0.967 mg/L

¹⁵ Includes Terrestrial Toxicity. 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).

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

- ABC 2013
 - 48-hour EC₅₀ (*Daphnia magna*) >106 mg/L
 - 48-hour EC₅₀ (*Chaoborus* sp., midge) = 180 mg/L
 - 96-hour EC₅₀ (*Americamysis bahia*, crustacean) = 5.4 mg/L
 - 48-hour EC₅₀ (*Cloeon* sp., invertebrate) = 0.014 mg/L
 - 48-hour EC₅₀ (*Chironomus riparius*, midge) = 0.035 mg/L

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Very High was assigned. The most conservative measured acute aquatic toxicity values for thiamethoxam were an LC₅₀ of 0.976 mg/L in crayfish and an EC₅₀ of 0.014 mg/L in *Cloeon* sp, which both correspond to a score of Very High. In addition, both the authoritative lists R50 and H400 correspond to a score of Very High.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): L

Thiamethoxam was assigned a score of Low for chronic aquatic toxicity based on its measured NOEC values in aquatic organisms being greater than 10 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic NOECs > 10 mg/L (CPA 2012b). Confidence in the score is reduced because no chronic toxicity data were identified for the most sensitive aquatic invertebrate species.

- Authoritative and Screening Lists
 - *Authoritative:* EU Risk Phrase R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment¹⁸.
 - *Screening:* EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects¹⁹.
- SCBP 2012
 - 7-days NOEC (*Lemna gibba*, aquatic plant) > 90.2 mg/L
 - 28-days NOEC (*rainbow trout*, fish) = 100 mg/L
 - 88-days NOEC (*rainbow trout*, fish) = 20 mg/L
 - 21-days NOEC (*Daphnia magna*, invertebrates) = 100 mg/L

ToxServices' summary and conclusion:

- Based on the weight of evidence, a score of Low was assigned. Available measured chronic aquatic toxicity values for thiamethoxam are clearly above 10 mg/L, which correspond to a score of Low. However, as observed in acute aquatic toxicity studies, aquatic invertebrates are the most sensitive trophic level, and the only species tested in chronic studies is daphnia, which is among the least sensitive species. Therefore, the confidence in the score was reduced.

Acute Terrestrial Vertebrates²⁰ Toxicity Score (ATV) Score (vH, H, M, or L): L

Thiamethoxam was assigned a score of Low for acute terrestrial vertebrate toxicity based on its measured oral LD₅₀ values in quail and duck being between 501 and 2,000 mg/kg and dietary LC₅₀ values in quail and duck being between 1,001 and 5,000 ppm. GreenScreen® criteria classify

¹⁸ This is an authoritative EU R-phrases that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation

¹⁹ This is a screening EU H-Statement that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation

²⁰ Includes birds and mammals

chemicals as a Low hazard for acute terrestrial vertebrate toxicity when acute avian toxicity values are between 501 and 2,000 mg/kg (oral exposure) or 1,001 and 5,000 ppm (dietary exposure) as per the U.S. EPA DfE criteria (CPA 2012b, DfE 2011). Confidence in the score is high because it is based on experimental data from well conducted studies.

- SCBP 2012 and ABC 2013
 - Oral: LD₅₀ (mallard duck) = 576 mg/kg
 - Oral: LD₅₀ (quail) = 1,552 mg/kg
- SCBP 2012
 - Dietary: LC₅₀ (Bobtail quail and mallard duck) >5200 ppm
 - Dietary: LC₅₀ (Bobwhite quail) > 1,929 g/kg
 - Dietary: LC₅₀ (mallard duck) > 1,175 g/kg

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

Thiamethoxam 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. Two toxicity studies of thiamethoxam to birds were identified and are described below.

- SCBP 2012 and ABC 2013
 - In a reproductive toxicity study, bobwhite quail were administered 100, 300 and 900 ppm of thiamethoxam. Authors defined a NOEL of 300 ppm and a LOEL of 900 ppm based on large differences in number of eggs laid.
 - In a reproductive toxicity study mallard ducks were administered 100, 300 and 900 ppm of thiamethoxam. Authors defined a NOEL at 300 ppm and a LOEL at 900 ppm based on parental effects and non-significant effects in several parameters

Acute Foliar Invertebrates and Pollinators²¹ (AFI) Toxicity Score (H, M, or L): H

Thiamethoxam was assigned a score of High for acute foliar invertebrates and pollinators toxicity based its measured oral and dermal LD₅₀ values in bees being less than 2 µg/bee. GreenScreen[®] criteria classify chemicals as a High hazard for acute foliar invertebrates and pollinators toxicity when the oral and dermal LD₅₀ 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.

