Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

Zinc Oxide (CAS #1314-13-2) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Washington States Department of Ecology

Prepared by:

ToxServices LLC

October 14, 2014

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

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

TABLE OF CONTENTS

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

TABLE OF FIGURES

TABLE OF TABLES

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

GreenScreen® Executive Summary for Zinc Oxide (CAS #1314-13-2)

Zinc oxide is a chemical that is used in pesticides and as a dermatologic agent.

Zinc oxide was assigned a GreenScreen® Benchmark Score of 1("Avoid—Chemical of High Concern") as it has Very High ecotoxicity (chronic aquatic toxicity (CA)), High Group II* toxicity (systemic toxicity (repeated dose (STr*)) and respiratory sensitization (SnR*)), and Very High persistence (P). This corresponds to GreenScreen® benchmark classification 1c ("vPT = very High P + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]") in CPA 2011. Data gaps (DG) exist for endocrine activity (E), neurotoxicity (single (Ns) and repeated dose (Nr*)), and bioaccumulation (B). As outlined in CPA (2013) Section 12.2 (Conduct a Data Gap Analysis to assign a final Benchmark score), zinc oxide meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gaps. In a worst-case scenario, if zinc oxide were assigned a High score for the data gaps endocrine activity (E), neurotoxicity (single (Ns) and repeated dose (Nr*)), and bioaccumulation (B), it would still be categorized as a Benchmark 1 Chemical.

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

GreenScreen® Hazard Ratings for Zinc Oxide

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	**M**	**L**	**L**	DG	**L**	**L**	**H**	DG	DG	**L**	*H*	**L**	**L**	**vH**	**vH**	**vH**	DG	**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.

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

GreenScreen® Assessment for Zinc Oxide (CAS #1314-13-2)

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

Chemical Name: Zinc Oxide

CAS Number: 1314-13-2

GreenScreen® Assessment Prepared By:
Name: Zach Guerrette, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: July 29, 2014
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 14, 2014

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

Chemical Structure(s):

Also called:
Pigment white 4; C.I. 77947; C.I. Pigment White 4; Chinese White; CI 77947; CI Pigment white 4; EINECS 215-222-5; Emanay zinc oxide; Flowers of zinc; Zinc gelatin; Zinc monoxide; Zinc White; zincum oxidatum; Zinc oxide (ZnO); Zinc oxide fume (ChemIDplus 2014)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
No chemical surrogates were used for this assessment as sufficient data were identified to assign a Benchmark 1 score for zinc oxide.

Identify Applications/Functional Uses: (HSDB 2006)
1. Used in pesticides
2. Used as a dermatologic agent

GreenScreen® Summary Rating for Zinc Oxide[4]: Zinc oxide was assigned a GreenScreen® Benchmark Score of 1("Avoid—Chemical of High Concern") as it has Very High ecotoxicity (chronic aquatic toxicity (CA)), High Group II* toxicity (systemic toxicity (repeated dose (STr*)) and respiratory sensitization (SnR*)), and Very High persistence (P). This corresponds to GreenScreen® benchmark classification 1c ("vPT = very High P + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]") in CPA 2011. Data gaps (DG) exist for endocrine activity (E), neurotoxicity

[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

[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.

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

(single (Ns) and repeated dose (Nr*)), and bioaccumulation (B). As outlined in CPA (2013) Section 12.2 (Conduct a Data Gap Analysis to assign a final Benchmark score), zinc oxide meets requirements for a GreenScreen® Benchmark Score of 1 despite the hazard data gaps. In a worst-case scenario, if zinc oxide were assigned a High score for the data gaps endocrine activity (E), neurotoxicity (single (Ns) and repeated dose (Nr*)), and bioaccumulation (B), it would still be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Zinc Oxide

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	**M**	**L**	**L**	DG	**L**	**L**	**H**	DG	DG	**L**	*H*	**L**	**L**	**vH**	**vH**	**vH**	DG	**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]

No transformation products were identified for zinc oxide. Potential processes affecting zinc oxide include reduction in the environment to form zinc (CAS #7440-66-6). Zinc is an LT-P1 chemical based on chronic aquatic toxicity. Since zinc oxide is a Benchmark 1 chemical, the transformation products do not modify the Benchmark score for zinc oxide.

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Feasible and Relevant?	List Translator Results[6,7]
NA	End of Life	Reduction	Zinc	7440-66-6	Yes	LTP1: H410 – very toxic to aquatic life with long-lasting effects.

Introduction

Zinc oxide is a white powder, and used in a variety of ways. Some examples include the manufacture of rubber, tires, and general rubber goods, glass and ceramics, ferrites, varistors, and catalysts, animal feed,

[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 2014) 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).

raw material for the production of zinc chemicals, fuel and lubricants additives, paints, and cosmetics and pharmaceuticals (ESIS 2008).

ToxServices assessed zinc oxide 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 2014) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. It checks all of the lists in the List Translator with the exception of the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b) and these should be checked separately in conjunction with running the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for zinc oxide can be found in Appendix C and a summary of the results can be found below:

- Very High Hazard
  - Acute Aquatic Toxicity
    - GHS Hazard Statement H400 – Very toxic to aquatic life
    - EU Risk Phrase R50/53 – Very toxic to aquatic organisms, may cause long lasting effects
    - GHS Japan Category 1 – Hazardous to the aquatic environment (acute)
    - GHS New Zealand Category 9.1A (fish, crustacean, algae) – Very ecotoxic in the aquatic environment (equivalent to GHS Category 1 acute aquatic toxicity)
  - Chronic Aquatic Toxicity
    - GHS Hazard Statement H410 – Very toxic to aquatic life with long lasting effects
    - GHS Japan Category 1 – Hazardous to the aquatic environment (chronic)
- High Hazard
  - Mammalian Toxicity
    - GHS Japan Category 1 – Specific target organs/systemic toxicity following single and repeated exposure.
- Medium Hazard
  - Respiratory Toxicity
    - AOEC Asthmagen (ARs) – sensitizer-induced, inhalable forms only

Zinc oxide is not listed on the U.S. DOT (2008a,b) lists.

PhysicoChemical Properties of Zinc Oxide

Zinc oxide is a white powder under standard temperature and pressure. It is slightly soluble in water (2.9 mg/L at 20°C). It is an inorganic chemical so it is persistent in the environment.

Table 1: Physical and Chemical Properties of Zinc Oxide (CAS #1314-13-2)

Property	Value	Reference
Molecular formula	Zn-O	ChemIDplus 2014

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

Table 1: Physical and Chemical Properties of Zinc Oxide (CAS #1314-13-2)		
Property	**Value**	**Reference**
SMILES Notation	O=[Zn]	ChemIDplus 2014
Molecular weight	81.389 g/mol	ChemIDplus 2014
Physical state	Solid	ECHA 2014
Appearance	White powder	ECHA 2014
Melting point	>1,000°C at 1 atm (EU Method A.1)	ECHA 2014
Vapor pressure	Not identified	
Water solubility	2.9 mg/L at 20°C (OECD 105)	ECHA 2014
Dissociation constant	Not identified	
Density/specific gravity	5.68 g/cm³ at 22°C (EU Method A.3)	ECHA 2014
Partition coefficient	Not identified	
Particle size	100-10,000 nm	ESIS 2008
Structure	Not identified	
Bioavailability	Not identified for zinc oxide; Absorption of zinc following oral exposure is dependent on protein content in diet and other factors	ATSDR 2005

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Zinc oxide was assigned a score of Low for carcinogenicity based on the lack of evidence suggesting that zinc oxide is a carcinogen. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012a). The confidence was adjusted based on the lack of animal bioassays directly investigating the carcinogenic potential of zinc oxide.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Logue et al. 1982
  - *Epidemiology*: A cohort study of 4,802 refinery workers in nine electrolytic zinc and copper refining plants (i.e. one zinc, one copper and zinc, and seven copper refineries), who had been employed between 1946 and 1975, reported slightly reduced mortality in the 1,247 workers who had been exposed to "zinc" alone (978) or in combination with "copper" (269). Employees were incorporated in the study when they had worked in the electrolytic department for at least one year. Age-adjusted Standardized Mortality Ratios were calculated on the basis of comparison with the mortality rates for the entire US population for the year 1970. Of the 1,247 workers who were exposed to "zinc" (either alone or in combination with "copper"), 88 died before the end of the follow-up. For 12 of these, the cause of death could not be retrieved. 143 workers were lost to follow-up entirely. Cancer rates were only analyzed for the entire cohort of refinery workers (i.e. all 4,802 participants). An association between cancer mortality and employment in zinc and/or copper refinery was not found. However, the study does not permit drawing a conclusion about any association

between cancer mortality and zinc exposure because cancer mortality for "zinc" workers was not analyzed separately from cancer mortality for "copper" workers.

