N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Washington State Department of Ecology

Prepared by:

ToxServices LLC

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TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

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N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is a chemical that functions as an herbicide and biocide booster.

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search For Safer Substitutes") as it has High persistence-P, Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and endocrine activity-E), Group II Human Toxicity (systemic toxicity (single dose)-STs and neurotoxicity (single dose)-Ns), and Group II* Human Toxicity (systemic toxicity (repeated dose)-STr* and skin sensitization-SnS*), and Very High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA). This corresponds to GreenScreen® benchmark classifications 2c, 2e, and 2f in CPA 2011. Data gaps (DG) exist for neurotoxicity (repeated dose)-Nr* 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), N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) were assigned a High score for the data gaps Nr* or SnR*, it would still be categorized as a Benchmark 2 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 2 ("Use but Search for Safer Substitutes") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio)

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	P	B	Rx	F
						single	repeated*	single	repeated*										
M	L	*M*	L	*M*	L	*M*	M	M	DG	M	DG	L	L	vH	vH	H	L	*L*	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated 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.

GreenScreen® Assessment for N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS #28159-98-0)

Method Version: GreenScreen® Version 1.2[1]
Assessment Type[2]: Certified

Chemical Name: N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio)

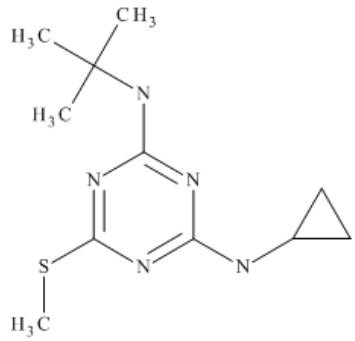
CAS Number: 28159-98-0

GreenScreen® Assessment Prepared By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: September 22, 2014
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: December 1, 2014

Confirm application of the *de minimus* rule[3]: N/A

Chemical Structure(s):



Also called: Cybutryne; Irgarol 1051; 1,3,5-Triazine-2,4-diamine, N-cyclopropyl-N'-(1,1-dimethylethyl)-6-(methylthio)-; N'-tert-Butyl-N-cyclopropyl-6-(methylthio)-1,3,5-triazine-2,4-diamine (ChemIDplus 2014)

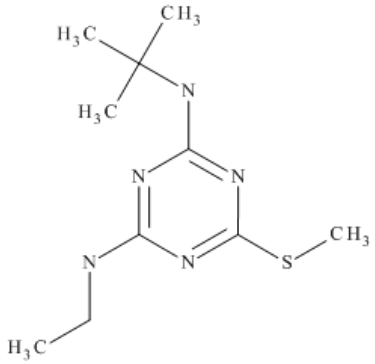
Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
An incomplete dataset was identified for N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio). Terbutryn was identified as a chemical surrogate based on structural similarity. Terbutryn was identified by the U.K. Health and Safety Executive Biocides & Pesticides Assessment Unit as an acceptable surrogate for N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) as it is a related S-triazine compound with a similar metabolic pathway and repeated dose toxicity profile. It differs from N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) in that it dose not contain a cyclopropyl moiety, but toxiciokinetic data indicate that the

[1] Use GreenScreen® Assessment Procedure (Guidance) V1.2

[2] 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)

[3] 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

cyclopropyl moiety does not significantly alter metabolism of triazines (HSE 2005). Terbutryn was used to fill data gaps for carcinogenicity, reproductive toxcity, and endocrine activity.



Terbutryn (CAS# 886-50-0)

Identify Applications/Functional Uses: (HSE 2005)
1. Herbicide
2. Booster biocide

GreenScreen® Summary Rating for N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio)[4]: N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search For Safer Substitutes") as it has High persistence-P, Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and endocrine activity-E), Group II Human Toxicity (systemic toxicity (single dose)-STs and neurotoxicity (single dose)-Ns), and Group II* Human Toxicity (systemic toxicity (repeated dose)-STr* and skin sensitization-SnS*), and Very High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA). This corresponds to GreenScreen® benchmark classifications 2c, 2e, and 2f in CPA 2011. Data gaps (DG) exist for neurotoxicity (repeated dose)-Nr* 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), N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) were assigned a High score for the data gaps Nr* or SnR*, it would still be categorized as a Benchmark 2 Chemical.

Figure 1: GreenScreen® Hazard Ratings for N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio)

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	P	B	Rx	F
						single	repeated*	single	repeated*										
M	L	*M*	L	*M*	L	*M*	M	M	DG	M	DG	L	L	vH	vH	H	L	*L*	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four

[4] 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.

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**[5]

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is not readily biodegradable and is hydrolytically stable. The major degradation product is 2-amino-4-tert-butylamino-6-methylthio-s-triazine (CIRCABC 2011), which is also known as GS-26575 (HSE 2005). Two other products, CGA-234575 and CGA-234576 have been produced by photolysis (HSE 2005). These compounds are not listed in the Pharos database and therefore do not impact the Benchmark score. No other degradation products were identified.

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Feasible and Relevant?	GreenScreen® List Translator Score or Benchmark Score [6,7]
Biocide	Use, end of life	Photolysis	GS-26575 (2-amino-4-tert-butylamino-6-methylthio-s-triazine)	N/A	Y	Not in Pharos database
Biocide	Use, end of life	Photolysis	CGA-234575 -	N/A	Y	Not in Pharos database
Biocide	Use, end of life	Photolysis	CGA-234576 -	N/A	Y	Not in Pharos database

Introduction

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is a triazine herbicide that is used as a booster biocide in antifouling products to enhance the efficacy of copper or triorganotins (HSE 2005).

ToxServices assessed N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.69 (GreenScreen® Hazard Assessment) (ToxServices 2013).

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2014a) is an

[5] 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.

[6] 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 2014a) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.

