GreenScreen® Chemical Assessment

Zircon (14940-68-2)

Method Version: GreenScreen® for Safer Chemicals v1.4

Assessment Details:

Assessment Type:	Certified
Assessment Prepared By:	WAP Sustainability Consulting, LLC (Eric Rosenblum Ph.D. DABT Donald K. Ward, NSF International
Assessment Prepared For:	Tile Council of North America (TCNA)
Date Assessment Completed:	January 31st, 2021
Assessment Expiration Date:	January 31st, 2026
Assessor Type:	Licensed GreenScreen® Profiler

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GREENSCREEN BENCHMARK™ SUMMARY:

This chemical assessment report includes a GreenScreen Benchmark™ score and results for Zircon (14940-68-2) only. No marketing claims can be made without licensing through Clean Production Action.

GreenScreen Benchmark Score: BM-2

Zircon (14940-68-2) was assigned a was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") based on the moderate hazard for a human group II* repeat dose systemic toxicity, and the combination of skin sensitization and respiratory sensitization and very high for persistence. This corresponds to GreenScreen® benchmark classification 2b in CPA 2018. Data gaps (DG) exist for endocrine activity, neurotoxicity, and chronic aquatic toxicity. As outlined in CPA (2018) Annex 5 (Conduct a Data Gap Analysis to assign a final Benchmark score), Zircon meets the requirements for a GreenScreen® Benchmark Score of 2. In a worst-case scenario, if Zircon were assigned a High score for endocrine activity or a very high score for chronic aquatic toxicity it would continue to categorized as a Benchmark 1 Chemical.

HAZARD CLASSIFICATION SUMMARY

Table 1. GreenScreen Hazard Summary Table:

GreenScreen Hazard Summary Table for Zircon – BM-2																			
Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
Carcinogenicity	Genotoxicity/Mutagenicity	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
						single	repeat*	single	repeat*	*	*								
L	*L*	**L**	*L*	DG	**L**	*L*	*M*	DG	*L*	*M*	*M*	**L**	**L**	**L**	DG	vH	vL	**L**	*L*

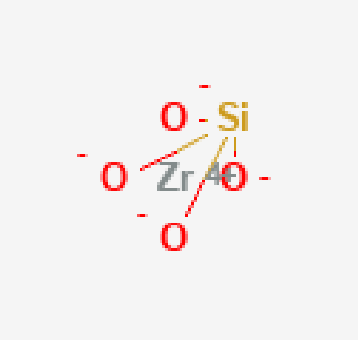
Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in italics reflect lower confidence in the hazard classification while hazard levels in BOLD font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that Group II Human Health endpoints 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. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints.

SCOPE OF ASSESSMENT

Zircon (14940-68-2) only:

Also Called: Zirconium(IV) silicate; Zirconite; Zircon; Zircon (Zr(SiO4)); Everest HPC; Hyacinth; Zircosil; Excelopax; Micro-Pax (PubChem 2019)

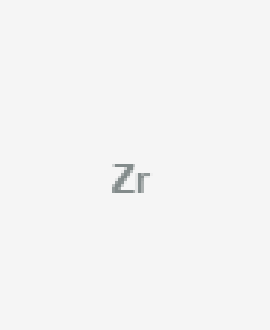
Chemical Structure:



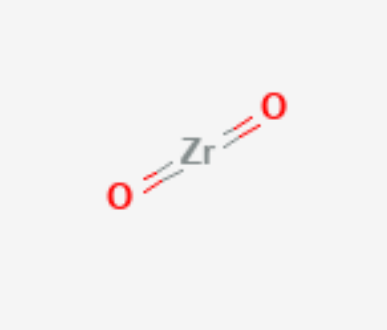
67

Suitable analogs or moieties of chemicals used in this assessment (CASRN(s)):

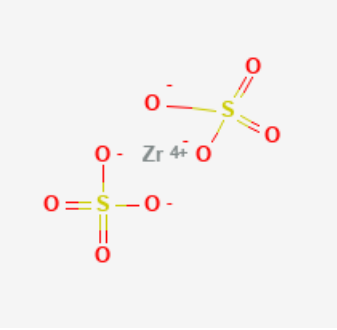
Chemical Structure(s) of suitable analog(s) and/or moieties:



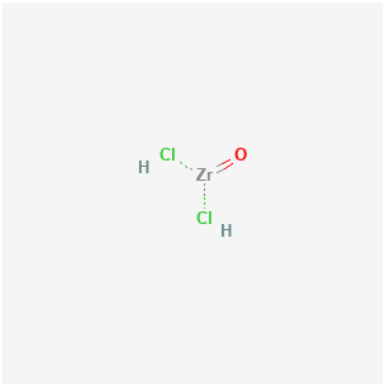
Zirconium
(CAS# 7440-67-7)



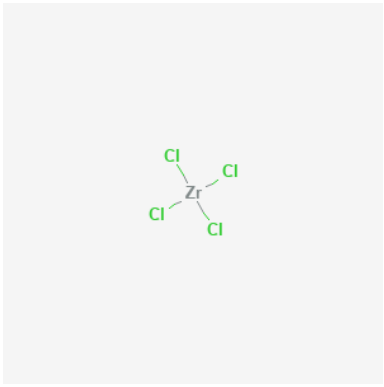
Zirconium Dioxide
(CAS# 1314-23-4)



Zirconium Sulfate
(CAS# 14644-61-2)



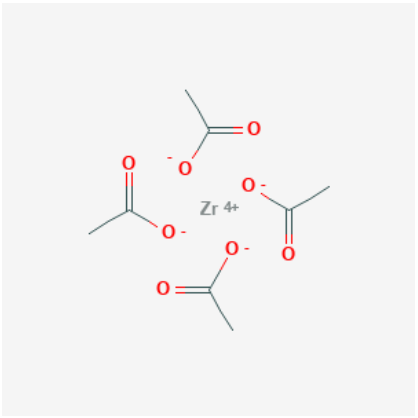
Zirconium Oxychloride
(CAS# 7699-43-6)



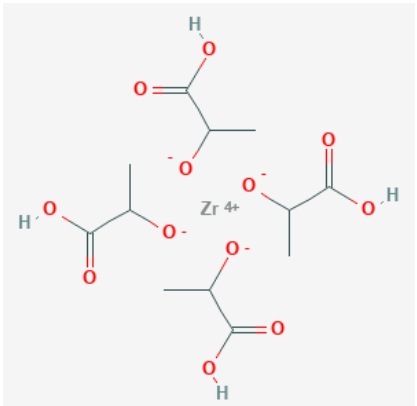
Zirconium Tetrachloride
(CAS# 10026-11-6)

N/A

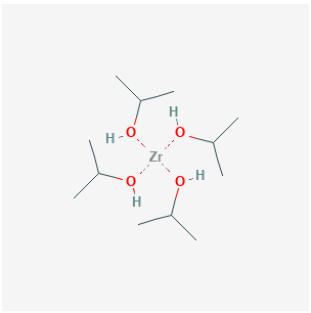
Zirconyl Chloride
(CAS# 13520-92-8)

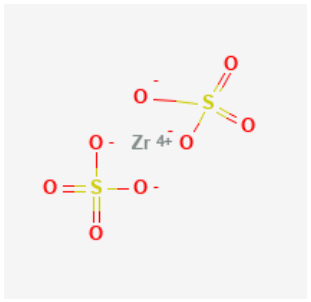


Zirconium Acetate
(CAS# 4229-34-9)



Zirconium Lactate
(CAS# 60676-90-6)





Zirconium
Tetraisopropoxide
(CAS# 2171-98-4)

For Inorganic Chemicals and relevant particulate organics (if not relevant, list NA)

Define Properties:

- Particle size (e.g., silica of respirable size): N/A
- Structure (e.g., amorphous vs. crystalline): N/A
- Mobility (e.g., water solubility, volatility): N/A
- Bioavailability: N/A

Identify potential applications/functional uses of the chemical:

- Used as an input in industrial refractory products
- Used in synthetic dye and pigment manufacturing
- Used to treat chronic kidney disease in patients with hyperkalemia
- Used as a whitening agent in some brands of toothpaste (PubChem 2019)

Table 2. Environmental Transformation Products Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen List Translator Score or GreenScreen Benchmark Score
		None				

HAZARD CLASSIFICATION SUMMARY

GROUP I HUMAN HEALTH EFFECTS (GROUP I HUMAN)

Carcinogenicity (C): L

Zircon was assigned a hazard classification level of Low for carcinogenicity based on no increased tumor incidences in orally exposed rats and mice. The hazard conclusion is based on chronic exposures using the high quality analog zirconium sulfate. The studies however where not specific to carcinogenicity and were of low concentration and therefore the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

Inchem 1997

There is no evidence regarding the carcinogenicity of zirconium in humans (REPROTEXT, 1997). However, there is an increased risk of gastric cancer following severe mucosal damage after corrosive ingestion.