- Oral
 - SCBP 2012
 - LD₅₀ (honeybee, *Apis mellifera*) = 0.005 µg/bee
 - LD₅₀ (honeybee, *Apis mellifera*) = 0.024 µg/bee
 - 48-hour EC₅₀ (*Cloeon Sp. (Ephemeroptera)*, insect) = 0.014 mg/L
 - Poquet et al. 2015
 - In an acute toxicity study honey bee workers (*Apis mellifera*) were exposed to thiamethoxam (purity 98.5%) either on the thorax or on the wings at doses of 0, 5, 10, 25, 50, 60, 80, 100 and 200 ng/bee. Eight replicates of 30 bees per contact area were performed. Bees were observed for mortality 24, 48, 72, 96 and 120 hours after exposure. Authors determined 120 hour LD₅₀ values of 27.03 ng thiamethoxam for wing exposure and 12.13 ng thiamethoxam for the thorax exposure.

²¹ Includes bees

- Blacquiere et al. 2012
 - LD₅₀ (honey bee, *Apis mellifera*) = 0.005 µg/bee
 - LD₅₀ (honey bee, *Apis mellifera*) = 0.004 µg/bee
- *Dermal*
 - Iwasa et al. 2004
 - LD₅₀ (honey bee, *Apis mellifera*) = 29.9 ng/bee
 - Blacquiere et al. 2012
 - LD₅₀ (honey bee, *Apis mellifera*) = 0.024 µg/bee
 - LD₅₀ (bumble bee, *Bombus terrestris*) = 33 ng/bee

Chronic Foliar Invertebrates and Pollinators (CFI) Toxicity Score: N/A

Thiamethoxam 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 thiamethoxam to bees were identified and these are described below.

- Blacquiere et al. 2012
 - Chronic (11 day) dermal exposure to 0.1 ng/bee thiamethoxam reduced olfactory learning of the proboscis extension reflex but did not cause long term effects; recovery of memory was seen after 48 hours.
- Catae et al. 2014
 - In a terrestrial toxicity study, the toxic effects of thiamethoxam in the midgut and Malpighian tubule cells of Africanized *Apis mellifera* was investigated. Africanized honeybees (25/dose) were exposed to thiamethoxam (purity 92.5%) at a concentration of 0.428 ng/µL/day. Bees were collected at intervals of 1, 3, 5 and 8 days (5 samples/time) and the midgut and Malpighian tubules were removed for evaluation. Effects of thiamethoxam were most evident in midguts of bees after 1 day exposures; authors observed decreased mitochondrial cristae in digestive cells, dilated and disorganized cisterns with lower amounts of ribosomes in the rough endoplasmic reticulum and irregularly shaped nuclei. A distinct disorganization of the basal labyrinth was evident in the Malpighian tubules. At day 3 of exposure, digestive cells had more regular shaped nuclei and mitochondria and vacuoles were present. The basal labyrinth showed characteristics of degeneration and there was a pronounced increase in the amount of the smooth endoplasmic reticulum. At day 5 of exposure the nuclei of digestive cells had no irregularities and contained decondensed chromatin. The Malpighian tubules had disruption of the cytoplasm and basal labyrinth, loss of cytoplasmic organelles, and alterations to the mitochondria and microvilli. At day 8 of exposure digestive cells showed morphology most similar to the control group; however, there was near complete loss of the basal labyrinth of the Malpighian tubules with clear spaces in the cytoplasm and dilated microvilli. Authors concluded thiamethoxam is toxic to the midgut and Malpighian tubules of honey bees and greatly affects the absorption and excretion functions, impairing the physiology of Africanized honeybees.
- Tavares et al. 2015
 - In an OECD Guideline 237 terrestrial toxicity study, the sub-lethal effects of thiamethoxam on the morphology of the developing larval brain of the Africanized honey bee *Apis mellifer* was investigated. Honey bee larva were reared *in vitro* and exposed to thiamethoxam (purity 99.6%) at a concentration range of 0.1 – 200 ng/µL in the diet. Authors observed and characterized development of larvae and monitored mortality. In a second experiment, larvae were exposed to thiamethoxam at a concentration of 1.43