[7] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

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 N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) can be found in Appendix C and a summary of the results can be found below:

Mammalian Toxicity
New Zealand HSNO/GHS (GHS-New Zealand) 6.1E (oral) - Acutely toxic (Category 5)
Skin Sensitization
New Zealand HSNO/GHS (GHS-New Zealand) 6.5B (contact) - Contact sensitizers (Category 1)
Eye Irritation
New Zealand HSNO/GHS (GHS-New Zealand) 6.4A - Irritating to the eye (Category 2A)
Aquatic Toxicity
New Zealand HSNO/GHS (GHS-New Zealand) 9.1A (algal) - Very ecotoxic in the aquatic environment (Category 1)
New Zealand HSNO/GHS (GHS-New Zealand) 9.1A (fish) - Very ecotoxic in the aquatic environment (Category 1)
New Zealand HSNO/GHS (GHS-New Zealand) 9.1B (crustacean) - Very ecotoxic in the aquatic environment (Category 2)
New Zealand HSNO/GHS (GHS-New Zealand) 9.1B (other) - Very ecotoxic in the aquatic environment (Category 2)
Other
German FEA - Substances Hazardous to Waters (VwVwS)

When appropriate, the equivalent GHS hazard classifications were identified for GHS New Zealand classifications (EPA 2012)

PhysicoChemical Properties of N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio)

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is a solid at room temperature. Its low vapor pressure of 6.6×10^{-7} mmHg indicates that it is not likely to form a gas. It is slightly soluble in water (1.8-11 mg/L), and its log K_{ow} of 2.8 indicates low potential for bioaccumulation.

Table 1: Physical and Chemical Properties of N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS #28159-98-0)

Property	Value	Reference
Molecular formula	C11-H19-N5-S	ChemIDplus 2014
SMILES Notation	c1(nc(NC(C)(C)C)nc(n1)SC)NC1CC1	ChemIDplus 2014
Molecular weight	253.372	ChemIDplus 2014
Physical state	Solid	HSE 2005
Appearance	White to yellowish, granular	HSE 2005
Melting point	127-133°C	HSE 2005
Vapor pressure	0.088 mPa (6.6×10^{-7} mmHg) at 25°C	HSE 2005
Water solubility	1.8-11.1 mg/L at 20°C	HSE 2005

Table 1: Physical and Chemical Properties of N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS #28159-98-0)		
Property	**Value**	**Reference**
Dissociation constant	Not identified	
Density/specific gravity	1.17	HSE 2005
Partition coefficient	Log K_{ow} = 2.8 at 20°C	HSE 2005

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Moderate for carcinogenicity based on an oral carcinogenicity study of the surrogate terbutryn in rats that reported tumors of the mammary gland, liver, thyroid, and testes. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited or marginal evidence of carcinogenicity in animals (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - No carcinogenicity data are available for N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio). Data for structurally similar S-triazines and chlorotriazines indicate that these substances are carcinogenic in rats, but mechanistic data are inadequate to determine the relevance of these studies to human health. These compounds are considered to be non-genotoxic carcinogens based on negative genotoxicity studies. HSE concluded that the worst case assumption is that N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is a non-genotoxic carcinogen.

Terbutryn (CAS# 886-50-0)

- HSE 2005
  - In a 2-year oral carcinogenicity study in male and female CD1 rats, animals (number not specified) were administered terbutryn (purity not specified) in the diet to produce doses of 0, 0.1, 15, or 150 mg/kg/day assuming a body weight of 400 g/day and food consumption of 20 g/day. In females, significant increases in the combined incidence of mammary gland adenoma/adenocarcinoma and hepatocellular adenoma/adenocarcinoma were seen at the high dose. In males, significant increases in thyroid follicular cell adenoma/carcinoma and testicular interstitial cell adenoma were seen. Incidences exceeded the upper limit of the historical control range for thyroid, liver, and testicular tumors, and for malignant but not benign mammary tumors. HSE notes that there is a high background spontaneous incidence of mammary and testicular tumors in this strain, and concluded that terbutryn is a non-genotoxic carcinogen in rats but that the relevance to human health is unknown due to the lack of mechanistic data.
- U.S. EPA 1986
  - In a 2-year oral carcinogenicity study in CD1 mice, no evidence of carcinogenicity was seen when animals were administered technical grade terbutryn in the diet at concentrations of 0,

3, 1,000, or 3,000 ppm (0, 0.555, 185, or 555 mg/kg/day[8]). No additional details were provided.

- Based on the weight of evidence, a score of Moderate was assigned. The structurally similar surrogate terbutryn is considered to be a non-genotoxic carcinogen in rats, producing tumors of the mammary gland, liver, thyroid, and testes. Although HSE noted that the relevance to humans is unknown, GreenScreen® criteria specify a score of Moderate when there is limited or marginal evidence of carcinogenicity in animals.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Low for mutagenicity/genotoxicity based on negative results in *in vitro* bacterial and mammalian cell mutagenicity assays, a mammalian cell chromosome aberration assay, and a UDS assay. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and are negative for both mutagenicity and clastogenicity, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98% purity) was negative in a bacterial reverse mutation assay in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 when tested at concentrations of 0, 20, 78, 313, 1,250, and 5,000 µg/mL with and without metabolic activation.
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98% purity) was negative in an *in vitro* mammalian cell mutagenicity assay in Chinese hamster lung cells (V79-HPRT) when tested at concentrations of 50-1,000 µg/mL without metabolic activation and 2.5-5.0 µg/mL with metabolic activation. No evidence of mutagenicity was seen in an initial or confirmatory study.
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98% purity) was negative in an *in vitro* mammalian cell chromosome aberration study in Chinese hamster ovary (CHO) cells when tested at concentrations up to 150 mg/mL with and without metabolic activation. No increase in chromosomal aberrations was seen in an initial or confirmatory study.
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98% purity) was negative in an *in vitro* unscheduled DNA synthesis assay in adult male Tif.RAI (SPF) rat primary hepatocytes when tested at concentrations of 0.3-30 µg/mL. A marginal increase in grains/cell was seen at 3 µg/mL in the initial study but not in the confirmatory study, and authors concluded that there was no evidence of UDS.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Moderate for reproductive toxicity based on effects on male fertility and pup weight in a 3-generation study in rats for the surrogate terbutryn. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity in animals (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists

[8] 3,000 mg/kg food/day * 0.185 kg food/kg BW/day = 555 mg/kg/day (mouse average food factor values for chronic study from TERA undated)

- *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- No data were identified

Terbutryn (CAS# 886-50-0)

- HSE 2005
  - In a 3-generation reproductive toxicity study in rats, animals were administered doses of 0.1, 15, or 150 mg/kg/day terbutryn (route not specified). Male fertility was slightly impaired at the high dose in the F1a and F1b litters, and the fertility index of the F3a litter was reduced. Mean pup weights on lactation day 21 were decreased in all top dose litters. No additional details were provided. HSE identified a NOAEL of 15 mg/kg/day and LOAEL of 150 mg/kg/day for reproductive effects.
- Based on the weight of evidence, a conservative score of Moderate was assigned, as data for the surrogate terbutryn provide limited or marginal evidence of reproductive effects in animals. Confidence in this score is reduced as few experimental details were available for this study.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Low for developmental toxicity based on negative results in a prenatal developmental toxicity study in rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate data are available and are negative for developmental toxicity, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - In a prenatal developmental toxicity study in Sprague-Dawley rats, dams (25-33/dose) were administered 0, 50, 150, or 300 mg/kg/day N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98-99% purity) via gavage on gestation days 6-15 and were sacrificed on gestation day 20. Clinical signs of maternal toxicity (pushing of nose through sawdust and extreme soiling of the cage) were seen at the mid and high dose. At the high dose, body weight gain was significantly decreased by 48% compared to controls during treatment on gestation days 6-15, and returned to control values by gestation day 20. Mean body weight was decreased by 6-8% during treatment in this group. Food consumption on gestation days 6-10 was decreased by 20 and 25% in the mid and high dose groups, respectively. No effects on the number of corpora lutea, implantations, resorptions (early and late), mean number of live fetuses, number of fetuses per dam, mean litter weight, or fetal sex ratio were seen. There was no treatment-related increase in the incidence of visceral malformations or skeletal malformations, and there were no effects on ossification. HSE identified a NOAEL of 50 mg/kg/day for maternal toxicity, and 300 mg/kg/day for developmental toxicity based on the lack of effects.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Moderate for endocrine disruption based on presence of the surrogate on screening lists. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine disruption when the chemical is classified as Category 1 potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors and as a

potential endocrine disruptor in TEDX, and data show evidence of endocrine activity without related human health effects (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- 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.
- No data were identified
- High Throughput Screening (HTS) Data –
    - HTS data were identified for N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) using PubChem (http://pubchem.ncbi.nlm.nih.gov/).
    - The data included the following results:
        - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was active in 0/3 androgen receptor agonist assays and 0/6 androgen receptor antagonist assays.
        - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was active in 0/3 estrogen receptor-alpha agonist assays and 0/6 estrogen receptor-alpha antagonist assays.
        - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was active in 0/1 thyroid receptor agonist assay and 0/3 thyroid receptor antagonist assays.
        - The activity of N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) towards the thyroid stimulating hormone receptor was not evaluated.

Terbutryn (CAS# 886-50-0)

- 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.
- Pharos 2014b
    - Terburtyn is listed as a Category 1 potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors and as a potential endocrine disruptor in TEDX.
- TEDX 2011
    - Terbutryn is classified as a potential endocrine disruptor based on its carcinogenic properties in the mammary gland and testes, and the common mode of antithyroid induced carcinogenicity of several pesticides, as summarized in Hurley et al. 1998.
- Based on the weight of evidence, a score of Moderate was assigned. The surrogate terbutryn is classified as Category 1 potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors and as a potential endocrine disruptor in TEDX, which corresponds to a score of Moderate to High. Although there is evidence of mammary, testicular, and thyroid carcinogenicity in rats, HSE notes that the relevance to humans is unknown. As GreenScreen criteria require "evidence of endocrine activity and related human health effect" to classify as a High, the score of Moderate, which corresponds to "evidence of endocrine activity", is appropriate. Confidence in this score is reduced because it is based on screening lists.

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): L

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Low for acute toxicity based on an oral LD_{50} of 5,000 mg/kg and a dermal LD_{50} of greater than 2,000 mg/kg in rats. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* New Zealand HSNO/GHS (GHS-New Zealand) 6.1E (oral) - Acutely toxic (Category 5)

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - *Oral*: LD_{50} (rat, male and female Tif:RAI (SPF)) = 5,000 mg/kg
  - *Dermal*: LD_{50} (rat male and female Tif:RAI (SPF)) > 2,000 mg/kg
  - *Dermal*: LC_{50} (rat male and female Tif:RAI (SPF)) > 2,000 mg/kg > 4.09 mg/L