US EPA 2012

The test drinking water containing 5 ppm zirconium sulfate was provided to 56 male and 58 female Long-Evans rats (the offspring of pregnant Long-Evans rats purchased for the study) from weaning to natural death (a maximum of 1347 days). An equal number of rats served as controls. The experimental rats also were fed a diet containing 2.66 µg/g zirconium (thus zirconium was in the food and water). Using time-weighted average body weight and default water consumption in Long-Evans rats, the dose of 5 ppm zirconium sulfate in drinking water was converted to 0.60 mg/kg-day for males (0.057 L/day × 5 mg/L/0.472 kg = 0.60 mg/kg-day) and 0.67 mg/kg-day for females. The dose of 2.66 mg/kg zirconium in feed was converted (also using time-weighted average body weights and food consumption) to 0.19 mg/kg-day for males and 0.22 mg/kg-day for females. These doses were also adjusted for the fraction of zirconium sulfate that is zirconium. Actual food consumption data was not shown. Data related to the differential bioavailability between drinking water and dietary zirconium was not available. Because the rats ingested both drinking water and feed, the doses were summed for a total equivalent dose (TED) of 0.79 mg/kg-day in males and 0.89 mg/kg-day in females. The rats were weighed weekly from weaning until 6 weeks of age, and then monthly. As the rats died, they were weighed and dissected to identify grossly visible tumors and other lesions in the heart, lung, kidney, liver, and spleen. During the study, an epidemic of virulent pneumonia struck the rat colony, and killed 19 males and 12 females (controls) and 5 males and 4 females (zirconium-exposed) in a 3-week period. According to the authors, these animals were removed from the series and survival numbers were corrected for that time period. Zirconium did not consistently affect the growth rates of the

rats (Schroeder et al., 1970). Males administered zirconium were significantly heavier than controls at 30, 150, and 180 days and lighter than controls at 360 and 540 days, while females were significantly heavier than controls at 30, 150, and 540 days. There was no significant difference in survival of the zirconium-administered rats compared to controls. Females administered zirconium showed significantly higher fasting serum glucose levels than controls and males administered zirconium had significantly higher cholesterol levels. Glycosuria (glucose in the urine) was noted in 23% of the controls and in 52% of 56 rats (study does not say whether in males or females) administered zirconium (significantly different by chi-square analysis at $p < 0.01$). No differences were observed in the mean body weights of the rats administered zirconium compared to controls, while the hearts of males administered zirconium weighed 14.6% less than controls, the hearts of females weighed 7.4% more. No significant increase was reported in the number of tumors in rats administered zirconium compared to the controls (Schroeder et al., 1970; Kanisawa and Schroeder, 1969). The study authors did not identify a NOAEL or LOAEL from this study. A LOAEL of 0.79 mg/kg-day (males) and 0.89 mg/kg-day (females) is identified based on significantly increased incidence of glycosuria, higher fasting glucose levels in females and higher cholesterol levels in males. A NOAEL is not determined because only one dose (in addition to controls) was tested.

Schroeder et al. (1968) administered one of four trace elements (i.e., zirconium, niobium, antimony, or fluorine) to different groups of mice in both drinking water and feed. The test drinking water containing 5 ppm zirconium sulfate was administered to 54 male and 54 female Charles River CD-1 mice (born from random-bred pregnant females) over the lifetime (from weaning until death) of the mice. An equal number of mice served as controls. The experimental mice also were fed a diet reported to contain 2.66 µg/g zirconium. Using standard assumptions for body weight and water consumption in mice, 5 ppm zirconium sulfate in drinking water was calculated to be equivalent to 1.23 mg/kg-day for males and 1.26 mg/kg-day for females. The dose of 2.66 µg/g zirconium in feed was calculated, also using standard assumptions, to represent 0.48 mg/kg-day for males and 0.49 mg/kg-day for females. Because the experimental mice ingested both drinking water and feed, the doses were summed for a total equivalent dose of 1.71 mg/kg-day in males and 1.75 mg/kg-day in females. This study was conducted before GLP guidance was developed by EPA in 1983. The mice were weighed weekly for 8 weeks and then at monthly intervals. The dead animals were dissected, grossly visible tumors and other lesions were noted, and abnormal tissues were sectioned. For the elemental analysis, hearts, lungs, kidneys, livers, and spleens were pooled in samples of 5 to 15 from the various age groups and analyzed. Significantly decreased body weights were noted in male mice at 90 and 540 days and female mice at 540 days. Schroeder et al. (1968) reported a significant increase in body weights in females at 60 days. The study authors noted that administration of zirconium was associated with shortened life spans by 27 to 47 days in males and 67 to 85 days in females, at 5 out of 6 intervals, and that the difference in females was statistically significant. As in Schroeder et al. (1970), the study continued until natural death of each animal. Schroeder et al. (1968; Kanisawa and Schroeder, 1969) noted a significant change in body weights of males at 540 days. No significant increase was noted in the number of tumors compared with control mice. The study authors did not identify a NOAEL or LOAEL from this study. A LOAEL is identified

by EPA because the decrease in body weight was greater than 10%. The LOAEL in male mice is 1.71 mg/kg-day while the FEL (based on significantly increased mortality) in female mice is 1.75 mg/kg-day.

MAK 2007

The liver tumour-inducing effect of neutron irradiation was tested in 240 female Wistar rats. Pretreatment with zirconium oxide (Zirconotrast) in a dose of 120 µl i.v. did not result in an increase in the tumour incidence. The number of tumours in a group treated only with zirconium was not different from that in the untreated control group (Spiethoff et al. 1992).

Estimated Data- None

Mutagenicity/Genotoxicity (M): L

Zircon was assigned a hazard classification level of Low for mutagenicity/genotoxicity based on negative results for zirconium dioxide and an insoluble form of zirconium. The studies summarized that report a "positive" or "ambiguous result are for Zirconium oxychloride. This is a water-soluble compound whereas zircon is insoluble. The pH is very high, 20% solution with pH <1. In addition, there are problems with these studies that make them unacceptable for use in classifying mutagenicity/genotoxicity for zirconium silicate. Due to the discounting of week mutagenicity/genotoxicity effects reported for soluble zirconium compounds, the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

A chromosome aberration test was performed according to OECD guideline 473. Cultured peripheral human lymphocytes were exposed for 3 hours to 10, 33 and 100 µg zirconium dioxide/mL culture medium with and without S9-mix (dose range finding test/first cytogenetic assay); at 24 and 48 h continuous exposure time blood cultures were treated with 1, 3, 10, 33, 100, 333 and 1000 µg zirconium dioxide/mL culture medium without S9-mix. A second cytogenicity test was performed as follows: without S9-mix: 10, 33 and 100 µg/mL culture medium (24 and 48h exposure time, 24h and 48h fixation time); with S9-mix: 10, 33 and 100 µg/mL culture medium (3h exposure time, 48h fixation time). Vehicle and positive control substances were tested simultaneously and considered valid. Zirconium dioxide tested negative with and without metabolic activation. No cytotoxicity was observed.

A mouse lymphoma test was performed according to OECD guideline 476. Mouse lymphoma L5178Y cells were exposed to 0.03, 0.1, 1, 3, 10, 33 and 100 µg/mL zirconium dioxide with and without metabolic activation. In a first experiment, cell cultures were exposed for 3 hours to zirconium dioxide in exposure medium in the absence and presence of S9-mix. In a second experiment, cell cultures were exposed to Zirconium dioxide in exposure medium for 24 hours in the absence of S9-mix and for 3 hours in the presence of

S9-mix. Zirconium dioxide tested negative in both experiments with and without metabolic activation. No cytotoxicity was observed and positive and vehicle controls were considered valid.

ECHA 2019b

Laus (2008) performed a bacterial reverse mutation study according to OECD guideline 471 and EU method B13/14. This study was used as key study for this endpoint. Salmonella typhimurium strains TA97a, TA98, TA100, TA102 and TA1535 were exposed to 50 to 4998 µg/plate with and without metabolic activation in 2 independent experiments. Vehicle and positive controls were valid. Zirconium dioxide did not induce mutation with and without metabolic activation and no cytotoxicity was observed.

Braz et al. (2008) performed a Comet assay according to the following guideline: Single Cell Gel/Comet Assay: Guidelines for in vitro and in vivo genetic toxicology testing. Human lymphocytes were exposed to 1, 100 and 1000 µg/L zirconium dioxide without metabolic activation. Vehicle and positive control were tested simultaneously and considered valid. Zirconium dioxide tested negative in human lymphocytes without metabolic activation. No cytotoxicity was observed.

US EPA 2012

Zirconium oxychloride was negative when tested in Salmonella typhimurium TA97, TA98, TA1535, TA1537, and TA100, with and without rat and hamster liver S-9 metabolic activation (Mortelmans et al., 1986).

