Zinc Pyrithione (CAS# 13463-41-7) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

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GreenScreen® Executive Summary for Zinc Pyrithione (CAS #13463-41-7)

Zinc pyrithione is used in antifoulant boat paints to control the growth of slime, algae, and marine fouling organisms (i.e., barnacles, tubeworms, etc.) below the water line on recreational and commercial boat hulls. It is used as a preservative in a number of food/drinking water contact, and non-food contact articles. It is also used as a preservative, and antidandruff, antiseborrhoeic, and hair conditioning agent in personal care product formulations, and is the active ingredient in many anti-dandruff shampoos.

Zinc pyrithione was assigned a **GreenScreen Benchmark™ Score of 1_{TP}** ("Avoid – Chemical of High Concern") due to its environmental transformation product of zinc. Zinc pyrithione itself was assigned a GreenScreen Benchmark Score of 2 ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2c
  - High P + Moderate Group I Human Toxicity (developmental toxicity (D) and endocrine activity (E))
  - High P + Very High Group II Human Toxicity (acute toxicity (AT), single dose systemic toxicity (STs), and eye irritation (IrE))
  - High P + High Group II* Human Toxicity (repeated dose systemic toxicity (STr*), repeated dose neurotoxicity (Nr*), and respiratory sensitization (SnR*))
  - High P + Moderate Group II Human Toxicity (single dose neurotoxicity (Ns))
  - High P + Very High Ecotoxicity (acute aquatic toxicity (AA) and chronic aquatic toxicity (CA))
- Benchmark 2e
  - Moderate Group I Human Toxicity (developmental toxicity (D) and endocrine activity (E))
- Benchmark 2f
  - Very High Ecotoxicity (acute aquatic toxicity (AA) and chronic aquatic toxicity (CA))
  - Very High Group II Human Toxicity (acute toxicity (AT), single dose systemic toxicity (STs), and eye irritation (IrE))
  - High Group II* Human Toxicity (repeated dose systemic toxicity (STr*), repeated dose neurotoxicity (Nr*), and respiratory sensitization (SnR*))

No data gaps exist.

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 Zinc Pyrithione

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*										
L	L	L	*M*	*M*	vH	vH	H	M	H	L	*H*	L	vH	vH	vH	*H*	vL	L	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in

BOLD font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Assessment for Zinc Pyrithione (CAS #13463-41-7)

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

Chemical Name: Zinc Pyrithione

CAS Number: 13463-41-7

GreenScreen® Assessment Prepared By:
Name: Sara M. Ciotti, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: June 24, 2015
Assessor Type: Licensed GreenScreen® Profiler

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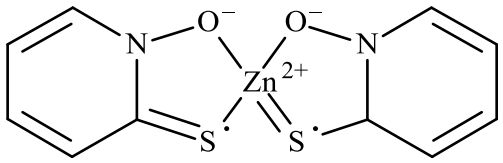
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: June 25, 2015

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

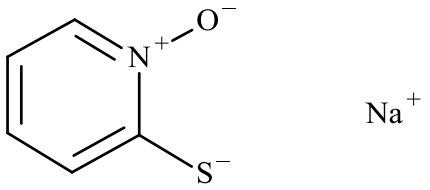
Chemical Structure(s):



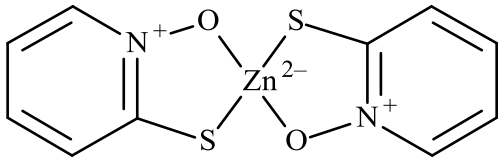
Also called: Bis(1-hydroxy-2(1H)-pyridinethionato)zinc; Pyrithione zinc; Pyrithione zinc [USAN:INN]; Zinc bis(2-pyridylthio)-N-oxide; Zinc, bis(1-hydroxy-2(1H)-pyridinethionato)-; 2(1H)-Pyridinethione, 1-hydroxy-, zinc complex; 2-Mercaptopyridine 1-oxide zinc salt; 2-Pyridinethiol-1-oxide, zinc salt; AI3-62421; BC-J; Biocut ZP; Bis(2-pyridinethiol-1-oxide)zinc; Bis(2-pyridylthio)zinc 1,1'-dioxide; Breck One Dandruff Shampoo; Caswell No. 923; CCRIS 4894; EC 236-671-3; EINECS 236-671-3; EPA Pesticide Chemical Code 088002; Evafine P 50; Finecide ZPT; FSB 8332; Head & Shoulders Conditioner; Head and Shoulders; Hokucide ZPT; HSDB 4498; Niccanon SKT; NSC 290409; OM-1563; Omadine Zinc; Sebulon Shampoo; Tomicide Z 50; Tomicide ZPT 50; Top Brass; UNII-R953O2RHZ5; Vancide P; Vancide ZP; Wella Crisan; Zinc – pyrion; Zinc 1-hydroxy-2-pyridinethione; Zinc 2-mercaptopyridine N-oxide; Zinc Omadine; Zinc PT; Zinc pyrethion; Zinc pyridine-2-thiol 1-oxide; Zinc pyridine-2-thiol-1-oxide; Zinc pyridinethione; Zinc, bis(2-pyridinylthio)-, N,N'-dioxide; Zinc, bis(2-pyridylthio)-, 1,1'-dioxide; Zinc, bis(2-pyridylthio)-, N,N'-dioxide; Zinci pyrithionum; Zincon Dandruff Shampoo; Zincopan; Zincpolyanemine; Zn – pyrion; ZNP Bar; ZnPT; ZPT; (T-4)-Bis(1-hydroxy-2(1H)-pyridinethionato-O,S)zinc; Zinc, bis(1-(hydroxy-kappaO)-2(1H)-pyridinethionato-kappaS2)-, (T-4)-; Zinc, bis(1-hydroxy-2(1H)-pyridinethionato)- (8CI); Zinc, bis(1-hydroxy-2(1H)-pyridinethionato-O,S)-(T-4)-; Zinc 2-pyridinethiol-1-oxide; Zinc, bis(1-hydroxy-2(1H)-pyridinethionato)- (ChemIDplus 2015)

[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

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
Read across substances identified by the SCCS (2014) and U.S. EPA (2004a) were used as surrogates in this GreenScreen®. Zinc pyrithione and 2-mercaptopyridine-N-oxide zinc (CAS# N/A) are highly structurally similar; the only differences include the presence of double bonds and the electrical charge of the sulfur and oxygen ions. Data on the metabolism of zinc pyrithione indicate that the zinc ion is cleaved from the molecule after uptake. Therefore, the use of sodium pyrithione (CAS# 3811-73-2) is considered appropriate. Further, metabolic studies in pigs using sodium pyrithione and zinc pyrithione indicate that they have a common metabolic a pathway. Zinc and sodium ions are not considered neurotoxic; the neurotoxicity of zinc pyrithione is due to the pyrithione moiety (SCCS 2014).



Sodium Pyrithione (CAS# 3811-73-2)



2-Mercaptopyridine-N-Oxide Zinc (CAS# N/A)

Identify Applications/Functional Uses: (U.S. EPA 2015; EC 2015)
1. Used in antifoulant boat paints
2. Used as a preservative in food/drinking water contact, and non-food contact articles
3. Used as a preservative, and antidandruff, antiseborrhoeic, and hair conditioning agent in personal care product formulations

GreenScreen® Summary Rating for Zinc Pyrithione[4]: Zinc pyrithione was assigned a **GreenScreen Benchmark™ Score of 1_{TP}** ("Avoid – Chemical of High Concern") due to its environmental transformation product of zinc. Zinc pyrithione itself was assigned a GreenScreen Benchmark Score of 2 ("Use but Search for Safer Substitutes") (CPA 2014). This score is based on the following hazard score combinations:

- Benchmark 2c
    - High P + Moderate Group I Human Toxicity (developmental toxicity (D) and endocrine activity (E))
    - High P + Very High Group II Human Toxicity (acute toxicity (AT), single dose systemic toxicity (STs), and eye irritation (IrE))
    - High P + High Group II* Human Toxicity (repeated dose systemic toxicity (STr*), repeated dose neurotoxicity (Nr*), and respiratory sensitization (SnR*))
    - High P + Moderate Group II Human Toxicity (single dose neurotoxicity (Ns))

[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.

  - High P + Very High Ecotoxicity (acute aquatic toxicity (AA) and chronic aquatic toxicity (CA))
- Benchmark 2e
  - Moderate Group I Human Toxicity (developmental toxicity (D) and endocrine activity (E))
- Benchmark 2f
  - Very High Ecotoxicity (acute aquatic toxicity (AA) and chronic aquatic toxicity (CA))
  - Very High Group II Human Toxicity (acute toxicity (AT), single dose systemic toxicity (STs), and eye irritation (IrE))
  - High Group II* Human Toxicity (repeated dose systemic toxicity (STr*), repeated dose neurotoxicity (Nr*), and respiratory sensitization (SnR*))

No data gaps exist.

Figure 1: GreenScreen® Hazard Ratings for Zinc Pyrithione

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*										
L	L	L	*M*	*M*	vH	vH	H	M	H	L	*H*	L	vH	vH	vH	*H*	vL	L	L

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

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[5].

Zinc pyrithione is hydrolytically stable in water and simulated sea water. Extrapolated half-lives for pH 5, 6, 9, and simulated sea water are 99, 120, 123, and 96 days (U.S. EPA 2004b). Zinc pyrithione is rapidly degraded to form more persistent products (i.e., pyridine sulfonic acid, pyrithione sulfonic acid, and zinc) which are presented in the table below. Zinc is a LT-P1 chemical. It is a known acute aquatic toxicant (H400 – Very toxic to aquatic life) and it is persistent; therefore, with a full GreenScreen® assessment it would likely be a BM1 chemical. ToxServices' past GreenScreen® evaluations of zinc oxide (CAS #1314-13-2) and zinc salts indicate that these compounds are Benchmark 1 chemicals due to aquatic toxicity in combination with very high persistence, meeting the criteria for benchmark 1c. Therefore, the benchmark score of zinc pyrithione was adjusted due to its transformation product zinc likely being a BM 1 chemical.

[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.