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M, or L):** *M*

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Moderate for systemic toxicity (single dose) based on pathological changes to the lungs in an acute inhalation study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when available data indicate that GHS Category 3 classification for respiratory tract irritation may be warranted (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - *Oral*: In the acute oral toxicity study in male and female Tif:RAI (SPF) rats that identified an LD_{50} of 5,000 mg/kg, animals (5/sex/dose) were administered a single oral dose of 2,000 or 5,000 mg/kg N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98.6% purity) via gavage and were observed for 14 days. No mortality was seen at the low dose. Dyspnea, ruffled fur, and curved body position were seen at the 2,000 mg/kg/day dose and above. Sedation was observed at the 5,000 mg/kg/day dose. No gross lesions were observed at necropsy.
  - *Dermal*: In the acute dermal toxicity study in male and female Tif:RAI (SPF) rats that identified an LD_{50} of > 2,000 mg/kg, animals (5/sex) received a single dermal dose of 2,000 mg/kg N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98.6% purity) to shaved skin under occlusion for 24 hours, and were observed for 14 days. No mortality was observed. Transient sedation and curved body position, dyspnea, ruffled fur, and ventral body position were observed. No gross lesions were observed at necropsy.
  - *Inhalation*: In the acute inhalation toxicity study in male and female Tif:RAI (SPF) rats that identified an LC_{50} of > 4.09 mg/L, animals (5/sex/dose) were exposed to N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98.6% purity) aerosol 0.2, 0.75, or 4.09 mg/L N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) aerosol for 4 hours and were observed for an unspecified duration. Depressed activity and movement and nasal discharge were seen in both sexes. Red foci were seen on the lungs at the mid and high doses.
  - *Inhalation*: One case of respiratory tract irritation has been reported due to occupational exposure by an operator preparing a formulation containing N-cyclopropyl-N'(1,1-

dimethyl)-6-(methylthio). It cannot be determined whether irritation is due to this compound or to others in the formulation.

- Based on the weight of evidence, a conservative score of Moderate was assigned to account for the possibility of respiratory tract irritation with inhalation exposures. Signs including dyspnea, ruffled fur, and curved body position at a dose of 2,000 mg/kg were not considered by ToxServices to be sufficient to warrant GHS classification for systemic toxicity considering the lack of gross pathological effects. However, the presence of red foci on the lungs of rats in the acute inhalation toxicity study suggest that respiratory tract irritation is possible, and GHS guidance specifies that histopathology can be used in the weight of evidence evaluation of respiratory tract effects. There is also one case of respiratory tract irritation in humans following inhalation exposure. Confidence in this score is reduced as it is not possible to determine if irritation in the human case study can be attributed solely to N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio).

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Moderate for systemic toxicity (repeated dose) based on effects on body weight, hematology, and clinical chemistry at a dose of 62.5 mg/kg/day in a 90-day oral toxicity study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when evidence of systemic toxicity is seen between 10 and 100 mg/kg/day in an oral toxicity study (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

<u>N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)</u>

- HSE 2005
  - *Oral*: In a 28-day oral toxicity study in male and female Tif:RAI F3 hybrid rats, animals (10-sex/dose) were administered N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98% purity) in the diet at concentrations of 0, 100, 600, 1800 or 5,000 ppm (0, 7.5, 45.1, 132, or 360 mg/kg/day). At the end of the 28-day treatment period (5 rats/sex/dose) were maintained on the control diet for a 2-week recovery period. Mean body weight decreased significantly with dose starting at week 1 in males at the low dose (by 5-6%) and above (by 12-31%) and at weeks 1-2 in females at the 45.1 mg/kg/day dose (by 3-8%) and above (by 7-15%). Body weight decreases at the two highest doses did not reverse during the recovery period. Food consumption decreased with dose in both sexes during treatment and returned to control levels during recovery. Mild regenerative anemia and slight decreases in plasma hematocrit, hemoglobin concentration, and erythrocyte count, which were occasionally significant, were seen at 45.1 mg/kg/day and above, and resolved by the end of the recovery period. Plasma cholesterol was significantly increased in both sexes by 27-30% at 132 mg/kg/day and 74-86% at 360 mg/kg/day and reversed following the recovery period. Plasma ALP increased significantly in both sexes at 132 mg/kg/day and above, and did not reverse during the recovery period in males. Plasma ALT activity increased significantly (by 70%) in males at the high dose and resolved during recovery. Changes in relative organ weights were considered by HSE to be due to changes in body weight. Minimal centrilobular hypertrophy was seen in 9/10 animals at the high dose after treatment, and in 1/5 males in each of the two highest dose groups after recovery. Hepatocellular glycogen depletion was seen in males at 45.1 mg/kg/day and above and females at 360 mg/kg/day, and resolved after the recovery period. A treatment related increase in incidence and severity of hemosiderosis of the spleen, which did not resolve during recovery, was seen in both sexes at 45.4 mg/kg/day and

above. HSE identified a NOAEL of 7.5 mg/kg/day and above. The LOAEL of 45.1 mg/kg/day is compared to triple guidance values due to the 28-day length of the study.

- *Dermal*: In a 21-day dermal toxicity study in male and female Tif:RAI F3 hybrid rats, animals (5/sex/dose) were administered 0, 10, 100, or 1,000 mg/kg/day N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98% purity) under gauze to shaved intact skin for 6 hours/day, 5 days/week. No treatment-related mortality, clinical toxicity, effects on body weight, or gross pathological changes was seen. HSE identified a NOAEL of 300 mg/kg/day based on the lack of effects. This is equivalent to 214 mg/kg/day[9] based on a 7 day week treatment frequency.
- *Oral*: In a 90-day oral toxicity study in male and female Tif:RAI F3 hybrid rats, animals (20/sex/dose at control and high dose, 10/sex/dose at low and mid dose) were administered N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (99% purity) in the diet at concentrations of 0, 20, 150, or 1,000 ppm (0, 1.1, 9.7, or 62.5 mg/kg/day). At the end of the 90-day treatment period, 10 animals in the control and high dose group were maintained on a control diet for a 4-week recovery period. No clinical signs of toxicity were seen. Body weight was significantly decreased by 17% in males and 9% in females from week 2 though the conclusion of the study. Food consumption was decreased by 8% in both sexes at this dose. During the recovery period, food consumption increased in both sexes and body weight in males, but not females, recovered. Slight decreases of 2-5% in erythrocyte count, hemoglobin concentration and plasma hematocrit were seen in both sexes at the high dose, and reversed during recovery. Plasma cholesterol concentration was significantly increased by 18-19% in both sexes after 90 days at the high dose, and reversed during recovery. Plasma ALP activity increased significantly by 39% in females at the high dose, and remained 27% higher than controls after the recovery period. An increase of 10% in relative liver weight was seen in both sexes, but was attributed to body weight changes. No histopathological changes were seen in any tissue after either the treatment or recovery period. HSE identified a NOAEL of 9.7 mg/kg/day and LOAEL of 62.5 mg/kg/day based on effects on body weight, hematology, plasma cholesterol, and ALP activity at the high dose.

