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Toxicology Directorate

Toxicology Assessment for Work Unit Toxic Metal Reduction (TMR) 19-01
Zinc Nickel Alternative to Cadmium Electroplating
October 2019–October 2021

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14. ABSTRACT The goal of this project is to qualify Low Hydrogen Embrittlement (LHE) Alkaline ZnNi electroplating as a replacement for Cadmium (Cd) plating at the Corpus Christi Army Depot (CCAD). The replacement product should have reduced impact upon human health and the environment. None of the components of the new electroplating solution pose a high health risk to workers and the environment if it is used with adequate occupational health and environmental safeguards. A complete analysis of all formulations could not be conducted since some of the components have not been completely tested and the identity of some components was withheld as CBI.					
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TOXICOLOGY REPORT NO. S.0059709-19
TOXICOLOGY ASSESSMENT FOR TOXIC METAL REDUCTION (TMR) 19-01
ZINC NICKEL ALTERNATIVE TO CADMIUM ELECTROPLATING

1 SUMMARY

1.1 Overview

Research, development, testing, evaluation (RDT&E), training, and use of substances potentially less hazardous to human health and the environment are vital to the readiness of the U.S. Army. Safeguarding the health of Soldiers, Civilians, and the environment requires an assessment of alternatives before such substances are fielded. Hexavalent chromium (Cr⁶⁺ or Cr(VI))-based post sealers are known carcinogens, subject to obsolescence issues and regulatory constraints. Cadmium deposition requires the toxic chemical, cyanide in the plating bath. Cyanide hazards require additional safety precautions, and are environmentally difficult/taxing for disposal. Reduction of cyanide use will reduce alarms/evacuations, exposures and plating downtime. Finding alternatives to these formulations offers cost savings by reducing hazardous waste disposal and extending the service life of parts in the field. ZnNi plating is highly corrosion resistant, and extremely useful for depositing thin layers in low tolerance applications. ZnNi is very ductile, making it an excellent choice for applications where forming or manipulation will take place later. ZnNi also has great tolerance to high temperatures and galvanic corrosion which benefit the science to support Army Aviation.

1.2 Purpose

The purpose of this work unit is to qualify Low Hydrogen Embrittlement (LHE) Alkaline ZnNi electroplating as a replacement for Cadmium (Cd) plating at the Corpus Christi Army Depot (CCAD), Texas.

1.3 Conclusions

ZnNi electroplating coating formulations are complex mixtures of inorganics intended for corrosion protection. Quantitative toxicity information is not available for all of these substances, with the polyamines having minimal toxicity information available. The manufacturers also failed to adequately provide information of the surfactants being used; however, these surfactants account for a small percentage of the formulation for DIPSOL 523-SC. The most hazardous components, present at sufficient concentration to pose a hazard to skin, eyes, and the respiratory system are potassium hydroxide and sodium hydroxide. Other compounds that have both acid and base characteristics, such as tartaric acid, oxalic acid, and sodium chloride, can potentially result in skin corrosion and eye damage. Additionally, the metal anions in cobalt (II) nitrate and nickel (II) sulfate may be genotoxic with sufficient exposure. Use of chemical handling protective equipment, such as goggles or face shields, chemical protective gloves, and (in some cases) respirators is necessary. Ingestion of these solutions is highly hazardous, therefore necessary protective measures should be followed.

The mention of any non-federal entity and/or its products is not to be construed or interpreted, in any manner, as federal endorsement of that non-federal entity or its products.
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1.4 Recommendations

These preparations are commercially available and designed to replace more toxic formulations, and appear to be generally less toxic and more sustainable than those that use Cr(VI), cadmium and cyanide, but information on some of the components was not uniformly accessible for this review. Specifically, little toxicity information exists for polyamine-1 and polyamine-2 which are approved for use as inert ingredients and secondary food additives by the U.S. Food and Drug Administration (FDA), and the manufacturer failed to provide specific compound information for the surfactants used in DIPSOL 523-C. The authors of this report recommend the formulations continue in the evaluation process with the stipulation that no variation in approved use occurs and the manufacturer provides notice if constituents are added, replaced or removed. Materials must be disposed in the appropriate manner and all safety guidelines must be adhered to when using these products.