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[6,7]**
Antifoulant boat paint, preservative, and antidandruff, aniseborrhoeic, and hair conditioning agent	In use and disposal	Degradation	2-Pyridine sulfonic acid	15103-48-7	Y	Not in Pharos
Antifoulant boat paint, preservative, and antidandruff, aniseborrhoeic, and hair conditioning agent	In use and disposal	Degradation	Pyrithione sulfonic acid	N/A	Y	Not in Pharos
Antifoulant boat paint, preservative, and antidandruff, aniseborrhoeic, and hair conditioning agent	In use and disposal	Degradation	Zinc	7440-66-6	Y	LT-P1

Introduction

Zinc pyrithione is used in antifoulant boat paints to control the growth of slime, algae, and marine fouling organisms (i.e., barnacles, tubeworms, etc.) below the water line on recreational and commercial boat hulls (U.S. EPA 2015). It is used as a preservative in a number of food/drinking water contact, and non-food contact articles (U.S. EPA 2015). It is also used as a preservative, and antidandruff, antiseborrhoeic, and hair conditioning agent in personal care product formulations, and is the active ingredient in many anti-dandruff shampoos (EC 2015).

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

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012a). Pharos (Pharos 2015) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for zinc pyrithione can be found in Appendix C and a summary of the results can be found below:

Respiratory

ZOEC – Asthmagens – Asthmagen (ARs) – sensitizer-induced – inhalable forms only

[6] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2012a). Pharos (Pharos 2015) 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).

Cancer

U.S. EPA – IRIS Carcinogens – (1986) Group D – Not classifiable as to human carcinogenicity

Restricted List

German FEA – Substances Hazardous to Waters (VwVwS) – Class 3 Severe Hazard to Waters

Environment Canada – Domestic Substances List – Inherently Toxic in the Environment

Persistent

Environment Canada – Domestic Substances List – DSL substances that are Persistent

Physiochemical Properties of Zinc Pyrithione

Zinc pyrithione is a solid at room temperature. It is slightly soluble in water. Its vapor pressure indicates that it will exist mostly in the solid phase and its partition coefficient indicates that it is not likely to bioaccumulate.

Table 2: Physical and Chemical Properties of Zinc Pyrithione (CAS #13463-41-7)

Property	Value	Reference
Molecular formula	C10-H8-N2-O2-S2-Zn	ChemIDplus 2015
SMILES Notation	C12N(C=CC=C2)[O-][Zn+2]2(=[S]1)[S]=c1n(cccc1)[O-]2	ChemIDplus 2015
Molecular weight	320.7309	ChemIDplus 2015
Physical state	Solid	SCCS 2014
Appearance	White to slightly yellow crystals	SCCS 2014
Melting point	240°C (Decomposition)	SCCS 2014
Vapor pressure	< 0.000001 Pa at 25°C (GLP, OECD 104) (equivalent to 7.9 x 10^{-9} mm Hg[8])	ECHA 2015
Water solubility	6.3 ppm at 20°C (GLP, OECD 105) (equivalent to 6.3 mg/L)	ECHA 2015
Dissociation constant	N/A	
Density/specific gravity	1.76 g/cm^3 (GLP, OECD 109)	ECHA 2015
Partition coefficient	Log K_{ow} = 0.9 (GLP, OECD 107)	ECHA 2015

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

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

Zinc pyrithione was assigned a score of Low for carcinogenicity based on negative findings in oral studies using zinc pyrithione and oral and dermal studies using sodium pyrithione. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and negative, the chemical has no structural alerts, and the chemical is not GHS classified (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* US EPA – IRIS Carcinogens – (1986) Group D – Not classifiable as to human carcinogenicity
  - *Screening:* not on any screening lists

[8] 0.000001 Pa * 0.0075 = 7.9 x 10^{-9} mm Hg

Zinc Pyrithione (CAS# 13463-41-7)

- ECHA 2015
    - *Oral:* In a GLP-compliant carcinogenicity study conducted according to EPA OPP 83-2, male and female Crl:Cd-1 rats (50/sex/dose) received 0, 0.5, 1.5, or 5.0 mg/kg/day zinc pyrithione (41.2% purity) via oral gavage daily for 104 weeks. The high dose was reduced to 3.5 mg/kg/day after 12 weeks due to treatment-related reduction in body weight gain in high dose animals. The body weights of high dose animals were 8% lower than controls after 8 weeks of treatment. Body weights of high dose animals remained approximately 10% below controls for the remainder of the study. The study authors found no treatment-related incidences of neoplasia.
    - *Oral:* In a carcinogenicity study, male and female rats (strain not reported, 10/sex/dose) received 0, 2, 5, 10, 25, or 50 ppm zinc pyrithione (equivalent to 0, 0.156, 0.39, 0.78, 1.95, and 3.9 mg/kg/day[9]) in their feed for 2 years. Treatment had no effect on tumor incidence.

Sodium Pyrithione (CAS# 3811-73-2)

- ECHA 2015; SCCS 2014
    - *Oral:* In a GLP-compliant combined chronic toxicity/carcinogenicity study conducted according to OECD Guideline 453, male and female Sprague-Dawley rats (56/sex/dose) received 0.5, 1.5, or 4.0 mg/kg/day sodium pyrithione (40%) via oral gavage 7 days per week for at least 104 weeks. The high dose was reduced during the course of the study to 2.8 mg/kg/day in males and 2.1 mg/kg/day in females due to a severe reaction to treatment. The study summary did not report when the dose was lowered. Lower body weights were observed in high dose males and females, mid dose females, and low dose males. The study authors found no incidences of neoplasia in treated animals.
    - *Dermal:* In a GLP-compliant carcinogenicity study conducted according to US-EPA 83-2, Crl:CD-1 (ICR) BR mice (50/sex/dose) were dermally administered 0, 5, 15, or 40 mg/kg/day sodium pyrithione (41.2% in aqueous solution) once per day for 80 weeks (no occlusion). Treatment had no effect on tumor incidence.

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

Zinc pyrithione was assigned a score of Low for mutagenicity/genotoxicity based on negative findings for both *in vivo* and *in vitro* chromosomal aberration and *in vitro* gene mutation assays using zinc pyrithione. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and negative for both chromosomal aberrations and gene mutations, the chemical has no structural alerts, and the chemical is not GHS classified (CPA 2012b).

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

Zinc Pyrithione (CAS# 13463-41-7)

- ECHA 2015; SCCS 2014
    - *In vitro:* Zinc pyrithione was not mutagenic in a GLP-compliant Ames assay conducted according to OECD Guideline 471 in *S. typhimurium* tester strains TA98, TA100, TA1535, and TA1538 in the presence and absence of metabolic activation at concentrations up to 100 µg/plate (purity = 97.9%).

[9] Doses were calculated using male and female rat food factor values for chronic studies (TERA Undated).
2 ppm = 2 mg/kg food * 0.078 kg food/kg rat/day = 0.156 mg/kg/day

  - *In vitro:* Zinc pyrithione was not mutagenic in a GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476 in Chinese hamster lung fibroblasts (V79) in the presence and absence of metabolic activation at concentrations up to 6.25 µg/mL (purity = 97.9%).
  - *In vitro:* Zinc pyrithione induced chromosomal aberrations in a GLP-compliant chromosomal aberration test conducted according to OECD Guideline 473 in Chinese hamster lung fibroblasts. Concentrations up to 6.25 µg/mL zinc pyrithione (purity = 97.9%) in the presence and absence of metabolic activation were tested. No further details were provided.
  - *In vitro:* Zinc pyrithione was not mutagenic in a GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476 in Chinese hamster ovary cells at concentrations up to 100 µg/mL in the absence of metabolic activation and 103.5 µg/mL in the presence of metabolic activation (purity = 41.4%).
  - *In vitro:* Zinc pyrithione was not clastogenic in a GLP-compliant chromosome aberration test in human lymphocytes with and without metabolic activation at concentrations up to 12 µg/mL (purity = 96.3%).
  - *In vitro:* No conclusions were drawn in a GLP-compliant DNA damage and repair assay conducted according to US EPA 84-4 in rat hepatocytes. Cells were tested at concentrations up to 220 ng/mL.
  - *In vivo:* Zinc pyrithione was not genotoxic in a GLP-compliant mammalian erythrocyte micronucleus test conducted according to OECD Guideline 474 in male and female Crl:NMRIBR mice. Mice (5/sex/dose) received a single dose of 80, 100, or 130 mg/kg zinc pyrithione (purity = 97.9%) via oral gavage. Treatment did not produce an increase in the numbers of micronuclei in polychromatic erythrocytes.
  - *In vivo:* Zinc pyrithione was not genotoxic in a GLP-compliant micronucleus test conducted according to EPA OPP 84-2 in male and female Sprague-Dawley mice.[10] Mice (5/sex/dose) received a single dose of 0, 11, 22, or 44 mg/kg zinc pyrithione (purity not reported) via intraperitoneal injection. Treatment did not produce an increase in the numbers of micronuclei in polychromatic erythrocytes.
  - *In vivo:* Zinc pyrithione was not genotoxic in a GLP-compliant chromosome aberration test using blood lymphocytes from Cynomolgus Monkeys. Monkeys (2/sex/dose) received a doses of 5.5, 11, or 22 mg/kg zinc pyrithione (purity = 96.3%) via an oral capsule for 28 days. Treatment did not produce an increase in the numbers of micronuclei in polychromatic erythrocytes.
- SCCS 2014
  - Due to the equivocal results found in an *in vitro* mutation assay using 2-mercaptopyridine-N-oxide zinc (discussed below) and the absence of *in vivo* mutagenicity studies, the SCCS stated that no firm conclusion could be drawn with respect to the genotoxicity/mutagenicity of zinc pyrithione.
- HSE 2003
  - The HSE concluded that zinc pyrithione does not pose a genotoxic hazard.
- MAK 2012
  - Zinc pyrithione is non-genotoxic and non-mutagenic.
- U.S. EPA 2004a
  - The available data indicate that zinc pyrithione is non-mutagenic.

[10] Both the ECHA REACH Dossier and the SCCS summary refer to the test animal as a Sprague-Dawley mouse. However, authors of the SCCS study summary indicate that the study summary provided in ECHA appears to be identical to a study described in HSE (2003), which refers to the test animal as a mouse and does not specify the strain.