- Neuberger and Hollowell 1982
  - *Epidemiology*: Neuberger and Hollowell (1982) studied an excess in lung cancer mortality associated with residence in an old lead/zinc mining and smelting area in the US. The age- and sex-adjusted mortality rates were compared to state and national rates. The analysis determined that lung cancer mortality was elevated in the region. Quantification of inhabitant's exposure to zinc was not part of the study. The authors mentioned several possible causes for the increased lung cancer rates such as smoking habits, occupational exposure (e.g. in mining and associated activities), and residence. Ore contaminants were arsenic, cadmium, iron, sulphur, germanium, and radioactivity. Tuberculosis and silicosis were commonly seen among the region's inhabitants. From this study, any conclusion on a possible association between exposure to environmental levels of lead or zinc and the increased lung cancer rate cannot be drawn.
- Leitzmann et al. 2003
  - *Epidemiology*: Leitzmann et al. (2003) examined the association between supplemental zinc intake (level and duration) and prostate cancer among 46,974 US men participating in the Health Professionals Follow-Up Study. During 14 years of follow-up (from 1986 through 2000), 2,901 new cases of prostate cancer were ascertained, of which 434 cases were diagnosed as advanced cancer. Approximately 25% of the study population used zinc supplements (24% in amounts ≤ 100 mg/day, 1% in amounts > 100 mg/day). Supplemental zinc intake at doses of up to 100 mg/day was not associated with prostate cancer risk. However, compared with non-users, users with an excessively high supplemental zinc intake (> 100 mg/day) had a relative risk of advanced prostate cancer of 2.29 (95% CI 1.06 to 4.95). Increasing the duration of supplemental zinc use was unrelated to the risk of total prostate cancer. However, for chronic users (> 10 years) the relative risk of advanced prostate cancer was 2.37 (95% CI 1.42 to 3.95). According to the authors residual confounding effects by supplemental calcium intake or some unmeasured correlate of zinc supplement use cannot be ruled out. They also indicate that strong evidence to support a specific mechanism for the association is lacking at present, and that further exploration for the possible role of chronic zinc oversupply in prostate carcinogenesis is needed.
- Deknudt and Gerber 1979; Léonard et al. 1986
  - *Animal bioassay*: Although no direct carcinogenic actions of dietary zinc deficiency or supplementation are known, the growth rate or frequency of transplanted and chemically induced tumors are influenced by the zinc content in the diet. Both promoting and inhibiting actions have been reported depending on the experimental conditions. Experiments with rodents suggest that cancer growth is retarded by zinc deficiency and may be promoted by large amounts of zinc intake. These effects may be explained by the fact that zinc is needed in DNA synthesis and cell replication.

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

Zinc oxide was assigned a score of Moderate for mutagenicity/genotoxicity based on equivocal or positive results for mutagenicity, clastogenicity, and/or genotoxicity in *in vitro* tests, and a weakly positive result for an *in vivo* chromosome aberration test. GreenScreen® criteria classify chemicals as a Moderate hazard for mutagenicity/genotoxicity when limited or marginal evidence of mutagenicity is observed in animals (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.

  - *Screening:* Not listed on any screening lists for this endpoint.
- CCRIS 2010
  - *In vitro*: A mouse lymphoma assay was positive for mutagenicity in the presence of metabolic activation at doses of 5.0-24 µg/mL.
  - *In vitro*: A mouse lymphoma assay was positive for mutagenicity in the absence of metabolic activation at doses of 1.0-4.9 µg/mL.
  - *In vitro*: Ames assays were performed on *Salmonella typhimurium* tester strains TA98 and TA100 in the presence and absence of metabolic activation and determined to be negative for mutagenicity.
  - *In vitro*: An *in vitro* chromosomal aberration was performed in the absence of metabolic activation and determined to be positive (structural changes) at a concentration of 180 µM.
- ECHA 2014
  - *In vitro*: A non-GLP-compliant Ames assay conducted in a manner similar to OECD 471 (no data on negative control) was performed with *S. typhimurium* tester strains TA 98, TA 100, TA 1535, and TA 1537 treated with zinc oxide (99% purity) at 1,000-5,000 µg/plate with and without metabolic activation, and determined to be negative for mutagenicity.
  - *In vitro*: A GLP-compliant chromosome aberration test conducted according to OECD 473 was performed with Chinese hamster lung fibroblasts (V79) exposed to zinc oxide (98% purity) at 1-50 µg/mL with and without metabolic activation. Negative results were obtained.
  - *In vitro*: A chromosome aberration test conducted according to OECD 473 was performed with human dental pulp cells (D824) exposed to zinc oxide (greater than 99% purity) at 30-300 µM (use of metabolic activation is not clear). Zinc oxide induced an increase in the frequency of chromosome aberrations
  - *In vitro*: An increase in the incidence of chromosome aberrations was observed in an OECD 473 test following exposure of Syrian hamster embryo cells to zinc oxide (greater than 99% purity) at 60-180 µM without metabolic activation.
  - *In vitro*: A GLP-compliant OECD 476 mammalian cell gene mutation test produced ambiguous results for mutagenicity. Mouse lymphoma L5178Y cells were exposed to zinc oxide (98% purity) at 1-6 µg/mL without metabolic activation and 2.5-10 µg/mL with metabolic activation. Increased mutation frequencies were observed in conjunction with increased cytotoxicity.
  - *In vitro*: A GLP-compliant OECD 471 Ames test was negative for mutagenicity. *S. typhimurium* tester strains TA 98, TA 100, TA 102, TA 1535, and TA 1537 were exposed to zinc oxide (greater than 99% purity) at 20-5,000 µg/plate, with and without metabolic activation. No increase in the mutation frequency was observed with treatment.
  - *In vitro*: A non-GLP-compliant unscheduled DNA synthesis assay produced positive results for genotoxicity. Syrian hamster embryo cells were exposed to zinc oxide (99% purity) at 0.3-30 µg/mL without metabolic activation. DNA damage was observed at levels greater than 1 µg/mL without metabolic activation.
  - *In vivo*: A GLP-compliant mammalian micronucleus test conducted according to OECD 474 produced negative results for clastogenicity. Male NMRI mice (5/dose group) were administered single intraperitoneal injections of zinc oxide (96-99% purity) in fetal calf serum at 15, 30, or 60 mg/kg. The animals were sacrificed 24 or 48 hours following the injection and the femoral bone marrow was isolated for evaluation of micronuclei. No increase in the frequency of micronuclei was observed with treatment.
  - *In vivo*: A chromosome aberration assay was performed with female Wistar rats (number not reported) administered inhalation exposures to zinc oxide (purity not specified) at 0.1 or

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

0.5 mg/m^3 (equivalent to 0.0001 and 0.0005 mg/L, respectively) continuously for 5 months. A weakly positive increase in the frequency of hyperdiploid cells of bone marrow was observed with treatment.