- ng/ μ L and collected for morphology and immunocytochemical analysis at 24, 48 and 72 hours. Authors observed a dose dependent increase in larval development time, thiamethoxam exposed larvae showed a biphasic pattern characterized as one hyperbola. Additionally, exposure to high concentrations of thiamethoxam causes a reduction in body size; authors defined a 48 hour LC₅₀ of 14.34 ng/ μ L of diet. Morphological analysis of the brain showed the most pronounced effects of thiamethoxam exposure to occur in the optic lobes. Cellular condensation was evident in the medulla layer of all samples; no morphological changes were observed in the other analyzed brain structures. Authors concluded thiamethoxam can alter normal patterns of development in the Africanized honey bee.
- Henry et al. 2012
 - In a terrestrial toxicity study, the impact of thiamethoxam exposure to honey bee (*Apis mellifera*) hive death rate through homing failure in foraging bees was investigated. Authors monitored free-ranging honey bees (653 bees) with radio-frequency identification tagging and recorded forager mortality and homing failure and their effects on colony dynamics. Bees were exposed to thiamethoxam at a dose of 1.34 ng in 20 μ L sucrose solution and released away from their colonies. An increase in homing failure was evident for treated bees compared to controls, the number of treated forager bees returning to the colony was significantly lower than control forager. Authors concluded thiamethoxam exposure can affect forager survival and consequently contribute to colony collapse risk.
 - Elston et al. 2013
 - In a terrestrial toxicity study the effect of thiamethoxam exposure on nest building and brood production in queenless *Bombus terrestris* microcolonies was investigated. Microcolonies (10/dose) were exposed to thiamethoxam (purity not reported) at doses of 1 or 10 μ g/kg in an artificial nectar solution and pollen paste for 28 days. Authors observed for honey water consumption, mortality, onset of nest building and egg and larvae production. No bee mortality was observed, however, uncoordinated movement and extensive grooming were evident in bees exposed to both dose levels. Bees exposed to thiamethoxam at both dose levels consumed significantly less nectar compared to controls. High dose bees (10 μ g/kg) displayed significantly different time to initiation of nest building compared to controls, with a significant relationship between the number of wax cells built and treatment; significantly fewer were produced in both dose groups compared to controls. Exposure to the high dose (10 μ g/kg) significantly decreased the number of egg and larvae produced over the experimental period. Authors concluded constant exposure to high levels of thiamethoxam in pollen and nectar has the potential to affect the initiation and development of bumble bee microcolonies under conditions of the study.
 - Laycock et al. 2013
 - In a terrestrial toxicity study, the effect of field-realistic doses of thiamethoxam on microcolonies of worker bumble bees (*Bombus terrestris*) was investigated. Authors characterized dose response relationships that describe thiamethoxam's effects on brood production, food consumption and days survived by workers. Bumble bee colonies were exposed to thiamethoxam (purity not reported) at doses of 98.43, 39.37, 15.75, 6.30, 2.52, 1.01, 0.40, 0.16 and 0.06 μ g/kg *ad libitum* in syrup for 17 days. Microcolonies were monitored daily for worker mortality and the appearance of wax covered eggs. *Per capita* consumption of syrup and pollen in microcolonies was significantly affected by thiamethoxam; a significant reduction in food consumption was evident in microcolonies