2-Mercaptopyridine-N-Oxide Zinc (CAS# N/A)

- SCCS 2014
    - *In vitro:* In a GLP-compliant mammalian cell gene mutation assay conducted according to US EPA 84-2, Chinese hamster ovary (CHO) cells were treated with up to 30 µg/mL and 2.2 µg/mL 2-mercaptopyridine-N-oxide zinc (purity not reported) with and without metabolic activation, respectively. In the initial experiment, a statistically significant increase in mutation frequency was increased in cells treated with 2.0 µg/mL without metabolic activation. No increase in mutation frequency was found in the presence of metabolic activation. In the confirmatory experiment, no increase in mutation frequency was found in cells treated without metabolic activation; however, in the presence of metabolic activation a small increase was found in cells treated with 2.5 and 20 µg/L. The study authors did not consider the observed increases in mutation frequencies biologically relevant because the frequency was only slightly greater than controls, there was no dose-response relationship, and the results were not reproduced in each experiment.
- Based on the weight of evidence, a score of Low was assigned. Negative results were identified for both *in vivo* and *in vitro* chromosomal aberrations and *in vitro* gene mutations. One study using the structurally similar, 2-mercaptopyridine-N-oxide zinc reported increases in mutation frequencies in CHO cells; however, the study authors did not consider the increases to be biologically relevant and concluded that the test substance was not mutagenic. Due to the ambiguous results of this study and the absence of an *in vivo* mutagenicity study, the SCCS (2014) stated that a firm conclusion with respect to the genotoxicity/mutagenicity of zinc pyrithione could not be made. However, they acknowledged that the HSE (2003) and MAK (2012) have concluded that it is non-genotoxic and non-mutagenic. Based on the negative findings for both *in vivo* and *in vitro* chromosomal aberrations and *in vitro* gene mutations and negative carcinogenicity studies (discussed above), a high confidence score of Low was assigned.

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

Zinc pyrithione was assigned a score of Low for reproductive toxicity based on the absence of reproductive effects in various studies with rats and rabbits. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and negative, the chemical has no structural alerts, and the chemical is not GHS classified (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any authoritative lists
- A number of reproductive toxicity studies were identified for zinc pyrithione and sodium pyrithione. However, the study summaries provided by ECHA (2015), SCCS (2014), and U.S. EPA (2004a) were similar but differed slightly in their description of the treatment-related effects; therefore, it was difficult to discern if the same study was described each document, or if different studies were described. As a result, only the conclusions of authoritative bodies in regard to the reproductive toxicity of zinc pyrithione and the summary of one well-described study are presented below.

Sodium Pyrithione (CAS# 3811-73-2)

- U.S. EPA 2004a
    - *Oral:* In a two generation study, Crl:CD(SD)BR rats received 0, 0.5, 1.5, or 4.5 mg/kg/day sodium pyrithione (40%) via oral gavage. The high dose was reduced to 3.5 mg/kg/day due to toxicity. One female parental animal in the F0 generation and two females in the F1 generation were sacrificed due to systemic toxicity. Clinical signs

included hunched posture, impaired hindlimb mobility, rapid breathing, and peri-orbital, peri-nasal, and abdomen staining. Excessive salivation was observed in male and female rats treated with 1.5 and 3.5 mg/kg/day. Decreased body weight was observed in high-dose parental females and F0 males. Histological examination of 1.5 and 3.5 mg/kg/day male and female animals of both generations of parental rats found skeletal muscle atrophy. Treatment with 3.5 mg/kg/day caused reproductive toxicity in the F0 parents and F1 offspring. A significant reduction in the mating and fertility index was significantly reduced in males. Additionally, the number of estrous cycles per mating was increased in F0 females. Treatment had no effect on the total number of live pups, mean number of live pups per litter, live birth index, viability index, or lactation index in F1 pups. Mating and fertility indices were reduced in all treated animals relative to controls. However, the authors of the study summary indicate that atrophy of the hindlimb muscles in males would likely impact mating success and therefore result in the decreased mating and fertility indices. The authors identified a systemic toxicity NOAEL of 0.5 mg/kg/day and a LOAEL of 1.5 mg/kg/day based on histological alterations of the hindlimb skeletal muscle in F0 males and F1 males and females. The authors identified reproductive toxicity NOAEL and LOAEL values based on adverse developmental effects that are not relevant for this endpoint. As the authors of the U.S. EPA assessment considered the adverse effects on fertility were likely due to treatment-related atrophy of the hindlimb muscles, ToxServices identified a reproductive NOAEL of 3.5 mg/kg/day based on the absence of treatment-related reproductive effects.

<u>Zinc Pyrithione (CAS# 13463-41-7)</u>

- ECHA 2015
    - Two 2-generation study studies are provided in the ECHA REACH Dossier. These studies exposed rats to doses up to 3.5 mg/kg/day via oral gavage. The reported treatment-related systemic effects are similar to those described in the study above. Authors of the REACH Dossier state that the various adverse reproductive effects (i.e., increased uterine weights, decreased epididymis weights, decreased mating and fertility indices) are secondary to systemic toxicity. Therefore, zinc pyrithione is not considered a reproductive toxicant.
- HSE 2003
    - There was no evidence of reproductive toxicity at doses up to 3.5 mg/kg/day sodium pyrithione.
    - Based on the available animal data there is no concern regarding the adverse effects of zinc pyrithione on fertility.
- SCCS 2014
    - Dermal reproductive toxicity studies show that zinc pyrithione caused no adverse effects on fertility at doses up to 100 mg/kg/day in rabbits.
    - Topical application of shampoo formulations (dose = 400 mg/kg/day zinc pyrithione) caused no reproductive effects.
    - The available two-generation toxicity studies show no adverse reproductive effects.
    - The available data indicate that there is no concern to humans for adverse effects on fertility.

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

Zinc pyrithione was assigned a score of Moderate for developmental toxicity based on increased post-implantation loss at 1.5 mg/kg/day in the rabbit. GreenScreen® criteria classify chemicals as a

Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity in animals (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any authoritative lists
- ECHA 2015; U.S. EPA 2004a
    - *Oral:* In a GLP-compliant prenatal developmental toxicity study conducted according to EPA OPP 83-3, New Zealand White rabbits (20/group) received 0.5, 1.5, and 3.0 mg/kg zinc pyrithione (48% aqueous solution) via oral gavage on gestation days 6 – 18. Decreased weight gain and food consumption was observed in the mid and high dose animals. Embryotoxic effects were observed in the mid and high dose groups. One high dose animal aborted her litter on gestation day 27, whole litter resorptions were observed in one mid dose animals and 5 high dose animals, and an increase in the mean post-implantation loss and a decrease in the number of viable fetuses were observed in high dose animals. No significant differences in the mean number of corpora lutea or fetal sex ratio were found. An increased incidence of malformations, primarily in the cephalic and limb regions was found in the high dose group. There were no treatment-related differences in the incidence of developmental variations between control and treated animals. The study authors identified a maternal toxicity and embryotoxicity NOAEL of 0.5 mg/kg/day. Authors of the U.S. EPA assessment state that it is not clear if the increase in resorptions is due to maternal or developmental toxicity, and assigned a LOAEL of 1.5 mg/kg/day based on increased post-implantation loss and decreased number of viable fetuses.
    - *Oral:* In a GLP-compliant prenatal developmental toxicity study conducted according to EPA OPP 83-3, Sprague-Dawley rats (30/group) received 0, 0.75, 3.0, or 15.0 mg/kg zinc pyrithione (52% in water) via oral gavage on gestation days 6 – 15. Decreased weight gain was observed in the high dose animals. Uterine effects were observed in the mid and high dose groups. A significant increase in the mean post-implantation loss, a reduction in the mean number of viable fetuses, a reduction in the mean gravid uterine weight, and a reduction in the mean fetal body weight were observed in high dose animals. A whole litter re-adsorption occurred three of the high-dose dams. Increased mean post-implantation loss and reduction in mean gravid uterine weight was observed in mid dose animals. A significant increase in the incidence of litters with fetal malformations; vertebral malformation with or without an associated rib malformation was observed in 89% of fetuses. The incidence of malformations was also increased in the mid dose group (not significantly); skeletal malformations included absent lumbar and caudal vertebrae, a pelvic malformation, and fused skull bones. The study authors noted that with the exception of fused ribs, the skeletal malformations observed in high dose animals were not seen in mid dose animals. High dose animals also had an increased incidence of developmental variations relating to the vertebrae, ribs, and sternebrae relative to controls. The study authors concluded that zinc pyrithione is not a developmental toxicant because adverse developmental effects occurred at doses which caused maternal toxicity. They identified a maternal and teratogenicity NOAEL of 0.75 mg/kg/day.
- ECHA 2015; U.S. EPA Undated
    - *Dermal:* In a GLP-compliant prenatal developmental toxicity study conducted according to EPA OPPTS 870.3700, Crl:CD(SD)IGS BR rats (25/dose) were dermally administered 0, 10, 15, 30, or 60 mg/kg/day for 6 hours per day on gestation days 0 – 20. Maternal

toxicity was observed in animals in treated with 30 and 60 mg/kg/day. A significant increase in fetal malformations was observed in the high dose group; malformations were primarily incomplete ossification of the sternal cetra and wavy ribs. The study authors concluded that zinc pyrithione is not a developmental toxicant because the adverse developmental effects occurred at doses which caused maternal toxicity. They identified a maternal NOAEL of 15 mg/kg/day and a teratogenicity NOAEL of 30 mg/kg/day.

- HSE 2003
    - Adverse developmental effects such as increased post-implantation loss, reductions in the number of live fetuses, decreased fetal body weight, and increased numbers of malformations have been reported in rats and rabbits. However, these effects are considered to occur secondary to maternal toxicity. Therefore, zinc pyrithione is not considered to be a developmental toxicant.
- Based on the weight of evidence, a score of Moderate was assigned. Adverse developmental effects such as increased post-implantation loss, reduction in the number of live fetuses, decreased fetal weight, and increased number of malformations have been reported. HSE (2003) reports that they effects occurred at doses which were maternally toxic; therefore, they did not consider zinc pyrithione to be a developmental toxicant. However, one study assessed by the U.S. EPA found an increase in post-implantation losses at a dose of 1.5 mg/kg/day and they indicated that it was not clear if the increase was due to maternal or developmental toxicity. As the available data are insufficient to determine if toxicity was due to maternal or developmental toxicity, ToxServices considered both to be sensitive at the dose level of 1.5 mg/kg/day in the rabbit and assigned a Moderate score. Confidence level was reduced due to insufficient data available to determine if the effects were secondary to maternal toxicity.