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

Zinc oxide was assigned a score of Low for reproductive toxicity based on weight of evidence. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Schlicker and Cox 1968
  - In rats, the administration of 0.4% of Zn^{2+} as ZnO (corresponding to 200 mg Zn^{2+}/kg bw/day[8]) via the diet for 21 days prior to mating until day 15 of gestation resulted in resorption of all fetuses. Administration of 0.4% dietary Zn^{2+} from day 0 to day 15, 16, 18 or day 20 of gestation, but not prior to mating, resulted in decreased live fetal body weights and in 4-29% fetal resorptions. When the concentration of Zn^{2+}in the feed was reduced to 0.2% (corresponding to 100 mg Zn^{2+}/kg bw/day), starting 21 days prior to mating until day 15 of gestation, no resorptions or effects on fetal body weights were observed. Treatment with dietary zinc did not result in external malformations, irrespective of dose level or treatment regimen. A dose-related significant increase in liver total zinc and liver zinc concentrations and a significant decrease in the liver copper concentration were found in fetuses and mothers on all zinc regiments. No other information was given with respect to the health status of the mother animals. Although some of the animals were exposed from day 21 before mating up to study termination, no data were provided on possible consequences for female fertility.
- Bleavins et al. 1983
  - Bleavins et al. (1983) exposed groups of mink (11 females and 3 males/group) to a basal diet (containing 20.2 mg Zn^{2+}/kg diet and 3.1 mg Zn^{2+}/kg diet) or to a diet supplemented with 1,000 mg ZnO/kg. No exposure period was provided. No maternal effects were seen. All females on the basal diet produced offspring, 8/11 females of the Zn-supplemented diet group had young. None of the animals (males, females, and kits) were sacrificed, so they were only macroscopically examined. The kits were kept on the basal and supplemented diets. The body weight of male kits on the supplemented diet was significantly lower at 12 weeks of age. Eight-week old kits on the supplemented diet showed a significant decrease of the Ht-value, the other blood parameters were comparable to the kits on the basal diet. The decreased T-cell mitotic response observed in the Zn-supplemented kits was reversible when the kits were placed on the basal diet. Kits (3-4 weeks old) of females fed the Zn-supplemented diet showed effects consistent with copper deficiency, such as grey fur around eyes, ears, jaws, and genitals together with hair loss and dermatosis in these areas.
- ESIS 2008
  - When male rats were dosed with approximately 200 mg Zn^{2+}/kg bw via the food for 30-32 days before mating, a statistically significant reduction in male reproductive performance was observed. This effect was attributed to a reduction in sperm motility. In females receiving 200 mg Zn^{2+}/kg bw, reduced conception was observed when they were dosed after

8 $\frac{200\,\text{mg Zn}}{\text{kg bw}} \times \frac{\text{g Zn}}{1{,}000\,\text{mg Zn}} \times \frac{\text{mol Zn}}{65.39\,\text{g Zn}} \times \frac{\text{mol ZnO}}{\text{mol Zn}} \times \frac{81.39\,\text{g ZnO}}{\text{mol ZnO}} \times \frac{1{,}000\,\text{mg ZnO}}{\text{g ZnO}} = \frac{249\,\text{mg ZnO}}{\text{kg bw}}$

mating, but not when they were dosed before and during pregnancy. It is not known whether the reduced sperm motility in males and the contradictory effects on conception in females are a direct effect of zinc on the sperm cells, embryos, or uterine function, or whether they are the result of disturbances in other physiological functions.

- Available data in animals on zinc excess indicate that adverse effects on fertility and fetal development may occur at dose levels of 200 mg Zn^{2+}/kg bw/day[9], in conjunction with other effects such as perturbation of parental and fetal copper homeostasis. In humans a small disturbance (if any) of normal physiology, presumably indicative of copper deficiency, has been demonstrated at zinc excesses of 50 and 150 mg Zn^{2+}/day (0.83 and 2.5 mg Zn^{2+}/kg bw/day, respectively), while 150 mg Zn^{2+}/day (2.5 mg Zn^{2+}/kg bw/day) resulted in clinical signs[10].
- Zinc deficiency is known to result in impairment of fertility and of fetal development. In humans, additional zinc up to 0.3 mg Zn^{2+}/kg bw/day during pregnancy did not result in adverse effects. As the margin between the dose at which clinical signs in humans are manifested and the dose at which in animals reproductive effects have been reported is so high (viz. 80), it is considered unlikely that reproductive effects in humans will occur at exposure levels at which clinical signs are not manifest. Therefore, neither fertility nor developmental toxicity are considered end-points of concern for humans. Based on the available information, there is no reason to classify metallic zinc nor any of the zinc compounds considered as reproductive toxicants.

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

Zinc oxide was assigned a score of Low for developmental toxicity based on the lack of developmental toxicity observed in a GLP-complaint OECD 414 test in rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Ketcheson et al. 1969
  - Groups of Sprague-Dawley rats (10/group) were fed diets containing 2,000 or 5,000 mg ZnO/kg feed (calculated to be 150 or 375 mg ZnO/kg bw [≈120 or 300 mg Zn^{2+}/kg bw/day]) from day 0 of gestation to day 14 of lactation, then mothers and remaining pups were killed. The control animals received a basal diet containing 9 mg Zn^{2+}/kg feed. Maternal weight, daily food intake, duration of gestation, and the number of viable young/litter were not affected. No external malformations were seen. Two females at 5,000 mg/kg feed had all stillborn litters containing edematous pups. At 2,000 mg/kg feed, 4 stillborn pups (not edematous) were observed. Dry liver weights of pups (newborn and 14 days old) were decreased at 5,000 mg/kg feed. A dose-related increase in zinc content and a dose-related decrease in iron content were observed. The livers of newborns of zinc-treated dams,

9 $\frac{200\,\text{mg Zn}}{\text{kg bw}} \times \frac{\text{g Zn}}{1{,}000\,\text{mg Zn}} \times \frac{\text{mol Zn}}{65.39\,\text{g Zn}} \times \frac{\text{mol ZnO}}{\text{mol Zn}} \times \frac{81.39\,\text{g ZnO}}{\text{mol ZnO}} \times \frac{1{,}000\,\text{mg ZnO}}{\text{g ZnO}} = \frac{249\,\text{mg ZnO}}{\text{kg bw}}$

10 $\frac{0.83\,\text{mg Zn}}{\text{kg bw}} \times \frac{\text{g Zn}}{1{,}000\,\text{mg Zn}} \times \frac{\text{mol Zn}}{65.39\,\text{g Zn}} \times \frac{\text{mol ZnO}}{\text{mol Zn}} \times \frac{81.39\,\text{g ZnO}}{\text{mol ZnO}} \times \frac{1{,}000\,\text{mg ZnO}}{\text{g ZnO}} = \frac{1.03\,\text{mg ZnO}}{\text{kg bw}}$

$\frac{2.5\,\text{mg Zn}}{\text{kg bw}} \times \frac{\text{g Zn}}{1{,}000\,\text{mg Zn}} \times \frac{\text{mol Zn}}{65.39\,\text{g Zn}} \times \frac{\text{mol ZnO}}{\text{mol Zn}} \times \frac{81.39\,\text{g ZnO}}{\text{mol ZnO}} \times \frac{1{,}000\,\text{mg ZnO}}{\text{g ZnO}} = \frac{3.11\,\text{mg ZnO}}{\text{kg bw}}$

however, contained significantly more iron than the controls. This was not observed in the 14-day old pups. The copper levels in the liver were significantly lower only in the newborns of the 5,000 mg/kg level. After 14 days, the copper concentrations were significantly lower in all treated pups.

- Walsh et al. 1994; ATSDR 1994; WHO 1996
  - Clear evidence of zinc toxicity in human pregnancy has not been reported but this may be due to the fact that very high exposures to zinc in human pregnancy are unusual. In contrast, zinc deficiency during pregnancy can cause a variety of adverse effects on the fetus or may result in reduced fertility or delayed sexual maturation in animals as well as in humans.
- ECHA 2014
  - A GLP-compliant prenatal developmental toxicity study conducted according to OECD 414 was performed with pregnant female Wistar rats (25/dose group) administered nose/head only inhalation exposures of nanoscale ZnO (purity not specified) coated on its surface with triethoxycaprylylsilane (CAS #2943-75-1) at 0.3, 1.5, or 7.5 mg/m^3 (equivalent to 0.0003, 0.0015, and 0.0075 mg/L, respectively) for 6 hours/day on gestational days 6-19. The dams were sacrificed on gestational day 20. Maternal examinations included body weight, food consumption, gross pathology, and ovarian and uterine content. Fetal examinations consisted of evaluations of external, visceral, skeletal, and head abnormalities. In the high dose group, maternal toxicity was observed as slight inflammation and moderate alveolar lipoproteinosis. No adverse findings were observed for the fetuses. The study authors identified a NOAEC of 7.5 mg/m^3 (equivalent to 0.0075 mg/L) for developmental toxicity based on the lack of teratogenicity and embryotoxicity observed in the study.