- exposed at the two highest doses (39.37 and 98.43 µg/kg). The two high dose groups (39.37 and 98.43 µg/kg) had significantly higher frequencies of oviposition failure, significantly affecting the number of brood produced. Additionally, the highest dose of thiamethoxam (98.43 µg/kg) significantly affected worker mortality. Authors concluded high concentrations of thiamethoxam is toxic to bees and impairs their feeding behavior.
- Douglas et al. 2014
 - In a terrestrial toxicity study, the effect of thiamethoxam soya bean coating application on non-target molluscan herbivores and their insect predators was investigated. Authors examined disruption of *Deroceras reticulatum* slug predation through the dietary transfer of thiamethoxam from slug pests to their predators. Soya bean (34/dose) was treated with CruiserMaxx® (tradename for thiamethoxam) at either 0.0756 or 0.152 mg/seed. Slugs were placed with the plants and status of seedlings and slugs was monitored for 1 week. After 1 week, predatory beetles were introduced and their status was monitored for 1 week. Additionally, authors observed thiamethoxam effects in field conditions; 6 plots of soybean seeds exposed to 0.152 mg/seed of thiamethoxam were planted and monitored for crop productivity and activity density of slugs and their predators. In the lab, slugs were unaffected by thiamethoxam treatment; however, they transmitted the toxin to predaceous beetles, impairing or killing more than 60% of the population. In the field, thiamethoxam seed treatments depressed activity-density of arthropod predators resulting in less slug predation and a reduced soya bean density and yield. Authors concluded thiamethoxam can unintentionally reduce biological control and crop yield through trophic transfer.
 - Duso et al. 2013
 - In a terrestrial toxicity study the impact of thiamethoxam applied in apple orchards to the predatory mite *Kampimodromus aberrans* was investigated. Authors conducted field and laboratory experiments. Field experiments were performed on apple orchards located in Trentino. 30 g/hl of Actara 25WG (trade name for thiamethoxam) was applied in three applications. In laboratory studies, apple leaves were treated with thiamethoxam in the same dose as the field studies and mated *K. aberrans* (45-50/dose) were exposed on the leaves, mortality and egg hatching was observed for 72 hours. Surviving females were observed for an additional four days to assess fecundity. In the field, thiamethoxam application had no detrimental effect to predatory mites. In laboratory studies, thiamethoxam reduced female fecundity compared to controls. Thiamethoxam was not observed to eliminate predatory mites, but they inhibited their response to increasing prey populations. Authors concluded thiamethoxam has adverse effects on predatory mites that feed on thiamethoxam treated crops.
 - Miao et al. 2014
 - In a terrestrial toxicity study, the demographic growth and feeding behavior of the grain aphid (*Sitobion avenae*) after feeding on wheat plants treated with thiamethoxam was investigated. Wheat seeds were treated with thiamethoxam (purity not stated) at a concentration of 135 mg/kg and grown for seven days. Initially 10 adult aphids were placed on the treated plants, when >30 offspring were produced adults were removed and the development and reproduction of aphids was recorded daily. Authors observed the net reproductive rate, average generation lifespan, intrinsic rate of natural increase, finite rate of increase and population doubling time. For effects on feeding behavior, the probing behavior of adult aphids (15/dose) was recorded using a DC EPG amplifier and monitored for 12 hours after a 2 hour fast. Thiamethoxam exposure resulted in a significant decrease in net reproductive rates, a significantly altered intrinsic rate of

- increase, and significant increase in doubling time compared to controls. Authors observed significantly decreased time spent ingesting into/from phloem and a significantly longer duration of no-probing periods, resulting in a reduced time of ingestion in xylem. Authors concluded thiamethoxam wheat plant seed treatments have long term adverse effects on wheat aphid feeding, survival, fecundity and population increase.
- Seagraves and Lundgren 2012
 - In a terrestrial toxicity study, the effect of thiamethoxam soybean seed treatment on the aphid *Aphis glycines* and its predator *Orius insidiosus* was investigated. Cruiser 5FS (tradename for thiamethoxam) was applied to soybean seeds for six treatments over 2 years at a rate of 50 g/100 kg of seed in field conditions. Aphid and its predator population were monitored weekly. Additionally, authors observed aphid and its predator survival in a laboratory setting. Soybean aphid, thrips and grasshopper populations were unaffected by thiamethoxam treatment in the field. A loss of bioactivity of seed treatments against aphids was evident after 46 days in laboratory experiments. Pest and natural enemy communities were significantly reduced by thiamethoxam seed treatment compared to controls. Higher mortality of *O. insidiosus* - nymphs and adults was observed in the lab when exposed to thiamethoxam treated plants. Authors concluded thiamethoxam seed treatment has little benefit to soybean producers and adversely affects generalist predators.
 - Stamm et al. 2014
 - In a terrestrial toxicity study, the changes in gene expression of involved in plant defense pathways and general stress response in a soybean plant when exposed to thiamethoxam was investigated. Authors examined broad scale transcription effects of thiamethoxam seed treatment at three vegetative stages in soybean, and interactive effects of thiamethoxam seed treatment and drought stress using qRT-PCR of ten target genes. Soybean seeds were treated with Cruiser ® 5FS (tradename for thiamethoxam) at a labeled rate of 83 mL/100 kg of seed and grown. Total RNA was extracted from leaf tissues for expression analysis. Soybean plants were subject to drought stress for 7, 10 or 13 days in the VC stage and harvested for analysis. Thiamethoxam treated soybean revealed minor transcriptional differences when compared to controls, however, thiamethoxam seed treatment induced substantial transcriptional changes across vegetative stages. Several genes associated with phytohormone and oxidative stress responses were downregulated. Additionally, thiamethoxam exposure was observed to interact with drought stress by upregulating expression of thiamine biosynthetic enzyme and gibberellin regulated protein and downregulating expression of apetala 2, lipoxygenase and SAM dependent carboxyl methyltransferase. Authors concluded thiamethoxam treatment alters soybean gene expression related to plant defense and stress response.
 - The Xerces Society for Invertebrate Conservation 2013
 - Parasitoid wasps confined with citrus leaves that were treated with thiamethoxam had significantly higher mortality
 - All life stages of the multicolored Asian lady beetle (*Harmonia axyridis*) were susceptible to topical treatment of a dose at label rates of thiamethoxam. Larvae that fed on seedlings grown from seeds treated with thiamethoxam experienced significantly higher mortality and sub-lethal effects such as trembling, paralysis or loss of coordination.