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

Zinc pyrithione was assigned a score of Moderate for endocrine disruption based on the altered growth and reproduction of aquatic organisms. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine disruption when there is evidence of endocrine activity (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any authoritative 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 2015
    - Zinc pyrithione is a potential endocrine disruptor based on its impact on the growth and reproduction of aquatic organisms at levels below the LC_{50}.
- Based on the weight of evidence, a score of Moderate was assigned. The U.S. EPA has concluded that zinc pyrithione is a potential endocrine disruptor based on the altered growth and reproduction of aquatic organisms at levels below the LC_{50}. Confidence in this classification is reduced because it is not based on authoritative lists or mammalian studies.

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): vH

Zinc pyrithione was assigned a score of Very High for acute toxicity based on the most conservative LC_{50} of 0.14 mg/L in the rat. GreenScreen® criteria classify chemicals as a Very High hazard for acute toxicity when the inhalation LC_{50} (dust/mist/fumes) is less than 0.5 mg/L (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any authoritative lists
- ECHA 2015
  - *Oral:* LD_{50} = 302 mg/kg (purity = 48% in aqueous suspension) (male Wistar rats) (GLP, OECD 401)
  - *Oral:* LD_{50} = 221 mg/kg (purity = 48% in aqueous suspension) (female Wistar rats) (GLP, OECD 401)
  - *Oral:* LD_{50} = 774 mg/kg (purity not reported) (female Sprague-Dawley rats)(GLP, OECD 401)
  - *Dermal:* LD_{50} > 2,000 mg/kg (purity not reported) (male and female Sprague-Dawley rats) (GLP, EPA OPP 81-2)
  - *Dermal:* LD_{50} > 2,000 mg/kg (purity not reported) (male and female New Zealand White rabbits) (GLP, EPA OPP 81-2)
  - *Inhalation:* LC_{50} = 1.34 mg/L (aerosol, female Sprague-Dawley rats) (GLP, OECD 403)
  - *Inhalation:* LC_{50} = 0.84 mg/L (aerosol, female Sprague-Dawley rats) (GLP, OECD 403)
  - *Inhalation:* LC_{50} = 0.14 mg/L (aerosol, male and female Sprague-Dawley rats) (GLP)
- SCCS 2014
  - *Oral:* LD_{50} values range from 92 to 266 mg/kg in the rat and 160 to 1,000 mg/kg in the mouse.
  - *Dermal:* LD_{50} values range from < 2,000 mg/kg to 10,000 mg/kg in the albino rabbit.
  - *Inhalation:* LC_{50} = 5.08 mg/L (aerosol, male and female Sprague-Dawley rats) (GLP, OPPTS. 870.1300)
  - *Inhalation:* LC_{50} < 0.6 mg/L (aerosol dust, male and female Sprague-Dawley rats) (GLP, OECD 403)
- U.S. EPA 2004a
  - *Oral:* LD_{50} = 630 mg/kg (male rat)
  - *Oral:* LD_{50} = 460 mg/kg (female rat)
- Oral LD_{50} values range from 92 – 774 mg/kg and warrant a High score, dermal LD_{50} values are > 2,000 and warrant a Low score, and inhalation LC_{50} values range from < 0.6 – 5.08 mg/L (aerosol) and warrant a Very High score. In order to be protective of human health, ToxServices assigned a Very High score based on the most conservative inhalation LC_{50} value of 0.14 mg/L.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

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

Zinc pyrithione was assigned a score of Very High for systemic toxicity (single dose) based on the gross pathological changes in rats treated with oral doses ≥ 158 mg/kg. GreenScreen® criteria

classify chemicals as a Very High hazard for systemic toxicity (single dose) when adverse effects occur at oral doses less than 300 mg/kg (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any authoritative lists
- ECHA 2015
    - *Oral:* In a GLP-compliant acute oral toxicity study conducted according to OECD Guideline 401, male and female Wistar rats (5/sex/dose) received 125, 158, 200, 254, or 321 mg/kg zinc pyrithione (purity = 48% in aqueous solution) via oral gavage. The animals were observed for 14 days after treatment. All deaths occurred by day 5. Treated animals showed signs of ptosis, diarrhea, piloerection, chromomdacryorrhea, chromorhinorrhea, emaciation, bloated abdomen, alopecia, ocular abnormalities, alopecia of ventral surfaces, soiling of the body surfaces, and wetness and brown staining of the anogenital area. Treatment did not significantly affect body weight of the survivors; some survivors lost weight during the observation period, but they returned to normal by day 14. Necropsy found no gross pathological changes in animals treated with 125 mg/kg. Animals treated with ≥ 158 mg/kg showed abnormalities of the spleen adhesions in the peritoneal cavity, alopecia of the ventral surfaces brown staining of the anogenital area, and red staining around the eyes. The study authors identified an LD_{50} of 302 mg/L in males and 221 mg/kg in females. ToxServices identified a NOAEL of 125 mg/kg and a LOAEL of 158 mg/kg based on gross pathological changes.
    - *Oral:* In a GLP-compliant acute oral toxicity study conducted according to OECD Guideline 401, male and female Sprague-Dawley rats (5/sex in the 500 mg/kg group, 5 females/dose in the 707 and 1,000 mg/kg groups) received 500, 707, or 1,000 mg/kg zinc pyrithione via oral gavage. Animals were observed for 14 days. Deaths occurred within 7 days; treatment with 707 mg/kg caused 3 female deaths and treatment with 1,000 mg/kg caused 4 female deaths. All treated animals displayed signs of systemic toxicity, diuresis, hunched posture, and decreased respiratory rate. Diarrhea was observed in the 500 and 1,000 mg/kg treatment groups and labored respiration was observed in males treated with 500 mg/kg and females treated with 707 and 1,000 mg/kg. Females treated with 707 and 1,000 mg/kg had red/brown stains around the eyes or snout, piloerection, ptosis, and splayed or tiptoe gait. Treatment has no effect on body weight gain in surviving animals. Necropsy of surviving animals found no macroscopic changes. The study authors identified an LD_{50} of 774 mg/kg in females, no LD_{50} was identified in males. ToxServices identified a LOAEL of 500 mg/kg (lowest dose tested) based on clinical signs.
    - *Inhalation:* In a GLP-compliant acute inhalation toxicity study conducted according to OECD Guideline 403, male and female Sprague-Dawley rats (5/sex/concentration) were exposed to 0.53, 0.95, or 1.82 mg/L zinc pyrithione aerosol for 4 hours via nose only inhalation. Animals were observed for 14 days. All males and 3/5 females exposed to 1.82 mg/L died, 3/5 males and 2/5 females exposed to 0.95 mg/L died, and 1/5 males and 0/5 females exposed to 0.53 mg/L died. The study authors observed wet fur, hunched posture, pilo-erection, decreased respiratory rate, pallor of the extremities and ptosis, labored gasping and noisy respiration, red/brown staining around the eyes, snout, and mouth. Occasional incidences of increased respiratory rate, sneezing, dehydration, increased salivation, and stiffness in the hind legs were observed. Animals appeared normal 2 – 8 days after exposure. Reduced body weight gain was observed during week 1, but normal body weight gain returned during week 2. Dark foci on the lungs were

observed in one female exposed to 0.53 mg/L. The study authors identified an LC_{50} of 1.34 mg/L in females and 0.84 mg/L in males. ToxServices identified a LOAEC of 0.53 mg/L in females based on clinical signs and pathological changes of the lungs.

- *Inhalation:* In a GLP-compliant acute inhalation toxicity study, male and female Sprague-Dawley rats were exposed to 0.054, 0.14, 0.16, 0.82, 1.4, and 1.5 mg/L zinc pyrithione aerosol for 4 hours via whole body inhalation. Animals were observed for 14 days post exposure. All animals exposed to ≥ 0.82 mg/L died, all males and 2/5 females exposed to 0.16 mg/L died, 2/5 males and 1/5 females exposed to 0.14 mg/L died, and 0/5 males and 1/5 females exposed to 0.054 mg/L died. Treated animals showed signs of prostration, gasping, labored breathing, rales, trembling, and hunched posture. The average body weight of animals exposed to 0.054 – 0.14 mg/L was depressed during the post-exposure period. Body weights of animals treated with concentrations greater than 0.14 were not measured due to the high mortality rate. The treatment related effects were limited to the respiratory tract and were described as congestion. The test material was found in the trachea and esophagus. The study authors identified an LC_{50} of 0.14 mg/L.
- *Dermal:* In a GLP-compliant acute dermal toxicity study, male and female Sprague-Dawley rats were dermally exposed to 2,000 mg/kg zinc pyrithione under semi-occlusive conditions for 24 hours. Animals were observed for 14 days. No adverse systemic effects were observed. The study authors identified an LD_{50} > 2,000 mg/kg.
- *Dermal:* In a GLP-compliant acute dermal toxicity study, male and female New Zealand White rabbits (5/sex/dose) were dermally exposed to 2,000 mg/kg zinc pyrithione under occlusive conditions for 24 hours. One male rabbit died on day 2. Diarrhea and few feces were observed in treated animals. Body weight gain was normal in 6/9 survivors, while 3 animals lost weight during the observation period. Necropsy found no treatment-related effects in 8/9 survivors and 1 female exhibited brown staining of the anogenital area. The study authors identified an LD_{50} > 2,000 mg/kg.

- SCCS 2014
  - *Inhalation:* In a GLP-compliant repeated inhalation toxicity study conducted according to OPPTS. 870.1300, male and female Sprague-Dawley rats (5/sex/concentration) were exposed to 0.68, 1.19, and 2.25 mg/L zinc pyrithione aerosol for 4 hours via nose-only inhalation. Animals were observed for 14 days after exposure. Clinical signs included crusted eyes, piloerections, ptosis, respiratory gurgle, and sensitivity to touch and sound. Animals appeared normal by day 10. Treatment altered the body weight in several surviving animals. The study authors calculated an LC_{50} of 5.08 mg/L.
  - *Inhalation:* In a GLP-compliant repeated inhalation toxicity study conducted according to OECD 403, male and female Sprague-Dawley rats were exposed to 0.24 and 0.61 mg/L zinc pyrithione aerosol dust for 4 hours via nose-only inhalation. Clinical signs included salivation, labored breathing, and staining around the mouth. Animals appeared normal by day 5. Necropsy of surviving animals found no treatment-related effects. The study authors identified an LC_{50} of < 0.6 mg/L.
- Based on the weight of evidence, a score of Very High was assigned. Data from acute oral toxicity studies indicate that exposure to zinc pyrithione causes clinical signs such as diarrhea and poor grooming in rats. A GLP-compliant OECD Guideline study found abnormalities of the spleen in rats treated with doses > 158 mg/kg, which warrants a Very High score. No significant toxicological effects were reported in acute dermal toxicity studies. Inhalation exposure causes transient clinical signs and respiratory irritation. GHS Criteria indicates that substances which cause respiratory irritation should be classified as GHS Category 3, which warrants a Moderate

score. In order to be protective of human health, the most conservative score of Very High was assigned based on the oral NOAEL of 125 mg/kg.