Endocrine Activity (E) Score (H, M, or L): DG
Zinc oxide was assigned a score of Data Gap for endocrine disruption based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- 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 for this endpoint.

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
Zinc oxide was assigned a score of Low for acute toxicity based on oral LD_{50} values greater than 2,000 mg/kg, dermal LD_{50} values greater than 2,000 mg/kg, and inhalation LC_{50} values greater than 5.7 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral LD_{50} values are greater than 2,000 mg/kg, dermal LD_{50} values are greater than 2,000 mg/kg, and inhalation LC_{50} values are greater than 5 mg/L (dust) (CPA 2012a).

- Authoritative and Screening Lists

  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Loser 1977
  - *Oral*: LD_{50} (rat) = greater than 5,000 mg/kg (identified as Wistar rats and OECD 401 in ECHA 2014)
- Loser 1972
  - *Oral*: LD_{50} (rat) = 15,000 mg/kg
- Shumskaya et al. 1986
  - *Oral*: LD_{50} (mouse) = 7,950 mg/kg
- Klimisch et al. 1982
  - *Inhalation*: LC_{50} (rat) = greater than 5.7 mg/L (identified as 4-hour exposure and OECD 203 in ECHA 2014)
- ECHA 2014
  - *Oral*: LD_{50} (CD-ICR mouse) = greater than 5,000 mg/kg (20 nm ZnO OECD 401)
  - *Oral*: LD_{50} (CD-ICR mouse) = greater than 2,000 mg/kg and less than 5,000 mg/kg (120 nm ZnO OECD 401)
  - *Dermal*: LD_{50} (Wistar rat) = greater than 2,000 mg/kg (GLP-compliant, OECD 402)

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M, or L): L**
Zinc oxide was assigned a score of Low for systemic toxicity (single dose) based on the lack of systemic toxicity observed in acute toxicity studies and weight of evidence in humans. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when negative results, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS Japan Category 1 – Specific target organs/systemic toxicity following single exposure (based on metal fume fever in workers).
- ECHA 2014
  - *Oral*: No adverse systemic effects were observed in the study that identified an oral LD_{50} value of greater than 5,000 mg/kg in Wistar rats.
  - *Oral*: No systemic toxicity data were presented in the study that identified oral LD_{50} values of greater than 5,000 mg/kg for 20 nm ZnO and greater than 2,000 mg/kg and less than 5,000 mg/kg for 120 nm ZnO in CD-ICR mice.
  - *Inhalation*: No adverse systemic effects were observed in the study that identified an inhalation LC_{50} value of greater than 5.7 mg/L in rats.
  - *Dermal*: No adverse systemic effects were observed in the study that identified a dermal LD50 value of greater than 2,000 mg/kg in Wistar rats.
- ESIS 2008
  - Metal fume fever has been observed in workers exposed to zinc oxide by inhalation, but it is restricted to very specific operations at very high temperatures that form fresh ultra-fine particles (e.g. cutting or welding of galvanized steel). This effect is not associated with production and use of commercial grade zinc oxide.

***Group II* Score (repeated dose)* (H, M, or L): H**
Zinc oxide was assigned a score of High for systemic toxicity (repeated dose) based on it being classified as a Category 1 specific target organ/systemic toxicant (repeat dose). GreenScreen® criteria

classify chemicals as a High hazard for systemic toxicity (repeated dose) when a GHS Category 1 specific target organ/systemic toxicant (repeat dose) classification is available (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:*
        - GHS Japan Category 1 – Specific target organs/systemic toxicity following repeated exposure.
- Straube et al. 1980
    - *Oral*: Four groups of ferrets (3-5/group) were given 0, 500, 1,500, or 3,000 mg zinc oxide/kg feed (equivalent to 0, 81.3, 243.8, or 487.5 mg ZnO/kg bw, respectively). The length of exposure was not provided; however, animals were observed through day 191. Therefore, the length of the study overall can be assumed to be approximately 27 weeks at minimum. At the highest dose level (487.5 mg ZnO/kg bw) all animals (3) were killed in extremis within 13 days. Macroscopic examination showed pale mucous membranes, dark colored fluid in the stomach, blood in the intestines, orange colored liver and enlarged kidneys showing diffuse necrosis, hemorrhages in the intestine and severe macrocytic hypochromic anemia. Histology showed nephrosis and extramedullary hematopoesis in the spleen. At the mid dose level of 243.8 mg ZnO/kg bw, the animals (4) were killed on days 7, 14, and 21 (1/2 in extremis) showing poor condition. Macroscopy showed pale livers with fatty infiltration and enlarged kidneys. Histology was comparable with the highest dose group. The hemogram showed macrocytic hypochromic anemia, increased reticulocytes and leucocytosis. At the lowest dose level (81.3 mg ZnO/kg bw), the animals (3) were killed on days 48, 138, and 191, respectively. No clinical signs of toxicity or pathological changes were seen, apart from an extramedullary hematopoesis in the spleen. Therefore, the LOAEL for this study can be identified as 81.3 mg ZnO/kg bw based on extramedullary hematopoesis.
- Ellis et al. 1984 -
    - *Oral*: A 14-day and a 49-day feeding study were performed in 3 different breeds of sheep that were receiving feed containing 31 mg Zn^{2+}/kg. The sheep received additional amounts of Zn^{2+} (from ZnO) at dose levels of 261 and 731 (14 day study), or 731 and 1,431 mg Zn^{2+}/kg feed (49-day study). No effects were seen for 261 mg Zn^{2+}/kg in the feed. In all other groups, pancreatic lesions were seen.
- Smith and Embling 1993
    - *Oral*: Oral administration of 240 mg Zinc (as ZnO)/kg bw for 3 times/week during 4 weeks to 42 castrated sheep resulted in an increased incidence of pancreatic lesions.
- Conner et al. 1988; Conner et al. 1986; Lam et al. 1988; Lam et al. 1985
    - *Inhalation*: Several studies are available in which male Hartley guinea pigs were exposed to zinc oxide in particulate form for 3 hours per day from 1-5 days. The effects observed included increased number of nucleated cells in lavage fluid, an increase in neutrophils, and an increase in enzymatic activity. These effects were dose dependent. A decrease in total lung capacity, vital capacity, and diffusing capacity, as well as a decrease in alveolar volume were observed.
- Dinslage-Schlünz and Rosmanith 1976
    - *Inhalation*: 240 Female Wistar rats (80/group) were exposed by inhalation to 15 mg ZnO/m^3 for 1 hour, 4 hours, or 8 hours a day for 5 days a week. The length of exposure was not provided; however, the study states that sacrifice of animals took place at up to 84 days. Therefore, the length of the study overall can be assumed to be at least 12 weeks. 20 animals/group were sacrificed after 14, 28, 56, and 84 days and their lungs were examined

for zinc content. It appeared that the highest daily exposure time resulted in the highest dry lung weights, independent of the duration of the experiment, while the zinc content remained almost constant. The absolute and relative (relative to dried weights of lung tissue) zinc content in the lungs was influenced by the duration of the experiment. After 84 days of exposure, the zinc content was significantly higher compared to the 14 day exposure group, independent of the duration of the daily exposure.

- ECHA 2014
    - *Inhalation*: A GLP-compliant repeated dose toxicity study conducted according to OECD 413 (no females) was performed with male Wistar rats (65/dose group) administered nose-only inhalation exposures of zinc oxide aerosol (98% purity) at 0.3, 1.5, or 4.5 mg/m^3 (equivalent to 0.0003, 0.0015, and 0.0045 mg/L, respectively) for 6 hours/day, 5 days/week for 90 days. The equivalent concentrations for a 7 day/week exposure frequency are 0.0002, 0.0011, and 0.0032 mg/L, respectively. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. In the high concentration group, lactic dehydrogenase (LDH) was identified in the bronchiolo-alveolar lavage fluid. Bronchiolo-alveolar hyperplasia and mononuclear cell infiltration were observed in the high concentration group. The study authors identified a NOAEC of 1.5 mg/m^3 (equivalent to 0.0011 mg/L for a 7 day/week exposure frequency) based on histopathological changes in the lungs at 4.5 mg/m^3 (equivalent to 0.0032 mg/L for a 7 day/week exposure frequency).
        - The LOAEC of 0.0032 mg/L/6h/day is below the GHS guidance value of 0.02 mg/ L/6h/day for 90-day studies. Therefore, zinc oxide is classified to GHS category 1.