- Thiamethoxam is highly toxic to adults of rove beetle (*Atheta coriaria*) when applied to a growing medium at label rates.
- The minute pirate bug (*Orius insidiosus*) is a major predatory of soybean aphids that will feed on plant tissues when prey is scarce. This bug has high mortality when exposed to soybeans grown from thiamethoxam treated seeds.
- Ground beetle consumption of corn seeds treated with label rates of thiamethoxam caused nearly 100% mortality in 18 species tested; however, consumption of contaminated corn pollen caused no ill effects.
- Predaceous stink bug nymphs (*Podisus nigrispinus*) that consumed plant sap from thiamethoxam treated cotton plants had reduced survival; survival rates decreased with increasing amounts of thiamethoxam.
- Thiamethoxam was found not toxic on contact to *Anystis baccarum*, a predatory mite commonly found in apple orchards.
- Thiamethoxam was found not toxic to predatory mite *Neoseiulus fallacis*; however, it did significantly reduce reproduction.
- Time to find, identify and attack prey was significantly increased when predatory mites *Neoseiulus californicus* and *Phytoseiulus macropilis* are exposed to two-spotted spider mite eggs sprayed with thiamethoxam. Consequently, the predatory mites consumed significantly fewer pest mites.
- Higher predatory mortality due to applications of thiamethoxam in cotton resulted in a resurgence of bollworm larvae.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vH

Thiamethoxam was assigned a score of Very High for persistence based on a measured half-life for its main metabolite in soil being 337.95 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 in the score is reduced as modeling was used to predict the predominant compartment of thiamethoxam.

- **Authoritative and Screening Lists**
 - *Authoritative:* EU Risk Phrase R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment²².
 - *Screening:* EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects²³.
- **SCBP 2012**
 - Thiamethoxam was not biodegradable when tested in a ready biodegradation test. However in water it hydrolyzed under alkaline conditions to form the de-nitro metabolite NOA 407475 which has potential to bind to sediment. Its degradation in water occurs first by biological and then some photolytic processes. The measured hydrolysis half-lives for thiamethoxam in surface water were between 4.2-15.6 days at pH 9 or 640-572 days at pH 7.
 - Thiamethoxam was also degraded in soil when tested in field soil studies but its half-life depends mainly on the nature and biota of the soil. Degradation is relatively rapid under

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

anaerobic conditions with thiamethoxam yielding up to 62.3% of metabolite NOA 407475 at 120 days. In aerobic soil, thiamethoxam yields several metabolites, including CGA 322704 (clothianidin), which can reach up to 35.6%. The measured aerobic half-life in soil was 72 days at 10°C. The metabolite clothianidin is stable in water over a wide pH and temperature ranges and its measured aerobic half-lives in soils were 178 days at 20°C or 337.95 days at 12°C.