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

Zinc pyrithione was assigned a score of High for systemic toxicity (repeated dose) based on an inhalation LOAEC of 0.0025 mg/L/day and an oral LOAEL of 1.5 mg/kg/day. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when the chemical is classified as GHS Category 1 (CPA 2012b).

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

<u>Zinc Pyrithione (CAS# 13463-41-7)</u>

- Numerous repeated dose toxicity studies were identified for zinc pyrithione. As the nervous system is the target organ to zinc pyrithione toxicity (discussed below) (SCCS 2014) and neurotoxicity is not considered in this section, only the key dermal, inhalation, and oral toxicity studies identified in the U.S. EPA (2004a) assessment and the ECHA REACH Dossier (ECHA 2015), respectively, are summarized below.
- U.S. EPA 2004a
    - *Dermal:* In a 90-day dermal toxicity study, male and female CrlCD BR rats were administered 0, 20, 100, or 1,000 mg/kg/day zinc pyrithione under occlusion for 6 hours per day, 5 days per week, for 13 weeks. Decreased food consumption (91.6% of control), decreased body weight gain (48.9% of control), and decreased food efficiency (53.8% of control) was observed in high dose females. The authors identified a NOAEL of 100 mg/kg/day for females and 1,000 mg/kg/day for males. A LOAEL of 1,000 mg/kg/day was identified in females based on decreased body weight gain, food consumption, and food efficiency.
        - The GHS guidance values are based on 7 day per week treatment paradigms. Therefore, they were adjusted in order to account for study duration (i.e., 20 – 200 mg/kg/day adjusted to 28 – 280 mg/kg/day[11]). Because it is unknown if adverse effects occur at doses greater than the NOAEL of 100 mg/kg/day and less than the LOAEL of 1,000 mg/kg/day, zinc pyrithione is classified as GHS Category 2.
    - *Inhalation:* In a subchronic inhalation toxicity study, male and female Sprague-Dawley rats (15/sex/group) were exposed to 0.0005, 0.0025, or 0.01 mg/L zinc pyrithione aerosols (52.5% aqueous solution) for 6 hours per day, 5 days per week, for 13 weeks. Decreased body weights (23%), food consumption (10%), and food efficiency (53%) were observed in females exposed to 0.01 mg/L. No biologically significant changes in hematology, clinical chemistry, or urinalysis were found. The study authors found no treatment-related changes during the ophthalmologic examination and at gross necropsy. Increased lung weights (absolute and relative) were found in females treated with 0.0025 and 0.01 mg/L/day. Histopathological examination of the lungs found trace to mild subacute inflammation of the interstitial tissue and medial hypertrophy of pulmonary arteries, which were significant at 0.01 mg/L/day. The study authors identified a NOAEC of 0.0005 mg/L/day and a LOAEC of 0.0025 mg/L/day based on clinical signs and increased lung weights.
        - The GHS guidance values are based on 7 day per week treatment paradigms. Therefore, they were adjusted in order to account for study duration (i.e., 0.02 –

[11] 20 * 7 days / 5 days = 28 mg/kg/day

0.2 mg/L/day adjusted to 0.028 – 0.28 mg/L/day[12]). Based on the LOAEC of 0.0025 mg/L/day, zinc pyrithione is classified as GHS Category 1.

Sodium Pyrithione (CAS# 3811-73-2)

- ECHA 2015; SCCS 2014
  - *Oral:* In a previously described GLP-compliant combined chronic toxicity/carcinogenicity study conducted according to OECD Guideline 453, male and female Sprague-Dawley rats (56/sex/dose) received 0.5, 1.5, or 4.0 mg/kg/day sodium pyrithione (40%) via oral gavage 7 days per week for at least 104 weeks. The high dose was reduced during the course of the study to 2.8 mg/kg/day in males and 2.1 mg/kg/day in females due to a severe reaction to treatment. The study summary did not report when the dose was lowered. High mortality was reported in the mid and high dose females. Lower body weights were observed in high dose males and females, mid dose females, and low dose males. Significant reductions in kidney and spleen weights were observed in mid and high dose females. ToxServices identified a NOAEL of 0.5 mg/kg/day and a LOAEL of 1.5 mg/kg/day based on changes in mortality, body weight, and organ weight.
    - Zinc pyrithione contains 2 pyrithione moieties. The molecular weight of sodium pyrithione is 149.149 g/mol, and therefore 1.5 mg/kg/day / 149.149 mg/mmol = 0.01 mmol/kg/day. Each molecule of zinc pyrithione contains 2 pyrithione moieties. This level is equivalent to 0.01 mmol/kg/day * 320.7309 mg/mmol / 2 = 1.6 mg/kg/day zinc pyrithione. Based on the LOAEL of 1.6 mg/kg/day, zinc pyrithione is classified as GHS Category 1.
- Based on the weight of evidence, a score of High was assigned. A dermal repeated dose toxicity study identified a NOAEL of 100 mg/kg/day and a LOAEL of 1,000 mg/kg/day, which warrants a score of Moderate. LOAEC/L values of 0.0025 mg/L/day and 1.5 mg/kg/day from repeated inhalation and oral studies, respectively, warrant a High score.

Neurotoxicity (N)

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

Zinc pyrithione was assigned a score of Moderate for neurotoxicity (single dose) based on transient narcotic effects in rats following oral and inhalation exposure. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when the chemical is classified as GHS Category 3 (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any authoritative lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2015
  - *Oral:* In a previously described GLP-compliant acute oral toxicity study conducted according to OECD Guideline 401, male and female Wistar rats (5/sex/dose) received 125, 158, 200, 254, or 321 mg/kg zinc pyrithione (purity = 48% in aqueous solution) via oral gavage. The animals were observed for 14 days after treatment. Treated animals showed signs of lethargy and ataxia. ToxServices identified a LOAEL of 125 mg/kg based on clinical signs.
  - *Oral:* In a previously described GLP-compliant acute oral toxicity study conducted according to OECD Guideline 401, male and female Sprague-Dawley rats (5/sex in the 500 mg/kg group, 5 females/dose in the 707 and 1,000 mg/kg groups) received 500, 707,

[12] 0.02 * 7 days / 5 days = 0.028 mg/kg/day

or 1,000 mg/kg zinc pyrithione via oral gavage. Animals were observed for 14 days. All treated animals displayed signs of ataxia and lethargy. ToxServices identified a LOAEL of 500 mg/kg based on clinical signs.
    - *Inhalation:* In a previously described GLP-compliant acute inhalation toxicity study conducted according to OECD Guideline 403, male and female Sprague-Dawley rats (5/sex/concentration) were exposed to 0.53, 0.95, or 1.82 mg/L zinc pyrithione aerosol for 4 hours via nose only inhalation. Animals were observed for 14 days. The study authors observed lethargy and ataxia in treated animals. ToxServices identified a LOAEC of 0.53 mg/L in males and females based on clinical signs.
- SCCS 2014
    - *Inhalation:* In a previously described GLP-compliant repeated inhalation toxicity study conducted according to OPPTS. 870.1300, male and female Sprague-Dawley rats (5/sex/concentration) were exposed to 0.68, 1.19, and 2.25 mg/L zinc pyrithione aerosol for 4 hours via nose-only inhalation. Animals were observed for 14 days after exposure. Treated animals showed signs of decreased activity. ToxServices identified a LOAEC of 0.68 mg/L.
    - *Inhalation:* In a GLP-compliant repeated inhalation toxicity study conducted according to OECD 403, male and female Sprague-Dawley rats were exposed to 0.24 and 0.61 mg/L zinc pyrithione aerosol dust for 4 hours via nose-only inhalation. Animals showed signs of decreased activity and tremors. ToxServices identified a LOAEC of 0.24 mg/L.
- ECHA 2015; SCCS 2014
    - *Oral:* In a GLP-compliant neurotoxicity study conducted according to OECD Guideline 424, male and female Crl:CD(SD)IGS BR VAP/Plus® rats received a single dose of 0, 25, 75, or 150 mg/kg/day zinc pyrithione (98.3%) via oral gavage. Animals were subjected to functional observational battery (FOB) evaluations prior to treatment, 1 hour post dosage, and 7 and 14 days after dosage. The authors assessed hind limb muscle tone and mass of the calf muscle after FOB evaluations. No treatment-related lesions were found by neurohistological examination. The study authors identified a NOAEL of 25 mg/kg/day and a LOAEL of 75 mg/kg/day based on reductions in body temperature, and cumulative measured for motor activity 1 hour after dosage. It was noted that these changes were reversible and all groups had comparable values at the end of the study period.
- Based on the weight of evidence, a score of Moderate was assigned. Acute oral and inhalation toxicity studies observed transient narcotic effects (i.e., lethargy and ataxia) in animals following exposure. GHS Criteria specify that substances which cause transient narcotic effects in animals should be classified as GHS Category 3.

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

Zinc pyrithione was assigned a score of High for neurotoxicity (repeated dose) based on evidence of decreased forelimb and hindlimb strength and electrophysiological changes following oral and dermal exposure to zinc pyrithione in rats. GreenScreen® criteria classify chemicals as a High hazard for neurotoxicity (repeated dose) when the chemical is classified as GHS Category 1 (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any authoritative lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2015
    - No neurological abnormalities have been identified, even after 30 years of occupational

exposure to pyrithiones.