Zirconium tetrachloride also was negative in Salmonella typhimurium TA98, TA100, TA102, TA1537, and TA2637, without metabolic activation. When it was combined with 9-amino-acridine, it was positive for mutagenicity (Ogawa et al., 1987).

Ghosh et al. (1990, 1991) administered oral doses of zirconium oxychloride at 225, 750, or 2250 mg/kg in male mice and 220, 734, or 2200 mg/kg in female mice to study the effects on bone marrow chromosomes. No increase in mitotic division frequency or in chromosomal aberrations and breaks per cell were noted at the lowest dose, while the division frequency and the number of chromosomal aberrations was increased at the higher doses, in both males and females, as compared to controls. The frequency of chromosomal aberrations was slightly higher in females than in males, but was not statistically significant. The study authors concluded that zirconium oxychloride was potentially clastogenic, the effect being directly proportional to the dose used (Ghosh et al., 1991).

- Note: The results of the above study were not included in the hazard characterization for the following reasons:
    1. Only total chromosomal abnormalities are presented, which include structural chromosome aberrations and spindle disturbances, the latter being polyploidy. Polyploidy is a disturbance in mitotic processes and cell cycle progression. An increase in polypoloidy may indicate that a chemical has the potential to induce numerical aberrations. However, polyploidy is not related to clastogenicity, and should therefore be

included separately from the structural chromosome aberrations. As this study does not distinguish between the two, a conclusion on clastogenicity cannot be drawn.

2. An aqueous solution of zirconium oxychloride is given to the mice. It is known from water solubility/hydrolysis experiments that the substance in water will cause a drop in pH by the release of H+ ions. Apart from the fact that the mice have probably been dosed corrosive solutions, there is some evidence that H+ ions can cause chromosomal damage (refer to IARC monograph 54-8 (1992; p. 203) on hydrochloric acid). It can thus not be ruled out that the observed effects in the bone marrow have been caused by the low pH after dissolving the test substance in water.
3. 3) No data were presented on whether the substance has actually reached the bone marrow and whether this test is thus biologically relevant. Some evidence exists that zirconium oxychloride is poorly absorbed by mice after oral administration of an aqueous solution of 1500 mg/kg (Delongeas et al., 1983, J. Pharmacol. 14(4) 437-447). It reaches the blood and after 6 h a maximal blood concentration of 2.9 mg Zr/L (i.e. about 10 mg zirconium oxychloride per liter) was reached. In a similar but more extensive study in rats given aqueous solutions of 3000 mg zirconium oxychloride/kg, the maximal blood concentration was reached after 6 hours being about 0.3 mg Zr/L (i.e. about 1 mg zirconium oxychloride per liter). Using metabolic cages it was shown that within 24 hours 90-98% of the given dose was excreted via feces and minimal amounts via urine. This shows that the substance is hardly absorbed as it is excreted via feces. In the same study of Delongeas et al. (1983), tissue distribution reveals that the small absorbed fraction is distributed and fixed in the ovaries, liver and lung, and to a lesser degree in bone and CNS. All together this raises the question whether the substance in the current study has reached the bone marrow to a sufficient extent in order to induce effects.

In a study on human peripheral blood lymphocytes (Ghosh et al., 1992), aqueous solutions of zirconium oxychloride (20 µg/mL) were added to cultures from male and female volunteers ranging in age from newborns to 60 years old. The endpoints screened were chromosome and chromatid breaks, dicentrics, and rearrangements. The frequencies of chromosomal aberrations and sister chromatid exchanges were compared between the different age groups, in both males and females. The frequency of sister chromatid exchanges increased with the age of the female volunteers, but not the males.

- Note The results of the above study were not included in the hazard characterization for the following reasons:

4. In ECHA dossier for Zirconium dichloride oxide this study was not conducted similar to OECD 479, but the reliability is 3, and disregarded due to major methodological deficiencies.

Estimated Data- None

Reproductive Toxicity (R): L

Zircon was assigned a hazard classification level of Low for reproductive toxicity based on no reproductive effects reported following repeat dose inhalation and oral exposures to high quality analogs. While results from the inhalation study are poorly reported the oral study was performed according to OECD guideline 422 and under GLP principles. Therefore, the hazard score is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019b

The results of a 60-day repeated dose toxicity study after inhalation exposure to zirconium dioxide (Spiegl et al., 1956) showed no abnormal findings after histopathological evaluation of animal testes. This supports the assumption that exposure to zirconium dioxide does not affect at least the male reproductive organs. Specifically, Inhalation of 15.4 mg/m3 zirconium dioxide for 60 days produced no significant changes in mortality rate, growth, biochemistry, hematology values or histopathology. The NOAEC was deemed to be greater than (or equal to) 15.4 mg/m3.

The systemic toxic effects of the read across substance zirconium acetate after repeated oral dosing, as well as any toxic effects on reproduction and development, were investigated in Sprague Dawley rats up to early lactation (day 4 post partum) by Rossiello (2013). The study was performed according to OECD guideline 422 and under GLP principles. Three groups of 10 males and 10 females each received the test item, by oral gavage, at 100, 300 and 1000 mg anhydrous zirconium acetate/kg bw/day. A similar constituted control group received the vehicle alone during the treatment period. The overall dosing period was 32 days for males, which included 2 weeks before pairing and continuously thereafter up to the day before necropsy, and up to 50 days for females, including 2 weeks before pairing and thereafter during pairing, gestation and lactation periods until day 3 post partum. The parental animals were followed for daily clinical signs, weekly body weight, food consumption, neurotoxicity assessment, oestrous cycle, mating performance, clinical pathology evaluation including haematology and clinical chemistry, and offspring delivery. A detailed macroscopic examination, determination of organ weights, and histopathological examination, including the spermatogenic cycle, were performed. Pups were also checked for sex, body weight, clinical signs and macroscopic observations. No mortality occurred in the study. No treatment related findings were observed either during the in vivo phase or at post mortem examination of parent animals. Microscopically, a treatment related finding was seen in males receiving 300 and 1000 mg zirconium acetate/kg bw/day consisting of minimal focal vacuolation of squamous epithelium (limiting ridge) of the non-glandular region of the stomach. This change may be attributed to a local irritant effect of the compound

administered by oral gavage and since humans do not have a forestomach or structural analogue to the forestomach, this finding is not considered of toxicological relevance. In addition, no abnormalities were found during the evaluation of the spermatogenic cycle. No treatment related effects were observed in the number of oestrous cycle, pre-coital intervals, copulatory and fertility indices between treated and control groups. No effects were noted on reproduction at any dose. On the basis of the results obtained in this study, the NOAEL for reproduction/developmental toxicity was considered to be >= 1000 mg/kg bw/day (expressed as anhydrous zirconium acetate), i.e., the highest dose tested.

Estimated Data- None

Developmental Toxicity incl. Developmental Neurotoxicity (D): L

Zircon was assigned a hazard classification level of Low for developmental toxicity based on based on no significant differences observed in the number of implantations, corpora lutea, total litter size, pre-implantation loss, pre-birth loss and gestation length reported following repeat dose oral exposures to zirconium acetate. The oral study was performed according to OECD guideline 422 and under GLP principles using a high-quality analog. However, the 422 study does not evaluate skeletal and soft tissue alterations. Therefore, the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019b

There is sufficient evidence indicating that zirconium is barely absorbed neither from the gastrointestinal tract nor after exposure via inhalation or contact with the skin and thus, the probability to reach the reproductive organs and the unborn offspring is considered to be extremely low.

The systemic toxic effects of the read across substance zirconium acetate after repeated oral dosing, as well as any toxic effects on reproduction and development, were investigated in Sprague Dawley rats up to early lactation (day 4 post partum) by Rossiello (2013). The study was performed according to OECD guideline 422 and under GLP principles. Three groups of 10 males and 10 females each received the test item, by oral gavage, at 100, 300 and 1000 mg anhydrous zirconium acetate/kg bw/day. A similar constituted control group received the vehicle alone during the treatment period. The overall dosing period was 32 days for males, which included 2 weeks before pairing and continuously thereafter up to the day before necropsy, and up to 50 days for females, including 2 weeks before pairing and thereafter during pairing, gestation and lactation periods until day 3 post partum. The parental animals were followed for daily clinical signs, weekly body weight, food consumption, neurotoxicity assessment, oestrous cycle, mating performance, clinical pathology evaluation including haematology and clinical chemistry, and offspring delivery. A detailed macroscopic examination, determination of organ weights, and histopathological examination, including

the spermatogenic cycle, were performed. Pups were also checked for sex, body weight, clinical signs and macroscopic observations. No mortality occurred in the study. No treatment related findings were observed either during the in vivo phase or at post mortem examination of parent animals. Microscopically, a treatment related finding was seen in males receiving 300 and 1000 mg zirconium acetate/kg bw/day consisting of minimal focal vacuolation of squamous epithelium (limiting ridge) of the non-glandular region of the stomach. This change may be attributed to a local irritant effect of the compound administered by oral gavage and since humans do not have a forestomach or structural analogue to the forestomach, this finding is not considered of toxicological relevance. No significant differences were observed in the number of implantations, corpora lutea, total litter size, pre-implantation loss, pre-birth loss and gestation length between control and treated groups. No effects were noted on development at any dose. On the basis of the results obtained in this study, the NOAEL for reproduction/developmental toxicity was considered to be >= 1000 mg/kg bw/day (expressed as anhydrous zirconium acetate), i.e., the highest dose tested.