- Morrissey et al. 2015
 - *Soil*: $DT_{50}^{24} = 7 - 72$ days
 - *Surface water*: $DT_{50} = 2.7 - 39.5$ days
 - *Ground water*: $DT_{50} = 11.5$ days (pH 9)
- Goulson 2013
 - *Soil*: $DT_{50} = 7 - 353$ days
- Krupke and Long 2015
 - *Soil*: $DT_{50} = 5 - 100$ days
 - *Water*: $DT_{50} = 8 - 44$ days
- U.S. EPA 2012
 - The BIOWIN model predicted that thiamethoxam is not readily biodegradable. Using a fugacity model, thiamethoxam is predicted to appear mainly in the soil compartment (86.1%), with 13.7% 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 thiamethoxam is not readily biodegradable but it hydrolyzes in water under alkaline conditions to form the de-nitro metabolite NOA 407475 which has potential to bind to sediment. The measured hydrolysis half-lives for thiamethoxam in surface water are between 4.2-15.6 days at pH 9, which correspond to a score of Low, while the measured hydrolysis half lives in environmental conditions (pH 7) are 640-572 days, which correspond to a score of Very High. However, water is not predicted to be the predominant compartment for thiamethoxam. EPISuite predicts that thiamethoxam is going to mainly partition to soil. In soil, thiamethoxam has a measured aerobic half-life of 72 days at 10°C with clothianidin being the main metabolite. Clothianidin has measured aerobic half-lives in soils of 178 days at 20°C or 337.95 days at 12°C. Although the half lives in soil of 72 and 178 days for thiamethoxam and clothianidin, respectively, correspond to a score of High, the measured aerobic half-life in soil of 337.9 days for clothianidin at a lower temperature (but still environmentally relevant) of 12°C corresponds to a score of Very High. Based on this, ToxServices assigned a Very High score for this endpoint.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL

Thiamethoxam 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 a measured log K_{ow} .

²⁴ DT_{50} : Time required for 50% dissipation of the initial concentration.

- Authoritative and Screening Lists
 - *Authoritative:* EU Risk Phrase R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment²⁵.
 - *Screening:* EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects²⁶.
- SCBP 2012
 - Thiamethoxam has a measured log K_{ow} of -0.13 at 25°C.
- U.S. EPA 2012
 - BCFBAF predicts a BCF of 3.162 based on a measured log K_{ow} of -0.13 (see Appendix D).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): L

Thiamethoxam was assigned a score of Low for reactivity based on its NFPA and HMIS reactivity ratings and 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 in the score is 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 2015).
 - Thiamethoxam contains nitro chemical group (NO₂) which is associated with explosive properties (Appendix E). In addition, its calculated oxygen balance (as shown below) is greater than -200. Based on this, thiamethoxam is considered a potential explosive and according to GHS criteria further testing is necessary to determine the explosive property of thiamethoxam
 - Oxygen balance equation:
OB = -1600 x (2x+(y/2)-z)/MW Where C_xH_yO_z
Total number of carbons, hydrogens, and oxygens in thiamethoxam:
X = C = 8 Y = H = 10 Z = O = 3
OB = -1600 x (2(8)+(10/2)-3)/ 291.718 = - 98.7
- Santa Cruz 2015
 - Thiamethoxam has a reactivity rating of 0 from the NFPA (“Normally stable, even under fire exposure conditions, and is not reactive with water”) and HMIS (“Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives”).
- SCBP 2012
 - Thiamethoxam is not considered an explosive nor an oxidizing substance.

²⁵ This is an authoritative EU R-phrase that addresses a combination of hazards including aquatic toxicity, persistence, and/or bioaccumulation

²⁶ 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. Thiamethoxam contains a structural alert for explosivity and its calculated oxygen balance indicated a potential for explosivity. However it has received an NFPA and HMIS rating of 0 for physical hazards and reactivity which indicates that it is not explosive, and it was considered not explosive or oxidizing when evaluated by European Commission. It does not contain alerts for self-reactivity, or is a substance 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

Thiamethoxam was assigned a score of Low for flammability based on its NFPA and HMIS flammability ratings of 1 indicating a low hazard of flammability. GreenScreen[®] criteria classify chemicals as a Low hazard for flammability when they are not flammable solids and when they are not classified per GHS (CPA 2012b). Confidence in the score is 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
- SCBP 2012
 - Thiamethoxam is not considered a flammable substance.
- Santa Cruz 2015
 - A material safety data sheet for thiamethoxam states that it has an NFPA and HMIS flammability rating of 1. An HMIS and NFPA flammability rating of 1 correspond to “Materials that must be preheated before ignition can occur; includes liquids, solids and semi solids having a flash point above 200°F” (NFPA 2016 and ILPI 2015).