- *Oral:* The ability of zinc pyrithione to cause hind limb weakness in monkeys was investigated in a GLP-compliant repeated dose toxicity study conducted according to guidelines similar to EU Method B.7. Male and female Cynomolgus monkeys (number of animals per group was not reported) received oral doses 5.5, 11, or 22 mg/kg/day zinc pyrithione via a gelatin capsule for 28 days. No hind limb weakness was observed. ToxServices identified a neurotoxicity NOAEL of 22 mg/kg/day.
  - The GHS guidance values are based on 90 day studies. Therefore, they were multiplied by three in order to account for study duration (i.e., 10 – 100 mg/kg/day adjusted to 30 – 300 mg/kg/day). Based on the NOAEL of 22 mg/kg/day zinc pyrithione, insufficient data are available for classification.

- SCCS 2014
  - The neurotoxic effect of zinc pyrithione is due to the pyrithione moiety.
  - *Dermal:* In a 28-day dermal neurotoxicity study Sprague-Dawley rats were administered 0, 50, 150, or 200 mg/kg/day (male animals) or 0, 10, 25, 50, 75, or 100 mg/kg/day (female animals) zinc pyrithione. The treatment site was covered with plastic shielding. Male animals treated with 150 and 200 mg/kg/day had low muscle tone beginning on day 8 and 11 which persisted for the study duration. On days 14 and 48, decreases in hindlimb and forelimb strength, muscle tone, and body weight were observed in males treated with 150 and 200 mg/kg/day. Treatment did not alter plasma, red blood cell, or brain cholinesterase at any dose level. Males treated with 150 mg/kg/day had decreased electrophysiological measurements in terms of the maximum amplitude. In females, low muscle tone was observed in animals treated with doses ≥ 50 mg/kg/day. On day 14 grip strength was reduced in animals treated with 100 mg/kg/day, and on day 28 it was reduced in animals treated with ≥ 25 mg/kg/day. No consistent changes in plasma, red blood cell, or brain cholinesterase levels were observed at any dose. Females treated with 50 and 75 mg/kg/day had decreased in the maximum amplitude of electrophysiological measurements (measurements were not taken at 100 mg/kg/day). The authors identified a NOAEL of 25 mg/kg/day and the LOAEL of 50 mg/kg/day.
    - The GHS guidance values are based on 90 day studies. Therefore, they were multiplied by three in order to account for study duration (i.e., 20 – 200 mg/kg/day adjusted to 60 – 600 mg/kg/day). Based on the NOAEL of 25 mg/kg/day and LOAEL of 50 mg/kg/day, zinc pyrithione is classified as a GHS Category 1 (repeated dose neurotoxicant) because the LOAEL is less than 60 mg/kg/day.

- U.S. EPA 2004a
  - *Oral:* In a non-guideline toxicity study, CD male rats were divided into 63 pairs and one rat from each pair received 250 ppm zinc pyrithione (97%) (approximately 12.5 mg/kg/day) in the diet for 9 or 14 days. No morphological changes were found in the gastrocnemius or soleus muscles. Treatment did not alter the sciatic, sural, or spinal nerve roots. In rats which were allowed to recover for two weeks, myelinated sural nerve axons showed accumulation of dense granular axoplasmic deposits. Axons in the intramuscular lumbrical fibers were enlarged and contained abundant mitochondria and electron dense granules. There were no significant differences in sensory nerve conduction velocities between control and treated animals. Sensory nerve-evoked potential amplitudes remained significantly different from control animals after 2 weeks of recovery. The authors state that this study suggests zinc pyrithione targets the muscle fibers. ToxServices identified a LOAEL of 12.5 mg/kg/day (only dose tested).

        - The GHS guidance values are based on 90 day studies. Therefore, they were multiplied by six in order to account for study duration (i.e., 10 – 100 mg/kg/day adjusted to 60 – 600 mg/kg/day). Based on the LOAEL of 12.5 mg/kg/day zinc pyrithione, is classified as a GHS Category 1 (repeated dose neurotoxicant) because the LOAEL is less than 60 mg/kg/day.
    - *Oral:* In a repeated toxicity study, exposure to 50 ppm (2.5 mg/kg/day) zinc pyrithione in the diet caused a reduction in forelimb and hind limb grip strength and electrophysiological changes. No further details were provided. ToxServices identified a LOAEL of 2.5 mg/kg/day.
        - Because the oral LOAEL is less than 10 mg/kg/day, zinc pyrithione should be classified as GHS Category 1.

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

Zinc pyrithione was assigned a score of Low for skin sensitization based on negative skin sensitization tests in guinea pigs and a low potential to induce skin sensitization in humans. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative, the chemical has no structural alerts, and they chemical is not GHS classified (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any authoritative lists
- ECHA 2015; SCCS 2014
    - Zinc pyrithione was not sensitizing in a GLP-compliant guinea pig maximization study conducted according to OECD Guideline 406 with female Dunkin-Hartley guinea pigs (20 in the tested group and 10 in the control group). Animals were epicutaneously induced with 25% zinc pyrithione (purity = 97.9%) in petroleum under occlusive conditions and challenged with 10% zinc pyrithione in petroleum under occlusive conditions. Two of twenty (10%) animals has positive skin reactions after 24 hours.[13] The study authors noted that the percentage of sensitized animals (10%) is below the threshold for classification (30%) as a skin sensitizer.
    - Zinc pyrithione was not sensitizing in a GLP-compliant Buehler test conducted according to EPA OTS 798.4100 using male Hartley guinea pigs. Animals (10 animals induced, 5 animals naïve) were epicutaneously induced and challenged with 0.4 g zinc pyrithione in mineral oil. No skin reactions were observed. The study authors concluded that zinc pyrithione was not sensitizing under the conditions of this assay.
- ECHA 2015
    - Zinc pyrithione was not sensitizing to humans in patch-tests. One hundred human volunteers were epicutaneously induced with 1% zinc pyrithione in water containing 0.67% Tween 80 and epicutaneously challenged with 0.5% zinc pyrithione in water containing 0.67% Tween 80. No skin reactions were observed after the challenge dose. The study authors concluded that zinc pyrithione was not sensitizing under the conditions of this assay.
- SCCS 2014
    - Zinc pyrithione (48% suspension) was not sensitizing in a GLP-compliant guinea pig maximization assay conducted according to US EPA 81-6 using male Hartley Albino guinea pigs (10 dose animals, 5 control animals). Animals were epicutaneously induced

[13] This study appears to also be summarized in the ECHA REACH Dossier; however, the ECHA REACH Dossier study summary states that no animals had positive skin reactions.

and challenged with 0.4 mL zinc omadine. No positive skin reactions were reported. The study authors concluded that zinc pyrithione was not sensitizing under the conditions of this assay.
    - Zinc pyrithione (50% aqueous slurry) was not sensitizing in a Buehler assay using guinea pigs (strain not reported, n=40).
    - Zinc pyrithione (1%) was not sensitizing to guinea pigs when injected intracutaneously into depilated skin at a dose of 0.05 mL and nine subsequent doses of 0.1 mL on alternate weekdays. A challenge dose of 0.05 mL was injected 2 weeks later.
    - The SCCS reviewed the available human data and concluded that zinc pyrithione has a low potential to induce skin sensitization.
- U.S. EPA 2004a
    - Zinc pyrithione is not a skin sensitizer.

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

Zinc pyrithione was assigned a score of High for respiratory sensitization based on association with the authoritative AOEC ARs list. GreenScreen® criteria classify chemicals as a Moderate to High hazard for respiratory sensitization when the chemical is associated with the authoritative AOEC ARs list (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* AOEC – Asthmagens – Asthmagen (ARs) – sensitizer-induced – inhalable forms only – occupational risk only – applicable to all zinc compounds
    - *Screening:* not on any authoritative lists
- No data were identified.
- Based on association with the authoritative AOEC ARs lists as a zinc compound, a score of High was conservatively assigned. Confidence level was adjusted as the AOEC list is an authoritative B list, and no measured data were identified for zinc pyrithione.

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

Zinc pyrithione was assigned a score of Low for skin irritation/corrosivity based on negative findings in acute skin irritation studies. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative, the chemical has no structural alerts, and they chemical is not GHS classified (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any authoritative lists
- ECHA 2015
    - In a GLP-compliant acute skin irritation study conducted according to OECD Guideline 404, New Zealand White rabbits (n=3) were dermally exposed to 0.5 g of zinc pyrithione (purity = 97.9%) for 4 hours under semi-occlusive conditions. Irritation was assessed at 1, 24, 48, and 72 hours. No skin irritation was observed. The study authors concluded that zinc pyrithione was not irritating under the conditions of this study.
    - In a GLP-compliant acute skin irritation study conducted according to EPA OPP 81-5, New Zealand White rabbits (n=6) were dermally exposed to 0.5 g of zinc pyrithione (purity not reported) for 4 hours under semi-occlusive conditions. Irritation was assessed at 0.5, 1, 24, 48, and 72 hours. Mild erythema was observed at 0.5 and 1 hour, but was reversed by 24 hours. No edema was observed. The study authors concluded that zinc pyrithione was not irritating under the conditions of this study.
- SCCS 2014

  - In an acute skin irritation study, male New Zealand White rabbits (n=6) were dermally exposed to 0.5 g zinc pyrithione for 4 hours under occlusive conditions. Irritation was assessed at 0.5, 1, 24, 48, and 72 hours after treatment. Slight erythema (grade 1) and edema (grade 2) was observed after 0.5 and 1 hour in 3 and 2 animals, respectively. Erythema was fully reversible after 24 hours and edema after 48 hours. The study authors concluded that zinc pyrithione was mildly irritating under the conditions of this study.
  - A 20% suspension of zinc pyrithione was slightly irritating to rabbits, guinea pigs, and mice in open patch tests.
  - Zinc pyrithione was slightly irritating to humans in repeat insult patch tests.
- Based on the weight of evidence, a score of Low was assigned. Acute dermal exposure to zinc pyrithione caused no irritation to slight erythema and edema that was fully reversible within 48 hours. Based on these findings zinc pyrithione was not GHS Classified, and a score of Low was assigned.