Neurotoxicity (N)

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

Zinc oxide was assigned a score of Data Gap for neurotoxicity (single dose) based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- No data were identified.

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

Zinc oxide was assigned a score of Data Gap for neurotoxicity (repeated dose) based on insufficient data to assign a score for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- Kozik et al. 1980, 1981
    - Special studies were conducted to examine the morphological and histoenzymatic changes of the brain. Twelve Wistar rats were given daily doses of 100 mg ZnO (ca. 600 mg ZnO/kg bw ≈ 480 mg Zn^{2+}/kg bw) intragastrically for 10 consecutive days. A control group was included. After 10 days, the rats were sacrificed and the brains were examined for morphological and histoenzymatic changes. Morphological changes included degenerative changes of neurocytes, accompanied with moderate proliferation of the oligodendroglia, and glial proliferation in the white matter. Furthermore, endothelial edema was observed in the

small arterial and capillary walls. Histoenzymatic changes included decreased activities of ACP (acid phosphatase), ATPase (adenosinetriphosphatase), AChE (acetylcholine esterase), and BChE (Butyrylthiocholineesterase). The activities of TTPase (thiamine pyrophophatase) and NSE (non-specific esterase) were increased. No details on quantitative aspects of enzymatic changes were given. No change was seen in the alkaline phosphatase. The authors indicated that observed morphological and histoenzymatic changes were non-specific, indistinctive, and most likely reversible (Kozik et al. 1980). Examination of the neurosecretory function of the hypothalamus and the hypophysis in these animals showed an increased neurosecretion in cells of the supraoptic and paraventricularnucleus of the hypothalamus along with a declined neurosecretion in the hypophysis and an enhanced release of antidiuretic hormone in the neurohypophysis (Kozik et al. 1981). It is not clear whether these observations represent an adverse effect of zinc on the brain or whether they are secondary to changes somewhere else in the body.

- Since only one dose was utilized in this study, it is not possible to establish a dose-response relationship for the effects observed with treatment. Therefore, a data gap was assigned for this endpoint.

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

Zinc oxide was assigned a score of Low for skin sensitization based on negative results for sensitization in animal and human studies. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when negative data, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Malten and Kuiper 1974
  - In a human patch test performed with 100 selected leg-ulcer patients, 11/100 patients gave an allergic reaction with zinc ointment (60% ZnO and 40% sesame oil). However, 14/81 patients gave a positive response when treated with sesame oil alone. This study does not give any indication for a skin sensitizing potential of zinc oxide in humans.
- Söderberg et al. 1990
  - The authors studied the effect of zinc oxide on contact allergy to colophony. With 14 patients with earlier history of moderate patch test reactions to a colophony patch test, a patch test with 10% ZnO (2.3 mg Zinc/cm²) with and without colophony was performed. No positive response was observed in the 14 patients when only a 10% solution of zinc oxide was used. The addition of zinc oxide to colophony decreased the allergic reaction induced by colophony.
- Van Huygevoort 1999a1, 1999a2
  - The skin sensitization potential of zinc oxide (99.69% purity) was investigated in female Dunkin Hartley guinea pigs in 2 well-performed maximization tests, conducted according to Directive 96/54/EC B.6 and OECD guideline 406 (ECHA 2014 identifies these studies as GLP-compliant). Based on the results of a preliminary study, in the main studies experimental animals (10 in each test) were intradermally injected with a 20% concentration and epidermally exposed to a 50% concentration (i.e. the highest practically feasible concentration). Control animals (5 in each test) were similarly treated, but with vehicle (water) alone. Approximately 24 hours before the epidermal induction exposure, all animals were treated with 10% SDS. Two weeks after the epidermal application, all animals were challenged with a 50% test substance concentration and the vehicle. In the first study, in

response to the 50% test substance concentration, skin reactions of grade 1 were observed in 4/10 experimental animals 24 hours after the challenge (40% sensitization rate), while no skin reactions were evident in the controls. In contrast, in the second study no skin reactions were evident in the experimental animals (0% sensitization rate), while a skin reaction grade 1 was seen in one control animal. The skin reaction observed in one control animal is probably a sign of non-specific irritation.

- ESIS 2008
    - The data submitted fulfill the base-set requirements for skin sensitization testing. While some studies with guinea pigs produced conflicting results, the weight of evidence does not indicate that zinc oxide is a very potent sensitizing agent in animals, if any. In addition, the results of human patch tests do not indicate that zinc oxide acts as a sensitizing agent in humans. Zinc oxide does not have to be classified/labeled for skin sensitization. This is supported by the fact that zinc compounds, especially zinc oxide and zinc distearate, have been used for decades in a variety of pharmaceutical and cosmetic products (some of them even as dermatological preparations against skin irritation) without any such reported effects.

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

Zinc oxide was assigned a score of High for respiratory sensitization in the inhalable form based on it being classified as a sensitizer-induced asthmagen by the AOEC. GreenScreen® criteria classify chemicals as a Moderate to High hazard for respiratory sensitization when a chemical is classified as a sensitizer-induced asthmagen by the AOEC (CPA 2012a). ToxServices assigned a High score for the inhalable form in order to be protective of human health. Confidence level was adjusted due to the reliance on an Authoritative B list.

- Authoritative and Screening Lists
    - *Authoritative:*
        - AOEC Asthmagen (ARs) – sensitizer-induced, inhalable forms only
    - *Screening:* Not listed on any screening lists for this endpoint.
- No data were identified for this endpoint.

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

Zinc oxide was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation observed in animal studies. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when negative data, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- Agren 1990
    - No signs of skin irritation were noted when an occlusive 25% zinc oxide patch (2.9 mg Zn/cm^2) was placed on the human skin for 48 hours. The zinc oxide was incorporated in the adhesive (natural rubber, gum rosin, and white mineral oil; all pharmaceutical quality) of the patch.
- Derry et al. 1983
    - A rash and follicular pustules were observed developing in a patient who received a treatment with a 40% zinc oxide ointment treatment (15 g on 150 cm^2) under occlusive dressing at 24 hours post treatment. The dermal reaction disappeared 2 days after removal of the ointment and treatment with cool saline compresses, but reappeared after application

of 5% zinc oxide. From the study, it could not be determined whether the dermal effects were a result of zinc oxide or from other treatment-related stimuli. In 5 other patients who were treated with 40% zinc oxide ointment in a similar way and in 6 volunteers who received 100 g of 40% zinc oxide ointment on chest and legs, no signs of dermal reactions were reported.

- ECHA 2014
    - A dermal irritation study was performed with Dunkin-Hartley guinea pigs (8/dose group, sex not specified) administered dermal applications of a 20% zinc oxide (at least 98% purity) solution in 0.1% Tween 80 to shaved skin without dressing for 5 days. No irritation effects were observed following application of zinc oxide to the skin.
    - A dermal irritation study was performed with New Zealand White rabbits (4/dose group, sex not specified) administered dermal applications of a 20% zinc oxide (at least 98% purity) solution in 0.1% Tween 80 to clipped skin with and without occlusive dressing for 5 days. No irritation effects were observed following application of zinc oxide to the skin.
    - A GLP-compliant *in vitro* skin corrosion test conducted according to OECD 431 was performed with a reconstructed human skin model with exposures to zinc oxide (98% purity). The duration of treatment was 3 minutes or 1 hour, with two tissues per time point. Cell viability was 95% for the 3 minute and 1 hour time points. The study authors concluded that zinc oxide was not corrosive to skin.
    - A dermal irritation study was performed with TO (outbred) mice (6/dose group, sex not specified) administered dermal applications of a 20% zinc oxide (at least 98% purity) solution in 0.1% Tween 80 to clipped skin without dressing for 5 days. No irritation effects were observed following application of zinc oxide to the skin.
    - A dermal irritation study was performed with New Zealand White rabbits (2 total, sex not specified) administered dermal application of 500 mg zinc oxide (purity not specified) to the ear for 24 hours. An observation period of 7 days followed the exposure period. The overall irritation score at 24 hours was 0. The study authors concluded that zinc oxide was not irritating to the skin.