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

- (AA) Acute Aquatic Toxicity**
- (AFI) Acute Foliar Invertebrates and Pollinators Toxicity**
- (AT) Acute Mammalian Toxicity**
- (ATV) Acute Terrestrial Vertebrates Toxicity**
- (B) Bioaccumulation**
- (C) Carcinogenicity**
- (CA) Chronic Aquatic Toxicity**
- (CFI) Chronic Foliar Invertebrates and Pollinators Toxicity**
- (CTV) Chronic Terrestrial Vertebrates 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 Thiamethoxam (CAS# 153719-23-4)

		GreenScreen® Score Inspector																				
		Group I Human					Group II and II* Human							Ecotox		Fate		Physical				
Table 2: Chemical Details			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	
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	Thiamethoxam	153719-23-4	L	L	M	M	DG	M	L	M	H	L	L	DG	L	L	vH	L	vH	vL	L	L

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

Chemical Name	Preliminary GreenScreen® Benchmark Score
Thiamethoxam	1

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

Chemical Name	Final GreenScreen® Benchmark Score
Thiamethoxam	1

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

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

APPENDIX C: Pharos Output for Thiamethoxam (CAS# 153719-23-4)

[153719-23-4] thiamethoxam (ISO)

 General Information

 Hazards

 Life Cycle Research

 GreenScreen

Direct Hazards:

ACUTE AQUATIC



EC - CLP/GHS Hazard Statements - H400 - Aquatic Acute 1 - Very toxic to aquatic life / M-Factor of 10

+ 1



EC - Risk Phrases - R50: Very toxic to aquatic organisms.

CHRON AQUATIC



EC - CLP/GHS Hazard Statements - H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects

+ 1



EC - Risk Phrases - R53: May cause long-term adverse effects in the aquatic environment.

MAMMALIAN



EC - Risk Phrases - R22: Harmful if swallowed.

+ 1



EC - CLP/GHS Hazard Statements - H302 Harmful if swallowed

APPENDIX D: EPISuite Modeling Results for Thiamethoxam (CAS# 153719-23-4)

CAS Number: 153719-23-4
SMILES : C2OCN(C(N2C)=NN(=O)(=O))Cc1cnc(s1)CL
CHEM : THIAMETHOXAM
MOL FOR: C8 H10 CL1 N5 O3 S1
MOL WT : 291.71

----- EPI SUMMARY (v4.11) -----

Physical Property Inputs:

Log Kow (octanol-water): -0.13
Boiling Point (deg C) : -----
Melting Point (deg C) : -----
Vapor Pressure (mm Hg) : -----
Water Solubility (mg/L): -----
Henry LC (atm-m³/mole) : -----

Log Octanol-Water Partition Coef (SRC):

Log Kow (KOWWIN v1.68 estimate) = 0.80

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):

Boiling Pt (deg C): 395.22 (Adapted Stein & Brown method)
Melting Pt (deg C): 163.65 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 4.08E-007 (Modified Grain method)
VP (Pa, 25 deg C) : 5.43E-005 (Modified Grain method)
Subcooled liquid VP: 1.09E-005 mm Hg (25 deg C, Mod-Grain method)
: 0.00145 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):

Water Solubility at 25 deg C (mg/L): 1.771e+004
log Kow used: -0.13 (user entered)
no-melting pt equation used

Water Sol Estimate from Fragments:

Wat Sol (v1.01 est) = 1e+006 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 : 6.87E-015 atm-m³/mole (6.96E-010 Pa-m³/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: 8.843E-012 atm-m³/mole (8.960E-007 Pa-m³/mole)
VP: 4.08E-007 mm Hg (source: MPBPVP)
WS: 1.77E+004 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:

Log Kow used: -0.13 (user entered)
Log Kaw used: -12.551 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 12.421
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):

Biowin1 (Linear Model) : 0.0789
Biowin2 (Non-Linear Model) : 0.0014

Expert Survey Biodegradation Results:

Biowin3 (Ultimate Survey Model): 2.3393 (weeks-months)
Biowin4 (Primary Survey Model) : 3.2518 (days-weeks)