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

Zinc pyrithione was assigned a score of Very High for eye irritation/corrosivity based on severe eye irritation and irreversible effects on the eye. GreenScreen® criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when the chemical is classified as GHS Category 1 (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any authoritative lists
- ECHA 2015
  - In a GLP-compliant acute eye irritation study conducted according to OECD Guideline 405, zinc pyrithione (84 mg, purity = 97.9%) was instilled into the eyes of a New Zealand White rabbit (n=1). No control animals were used. Irritation was assessed at 60 minutes and 24 hours. Treatment produced irreversible corneal lesions (corneal perforation, leakage of aqueous humor), severe redness and swelling (score: 3 and 4). No observation of the iris was possible because of the severity of the chemosis and swelling. The study authors concluded that zinc pyrithione is a severe eye irritant and classified it as GHS Category 1.
  - In a GLP-compliant acute eye irritation study conducted according to EPA OPP 81-4, zinc pyrithione (0.1 mL) was instilled into one eye of New Zealand White rabbits (n=9). The treated eye of 6 rabbits remained unwashed, while the treated eye of 3 rabbits were washed 30 seconds after instillation. Ocular responses were recorded at 1h and on days 1, 2, 3, and 7 in animals with an unwashed eye, and on days 1, 2, 3, 7, 14, and 21 in animals with a washed eye. Corneal opacity, iritis, and severe eye irritation was observed in animals with unwashed eyes (scores not reported). Severe chemosis and discharge prevented the study authors from assessing the damage in some instances. Animals were sacrificed on day 7 because the damage was judged to be irreversible. Corneal opacity, iritis, and moderate to severe conjunctival irritation was observed in all three animals with washed eyes, and persisted through day 21 in two animals. The study authors concluded that zinc pyrithione is a severe eye irritant and classified it as GHS Category 1.
- SCCS 2014
  - In an acute eye irritation study, 0.1 mL of powdered zinc pyrithione was instilled into one eye New Zealand White rabbits (n=6). Irritation was assessed at 1, 24, 48, and 72 hours. Corneal opacity, conjunctival redness, conjunctival chemosis, and iridial effects were observed. Mean scores of 3, 3, 4, and 1.2 were reported, respectively. The study authors

concluded that zinc pyrithione is a severe eye irritant.
    - In an acute eye irritation study, 0.1 mL of a 48% aqueous dispersion of zinc pyrithione was instilled into the conjunctival sac of New Zealand White rabbits (n=6). Treated eyes were rinsed 24 hours post instillation. Irritation was assessed at 24, 48, and 72 hours. Mean scores of 2.5, 2.5, 3 and 1 were reported for corneal opacity, conjunctival redness, and conjunctival, chemosis, and iridial effects.
- Based on the weight of evidence, a score of Very High was assigned. Severe eye irritation and/or irreversible effects were reported in all acute eye irritation studies. Therefore, zinc pyrithione was classified as GHS Category 1 and a score of Very High was assigned.

Ecotoxicity (Ecotox)

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

Zinc pyrithione was assigned a score of Very High for acute aquatic toxicity based on L/EC_{50} values of 0.0026 mg/L in fish, 0.0032 mg/L in daphnia, and 0.0012 mg/L in algae. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when the LC_{50} or EC_{50} values are less than 1 mg/L (CPA 2012b).

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any authoritative lists
- ECHA 2015
    - 96h LC_{50} = 2.6 µg/L (0.0026 mg/L) (*Pimephales promelas,* fish) (GLP, EPA OPP 72-1)
    - 96h LC_{50} = 0.4 mg/L (*Cyprinodon variegatus,* fish) (GLP, U.S. EPA-FIFRA, Guideline 72-3)
    - 96h LC_{50} = 54 µg/L (0.054 mg/L) (*Oncorhynchus mykiss,* fish) (GLP, EPA OPP 72-1)
    - 96h LC_{50} = 150 µg/L (0. 150 mg/L) (*Oncorhynchus mykiss,* fish) (GLP)
    - 96h LC_{50} = 30 µg/L (0.030 mg/L) (*Pimephales promelas,* fish) (GLP, EPA OPP 72-1)
    - 96h LC_{50} = 1.1 mg/L (*Cyprinodon variegatus,* fish) (GLP, EPA OPP 72-3)
    - 96h LC_{50} = 68.5 mg/L (*Pimephales promelas,* fish) (GLP, EPA OPP 72-1)
    - 96h LC_{50} = 58.8 mg/L (*Pimephales promelas,* fish) (GLP, EPA OPP 72-1)
    - 96h LC_{50} = 92.3 mg/L (*Oncorhynchus mykiss,* fish) (GLP, EPA OPP 72-1)
    - 96h LC_{50} = 57.1 mg/L (*Oncorhynchus mykiss,* fish) (GLP, EPA OPP 72-1)
    - 96h LC_{50} = 3.2 µg/L (0.0032 mg/L) (*Oncorhynchus mykiss,* fish) (GLP, EPA OPP 72-1)
    - 48h EC_{50} = 8.2 µg/L (0.008 mg/L) (*Daphnia magna,* daphnia) (GLP, EPA OPP 72-2)
    - 96h EC_{50} = 6.3 µg/L (0.0063 mg/L) (*Daphnia magna,* daphnia) (GLP, EPA OPP 72-3)
    - 48h EC_{50} = 50 µg/L (0.050 mg/L) (*Daphnia magna,* daphnia) (GLP, OECD 202)
    - 48h EC_{50} = 34 µg/L (0.034 mg/L) (*Daphnia magna,* daphnia) (GLP, EPA OPP 72-2)
    - 48h EC_{50} > 127 mg/L (*Daphnia magna,* daphnia) (GLP, EPA OPP 72-2)
    - 48h EC_{50} = 13 µg/L (*Daphnia magna,* daphnia) (GLP, EPA OPP 72-2)
    - 120h ErC_{50} = 4.1 µg/L (0.0041 mg/L) (*Navicula pelliculosa*, algae) (GLP, EPA OPP 122-2)
    - 120h EC_{50} = 1.2 µg/L (0.0012 mg/L) (*Skeletonema costatum,* algae) (GLP, EPA OPP 122-2)
    - 96h EC_{50} = 1.3 µg/L (0.0013 mg/L) (*Skeletonema costatum,* algae) (GLP, EPA OPP 122-2)
    - 120h EC_{50} = 36.3 mg/L (0.0363 mg/L) (*Selenastrum capricornutum,* algae) (GLP, EPA OPP 122-2)
    - 72h ErC_{50} = 110 µg/L (0.110 mg/L) (*Selenastrum capricornutum,* algae) (GLP, OECD 201)
    - 72h EbC_{50} = 67 µg/L (0.110 mg/L) (*Selenastrum capricornutum,* algae) (GLP, OECD 201)
    - 120h ErC_{50} = 16 µg/L (0.016 mg/L) (*Anabaena flos-aquae*, algae) (GLP, EPA OPP 122-2)
    - 120h EC_{50} = 0.14 mg/L (*Selenastrum capricornutum*, algae) (GLP, EPA OPP 122-2)
    - 120h EC_{50} = 28 µg/L (0.028 mg/L) (*Selenastrum capricornutum*, algae) (GLP, EPA OPP

122-2)
  - 120h EC_{50} = 28.9 mg/L (*Selenastrum capricornutum*, algae) (GLP, EPA OPP 122-2)
- U.S. EPA 2004c
  - LC_{50} = 3.6 ppb (0.0036 mg/L)(*Oncorhynchus mykiss,* fish)
  - LC_{50} = 2.68 ppb (0.00268 mg/L)(*Pimephales promelas,* fish)
  - LC_{50} = 400 ppb (0.4 mg/L)(*Cyprinodon variegatus,* fish)
  - EC_{50} = 8.25 ppb (0.00825 mg/L)(*Daphnia magna,* daphnia)
  - EC_{50} = 28 ppb (0.028 mg/L)(*Selenastrum capricornutum,* algae)
  - EC_{50} = 7.1 ppb (0.0071 mg/L)(*Anabaena flos-aquae,* algae)
- Based on the most conservative L/EC_{50} values of 0.0026 mg/L in fish, 0.0063 mg/L in daphnia, and 0.0013 mg/L in algae, a score of Very High was assigned.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): vH
Zinc pyrithione was assigned a score of Very High for chronic aquatic toxicity based on NOEC values of 0.00122 mg/L in fish, 0.0027 mg/L in daphnia, and 0.00046 mg/L in algae. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when NOEC values are less than 0.1 mg/L (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any authoritative lists
- ECHA 2015
  - 28d NOEC = 1.22 µg/L (0.00122 mg/L) (*Pimephales promelas,* fish) (GLP, OECD 210)
  - 21d NOEC (1st generation survival/sublethal effects) = 22 µg/L (0.022 mg/L) (*Daphnia magna,* daphnia) (GLP, EPA OPP 72-4)
  - 120h NOErC = 2.4 µg/L (0.0024 mg/L) (*Navicula pelliculosa,* algae) (GLP, EPA OPP 122-2)
  - 120h NOEC = 0.46 µg/L (0.00046 mg/L) (*Skeletonema costatum,* algae) (GLP, EPA OPP 122-2)
  - 120h NOEC = 11.8 mg/L (*Skeletonema costatum,* algae) (GLP, EPA OPP 122-2)
  - 72h NOEC = 37 µg/L (0.037 mg/L) (*Selenastrum capricornutum,* algae) (GLP, OECD 201)
  - 120h NOEC = 3.8 µg/L (0.016 mg/L) (*Anabaena flos-aquae,* algae) (GLP, EPA OPP 122-2)
  - 120h NOEC = 0.08 mg/L (*Selenastrum capricornutum*, algae) (GLP, EPA OPP 122-2)
  - 120h NOEC = 5.46 mg/L (*Selenastrum capricornutum*, algae) (GLP, EPA OPP 122-2)
- U.S. EPA 2004c
  - NOEC = 1.22 ppb (0.00122 mg/L)(*Pimephales promelas,*fish)
  - NOEC = 10 ppb (0.010 mg/L)(*Pimephales promelas,* fish)
  - NOEC = 2.7 ppb (0.0027 mg/L)(*Daphnia magna,* daphnia)
- Based on the most conservative NOEC values of 0.00122 mg/L in fish, 0.0027 mg/L in daphnia, and 0.00046 mg/L in algae, a score of Very High was assigned.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *H*
Zinc pyrithione was assigned a score of High for persistence based on its biodegradation half-life of less than 43 days in water, which is its most relevant environmental compartment. GreenScreen® criteria classify chemicals as a High hazard for persistence when the half-life in water is between 40 and 60 days (CPA 2012b).