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

Zinc oxide was assigned a score of Low for eye irritation/corrosivity based on the ocular irritation effects observed in animals being insufficient for classification of zinc oxide as a GHS eye irritant. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when negative data, no structural alerts, and no GHS classification for eye irritation are available (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- Loser 1977
    - In an eye irritation study in 2 New Zealand White rabbits, 50 mg ZnO/animal caused erythema (mean scores over 24-72 hours: 3 and 2) and edema (mean score over 24-72 hours: 1.3 and 0.3) up to 48 hours after treatment. In the first rabbit, erythema persisted for 7 days. No effects were seen on the iris and cornea. Zinc oxide is borderline positive for irritation to the rabbit eye in this study.
- Van Huygevoort 1999b
    - In a well-performed eye irritation/corrosion study, performed according to Directive 92/69/EEC B.5 and OECD guideline 405 (ECHA 2014 identifies this study as GLP-compliant), three male New Zealand White rabbits were treated by instillation of approximately 64 mg of zinc oxide (a volume of about 0.1 ml) into the conjunctival sac of

one eye. The other eye remained untreated and served as a control. After 24 hours, both eyes of two animals were rinsed with water. The eyes were examined at 1, 24, 48, and 72 hours after instillation. No symptoms of systemic toxicity were observed and no mortality occurred. Slight iridial irritation (grade 1) was observed in one animal, at 1 hour only. Slight irritation of the conjunctivae (grade 1-2) was seen as redness (mean scores over 24-72 hours 0.7, 1, and 1), which had completely resolved at 72 hours in all animals. Chemosis (grade 2) and discharge (grade 1) were also observed in all animals, but at 1 hour only. No corneal opacity or epithelial damage was observed in any of the animals.

- The effects observed in this study are not sufficient to classify zinc oxide as a GHS Category 2 eye irritant. The criteria for a GHS Category 2 eye irritant are as follows: corneal opacity ≥ 1, and/or iritis ≥ 1, and/or conjunctival redness ≥ 2, and/or chemosis ≥ 2.

- Thijssen 1978
  - In another eye irritation study using 2 NZW rabbits 50 mg ZnO/animal caused slight erythema (mean scores over 24-72 hours: 0.7 and 0.7) of the conjunctiva that lasted for 2 days. No effect on the iris or cornea was seen in the 7-day observation period. Zinc oxide is not irritating to the rabbit eye in this study.

Ecotoxicity (Ecotox)

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

Zinc oxide was assigned a score of Very High for acute aquatic toxicity based on it being associated with GHS Hazard Statement H400 supported by data. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when a chemical is associated with GHS Hazard Statement H400 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:*
    - GHS Hazard Statement H400 – Very toxic to aquatic life
    - EU Risk Phrase R50/53 – Very toxic to aquatic organisms, may cause long lasting effects
  - *Screening:*
    - GHS Japan Category 1 – Hazardous to the aquatic environment (acute)
    - GHS New Zealand Category 9.1A (fish, crustacean, algae) – Very ecotoxic in the aquatic environment (equivalent to GHS Category 1 acute aquatic toxicity)
- Van Woensel 1994
  - In a 96-h acute toxicity test with fish *Brachydanio rerio* (test compound "EPM-grade" ZnO, purity 99.37%), no effect was found for dispersed ZnO at 100 mg ZnO/L (limit test), thus the 96-h EC_{50} (and thus, LC_{50}) is >100 mg ZnO/L, nominal concentration, equivalent to >80 mg Zn/L. The actual dissolved zinc concentration in this ZnO dispersion was 4,700 µg Zn/L (4.7 mg Zn/L).
- Van Ginneken 1994a, LISEC 1997
  - The two tests with the unicellular algae *Pseudokierchneriella subcapitata* (formerly known as *Selenastrum capricornutum*), in which two different grades of ZnO were tested ("Red seal-grade", purity 99.77%, and "EPM-grade", purity 99.37%), resulted in 72-h E_rC_{50} values for dissolved zinc of 135 and 136 µg Zn/L, respectively, for endpoint specific to growth rate.
- Van Ginneken 1994b

  - A short-term *Daphnia magna* immobilization test with "EPM grade" ZnO (purity 99.37%) resulted in a 48 hr. EC_{50} for dissolved zinc of 1,760 μg/L and a 48-hr NOEC for dissolved zinc of 280 μg/L.
- ECHA 2014
  - 96-hour LC_{50} (*Danio rerio*, zebrafish) = 1.793 mg/L (non-GLP-compliant)
  - 96-hour hatching rate EC_{50} (*Danio rerio*, zebrafish) = 2.065 mg/L (non-GLP-compliant)
  - 48-hour mobility EC_{50} (*Daphnia magna*) = 1.7-9 mg/L (nano ZnO, OECD 202)
  - 48-hour mobility EC_{50} (*Daphnia magna*) = greater than 5-12 mg/L (bulk ZnO, OECD 202)
  - 72-hour growth rate IC_{50} (*Pseudokirchnerella subcapitata*, green algae) = 0.136 mg/L (GLP-compliant, OECD 201)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): vH
Zinc oxide was assigned a score of Very High for chronic aquatic toxicity based on a 72h NOAEC of 0.024 mg/L for green algae. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are no greater than 0.1 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:*
    - GHS Hazard Statement H410 – Very toxic to aquatic life with long lasting effects
  - *Screening:*
    - GHS Japan Category 1 – Hazardous to the aquatic environment (chronic)
- ECHA 2014
  - 35-day larval growth NOAEC (*Danio rerio*, zebrafish) = at least 0.54 mg/L (GLP-compliant, OECD 210)
  - 100-day survival LOAEC (*Corophium volutator*, amphipod) = 0.2 mg/L (GLP-compliant, ASTM E1367-99)
  - 72-hour growth rate NOAEC (*Pseudokirchnerella subcapitata*, green algae) = 0.024 mg/L (GLP-compliant, OECD 201)

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vH
Zinc oxide was assigned a score of Very High for persistence based on it being an inorganic chemical that persists in the environment. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when a chemical is recalcitrant (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- Zinc oxide is expected to persist in the environment based on the fact that it is an inorganic compound. Inherent properties of inorganic compounds cause them to persist in the environment.

Bioaccumulation (B) Score (vH, H, M, L, or vL): DG
Zinc oxide was assigned a score of Data Gap for bioaccumulation based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- No data were identified for this endpoint.

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

Physical Hazards (Physical)

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

Zinc oxide was assigned a score of Low for reactivity based on it not being classified as reactive under GHS criteria (2013). GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification can be assigned (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ESIS 2008
  - Zinc oxide is not explosive (based on expert judgment).
- ECHA 2014
  - Zinc oxide does not possess oxidizing properties.
- Based on the data presented above, ToxServices did not classify zinc oxide as a reactive chemical based on GHS criteria (UN 2013).

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

Zinc oxide was assigned a score of Low for flammability based on it not being classified as a flammable solid under GHS criteria (UN 2013). GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is assigned for this endpoint (CPA 2012a).

Authoritative and Screening Lists

- *Authoritative:* Not listed on any authoritative lists for this endpoint.
- *Screening:* Not listed on any screening lists for this endpoint.

- ESIS 2008
  - Zinc oxide is not flammable.
- Based on this information, ToxServices did not classify zinc oxide as a flammable chemical based on GHS criteria (UN 2013).

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

References

Agren, M.S. 1990. Percutaneous absorption of zinc from zinc oxide applied topically to intact skin in man. Dermatologica. 180:36-39 (as cited in ESIS 2008).

Agency for Toxic Substances and Disease Registry (ATSDR). 1994. Toxicological profile for zinc (update). Agency for Toxic Substances and Disease Registry, Atlanta (as cited in ESIS 2008).

Agency for Toxic Substances and Disease Registry (ATSDR). 2005. Toxicological profile for zinc. Public Health Service, U.S. Department of Health and Human Services. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp60.pdf.

Bleavins, M.R., R.J. Aulerich, J.R. Hochstein, T.C. Hornshaw, and A.C. Napolitano. 1983. Effects of excessive dietary zinc on the intrauterine and postnatal development of mink. J. Nutr. 113:2360-2367 (as cited in ESIS 2008).