Estimated Data- None

Endocrine Activity (E): DG

Zircon was assigned a hazard classification level of Data Gap for endocrine activity based on based on the lack of available studies that directly address endocrine activity following exposures to the compound. No analog data was available to fill the data gap.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data- None

Estimated Data- None

GROUP II AND II* HUMAN HEALTH EFFECTS (GROUP II AND II* HUMAN)

Note: Group II and Group II* endpoints are distinguished in the v1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT): L

Zircon was assigned a hazard classification level of Low for acute mammalian toxicity based on a reported oral LD50 of >200,000 mg/kg specific to zirconium silicate. Weight of evidence for other zirconium compounds suggest oral LD50s that are >2000 mg/kg. As study data specific to the compound of interest is available the toxicity values for zirconium chloride and barium zirconate, which fall into the moderate acute toxicity range, have been discounted. The hazard score is based on the compound of interest and supported by multiple other zirconium compounds and therefore is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

US EPA 2012

Stookey et al. (1967) administered doses ranging from 70 to 200 g/kg body weight zirconium silicate by oral intubation to 80 albino mice, with the purpose of determining the LD50 for zirconium silicate. A dosage of 200 g/kg of body weight resulted in a 37.5% mortality rate in the mice. Doses greater than 200 g/kg were not tested due to limitations of the mouse gastrointestinal tract, so the LD50 was not determined.

MAK 2012

Compound	Administration route	LD_{50}
zirconyl acetate	oral	4100
zirconium carbonate, basic	oral	> 10000
zirconium chloride	oral	1688
zirconyl chloride (zirconium oxychloride)	oral	3500
zirconium nitrate	oral	3200
zirconium sulfate	oral	3500
zirconium lactate	oral	> 10000
barium zirconate	oral	1980

ECHA 2019b

Acute toxicity: oral

One key study was identified (Klimisch 1). Acute toxicity of zirconium dioxide was determined via the acute class method (OECD Guideline 423 and EU Method B1 tris) in female Sprague-Dawley rats. The LD50 value was > 5000 mg/kg.

Acute toxicity: inhalation

One key study (Klimisch 1) was performed by WIL Research Laboratories. Acute inhalation toxicity was tested according to OPPTS Guideline 870.1300 and OECD Guideline 436. Zirconium dioxide was administered to 1 group of 3 male and 3 female Crl:CD(SD) albino rats via nose-only inhalation exposure as a dust aerosol at a concentration of 4.3 mg/L, which

was the maximum technically obtainable mean concentration, for 4 hours. The exposure atmosphere was characterized by a mean mass median aerodynamic diameter (± geometric standard deviation) of 2.0 µm ± 1.75 µm. As no mortality occurred during the study, the LC50 of zirconium dioxide was greater than 4.3 mg/L.

CIR 2019

Silica was reported to have an oral LD50 of > 40,000 mg/kg in rats and > 8000 mg/kg in mice.

The oral lethal dose of pyrogenic silica in humans is 15 g/kg.

Orally administered Aluminum Calcium Sodium Silicate had no adverse effects up to 800 mg/kg in mice.

The LD50 was > 5000 mg/kg for precipitated (hydrated) Silica and > 2000 mg/kg for silica gel on intact and abraded rabbit skin. Mild erythema was observed.

The acute inhalation of silica at 477 mg/m3 by rats resulted in restlessness, droopy eyelids, lethargy, and dyspnea during treatment. Clinical signs resolved quickly after treatment and necropsies were unremarkable.

In an inhalation study, the LC50 for 30% Potassium Silicate in rats was > 2.06 mg/l.

Estimated Data- None

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single): L

Zircon was assigned a hazard classification level of Low for single dose systemic toxicity/organ effects based on no clinical signs of significant systemic toxicity following oral exposures to high quality analogs at oral doses up to 2,000 mg/kg and inhalation exposures of 4.3 mg/L. The hazard score is based acute mammalian toxicity studies which are not specific to systemic toxicity and provide limited detail on systemic toxicity observations following exposure. Therefore, the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

Two groups, each of three female WISTAR Crl: WI(Han) rats, were treated with Zirconium by oral gavage administration at a dosage of 2000 mg/kg body weight. The animals were observed on delivery, on inclusion in the study and before administration for mortality/morbidity and other clinical signs. All animals were examined for clinical signs several times on the day of dosing and once daily until the end of the observation period. Their body weights were recorded on day 1 (prior to the administration) and on days 8 and 15. All animals were necropsied and examined macroscopically. Throughout the 14-day

observation period, all animals survived until the end of the study without showing any signs of toxicity.

The acute inhalation toxicity of zirconium dioxide was evaluated in a 4-hour, single-exposure study in rats. Zirconium dioxide was administered to 1 group of 3 male and 3 female Crl:CD(SD) albino rats via nose-only inhalation exposure as a dust aerosol at a concentration of 4.3 mg/L. The exposure atmosphere was characterized by a mean mass median aerodynamic diameter (± geometric standard deviation) of 2.0 µm ± 1.75 µm. Mortality, clinical observations, body weights, and body weight changes were evaluated over a 14-day post-exposure observation period. Necropsies were conducted on all animals. Mortality was 0/6 animals for the 4.3 mg/L group. There were no significant clinical observations immediately following exposure. Significant clinical observations for animals during the 14-day post-exposure observation period included decreased defecation and small feces. All animals were considered clinically normal by study day 3. All animals lost weight from study day 0 to 1. One male lost weight (9 grams) from study day 1 to 3. All animals surpassed their initial (study day 0) body weight by study day 14. There were no macroscopic findings for any animal at the scheduled necropsy.

ECHA 2019b

Well documented, scientifically sound GLP study performed according to OECD Guideline 423 and EU Method B.1 tris. However, 6 animals were dosed at once with zirconium dioxide rather than dosing 3 animals per step. No clinical signs related to the administration of the test substance were observed. The macroscopical examination of the animals at the end of the study did not reveal treatment-related changes.

No deaths occurred during either the preliminary test with the group of 20 adult male rats or the more extensive test with 50 younger adult male rats. All animals continued to grow at a normal rate and gross examination of the autopsied animals revealed nothing abnormal up to a dose of 10000 mg ZrO2/kg bw (calculated based on 20.9% ZrO2 in the test material HZC - hydrated zirconium carbonate).

Estimated Data- None

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*): M

Zircon was assigned a hazard classification level of Moderate for repeated dose systemic toxicity/organ effects based on mixed results reported following inhalation exposures to analog substances. In humans the weight of evidence suggests that inhalation exposures do not produce significant toxicological effects. However, some cases have reported pulmonary fibrosis after exposure to zirconium but results are equivocal due to exposure to other substances. Mixed results are also reported for animal inhalation studies. Inhalation studies report lung effects occurring in exposed animals at concentrations ≤ 0.02 mg/L which equates to a GreenScreen high score for the endpoint. This result however has been discounted as the exposure period (225-days) and the exposure duration (7-hours per day) exceed the standard 90-day, 6-hours per day used in guideline repeat dose toxicity studies. In addition, available 30-day and 60-day inhalation studies using zirconium oxide report no significant toxicological effect at the highest doses tested (75 mg/m3 and 11 mg/m3,

respectively). It is presumed based on the available evidence from studies in humans and experimental animals that zirconium substances have the potential to be harmful to human health following repeat inhalation exposure and fulfill the criteria of a GHS category 2 repeat dose systemic toxicant (equivalent to a GreenScreen Moderate). The available evidence does not support the classification of zirconium substances as a GHS category 1 repeat dose toxicant. For example, effects reported by Brown (1963) stated that the observed fibrogenic effect was minimal and general changes found in the lungs were due to a low a grade Irritant effect. The moderate classification for zircon is based on effects reported for forms or Zircon with particle sizes < 10 microns. Forms of Ziron > 10 microns would not be classified for this endpoint. Due to the mixed results reported in the available human and animal studies the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

US EPA 2012

Subchronic Studies Rats, guinea pigs, and dogs were exposed by inhalation to zirconium tetrachloride at 6 and 75 mg/m3 for 60 days (Seiler et al., 1988). Dogs showed slight decreases in hemoglobin and red blood cell counts and rats and guinea pigs demonstrated increased mortality (unspecified) at 6 mg/m3. Because equivocal effects were noted at the low dose but not the high dose, neither a NOAEL nor a LOAEL is identified.