- Based on the weight of evidence, a score of Moderate was assigned. Effects on body weight, hematology, and clinical chemistry were seen at a dose of 45.1 mg/kg/day (NOAEL = 7.5 mg/kg/day) in the 21-day oral study. These values, when compared to the tripled guidance values of 30-300 mg/kg/day, correspond to a score of Moderate to High. As both oral toxicity studies were of similar design and quality, the 90-day study was weighed more heavily in the assessment due to the longer duration of the study. Similar effects to those seen in the 28-day study were seen at a dose of 62.5 mg/kg/day (NOAEL = 9.7 mg/kg/day), which corresponds to a score of Moderate. Therefore a score of Moderate was assigned.

Neurotoxicity (N)

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Moderate for neurotoxicity (single dose) based on transient narcotic effects in acute oral, dermal, and inhalation toxicity studies in rats GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when available data indicate that GHS Category 3 classification for transient narcotic effects may be warranted (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists

[9] 300 mg/kg/day * 5 days/7 days = 214 mg/kg/day

- *Screening:* Not present on any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - *Oral*: In the acute oral toxicity study in male and female Tif:RAI (SPF) rats that identified an LD_{50} of 5,000 mg/kg described above for systemic toxicity-single dose, sedation was observed at 5,000 mg/kg. Sedation resolved within 5 hours-3 days.
  - *Dermal*: In the acute dermal toxicity study in male and female Tif:RAI (SPF) rats that identified an LD_{50} of > 2,000 mg/kg described above for systemic toxicity-single dose, sedation was observed and resolved within 5 hours.
  - *Inhalation*: In the acute inhalation toxicity study in male and female Tif:RAI (SPF) rats that identified an LC_{50} of > 4.09 mg/L described above for systemic toxicity-single dose, depressed activity and movement was observed and resolved by day 5.
- Based on the weight of evidence, a score of Moderate was assigned. Evidence of sedation was seen in acute toxicity studies via all routes of administration, and resolved within 5 days. This indicates that GHS Category 3 classification for transient narcotic effects may be warranted. This corresponds to a score of Moderate.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- No data were identified

Terbutryn (CAS# 886-50-0)

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- No data were identified.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Moderate for skin sensitization based on positive results in a guinea pig maximization assay. GreenScreen® criteria classify chemicals as a Moderate hazard for skin sensitization when available data indicate that GHS Category 1B classification is warranted (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* New Zealand HSNO/GHS (GHS-New Zealand) 6.5B (contact) - Contact sensitizers (Category 1)

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98.6% purity) was positive in a guinea pig maximization test in male and female Pirbright white guinea pigs (10/sex) that were induced with intradermal injections of a 1% solution of N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) and adjuvant followed one week later by topical induction with a 30% solution. Weak positive responses were seen after 2 weeks in 8/20 animals 24 hours after the first

challenge with a 30% solution and in 6/20 animals upon a second challenge with a 10% solution.

- Based on the weight of evidence, a score of Moderate was assigned. Positive responses were seen in 8/20 animals (40%) after in intradermal induction dose of 1%. This corresponds to GHS Category 1B, which applies to positive responses in ≥30 to < 60% of animals at a >0.1% to ≤ 1% intradermal induction dose. Therefore a score of Moderate was assigned.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Data Gap for respiratory sensitization based on a lack of data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- No data were identified.

Terbutryn (CAS# 886-50-0)

- No data were identified.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Low for skin irritation/corrosivity based on negative results in a dermal irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and are negative for dermal irritation, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98.6% purity) was not dermally irritating when 0.5 g of premoistened test substance was administered to the shaved skin of 3 female New Zealand white rabbits for 4 hours under gauze dressing. No evidence of irritation was seen 24, 48, or 72 hours after administration.

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Low for eye irritation/corrosivity based on negative results in an ocular irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when available data indicate that the chemical does not warrant GHS classification for eye irritation (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* New Zealand HSNO/GHS (GHS-New Zealand) 6.4A - Irritating to the eye (Category 2A)

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98.6% purity) produced mild irritation when instilled into the eyes of 3 male New Zealand white rabbits. The mean scores for

conjunctival redness were 0.67 and 0.33 at 24, 48, and 72 hours in 2/3 animals. No irritation was seen in the thirds animal. No other signs or irritation were seen.

- CCID 2014
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is classified as Category 6.4A-Irritating to the eye (equivalent to GHS Category 2A) in New Zealand based on a report that it was mildly irritating to the eyes of rabbits.
- Based on the weight of evidence, a score of Low was assigned. Although N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is classified as a Category 2A eye irritant in New Zealand, this classification is based on a report that it is mildly irritating, and no additional details were provided in the source cited by New Zealand EPA (NYSDEC 1996). Available data indicate that N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is mildly irritating, but the scores of 0.67 and 0.33 fall below the guidance value of 2 for conjunctival redness for GHS classification. Therefore this compound does not warrant GHS classification for eye irritation.