Chemical Carcinogenesis Research Information System (CCRIS). 2010. Entry for zinc oxide. United States National Library of Medicine. Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/search.

ChemIDplus. 2014. Entry for Zinc Oxide (CAS #1314-13-2). United States National Library of Medicine. Available at: http://chem.sis.nlm.nih.gov/chemidplus/rn/1314-13-2.

Clean Production Action (CPA). 2011. The GreenScreen® for Safer Chemicals Version 1.2 Benchmarks. Dated October 2011. Available at: http://www.greenscreenchemicals.org/.

Clean Production Action (CPA). 2012a. The GreenScreen® for Safer Chemicals Version 1.2 Criteria. Dated: November 2012. Available at: http://www.greenscreenchemicals.org/.

Clean Production Action (CPA). 2012b. List Translator. Dated February 2012. Available at: http://www.greenscreenchemicals.org/.

Clean Production Action (CPA). 2013. The GreenScreen® for Safer Chemicals Chemical Hazard Assessment Procedure. Version 1.2 Guidance. Dated August 31, 2013. Available at: http://www.greenscreenchemicals.org/.

Conner, M.W., W.H. Flood, A.E. Rogers, and M.O. Amdur. 1986. Pulmonary damage in guinea pigs caused by inhaled ultra-fine zinc oxide, evaluation by light and electron microscopy and analysis of pulmonary lavage fluid. Microb. Anal.. 21:589-590 (as cited in ESIS 2008).

Conner, M.W., W.H. Flood, and A.E. Rogers. 1988. Lung injury in guinea pigs caused by multiple exposures to ultra-fine zinc oxide. Changes in pulmonary lavage fluid. J. Toxicol. Environ. Health. 25:57-69 (as cited in ESIS 2008).

Deknudt, G. and G.B. Gerber. 1979. Chromosomal aberrations in bone-marrow cells of mice given a normal or a calcium deficient diet supplemented with various heavy metals. Mutat. Res. 68:163-168 (as cited in ESIS 2008).

Derry, J.E., W.M. McLean, and J.B. Freeman. 1983. A study of the percutaneous absorption from topically applied zinc oxide ointment. J. Parenter. Enteral. Nutr. 7:131-135 (as cited in ESIS 2008).

Dinslage-Schulnz, A. and J. Rosmanith. 1976. The zinc elimination from the rat lung after repeated zinc oxide inhalation. Beitr. Silikose-Forsch. (Pneumokon). 28:80-89 [In German] (as cited in ESIS 2008).

Ellis, T.M., H.G. Masters, and C. Mayberry. 1984. Examination of susceptibility of different breeds of sheep to zinc intoxication. Aust. Vet. J. 61:296-298 (as cited in ESIS 2008).

European Chemical Substances Information System (ESIS). 2008. Risk Assessment Report for Zinc Oxide. European Commission Joint Research Centre. Available at: http://esis.jrc.ec.europa.eu/doc/existing-chemicals/risk_assessment/REPORT/zincoxidereport073.pdf.

European Chemicals Agency (ECHA). 2014. REACH Dossier for Zinc Oxide (CAS #1314-13-2). Available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb185b3-df52-333c-e044-00144f67d031/DISS-9eb185b3-df52-333c-e044-00144f67d031_DISS-9eb185b3-df52-333c-e044-00144f67d031.html.

Grandjean, P. and P.J. Landrigan. 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368: 2167-2178.

Grandjean, P. and P.J. Landrigan. 2014. Neurobehavioral effects of developmental toxicity. The Lancet 13: 330-338.

Hazardous Substances Data Bank (HSDB). 2006. Entry for zinc oxide. United States National Library of Medicine. Available at: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

Ketcheson, M.R., G.P. Barron, and D.H. Cox. 1969. Relationship of maternal dietary zinc during gestation and lactation to development and zinc, iron, and copper content of the postnatal rat. J. Nutr. 98:303-311 (as cited in ESIS 2008).

Klimisch, H.J., B. Hildebrand, and K.O. Freisberg. 1982. Acute inhalation toxicity study (LC_{50}, 4 hours, rat) with zinc oxide containing manganese II. BASF Aktiengesellschaft, Abteilung Toxikologie, Ludwigshafen (as cited in ESIS 2008).

Kozik, M.B., L. Maziarz, and A. Godlewski. 1980. Morphological and histochemical changes occurring in the brain of rats fed large doses of zinc oxide. Folia Histochem. Cytochem. 18:201-206 (as cited in ESIS 2008).

Kozik, M.B., G. Gramza, and M. Pietrzak. 1981. Neurosecretion of the hypothalamo-hypophyseal system after intragastric administration of zinc oxide. Folia Histochem. Cytochem. 19:115-122 (as cited in ESIS 2008).

Lam, H.F., M.W. Conner, A.E. Rogers, S. Fitzgerald, and M.O. Amdur. 1985. Functional morphologic changes in the lungs of guinea pigs exposed to freshly generated ultra-fine zinc oxide. Toxicol. Appl. Pharmacol. 78:29-38 (as cited in ESIS 2008).

Lam, H.F., L.C. Chen, D. Ainsworth, S. Peoples, and M.O. Amdur. 1988. Pulmonary function of guinea pigs exposed to freshly generated ultra-fine zinc oxide with and without spike concentrations. Am. Ind. Hyg. Assoc. J. 49:333-341 (as cited in ESIS 2008).

Leitzmann, M.F., M.J. Stamper, K. Wu, G.A. Colditz, W.C. Willett, and E.L. Giovannucci. 2003. Zinc supplement use and risk of prostate cancer. J. Natl. Cancer Inst. 95:1004-1007 (as cited in ESIS 2008).

LISEC. 1997. Transformation/dissolution of metals and sparingly soluble metal compounds in aqueous media, "Zinc oxide Powers", final report NR BO-016 LISEC, Genk, Belgium.

Logue, J.N., M.D. Koontz, and M.A.W. Hattwick. 1982. A historical prospective mortality study of workers in copper and zinc refineries. J. Occup. Med. 24:398-408 (as cited in ESIS 2008).

Loser, E. 1972. Acute toxicity of anorganic pigments. Bayer Institut fur Toxikologie, Wuppertal-Elberfeld. [in German] (as cited in ESIS 2008).

Loser, E. 1977. Acute oral toxicity and skin and eye irritation studies. Bayer Institut fur Toxikologie, Wuppertal-Elberfeld. [in German] (as cited in ESIS 2008).

Malten, K.E. and J.P. Kuiper. 1974. Allergie cutanee de contact dans 100 ca d'ulceres varieux. Phlebologie. 27:417-420. [in Frenc] (as cited in ESIS 2008).

Neuberger, J.S. and J.G. Hollowell. 1982. Lung cancer excess in an abandoned lead-zinc mining and smelting area. Sci. Total Environ. 25:287-294 (as cited in ESIS 2008).

Pharos. 2014. Pharos Chemical and Material Library Entry for Zinc Oxide (CAS #1314-13-2). Available at: http://www.pharosproject.net/material/.

Schlicker, S.A. and D.H. Cox. 1968. Maternal dietary zinc, and development and zinc, iron, and copper content of the rat fetus. J. Nutr. 95:287-294 (as cited in ESIS 2008).

Shumskaya, N.I., V.V. Mel'nikova, V.N. Zhilenko, and L.I. Berezhnova. 1986. Hygenic assessment of zinc ions in rubber extracts in contact with food products. Gig. Sanit. 4:89-90 [in Russian] (as cited in ESIS 2008).

Smith, B.L. and P.P. Embling. 1993. Sequential changes in the development of the pancreatic lesion of zinc toxicosis in sheep. Vet. Pathol. 30:242-247.

Söderberg, T.A., T. Elmros, R. Gref, and G. Hallmans. 1990. Inhibitory effect of zinc oxide on contact allergy due to colophony. Contact Dermatitis. 23:346-351 (as cited in ESIS 2008).

Straube, E.F., N.H Schuster, and A.J. Sinclair. 1980. Zinc toxicity in the ferret. J. Comp. Pathol. 90:355-361 (as cited in ESIS 2008).