In another study, guinea pigs exposed continuously to several steps in the zirconium reduction process for 2 to 6 months did not exhibit any pulmonary changes after a histological examination (Clayton and Clayton, 1981−1982). No further details were provided.

Zirconium tetrachloride inhaled by laboratory animals (unspecified) for 1 year at 3.5 mg/m3 showed no adverse effects (Bingham et al., 2001). No further details were provided in the secondary source (HSDB, 2006) for this study. A NOAEL or LOAEL could not be determined due to the lack of data available on this study

MAK 2012

In a group of 32 workers who produced zirconium-containing metal elements for the reactor industry and had been exposed for 1 to 17 years, no significant differences from a control group were found in respiratory complaints, lung roentgenograms or lung function ; in all the lung function tests the control persons had better lung function parameters than the exposed persons but the differences were not significant. The measured zirconium exposure levels were between 0.7 and 3.2 mg/m3 (Hadjimichael and Brubaker 1981).

In 61 workers who had been exposed for several years (no other details) to lead titanate zirconate, a ceramic substance containing about 60 % lead and 20 % zirconium, no abnormalities were found in the roentgenogram or lung function parameters (Roy et al. 1989).

Likewise there were no abnormal findings in the roentgenograms or lung function parameters of 178 men who had handled substances containing zirconium for several years (no other details) (Marcus et al. 1996).

Pulmonary granulomas were not found in any of 22 workers who had been exposed to zirconium chloride, zirconium oxide and metallic zirconium for 1 to 5 years (exposure levels not specified). Mild bronchial asthma was diagnosed in 2 workers, in 5 others chronic bronchitis; some of the persons had, however, also been exposed to chlorine (Reed 1956).

In a group of 136 workers in Ceylon who were exposed to ilmenite, rutile and zircon for an average of 4.4 years (exposure levels not specified), no pathological differences from a control group were found in the lungs (Uragoda and Pinto 1972).

In another study, no abnormalities were found in the roentgenograms or during the pathological examination of the lungs of 5 persons exposed to zirconium dust for periods of 1 to 4 years. The particle concentrations were given as 390 to 916 particles per cm3 and the diameters of 80 % of the particles as 1 µm. From these data, a dust concentration of about 1.3 to 3.0 mg/m3 may be calculated (Barsi 1963).

A worker in the nuclear technology industry who carried out welding processes on the zirconium-containing tubular covers of the fuel elements (exposure duration 16 years) developed extrinsic-allergic alveolitis. Histological examination of the lungs revealed various stages of an epithelioid cell granulomatosis induced by foreign bodies, with foreign body inclusions in giant cells and fibrotic changes. Zirconium was shown to be a main component of the foreign bodies. Similar changes were also found in the skin. In addition, there were granulomatous changes in the mammary glands and in the axillary lymph nodes (Kotter and Zieger 1992, Schneider et al. 1994).

Another case of pulmonary fibrosis after exposure to zirconium has been reported but in this case there were also relevant levels of exposure to other substances (asbestos, quartz, etc.) (Bartter et al. 1991). Another case of interstitial lung disease with confluent granulomas after exposure to zirconium has been described (Romeo et al. 1994). Zirconium was detected in granulomatous alterations in the lungs of three persons (Abraham 1980). Lung changes (asthma, bronchitis, pneumoconiosis, sarcoid granulomatosis, granulomatous interstitial pneumonia) have been described in workers exposed to zirconium, but in some cases the persons were also exposed to other substances which can cause lung damage and no concentration data were provided (ACGIH 1992, McCallum 1967).

Six months after intratracheal administration of 50 mg zirconium and zirconium oxide dust to rats, thickening of the alveolar septa, fibrosis, peribronchial and perivascular sclerosis and moderate emphysema were found (Egorov and Mogilevskaya 1960). According to this same research group, soluble zirconium compounds (zirconyl chloride, zirconium sulfate, zirconium nitrate) are much more toxic as they form aggressive aerosols which cause tissue damage on exposed sites as well as systemic reactions (Mogilevskaja 1960, available only as an abstract).

Guinea pigs were exposed for 2–6 months, 24 hours daily, to unspecified concentrations of zirconium chloride, zirconium oxide and metallic zirconium (no other details). In the lungs there were no signs of fibrosis, chronic inflammation or granulomas (Reed 1956).

Rabbits (number not specified) were exposed to a mist containing sodium zirconium lactate in a concentration of 49000 mg/m3, 20 minutes daily for six weeks. The findings included bronchiolar abscesses, lobar pneumonia and peribronchial granulomas; in the musculature of the tongue of one of the animals there was a granuloma (Prior et al. 1960).

Groups of 10 guinea pigs, 10 Wistar rats and 10 hamsters were exposed for 225 days to 15 or 150 mg/m3 zirconium lactate or to 15 mg/m3 barium zirconate, 7 hours daily on 5 days per week; the concentrations are equivalent to zirconium concentrations of 4.7, 36 and 5.4 mg/m3. The lung weights were increased after exposure to either of the compounds in all animal species. In rats and hamsters the body weight gain was reduced relative to the control values. The pathological examination revealed signs of diffuse interstitial pneumonitis with only slight fibrogenic effects in all three species and also an increase in the zirconium level in the lungs. Histopathological examination of the liver, spleen and kidneys revealed no exposure-related effects in any animals (Brown et al. 1963).

Note this study exposed animals for 7-hours per day while the guidance value is 6-hours per day. In addition, the exposure duration is for 225-day which is longer than the exposure time 90-day exposure period typically used for repeat dose classification. Furthermore, the authors of this study states that “the fibrogenic effect of the zirconium lactate and barium zirconate in the present study was minimal. The general changes found in the lungs of animals following prolonged exposure were not specific in any way but are suggestive of a tissue response arising from a low-grade irritant.” Therefore, this study has not been used for the classification of zircon. The particle size of the Brown et al. 1963 were reported to be 1.5 microns. These are respirable particles (<3.5 microns) and therefore may have concerns for chronic effects due to their ability to reach the alveoli.

Groups of 10 male and 10 female rats were given a standard diet containing the equivalent of about 4% zirconium oxide (added to the feed in the form of 3ZrO2·CO2·H2O) for 17 weeks. The amount of zirconium taken up daily was about 4 g/kg body weight. There were no adverse effects (growth rate, blood and urine parameters, mortality) (Harrison et al. 1951).

Mice given drinking water with a zirconium concentration of 5 mg/l [Zr(SO4)2] for life had a shorter life-span than untreated mice. This was interpreted as evidence for slight toxicity. Measurement of the concentration in the feed revealed a zirconium level of 2.66 µg/g; thus the amount taken up daily with the drinking water was 0.9 mg/kg body weight and with the feed 0.4 mg/kg body weight (Schroeder et al. 1968). In the same study, the treatment had no effect on survival of Long-Evans rats but in these animals there was a significant increase in the incidence of glucosuria (Schroeder et al. 1970).

ECHA 2019b

Well documented, scientifically sound study that is similar to OECD 412 "Repeated Dose Inhalation Toxicity with the following deviations: (1) only one dose was used rather than 3;

(2) 2 dogs, 6 Rabbits, and 20 rats (sex not provided) were exposed rather than 5 animals/sex/dose; (3) complete list of tissues examined for gross and histopathology were not provided; (4) no urinalysis or clinical chemistry parameters were examined. In this 30 day repeated dose inhalation study, dogs, rabbits and rats were exposed to 75 mg Zr/m3. No significant changes in animals were observed regarding mortality rate, growth, hematology values or hitopathology. The NOAEC was deemed to be greater than 75 mg Zr/m3.

Well documented, scientifically sound study that is similar to OECD 413 "Subchronic Inhalation Toxicity: 90-day study" guideline with the following deviations: (1) only 1 dose tested rather than 3; (2) exposure was for 60 days rather than 90 days; (3) complete list of tissues examined for histopathology was not provided; (4) limited clinical chemistry and urinalysis; (5) 4 cats, 4 dogs, 20 Guinea pigs, 19 rabbits and 72 rats (sex not provided) were exposed rather than 10 rodents per sex per dose. In this 60 day repeated dose inhalation test, cat, dog, guinea pig, rabbit and rat were exposed to 11 mg Zr/m3. No significant changes in animals were observed in mortality rate, growth, biochemistry, hematology values or histopathology. The NOAEC was deemed to be greater than 11 mg Zr/m3.