MITI Biodegradation Probability:

Biowin5 (MITI Linear Model) : -0.1557
Biowin6 (MITI Non-Linear Model): 0.0032

Anaerobic Biodegradation Probability:

Biowin7 (Anaerobic Linear Model): -0.2458

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): 0.00145 Pa (1.09E-005 mm Hg)

Log Koa (Koawin est): 12.421

Kp (particle/gas partition coef. (m³/ug)):

Mackay model : 0.00206

Octanol/air (Koa) model: 0.647

Fraction sorbed to airborne particulates (phi):

Junge-Pankow model : 0.0694

Mackay model : 0.142

Octanol/air (Koa) model: 0.981

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant = 248.9384 E-12 cm³/molecule-sec

Half-Life = 0.043 Days (12-hr day; 1.5E6 OH/cm³)

Half-Life = 0.516 Hrs

Ozone Reaction:

No Ozone Reaction Estimation

Fraction sorbed to airborne particulates (phi):

0.106 (Junge-Pankow, Mackay avg)

0.981 (Koa method)

Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):

Koc : 265.8 L/kg (MCI method)

Log Koc: 2.425 (MCI method)

Koc : 7.095 L/kg (Kow method)
Log Koc: 0.851 (Kow 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) = -2.0438 days (HL = 0.009041 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.039 (BCF = 0.914)
Log BAF Arnot-Gobas method (upper trophic) = -0.039 (BAF = 0.914)
log Kow used: -0.13 (user entered)

Volatilization from Water:

Henry LC: 6.87E-015 atm-m³/mole (estimated by Bond SAR Method)
Half-Life from Model River: 1.456E+011 hours (6.065E+009 days)
Half-Life from Model Lake : 1.588E+012 hours (6.616E+010 days)

Removal In Wastewater Treatment:

Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.76 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	5.89e-008	1.03	1000
Water	13.7	900	1000
Soil	86.1	1.8e+003	1000
Sediment	0.208	8.1e+003	0

Persistence Time: 1.74e+003 hr

APPENDIX E: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups


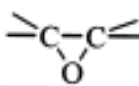
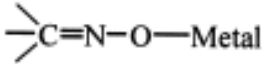
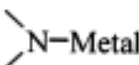
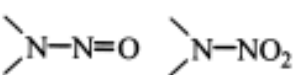
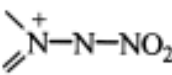
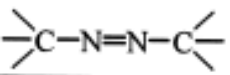
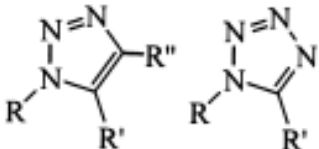
- Not classified if no chemical groups associated with explosivity, e.g.

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

© CHCS Module 17 CLP - Substances 31

Explosivity – Full List

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

Chemical group	Chemical Class
-C=C-	Acetylenic Compounds
-C=C-Metal	Metal Acetylides
-C=C-Halogen	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 <i>aci</i> -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) ₂ O, (ArN=N) ₂ S	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', $\begin{array}{c} \text{O} \\ \parallel \\ \text{---C} \\ \backslash \\ \text{OOR}' \end{array}$ [2]	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, $\begin{array}{c} \text{O} \\ \parallel \\ \text{---C} \\ \backslash \\ \text{OO}^- \text{Metal}^+ \end{array}$ [2]	Metal peroxides, Peroxoacids salts
-N ₃	Azides e.g. PbN ₆ , CH ₃ N ₃
$\text{O}^- \text{---C---N}_2^+$	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. perchlorates, bromates, etc
NX ₃ e.g. NCl ₃ , RNCI ₂	N-Halogen Compounds

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

Self-Reactive Substances



Screening procedures

- Not in CLP, but UN Manual of Tests and Criteria Appendix 6
- No explosive groups (see 2.1) plus

Structural feature	Chemical classes
Mutually reactive groups	Aminonitriles, haloanilines, organic salts of oxidising agents
S=O	Sulphonyl halides, sulphonyl cyanides, sulphonyl hydrazides
P-O	Phosphites
Strained rings	Epoxides, aziridines
Unsaturation	Olefins, cyanates

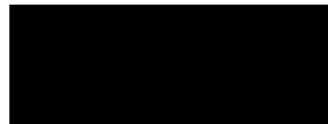
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