Thijssen, J. 1978. Eye irritation study with zinc oxide. Bayer Institut fur Toxikologie, Wuppertal-Elberfied. [in German] (as cited in ESIS 2008).

ToxServices. 2013. SOP 1.69: GreenScreen® Hazard Assessments. Dated: August 17, 2013.

United Nations (UN). 2013. Globally Harmonized System of Classification and Labeling of Chemicals (GHS). Fifth Revised Edition. ST/SG/AC/10/30/Rev.5. Available at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev05/05files_e.html.

United States Department of Transportation (U.S. DOT). 2008a. Chemicals Listed with Classification. 49 CFR § 172.101. Available at: http://www.gpo.gov/fdsys/pkg/CFR-2008-title49-vol2/pdf/CFR-2008-title49-vol2-sec172-101.pdf.

United States Department of Transportation (U.S. DOT). 2008b. Classification Criteria. 49 CFR § 173. Available at: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title49/49cfr173_main_02.tpl.

Van Huygevoort, A.H.B.M. 1999a1. Assessment of Contact Hypersensitivity to Zinc Oxide in the Albino Guinea Pig (Maximisation-Test). Project 254339. NOTOX B.V., 's-Hertogenbosch, The Netherlands (as cited in ESIS 2008).

Van Huygevoort, A.H.B.M. 1999a2. Assessment of Contact Hypersensitivity to Zinc Oxide in the Albino Guinea Pig (Maximisation-Test). (An extension of NOTOX Project 254339). Project 261214. NOTOX B.V., 's-Hertogenbosch, The Netherlands (as cited in ESIS 2008).

Van Huygevoort, A.H.B.M. 1999b. Acute Eye Irritation/Corrosion Study with Zinc Oxide in the Rabbit. Project 254352. NOTOX B.V., 's-Hertogenbosch, The Netherlands (as cited in ESIS 2008).

Van Ginneken, I. 1994a. The Effect of Zinc Oxide on the Growth of the Unicellular Green Alga Selenastrum capricornutum. Report No. AASc/0022 (year of test: 1993/1994). Janssen Pharmaceutica N.V., Beerse, Belgium (Sponsor: International Lead and Zinc Research Association Inc. (ILZRON), North Carolina, USA) (as cited in ESIS 2008).

Van Ginneken, I. 1994b. The Acute Toxicity of Zinc Oxide in the Waterflea *Daphnia magna*. Report No. ADK6/0034 (year of test: 1994). Janssen Pharmaceutica N.V., Beerse, Belgium (Sponsor: International Lead and Zinc Research Associated Inc. (ILZRO), North Carolina, U.S.A) (as cited in ESIS 2008).

Van Woensel, M. 1994. The Acute Toxicity of zinc Oxide in the zebrafish (*Brachidanio rerio*). Report No. AFBr/0025 (year of test: 1993). Janssen Pharmaceutica N.V., Beerse, Belgium (Sponsor: International Lead and Zinc Research Association Inc. (ILZRO), North Carolina, U.S.A.) (as cited in ESIS 2008).

Walsh, C.T., H.H. Sandstead, A.S. Prasad, P.M. Newberne, and P.J. Fraker. 1994. Zinc: Health effects and research priorities for the 1990s. Environ. Health Perspect. 102:5-46 (as cited in ESIS 2008).

World Health Organization (WHO). 1996. Zinc. In: Trace Elements in Human Nutrition and Health. WHO, Geneva, Chapter 5 (as cited in ESIS 2008).

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

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

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Zinc Oxide (CAS #1314-13-2)

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
Yes	Zinc Oxide	1314-13-2	*L*	M	L	L	DG	L	L	H	DG	DG	L	*H*	L	L	vH	vH	vH	DG	L	L

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Zinc Oxide	1

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Zinc Oxide	1

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

Table 5: Data Gap Assessment Table

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

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

APPENDIX C: Pharos Output for Zinc Oxide (CAS #1314-13-2)

ZINC OXIDE

CAS RN: 1314-13-2

Detailed Direct Hazard Listings — Quickscreen

RESPIRATORY	AOEC - Asthmagens (AOEC) Asthmagen (ARs) - sensitizer-induced - inhalable forms only - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only - HPD
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Specific target organs/systemic toxicity following repeated exposure - Category 1 - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Specific target organs/systemic toxicity following single exposure - Category 1 - GreenScreen Benchmark Unspecified (LT-U)
ACUTE AQUATIC	EC - CLP/GHS Hazard Statements (EU H-Statements) H400 - Aquatic Acute 1 - Very toxic to aquatic life - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only - HPD
ACUTE AQUATIC	EC - Risk Phrases (EU R-Phrases) R50: Very toxic to aquatic organisms. - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only - HPD
ACUTE AQUATIC	New Zealand HSNO/GHS (GHS-New Zealand) 9.1A (algal) - Very ecotoxic in the aquatic environment - GreenScreen Benchmark Unspecified (LT-U)
ACUTE AQUATIC	New Zealand HSNO/GHS (GHS-New Zealand) 9.1A (crustacean) - Very ecotoxic in the aquatic environment - GreenScreen Benchmark Unspecified (LT-U)
ACUTE AQUATIC	New Zealand HSNO/GHS (GHS-New Zealand) 9.1A (fish) - Very ecotoxic in the aquatic environment - GreenScreen Benchmark Unspecified (LT-U)
ACUTE AQUATIC	Japan METI/MOE - GHS Classifications (GHS-Japan) Hazardous to the aquatic environment (acute) - Category 1 - GreenScreen Benchmark Unspecified (LT-U)
CHRON AQUATIC	EC - CLP/GHS Hazard Statements (EU H-Statements) H410 - Aquatic Chronic 1 - Very toxic to aquatic life with long lasting effects - GreenScreen Benchmark Possible 1 (LT-P1) - occupational hazard only - HPD
CHRON AQUATIC	Japan METI/MOE - GHS Classifications (GHS-Japan) Hazardous to the aquatic environment (chronic) - Category 1 - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	US EPA - OPP - Registered Pesticides (EPA-FIFRA) FIFRA Registered Pesticide - Not included in GreenScreen
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Acute toxicity (inhalation: dust, mist) - Category 5 - GreenScreen Benchmark Unspecified (LT-U)

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

CHRON AQUATIC	EC - Risk Phrases (EU R-Phrases) R53: May cause long-term adverse effects in the aquatic environment. - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only
TERRESTRIAL	New Zealand HSNO/GHS (GHS-New Zealand) 9.3C - Harmful to terrestrial vertebrates - Not included in GreenScreen
PBT	Environment Canada - Domestic Substances List (DSL) DSL substances that are Persistent - GreenScreen Benchmark Unspecified (LT-U)
RESTRICTED LIST	German FEA - Substances Hazardous to Waters (VwVwS) Class 2 Hazard to Waters - GreenScreen Benchmark Possible 1 (LT-P1) - HPD
RESTRICTED LIST	Environment Canada - Domestic Substances List (DSL) Inherently Toxic in the Environment - GreenScreen Benchmark Unspecified (LT-U)

Compound Group Hazard Listings

RESPIRATORY	AOEC - Asthmagens (AOEC) Asthmagen (ARs) - sensitizer-induced - inhalable forms only - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only - HPD
CANCER	US EPA - IRIS Carcinogens (EPA-C) (2005) Inadequate information to assess carcinogenic potential - Not included in GreenScreen
CANCER	US EPA - IRIS Carcinogens (EPA-C) (1999) Data are inadequate for an assessment of human carcinogenic potential - Not included in GreenScreen
CANCER	US EPA - IRIS Carcinogens (EPA-C) (1986) Group D - Not classifiable as to human carcinogenicity - Not included in GreenScreen

Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

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/

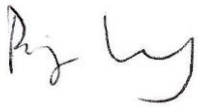
Template Copyright 2014 © Clean Production Action
Content Copyright 2014 © ToxServices

Licensed GreenScreen® Profilers

Zinc Oxide GreenScreen® Evaluation Prepared by:

Zach Guerrette, Ph.D.
Toxicologist
ToxServices LLC

Zinc Oxide GreenScreen® Evaluation QC'd by:



Bingxuan Wang, Ph.D.
Toxicologist
ToxServices LLC