CIR 2019

Short-term inhalation of silica up to 668 mg/m3 resulted in respiratory distress during treatment and a short-term inflammation response in the lungs, which resolved quickly when treatment ceased in rats. The lung clearance half-life was ~50 day for 50.5 and 154 mg/m3. The NOAEL was 10.1 mg/m3 in one study. In other studies, the NOEL was 1 and 46 mg/m3.

Subchronic inhalation of silica at 53 mg/m3 caused 44% mortality in rats from pulmonary vascular obstruction and emphysema. There was increased respiration rates and decreased weight gain during treatment. Necropsy findings included congestion of the lungs, lymph node enlargement, emphysema, vacuolated cells within alveolar spaces, and increased lung weights and collagen content. There were no mortalities at 31 mg/m3. The LOAEL was 53 mg/m3. The NOEL was 1.3 mg/m3.

In inhalation studies, mice bred to be susceptible to tumors exposed to aerosolized Silica at 0.5 g/d for a year had increased incidence of lung tumors with no obvious fibrosis of the lung tissue but fibrotic nodules in the tracheo-bronchial lymph nodes. At 53 mg/m3 for a year, treatment related deaths were 75% in rats from pulmonary vascular obstruction and emphysema starting in the 4th month. Guinea pigs exposed to Silica at 1.5 mg/ft3 for up to 24 months had no deaths. A chronic reaction of the lung tissue was established at 4 months and emphysema after 4 to 8 months. Histologically, there [were] periductal and peribronchiolar intra-alveolar accumulations of the giant cells. In the lymphoid tissue, medullary hyperplasia with the formation of slight amounts of reticulum was prominent during the second year of exposure. There were no macroscopically visible anomalies after 1 year of recovery

Rabbits chronically exposed to 0.2 and 5.0 mm aerosolized Silica had formation of nodular fibrotic or diffuse fibrotic changes in the lungs. Rats exposed to aerosolized Silica at 15 mg/m3 for 12 months had a few macrophages aggregated in the lungs. The LOAEL was 6 to 9 mg/m3. At 126 mg/m3 of Silica for up to 24 months, guinea pigs and rabbits had

increased lung weights and particle phagocytosing macrophages accumulated in alveoli, bronchioles, and lymphoid tissue. There was complete reversibility of Silica retention and inflammatory responses in guinea pigs within 6 months of recovery. Silicotic processes were completely absent. Rabbits exposed to aerosolized silica at 1.5 mg/ft3 for 12 months had progressive functional incapacitation and elevation of hematocrit levels observed in the majority of the rabbits, possibly due to the combined effect of pulmonary vascular obstruction and emphysema. During recovery, the cellular reactions and emphysema regressed but minor focal alveolar mural collagen persisted. In rabbits exposed to 360 mg/m3 for a year, emphysema, pulmonary emphysema, vascular stenosis, alveolar cell infiltration, sclerosis, and epithelization granulomatosis, macrophage catarrh were observed. Lesions were observed in the liver, spleen and kidney. The LOAEL was 28 mg/m3 .

Monkeys exposed to aerosolized silica at 15 mg/m3 for 12 months had initial decreased activity and body weight gain. There was emphysema at 3 months and considerable cellular infiltration of the alveoli and alveolar septa associated with distention of alveoli or accumulation of exudate and macrophages. After 12 months, the lesions were marked pulmonary emphysema, alveolar wall sclerosis, vascular occlusions, and cor pulmonale. The silica content remained low and decreased over time. At 50 and 100 mg/m3, there was interstitial fibrosis which did not resolve after 24 months. When monkeys were exposed to different types of Silica, the precipitated (hydrated) silica group had lower lung volumes. There were no changes in lung volume parameters, but in ventilatory performance and mechanical parameters, dynamic lung compliance, and forced expiratory flow when exposed to silica gel. The frequency and size of inflammatory cell aggregates varied with the type of Silica.

Estimated Data- None

Neurotoxicity (N-single): DG

Zircon was assigned a hazard classification level of Data Gap for single dose neurotoxicity based on based on the lack of available studies that directly address neurotoxicity following exposures to the compound. No analog data was available to fill the data gap.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data- None

Estimated Data- None

Neurotoxicity (N-repeated) (Group II*): L

Zircon was assigned a hazard classification level of Low for repeat dose neurotoxicity based on no effects reported following a neurobehavioral examination conducted under an OECD 422 combined repeated dose toxicity study with the reproduction / developmental toxicity screening test. Specifically, motor activity recorded at the end of treatment did not show significant differences between control and treated groups following oral exposures to 530

mg/kg zirconium (delivered as zirconium acetate). Exposure periods were from 32-days to 50-days which is shorter than the standard 90-day repeat dose toxicity study. In addition, the hazard score is based on an analog. Therefore, the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

In a one generation reproductive toxicity study performed under Good Laboratory Practices (GLP) and according to OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Three groups of 10 males and 10 females each received by oral gavage to 53, 159, 530 mg/kg bw/day zirconium (delivered as zirconium acetate). A similar constituted control group received the vehicle alone during the treatment period. The overall dosing period was 32 days for males, which included 2 weeks before pairing and continuously thereafter up to the day before necropsy, and up to 50 days for females, including 2 weeks before pairing and thereafter during pairing, gestation and lactation periods until day 3 post partum.Observations included neurobehavioural observations which occurred 5 days before necropsy and for females on Day 3 post partum. Battery of functions tested: grip strength; sensory reactivity to stimuli; motor activity assessment. Time schedule for examinations: once before commencement of treatment and at least once a week thereafter, each animal was given a detailed clinical examination. Battery of functions tested: removal (from cage); handling reactivity; lachrymation; palpebral closure; salivation; piloerection; rearing; spasms; myoclonia; mobility impairment; arousal (animal activity); vocalisation; stereotypies; unusual respiratory pattern; bizarre behaviour; urination; defecation; tremors; gait. Motor activity recorded at the end of treatment did not show significant differences between control and treated groups.

Estimated Data- None

Skin Sensitization (SnS) (Group II*): M

Zircon was assigned a hazard classification level of Moderate for skin sensitization based on low to moderate incidence of sensitization reactions in humans to zirconium compounds. Specifically, mixed reports indicate a low frequency of epithelioid cell granulomas following dermal exposures in humans to soluble zirconium compounds. While this hazard score is supported by inclusion on the German MAK list (an authoritative GreenScreen list), test results in animals using zirconium dioxide and zirconium lactate produced mixed results. The positive sensitization reactions reported in human and animal data is limited to soluble forms of zirconium while the data from the one study using an insoluble form of zirconium (zirconium dioxide) reported negative results for skin sensitization. Therefore, the hazard score is conservatively based on soluble forms of the compound and which are not considered high quality analogs for this endpoint. Therefore the hazard score is reported as low confidence.

Lists

- Authoritative: Sah German MAK (for Zirconium and its compounds)
- Screening: not included on any screening lists

Measured Data

MAK 2012

In the 1950s, zirconium compounds were used in cosmetics and for a short time also in dermatological therapy. After use of the water-soluble salt, sodium zirconium lactate, as a deodorant, the development of nodular inflammatory changes at the application site was reported on several occasions; the lesions regressed only very slowly in the course of some months. Histological examination revealed epithelioid cell granulomas (Epstein 1967, Epstein et al. 1963, Lever 1967, Rubin et al. 1956, Shelley and Hurley 1958).

In experimental studies it proved possible to induce epithelioid cell granulomas on the skin of one of 30 volunteers who had applied a stick containing 5 % zirconium to the skin, 5 minutes daily for 8 weeks. In another study for which a preparation containing 10 % zirconium was used, granulomatous sensitization was seen in 2 of 20 volunteers. Epicutaneous tests with the zirconium preparations yielded negative results. However, intracutaneous tests with 1 % and 0.1 % sodium zirconium lactate yielded positive results in the form of a reaction of delayed type (type IV). One volunteer produced a reaction to a concentration as low as 0.01 %. Similar tests carried out with 20 persons who had not been pretreated yielded negative results (Shelley and Hurley 1958).

Granulomatous skin reactions in the area of the application site were also observed with water-insoluble zirconium compounds such as zirconium oxide, which was used for a short period in the 1960s without success to treat a kind of dermatitis which is common in the USA and induced by certain Rhus species ("poison ivy"); the granulomatous reactions developed during a period of several weeks to months and were very persistent (Baler 1965, Epstein and Allen 1964, LoPresti and Hambrick 1965, Williams and Skipworth 1959).

No granulomas were detected on 54 volunteers treated topically with zirconium oxychloride (ACGIH 1992).

Allergic contact dermatitis after exposure to zirconium does not seem to have been reported. Several authors consider that the sensitizing potential for man is low (Epstein 1967).

Intradermal injection of a 10 % sodium zirconium lactate suspension into 48 mice and of an 8% to 20% sodium zirconium lactate suspension in sodium stearate to 58 mice resulted in the formation of local foreign body granulomas which persisted for more than 8 months. Epithelioid cell granulomas of the type associated with a delayed hypersensitivity reaction were, however, not observed (Shelley and Raque 1971).