2 REFERENCES AND GLOSSARY

See Appendix A for a list of references. See the Glossary for a list of acronyms and abbreviations.

3 AUTHORITY

Funding for this work was provided under the U.S Army Research, Development, and Engineering Command Military Interdepartmental Purchase Request No. 11225403 dated 24 July 2018. This Toxicology Assessment addresses, in part, the environment, safety, and occupational health (ESOH) requirements outlined in—

- Army Regulation (AR) 200-1, *Environmental Protection and Enhancement* (Department of the Army (DA) 2007a);
- AR 40-5, *Army Public Health Program* (DA 2020);
- AR 40-10, *Health Hazard Assessment Program in Support of the Army Acquisition Process* (DA 2007b);
- AR 70-1, *Army Acquisition Policy* (DA 2018);
- Department of Defense (DoD) Instruction 4715.23, *Pollution Prevention* (DoD 2018); and
- The Army Environmental Requirement and Technology Assessment (AERTA) PP-2-02-06 (AEC 2018) by eliminating cadmium and reducing hexavalent chromium in CCAD plating shop processes.

This toxicology assessment was performed as part of an on-going effort by the U.S. Army Safer Alternatives for Readiness (SAFR) program to reduce or eliminate the environmental impact from life-cycle use of new chemical formulations proposed for use in support of weapon systems or platforms. The sponsor is the ZnNi Alternative to Cadmium Program DEVCOM and the Principal Investigator is Nancy L. Lykins, Materials Engineer, U.S. Army Aviation and Missile Command, Redstone Arsenal, Alabama.

4 BACKGROUND

Current regulations require assessment of human health and environmental effects arising from exposure to substances in soil, surface water, and groundwater. When conducted after an item has been fielded, these assessments can reveal the existence of adverse environmental and human health effects that must be addressed retrospectively—often at substantial cost. It is more efficient to begin the assessment of exposure, effects, and environmental transport of military-related compounds/substances early in the RDT&E process in order to avoid unnecessary costs, to conserve physical resources, and to sustain the health of our forces and others potentially at risk of exposure.

In an effort to support this preventive approach, the U.S. Army Public Health Center (APHC) created a phased process to identify ESOH findings impacting readiness, training, and development costs. This report represents the status of information available for this work unit as of the date of report publication.

5 STATEMENT OF THE PROBLEM

The Army requires the capability to protect its materiel from corrosion, wear, fatigue, and other harsh environments, while at the same time protecting the health of the force and assuring its facilities remain environmentally sustainable. Currently, the Army relies on unsustainable and carcinogenic materials such as hexavalent chromium and cadmium in surface finishing during production and maintenance of weapons systems and components. These systems include hydraulic and pneumatic actuators, turbine engines, structural components, armaments (gun barrels, gun mounts, towed howitzer carriage, and trail systems), small components (hinges, brackets, bushings, bearings, and pins), electrical connectors, and fasteners. To accomplish its corrosion protection goals, the Army requires affordable coatings/processes that meet or exceed current performance requirements while reducing or eliminating the ESOH and energy costs.

6 METHODS

To determine the human health and environmental impact of compounds employed in these formulations, each compound needs correct identification and its physical, chemical, and toxicological properties assessed. Table 1 provides the compound name, percent formulation, and Chemical Abstracts Service Registry Number (CASRN) for the formulation. Note, water (H₂O, CASRN 7732-18-5) is not evaluated for toxicity in this report. While not all compounds have a CASRN, it can be used as a keyword to search online databases and are often cross-referenced with systematic and trivial (i.e., “common” or non-systematic) substance names. In some cases, synonyms and trade names are used to identify structures.