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

  - *Screening:* Environment Canada – Domestic Substances List – DSL substances that are Persistent
- ECHA 2015
  - Zinc pyrithione was not readily biodegradable in a GLP-compliant CO_2 Evolution test conducted according to OECD Guideline 301B with 39% degradation after 28 days.
  - Zinc pyrithione was not readily biodegradable in a GLP-compliant CO_2 Evolution test conducted according to OECD Guideline 301B with 17% degradation after 8 days and 54% degradation after 43 days.
- U.S. EPA 2004b
  - Zinc pyrithione is hydrolytically stable in water and simulated sea water. Extrapolated half-lives for pH 5, 6, 9, and simulated sea water are 99, 120, 123, and 96 days.
  - Under aerobic conditions zinc pyrithione has a degradation half-life of 0.6 hours in aqueous system and 0.89 days in sediment (appeared to be the rate of primary degradation)
  - Under anaerobic conditions zinc pyrithione degrades in water within 0.5 hours and in sediment in approximately 19 hours (appeared to be the rate of primary degradation).
  - Photolytically, zinc pyrithione degrades rapidly with a half-life of 13 minutes in buffered aqueous medium and 17 minutes in simulated sea water.
  - Based on the K_d, zinc pyrithione shows a tendency to bind to fresh and salt water soil and sediment.
  - Zinc pyrithione is not likely to persist in water, microbial soils, and sediments.
- Based on the weight of evidence, a score of High was assigned. Zinc pyrithione is associated with the DSL screening list, which warrants a High to Very High score. Two OECD Guideline 301B tests found that zinc pyrithione was not readily biodegradable with 39% degradation after 28 days and 54% degradation after 43 days. Although limited study details were provided and the authors did not indicate if zinc pyrithione was toxic to the inoculum, these studies suggest that the half-life of zinc pyrithione in water is less than 43 days even under the worst assumption that it inhibits the inoculum. Zinc pyrithione breaks down quite rapidly to form more persistent degradation products (i.e., pyridine sulfonic acid, pyrithione sulfonic acid, and zinc) which are assessed in the transformation products section (above) (U.S. EPA 2004b; DSL Undated). Data presented by the U.S. EPA suggest that zinc pyrithione undergoes rapid primary degradation under aerobic (half-life < 2 hrs) and anaerobic (half-life < 1 day) conditions. It is hydrolytically stable with extrapolated half-lives in freshwater and seawater ranging from 96 – 123 days. Based on its K_d, zinc pyrithione is expected to partition to the sediment. GHS Criteria state that data on the primary degradation of a chemical may be considered when the degradation products are not hazardous to the aquatic environment (UN 2013). As zinc is a known aquatic toxicant (H400 – Very toxic to aquatic life), primary degradation rate should not be used as the basis for the classification of this endpoint. Therefore, ToxServices focused on the rate of ultimate biodegradation as the basis for this endpoint. Modeling could not be performed to estimate the predominant environmental compartment or degradation half-lives, as organometallic compounds are outside the application domain of EPISuite™ (U.S. EPA 2012). Based on its major uses as a component of boat paints and a preservative in food, drink and personal care products, the most relevant environmental compartment is likely water. Ready biodegradation studies suggest that the ultimate degradation half-life of zinc pyrithione is less than 43 days, while U.S. EPA extrapolated a degradation half-life of 96 – 123 days in water. ToxServices considered measured data with more weight than extrapolated data. In addition, U. S. EPA concluded that zinc pyrithione is not likely to be persistent in water, which ToxServices interpreted as not warranting a Very High score. Therefore, ToxServices assigned a score of High for this endpoint. This is consistent with DSL's listing (a High to Very High score). Although the zinc moiety is

recalcitrant as a metal, ToxServices evaluated its toxicity and persistence in the environmental transformation product section previously. Confidence level was reduced due to lack of sufficient measured data on the biodegradation half-lives.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Zinc pyrithione was assigned a score of Very Low for bioaccumulation based on measured BCF values less than 50 and log K_{ow} values less than 1. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the BCF is less than 100 and the low K_{ow} is less than 4 (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any authoritative lists
- ECHA 2015
  - In a GLP-compliant bioaccumulation study conducted according to OECD Guideline 305E, oysters were exposed to zinc pyrithione at 0.0565 µg/L and 0.474 µg/L (measured) for 30 days. BCFs ranged from 0.05 – 0.5.
  - In a GLP-compliant bioaccumulation study conducted according to OECD Guideline 305C, carp were exposed to 0, 0.02, or 0.2 ng/L zinc pyrithione (nominal) for 8 weeks. BCF values ranged from < 5 - < 50.
  - Log K_{ow} = 0.9 (GLP, OECD 107)
  - Log K_{ow} = 0.883 (GLP, OECD 107)
- U.S. EPA 2004b
  - Zinc pyrithione is not expected to bioaccumulate in aquatic organisms.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): L
Zinc pyrithione was assigned a score of Low for reactivity based on the absence of explosive and oxidizing properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data are available and the chemical is not GHS classified (CPA 2012b).

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any authoritative lists
- ECHA 2015
  - Zinc pyrithione contains no explosive properties (GLP, EU Method A.14, drop hammer method, purity = 98.7%).
  - Zinc pyrithione contains no explosive properties (GLP, EU Method A.14, BAM fall hammer test, DAM friction test, Koenen steel tube test, purity = 98.7%).
  - Zinc pyrithione contains no oxidizing properties (GLP, EU Method A.17, purity = 98.7%).
  - Zinc pyrithione contains no oxidizing properties (GLP, EU Method A.17, purity = 97.9%).

Flammability (F) Score (vH, H, M, or L): L
Zinc pyrithione was assigned a score of Low for flammability based on negative findings in flammability tests. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data are available and the chemical is not GHS classified (CPA 2012b).

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

- ECHA 2015
  - Zinc pyrithione is not flammable (GLP, EU Method A.16, purity = 98.7%).
  - Zinc pyrithione is not flammable (GLP, EU Method A.10, purity = 97.6%).

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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 Zinc Pyrithione (CAS #13463-41-7)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
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	Zinc Pyrithione	13463-41-7	L	L	L	*M*	*M*	vH	vH	H	M	H	L	*H*	L	vH	vH	vH	*H*	vL	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
Zinc Pyrithione	2

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

Table 6

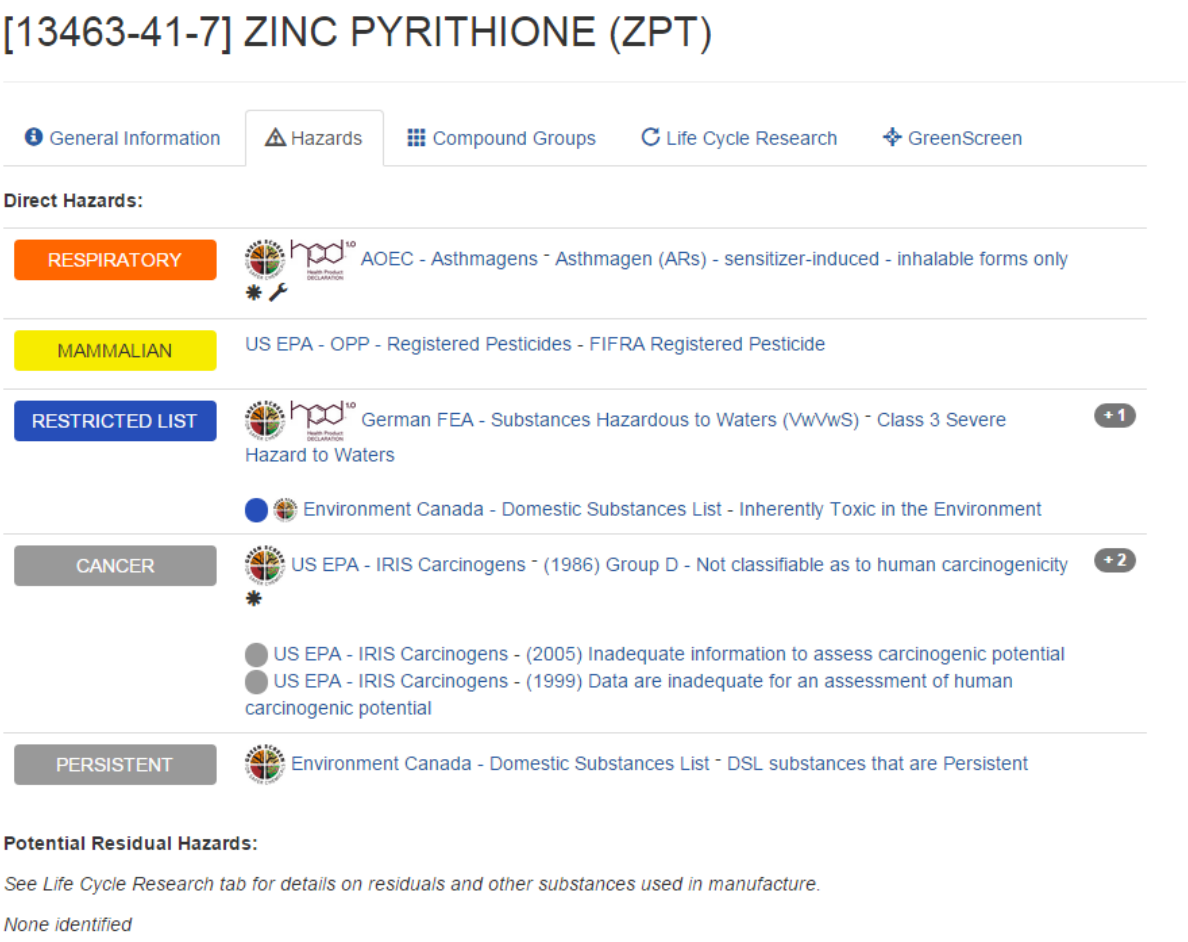
Chemical Name	Final GreenScreen® Benchmark Score
Zinc Pyrithione	2

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

Table 5: Data Gap Assessment Table

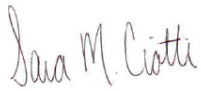
Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for Zinc Pyrithione (CAS #13463-41-7)



Licensed GreenScreen® Profilers

Zinc Pyrithione GreenScreen® Evaluation Prepared by:



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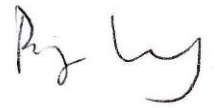
ToxServices LLC

Zinc Pyrithione GreenScreen® Evaluation QC'd by:



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