10 Hartley guinea pigs were immunized with a total dose of 1 mg sodium zirconium lactate (1.25 mg/kg body weight), whereby four injections were into the paws and one into the neck. After 2 weeks the animals were given intradermal injections of 25 µg sodium zirconium lactate in 0.1 ml saline, once weekly for 5 weeks. After 3 weeks in one guinea pig and after 8 weeks in all the animals, a hypersensitivity reaction of delayed type and nodular granulomas

were detected. This result could be confirmed in a modified split-adjuvant and maximization test (Turk and Parker 1977b, Turk et al. 1978). Intradermal injection of zirconium carbonate into guinea pigs did not result in granuloma formation, but injection of a zirconium aluminium glycine complex (ZAGS) did (Turk and Parker 1977a).

In a modified Magnusson and Kligman guinea pig sensitization test and in a mouse lymph node assay, zirconium chloride (ZrCl4) was not sensitizing. Induction was carried out by intradermal injection of a 1% solution into 5 guinea pigs, provocation with a 5% solution. The 3 Balb/c mice were treated with 50 µl intradermally on the abdomen and then after 5 days with an interdermal injection of 25 µl on each of 3 consecutive days (Ikarashi et al. 1996).

On rabbit skin (number of animals not specified) 24 hours after subcutaneous injection of 100 mg and after intracutaneous injection of 10 mg zirconium tetraisopropoxide, slight erythema developed. Seven weeks later the skin reacted to injection of the substance with a mild restricted erythema which disappeared after 24 hours. Percutaneous application produced no effects (Prior and Cronk 1959).

After subcutaneous and intracutaneous injection of a 42 % sodium zirconium lactate solution into rabbits (number not specified) acute inflammatory and granulomatous reactions developed. The inflammatory reactions were also seen after percutaneous application and increased after repeated injections (Prior et al. 1957).

ECHA 2019a

The traditional skin sensitization test was performed according to OECD guideline 406. Female Guinea pigs of the Hartley strain received following treatment: Intradermal sensitization Test agent group - E-FCA (equal volume (v/v) of "distilled injection water" and Freund's complete adjuvant (FCA) were mixed and emulsified in water-in-oil style - 2.5% test agent - 2.5% test agent/FCA emulsion Control group - E-FCA Positive control group - E-FCA - 0.1% DNCB/olive oil - 0.1% DNCB/FCA emulsion Patch sensitization Test agent group - 25% test agent Control group - “distilled injection water” Positive control group - 0.5% DNCB Elicitation Treatment Test group and control group - 25% test agent - 2.5% test agent Positive control group - 0.1% DNCB Zirconium dioxide was found to be not sensitising to the skin at level up to 25% whilst the positive control substance, DNCB, was found to have an extreme skin sensitising potential.

Estimated Data- None

Respiratory Sensitization (SnR) (Group II*): M

Zircon was assigned a hazard classification level of Moderate for respiratory sensitization based on a single report associating Granulomatous interstitial pneumonia with repeat inhalation exposure to zirconium silicate. The hazard score is based on a poorly reported human exposure which did not account for possible exposures to other clay minerals. It is also assumed that the frequency of respiratory sensitization is low in humans based on the absence of additional epidemiology studies associating zirconium exposures with Respiratory Sensitization. While this hazard score is supported by inclusion on the German

MAK list (an authoritative GreenScreen list), the hazard score is based on a single case report and professional judgement and therefore is reported as low confidence.

Lists

- Authoritative: German MAK (for Zirconium and its compounds)
- Screening: not included on any screening lists

Measured Data

MAK 2012

Granulomatous interstitial pneumonia with mild fibrosis which was interpreted as hypersensitivity pneumonitis was diagnosed in a worker who had been exposed for 3.5 years to dust containing zirconium. The dust load in the lungs was determined and found to be 100 times the normal background level and composed mainly of zirconium silicate and clay minerals. The dust concentration at the workplace, where glazes for ceramics were used, was 0.8–5.8 mg/m3; the dust contained 10–30 % w/w zirconium (Liippo et al. 1993).

Estimated Data- None

Skin Irritation/Corrosivity (IrS): L

Zircon was assigned a hazard classification level of Low for skin irritation/corrosivity based on negative results in an OECD 405 guideline study. The hazard score is based on a well reported GLP study using a high-quality analog and therefore is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

Two reliable studies, performed with ZrO2, have been identified (Klimisch 2). The study of Magnesium Elecktron Ltd (1986) is a GLP study, performed according to the OECD 404 guideline with minor deviations. The substance was determined not to be irritating to New Zealand White rabbit skin after 4 hours of exposure. These observations were supported by the Tosoh study (2000). This second GLP study followed also the OECD guideline 404 and the result is “not irritating”.

Estimated Data- None

Eye Irritation/Corrosivity (IrE): L

Zircon was assigned a hazard classification level of Low for eye irritation/corrosivity based on negative results in an OECD 405 guideline study. The hazard score is based on a well reported GLP study using a high-quality analog and therefore is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

In this GLP study, performed according to the OECD 405 guideline, Zirconium oxide was determined to be slightly irritating based on the AFNOR criteria using New Zealand White rabbits. Observed effects were fully reversible within 72 hours. Specifically, the acute ocular irritation index was determined to be 6.0 at 24 hours and the MOI after 48 hours was 2.0, therefore, this test agent was determined to be slightly irritating based on the AFNOR (1982) criteria. The Accident Value Test of Corneal Epithelium 24 hours after application was zero in all three animals.

Estimated Data- None

ECOTOXICITY (ECOTOX)

Acute Aquatic Toxicity (AA): L

Zircon was assigned a hazard classification level of Low for acute aquatic toxicity based on LC50 and EC50 values in all three trophic levels reported at >100 mg/L. The hazard score is based on well reported guideline studies using quality analogs and therefore is reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

A 96hr-acute toxicity of Zirconium dioxide to Brachydanio rerio studied under static conditions according to OECD Guideline 203 has been used for read-across for zirconium substance. Fish were exposed to nominal concentration of 100 mg ZrO2 /L. While the mortality/immobilization were observed daily, no mortality was observed during the test, neither in the control nor in the group exposed to zirconium dioxide. Therefore, the 96 hour LL50 and NOELR are > 100 mg ZrO2/L. In terms of zirconium element, the 96 hour LL50 and NOELR are > 74.03 mg Zr/L

A study performed with zirconium dichloride oxide (ZrOCl2) on Heteropneustes fossilis and Clarius sp. was disregarded because very few information was available for the fish toxicity test. Nevertheless, no effect was observed at a loading rate of 100 mg ZrOCl2/L (i.e 51 mg Zr/L).

The acute toxicity of ZrO2 to Daphnia magna was studied under static conditions according to EU method C2. Daphnids were exposed to control and test chemical at an initial loading rate of 100 mg/L for 48 hours. Mortality and immobilization were observed after 24 and 48 hours. No significant immobilization was observed. The 48 hours NOEC and the 48 hours EC50 were higher to 100 mg ZrO2/L.

The acute toxicity of zirconium dichloride oxide to Tubifex tubifex was studied under semi-static conditions according to APHA method. Tubifex tubifex were exposed to control and test chemical following a logarithmic scale for 96 hours. Mortality and immobilization were recorded at intervals of 30 min and 1, 2, 4, 8, 14, 33, 48 and 96 hours. No significant immobilization was observed after 96 hours exposure. The EC50 calculated for this experiment is above 100 mg/L expressed in zirconium element.

No adverse effect of zirconium metal was recorded on Hyallela azteca. LC50 values were >3150 µgZr/L for tap water and >1000 µgZr/L for soft water

By treating Chlorella cells with ZrOCl2, growth rate (optical density measurement) was inhibited and started at the lowest concentration used (20 mg/L). However, the reduction of growth was due to the lack of phosphate precipitated by the test material. To confirm this

assertion, the author conducts an additional experiment where Chlorella cells were treated with 100 mg/L and 200 mg/L of ZrOCl2 in phosphate-supplemented medium. No toxic effect on growth rate was observed on Chlorella sp. Therefore, it is concluded that the observed growth inhibition in the previous test was due to the unavailability of phosphate and not to Zirconium toxicity. The NOEC (14d) value is therefore > 200 mgZrOCl2/L i.e > 102.5 mgZr/L expressed in zirconium element.