Ecotoxicity (Ecotox)

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Very High for acute aquatic toxicity based on LC/EC_{50} values of 0.86 mg/L in rainbow trout, 0.49 mg/L in mysid shrimp, and 0.0014 mg/L in green algae. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when the most conservative acute LC/EC_{50} values are less than 1 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* New Zealand HSNO/GHS (GHS-New Zealand) 9.1A (algal) - Very ecotoxic in the aquatic environment (Category 1)
  - *Screening:* New Zealand HSNO/GHS (GHS-New Zealand) 9.1A (fish) - Very ecotoxic in the aquatic environment (Category 1)

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
  Note: Numerous acute aquatic toxicity studies were available. Only those of standard duration (96 hours for fish, 48 hours for invertebrates, and 72 hours for algae) were included in the assessment.
  - 96-hour LC_{50} (*Brachyanio rerio*, zebrafish) = 4.0 mg/L
  - 96-hour LC_{50} (*Lepomis macrochirus*, bluegill sunfish) = 2.9 mg/L
  - 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = 0.86 mg/L
  - 96-hour LC_{50} (*Menidia menidia*, inland silversides) = 1.76 mg/L
  - 96-hour LC_{50} (*Cyprinodon variegatus*, sheepshead minnow) = 3.5 mg/L
  - 48-hour EC_{50} (*Daphnia magna*, water flea) = 2.4 mg/L
  - 48-hour EC_{50} (*Mysidopsis bahia*, mysid shrimp) = 0.49 mg/L
  - 48-hour EC_{50} (*Crassostrea virginica*, eastern oyster) = 3.2 mg/L
  - 72-hour EC_{50} (*Pseudokirchneriella subcapitatum*, green algae) = 0.0014 mg/L (biomass); = 0.0049 mg/L (growth)
  - 72-hour EC_{50} (*Scenedesmus subspicatus*, green algae) = 0.0024 mg/L (biomass)

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Very High for chronic aquatic toxicity based on NOEC values of less than 0.029 mg/L in rainbow trout and less than 0.00022 mg/L in algae . GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when the most conservative chronic aquatic toxicity values are less than 0.1 mg/L (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* New Zealand HSNO/GHS (GHS-New Zealand) 9.1B (crustacean) - Very ecotoxic in the aquatic environment (Category 2)
    - *Screening:* New Zealand HSNO/GHS (GHS-New Zealand) 9.1B (other) - Very ecotoxic in the aquatic environment (Category 2)

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
    - 62-day NOEC (*Oncorhynchus mykiss*, rainbow trout) < 0.029 mg/L (growth)
    - 60-day NOEC (*Oncorhynchus mykiss*, rainbow trout) = 0.037 mg/L
    - 28-day NOEC (*Mysidopsis bahia*, mysid shrimp) = 0.169 mg/L (reproduction)
    - 72-hour NOEC (*Pseudokirchneriella subcapitatum*, green algae) < 0.001 mg/L (biomass); <0.001 mg/L (growth)
    - 72-hour NOEC (*Scenedesmus subspicatus*, green algae) < 0.00022 mg/L (biomass)

Environmental Fate (Fate)

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

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of High for persistence based on a measured half-life of 101 days in soil, its major compartment. GreenScreen® criteria classify chemicals as a High hazard for persistence when the chemical has a half-life between 60 and 180 days in soil (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
    - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was not readily biodegradable in a test according to OECD Guideline 301B (CO2 Evolution (Modified Sturm Test)) using pre-conditioned sludge inoculum. When tested according to the guideline without a vehicle, 1% (10 mg/L starting concentration) or 6% (20 mg/L starting concentration) biodegradation was observed after 41 days. When tested as an emulsified solution in Tween 20, 51% (10 mg/L starting concentration) or 18% (20 mg/L starting concentration) biodegradation was observed after 41 days. When dissolved in the solvent dichlorimethane, 1% (10 mg/L starting concentration) or 9% (20 mg/L starting concentration) biodegradation was observed after 41 days. HSE concluded that N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is not readily biodegradable.
    - In a GLP-compliant aerobic soil metabolism test according to U.S. EPA FIFRA Guideline 162-1, a 4.18 mg/L solution of ^{14}C N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) had a half-life of 101 days in sandy loam.
    - In a GLP-compliant aerobic aquatic metabolism study according to U.S. EPA Guideline 162-4, a 4.72 or 4.95 mg/L solution of ^{14}C N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) had a half-life of 201 days in seawater containing seawater sediment and 96.4 days in freshwater containing freshwater sediment.
    - In a GLP-compliant anaerobic aquatic metabolism study according to U.S. EPA Guideline 162-3^{14}C N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) had a half-life of 23 years in seawater and 5.6 years in freshwater.

  - In a freshwater hydrolysis study according to U.S. EPA FIFRA Guideline 161-1, less than 10% hydrolysis of ^{14}C N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) occurred at pH 5.3, 7.1, and 9.0 for 30 days. In a second hydrolysis study according to U.S. EPA FIFRA Guideline 161-1, no hydrolysis was observed in 30 days. Authors of both studies concluded that N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is hydrolytically stable.
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) undergoes slow photolysis in water, but studies according to U.S. EPA Guideline 161-2 are insufficient to determine a reliable half-life as levels of degradation were close to the limits of analytical sensitivity and did not conform to first-order kinetics.
- U.S. EPA 2012
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is not expected to be readily biodegradable. Fugacity modeling predicts 87.3% will partition to soil with a half-life of 120 days and 12.4% will partition to water with a half-life of 60 days.
- Based on the weight of evidence, a score of High was assigned. N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is not readily biodegradable, and modeling predicts that it partitions primarily to soil. N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) has a measured half-life of 101 days in soil and a modeled half-life of 120 days in soil, which both correspond to a score of High.