Estimated Data- None

Chronic Aquatic Toxicity (CA): DG

Zircon was assigned a hazard classification level of Data Gap for chronic aquatic toxicity y based on the lack of available studies that directly address chronic aquatic exposures to aquatic vertebrates and invertebrates. No analog data was available to fill the data gap.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

Vryenhoef and Mullee, 2010 investigated the effect of zirconium basic carbonate on the growth of Desmodesmus subspicatus over a 72 h period. As zirconium could not be detected (<LOQ) in the test solution, the results were based on nominal concentrations. The NOErC was 32 mg/L (based on zirconium basic carbonate). Phosphate monitoring during the test indicated that reduced growth rate was concurrent with phosphate depletion due to phosphate complexing with zirconium and precipitation of the formed complexes. The observed effect is clearly a secondary effect which is not considered environmentally relevant.

By treating Chlorella cells with ZrOCl2, growth rate (optical density measurement) was inhibited and started at the lowest concentration used (20 mg/L). However, the reduction of growth was due to the lack of phosphate precipitated by ZrOCl2. In fact, an experiment performed by treating the cells with 100 mg/L and 200 mg/L of ZrOCl2 in phosphate-supplemented medium, displayed no impact on growth rate of Chlorella sp. Therefore, the growth inhibition, which was observed, was considered due to the unavailability of phosphate and not to zirconium toxicity. The NOEC value is assessed at > 200 ppm of ZrOCl2.

Estimated Data- None

ENVIRONMENTAL FATE (FATE)

Persistence (P): vH

Zircon was assigned a hazard classification level of Very High for persistence based on being an inorganic material and is not expected to be biodegradable. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when substances are recalcitrant (CPA 2012a). The hazard score is based on physical/chemical properties of the substance and is therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening:
  - EC - CEPA DSL Persistent (correspond to High to very high)

Measured Data- None

Estimated Data- None

Bioaccumulation (B): vL

Zircon was assigned a hazard classification level of Very Low for bioaccumulation-based measurements made in BCF values of <100 measured in microalgae and cyanobacteries. Although no data are available on other aquatic organisms besides algae and cyanobacteria, it can be concluded that zirconium has no potential to bioconcentrate/bioaccumulate in the aquatic foodchain. Specifically, a rapid uptake of zirconium from the medium was observed as well as a rapid desorption. The BCF values obtained for cyanobacteria and microalgae were very low, the highest value being 0.064 L/kg ww . The hazard score is based on measured data using quality analogs and supported by professional judgement and therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

A study from Garnham et al. (1993) has considered the bioaccumulation of zirconium to microalgae and cyanobacteries. Accumulation of zirconium metal, by the microalgal and cyanobacterial species examined was due to a single phase metabolism-independent "biosorption" because values of Zr accumulation after 5 min or 4 hours were equivalents. Metal-ion binding to algal cell walls occurs partly through an ion-exchange mechanism, with binding sites arising from amino- and carboxyl- groups as well as sulphates and imidiazoles associated with polysaccharides and proteins in the cell wall. Biosorption is therefore highly dependent on cell wall structure and differences in amounts of Zr bound between the microalgal species is probably due to differences in the cell walls. According to the authors

of the studies presented in the present dossier, the biosorption of Zr was dependent on competing cations. Differences between organims may be attributed to (1) differences in cell wall structure, (2) different amounts of extracellular polysaccharide and (3) the result expressed in dry weight which does not take into account differences in the surface area available for Zr binding. Overall, BCF values showed little to nor bioaccumalation in microalage and are ranged between 0.1 - 0.6 L/kg.

Another publication of E. Ferrand studied the transfer of Zr from 2 type of soils (acidic and calcareous) to tomato and pea plants during 7 -days exposure. The 2 soils were amended with 3 forms of zirconium : ZrOCl2 and Zr acetate and Zr(OH)4. Zr accumulated mainly in the roots, with Zr adsoption to the root surface being of minor relevance. Translocation to aerial parts was limited. In that context, BSAF values for root were the highest for Zr acetate and the lowest for Zr(OH)4. They were all <= 0.1 BSAF values for aeria parts.

Estimated Data- None

PHYSICAL HAZARDS (PHYSICAL)

Reactivity (Rx): L

Zircon was assigned a hazard classification level of Low based on the structural composition of the compound, which is not reactive, explosive or oxidizing. The NFPA rating is 0 for reactivity. The hazard score is based on the physical properties of the compound and therefore reported as high confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019b

Zirconium dioxide is considered not to contain any chemical groups indicating explosive properties and is therefore considered not to be explosive.

Zirconium dioxide being a stable inorganic metal oxide is not sensitive to oxygen release. Experience in the day-to-day handling and use of the substance shows no oxidizing potential.

Fisher 2018

NFPA Instability/Reactivity rating: 0

Estimated Data- None

Flammability (F): L

Zircon was assigned a hazard classification level of Low for flammability based on a NFPA flammability rating of 0 for zirconium silicate. While several sources have reported that zirconium is highly flammable and associated with the GHS hazard code H250, the hazard score herein is based on data specific to zirconium silicate. The hazard scores for the silicate form of the compound differs greatly than the high flammability reported for the non-silicate zirconium compounds. Therefore, the hazard score is reported as low confidence.

Lists

- Authoritative: not included on any authoritative lists
- Screening: not included on any screening lists

Measured Data

ECHA 2019a

The temperature of the test item exceeded 400 °C at a corresponding oven temperature of 389 °C.

The relative self-ignition temperature was 389 °C, according to the testing guideline for autoflammability

(solids - determination of relative self-ignition temperature) in the sense of the European Commission Regulation (EC) No. 440/2008, Method A.16. No sharp temperature increase was observed.

The aim of the study was the determination of the flammability of Zirconium Shot. The test item is considered as highly flammable according to 67/548/EEC since the zone of reaction spread over the whole sample in less than 10 minutes. The test item is considered as flammable solid category 1 according to CLP 1272/2008 since the zone of reaction spread over the whole sample in less than 5 minutes.

NJHSFC 2008 -zirconium

NFPA flammability rating 4

Zirconium powder dust or granule is highly flammable and can explode spontaneously in air

TheremoFisher Scientific 2018 – zirconium silicate

NFPA flammability rating = 0

Estimated Data- None

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APPENDIX A: HAZARD CLASSIFICATION ACRONYMS

(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

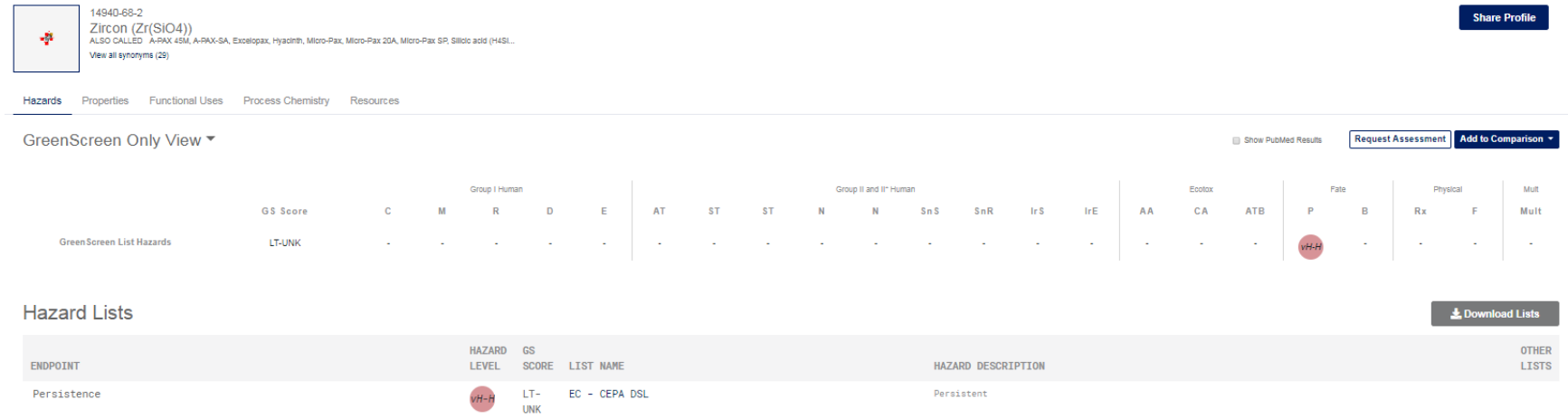
(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B – PHAROS OUTPUT FOR ZIRCON (14940-68-2)



14940-68-2
Zircon (Zr(SiO4))
ALSO CALLED A-PAX 45M, A-PAX-SA, Excelopax, Hyacinth, Micro-Pax, Micro-Pax 20A, Micro-Pax SP, Silicic acid (H4Si...
View all synonyms (29)

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Hazards | Properties | Functional Uses | Process Chemistry | Resources

GreenScreen Only View

Show PubMed Results | Request Assessment | Add to Comparison

		Group I Human					Group II and II* Human									Ecotox			Fate		Physical		Mult
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult
GreenScreen List Hazards	LT-UNK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	vH-H	-	-	-	-

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Persistence	vH-H	LT-UNK	EC - CEPA DSL	Persistent	