Bioaccumulation (B) Score (vH, H, M, L, or vL): L
N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Low for bioaccumulation based on measured BCF values of 160-250 in fish. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when the chemical has a BCF between 100 and 500 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

<u>N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)</u>

- HSE 2005
  - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (98% purity) has measured BCF values of 240 (35 µg/L) and 250 (3.5 µg/L) in sheepshead minnow (*Cyprindon variegatusm*), in a GLP-compliant bioaccumulation assay according to OECD Guideline 305E.
  - A BCF of 160 for N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (29 µg/L starting concentration) was measured in bluegill sunfish (*Lepomis macrochirus*) in a GLP-compliant bioaccumulation assay according to U.S. EPA Guideline 165-4.

<u>Physical Hazards (Physical)</u>

Reactivity (Rx) Score (vH, H, M, or L): *L*
N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Low for reactivity based on reports that it is not explosive and is not corrosive to metals. Confidence level was reduced due to lack of measure data. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when the chemical is not explosive or corrosive to metals, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- HSE 2005
    - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) is not expected to be explosive
    - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was not corrosive when stored in aluminum or tin.

Flammability (F) Score (vH, H, M, or L): L

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was assigned a score of Low for flammability based on being classified as not highly flammable in a test according to Directive 92/69/EEC, A.10. GreenScreen® criteria classify chemicals as a Low hazard for flammability when available data indicate that the chemical does not warrant GHS classification as a flammable solid, and the chemical is not present on authoritative or screening lists (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS# 28159-98-0)

- CIBA 2008
    - N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was not highly flammable in a flammability test according to Directive 92/69/EEC, A.10.
- According to Directive 92/69/EEC, A.10 a substance is classified as highly flammable if it has a burn time of less than 45 s for 100 mm (EU 1992). As N-cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) was classified as not highly flammable, it has a burn time of greater than 45 s for 100 mm (2.2 mm/s), and therefore does not warrant GHS classification as a flammable solid. Therefore a score of Low was assigned.

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS #28159-98-0)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
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	N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio)	28159-98-0	M	L	*M*	L	*M*	L	*M*	M	M	DG	M	DG	L	L	vH	vH	H	L	*L*	L

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio)	2

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

Table 6

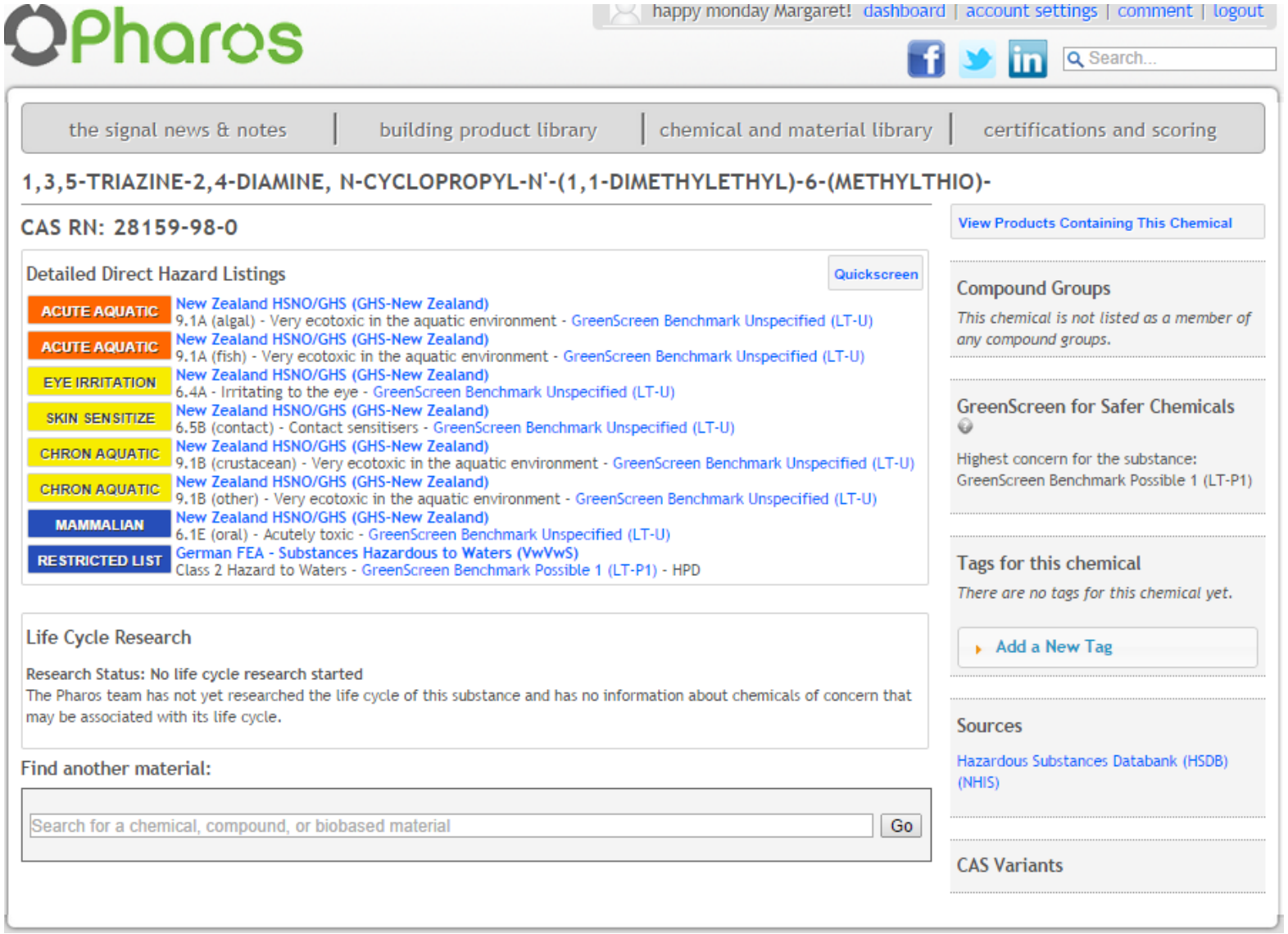
Chemical Name	Final GreenScreen® Benchmark Score
N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio)	2

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

Table 5: Data Gap Assessment Table

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

APPENDIX C: Pharos Output for N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS #28159-98-0)



APPENDIX D: EPISuite Modeling Results for N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) (CAS #28159-98-0)

CAS Number: 28159-98-0
SMILES: n(c(nc(n1)NC(C2)C2)NC(C)(C)C)c1SC
CHEM: IRGAROL 1051
MOL FOR: C11 H19 N5 S1
MOL WT: 253.37
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log K_{ow} (octanol-water): 2.80
Boiling Point (deg C): ------
Melting Point (deg C): 127.00
Vapor Pressure (mm Hg): 6.6E-007
Water Solubility (mg/L): 11.1
Henry LC (atm-m3/mole): ------

Log Octanol-Water Partition Coef (SRC):
Log K_{ow} (K_{ow}WIN v1.68 estimate) = 4.07

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 362.66 (Adapted Stein & Brown method)
Melting Pt (deg C): 148.44 (Mean or Weighted MP)
VP (mm Hg,25 deg C): 6.33E-006 (Modified Grain method)
VP (Pa, 25 deg C): 0.000844 (Modified Grain method)
Subcooled liquid VP: 6.74E-006 mm Hg (-999 deg C, user-entered VP)
: 0.000898 Pa (-999 deg C, user-entered VP)

Water Solubility Estimate from Log K_{ow} (WSK_{ow} v1.42):
Water Solubility at 25 deg C (mg/L): 47.29
log K_{ow} used: 2.80 (user entered)
melt pt used: 127.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 20.313 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Triazines, Aromatic

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method: 5.32E-009 atm-m3/mole (5.39E-004 Pa-m^3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.982E-008 atm-m^3/mole (2.009E-003 Pa-m^3/mole)
VP: 6.6E-007 mm Hg (source: User-Entered)
WS: 11.1 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [K_{oa}WIN v1.10]:
Log K_{ow} used: 2.80 (user entered)
Log K_{aw} used: -6.663 (HenryWin est)
Log K_{oa} (K_{oa}WIN v1.10 estimate): 9.463
Log K_{oa} (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model): -0.0150
Biowin2 (Non-Linear Model): 0.0000
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 1.9114 (months)
Biowin4 (Primary Survey Model): 3.0545 (weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model): -0.1190
Biowin6 (MITI Non-Linear Model): 0.0000
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.6509
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): 0.000899 Pa (6.74E-006 mm Hg)
Log K_{oa} (K_{oa}win est): 9.463
Kp (particle/gas partition coef. (m^3/ug)):
Mackay model: 0.00334
Octanol/air (K_{oa}) model: 0.000713
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model: 0.108
Mackay model: 0.211
Octanol/air (K_{oa}) model: 0.054

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 2.4123 E-12 cm^3/molecule-sec
Half-Life = 4.434 Days (12-hr day; 1.5E6 OH/cm^3)
Half-Life = 53.206 Hrs.
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.159 (Junge-Pankow, Mackay avg)
0.054 (K_{oa} method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (K_{oc}WIN v2.00):
K_{oc}: 253.6 L/kg (MCI method)
Log K_{oc}: 2.404 (MCI method)

K_{oc}: 84.6 L/kg (K_{ow} method)
Log K_{oc}: 1.927 (K_{ow} method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.998 (BCF = 9.944 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.0293 days (HL = 0.09347 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.375 (BCF = 23.72)
Log BAF Arnot-Gobas method (upper trophic) = 1.375 (BAF = 23.72)
log K_{ow} used: 2.80 (user entered)

Volatilization from Water:
Henry LC: 1.98E-008 atm-m^3/mole (calculated from VP/WS)
Half-Life from Model River: 4.702E+004 hours (1959 days)
Half-Life from Model Lake: 5.13E+005 hours (2.138E+004 days)

Removal In Wastewater Treatment:
Total removal: 12.52 percent
Total biodegradation: 8.54 percent
Total sludge adsorption: 3.98 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr.)	Emissions (kg/hr.)
Air	0.105	106	1000
Water	12.4	1.44e+003	1000
Soil	87.3	2.88e+003	1000
Sediment	0.193	1.3e+004	0

Persistence Time: 2.43e+003 hr.

Sources to Check for GreenScreen® Hazard Assessment

Note: For a GreenScreen® Hazard Assessment, data queries should be initially limited to the following references. If data gaps exist after these references have been checked, additional references may be utilized.

U.S. EPA High Production Volume Information System (HPVIS):
http://www.epa.gov/hpvis/index.html

UNEP OECD Screening Information Datasets (SIDS):
http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html

OECD Existing Chemicals Database: http://webnet.oecd.org/hpv/ui/SponsoredChemicals.aspx

European Chemical Substances Information System IUCLID Chemical Data Sheets:
http://esis.jrc.ec.europa.eu/index.php?PGM=dat

National Toxicology Program: http://ntp.niehs.nih.gov/

International Agency for the Research on Cancer:
http://monographs.iarc.fr/ENG/Classification/index.php

Human and Environmental Risk Assessment (HERA) on ingredients of household cleaning products:
http://www.heraproject.com/RiskAssessment.cfm

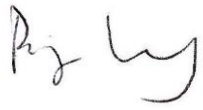
European Chemicals Agency (ECHA) REACH Dossiers: http://echa.europa.eu/

Licensed GreenScreen® Profilers

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) GreenScreen® Evaluation Prepared by:

Jennifer Rutkiewicz, Ph.D.
Toxicologist
ToxServices LLC

N-Cyclopropyl-N'(1,1-dimethyl)-6-(methylthio) GreenScreen® Evaluation QC'd by:



Bingxuan Wang, Ph.D.
Toxicologist
ToxServices LLC