Table 1. Percent Formulation for Candidate Products

Section/ Product	Constituents	CASRN	Percent Formulation
7.3 DIPSOL 523-SC			
	Potassium hydroxide	1310-58-3	10–20
	H ₂ O + surfactants	unknown	80–90
7.4 DIPSOL F-0529			
	Tartaric acid	87-69-4	10–45
	H ₂ O	7732-18-5	55–90
7.5 DIPSOL IZ-264			
	Cobalt (II) nitrate	10141-05-6	5–20
	H ₂ O	7732-18-5	80–95
7.6 DIPSOL IZ-264 T			
	Chromic chloride	10025-73-7	5–25
	H ₂ O	7732-18-5	75–95
	Sodium hydroxide	1310-73-2	
	Oxalic acid	144-62-7	
7.7 DIPSOL IZ-C17+B			
	Polyamine-2	25988-97-0	60–99
	Diethylenetriamine	111-40-0	1–3
	H ₂ O	7732-18-5	remainder
7.8 DIPSOL IZ-C17+Ni			
	Nickel (II) sulfate	7786-81-4	20–30
	Polyamine-1	9002-98-6	5–10
	H ₂ O	7732-18-5	60–75
7.9 Caustic Soda			
	Sodium hydroxide	1310-73-2	97–98.2
	Sodium chloride	7647-14-5	0–1.2
	Sodium carbonate	497-19-8	0.4–1
7.10 DIPSOL N-777			
	Sodium hydroxide	1310-73-2	30–40
	Zinc oxide	1314-13-2	5–15
	H ₂ O	7732-18-5	remainder

The properties necessary to assess fate and transport in the environment include:

- Molecular weight (MW in g per mol; g/mol).
- Boiling point (bp) in °C.

- Octanol-water partition coefficient ($\log K_{ow}$).
- Organic carbon partition coefficient ($\log K_{oc}$).
- Water solubility (mg/L or mL/L).
- Henry's Law constant (K_H).
- Vapor pressure (vp) in mm of mercury (Hg) – mmHg.

Toxicological information needed to estimate potential human health risks includes reported toxicity effects of oral, inhalation, dermal, and ocular exposures; potential for developmental or reproductive toxicity, neurotoxicity, genotoxicity, carcinogenicity, and mode(s) and mechanisms of toxicity. Toxicological information was derived directly from primary sources whenever possible. Values reported herein include median lethal dose (LD_{50} ; reported in mg/kg), no observed adverse effect level (or concentration) (NOAEL/C), lowest observed adverse effect level (or concentration) (LOAEL/C) reported in mg/kg or mg/L, median effect concentration (EC_{50}), median inhibitory concentration (IC_{50}), median lethal concentration (LC_{50}) typically reported as mass (g or mg) per m^3 or mg/L, clinical chemistry values may be reported in dL and some water quality values may be reported in μ /L or ppm. Toxicological information was derived directly from primary sources whenever possible. Where data gaps exist, *in silico* toxicity estimates were made using two quantitative structure activity relationship (QSAR) programs: TOPKAT (Toxicity Prediction Komputer Assisted Technology) (BIOVIA 2015) and ECOSAR™ (ECOLOGICAL Structure Activity Relationship) (EPA 2012). The ECOSAR program provides point estimates for aquatic endpoints (green algae, *Daphnia*, and fathead minnow acute toxicity and chronic values).

Basic physical and chemical properties are usually determined by consulting tertiary sources when such information is available. Where these data were unavailable, predictions from EPI Suites were used. Tertiary sources used in this search included the National Institutes of Health (NIH), the U.S. Environmental Protection Agency (EPA), the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR), the EPA ECOTOXicology Database System (ECOTOX), and the Defense Technical Information Center (DTIC®). Additional sources may include publications from the U.S. National Institute for Occupational Safety and Health (NIOSH), the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), and the European Chemical Agency (ECHA). Primary references are identified and retrieved by PubMed®, EBSCOhost® Research Databases and Google Scholar®.

Persistence, bioaccumulation, human health toxicity, and ecotoxicity were assigned to general categories of risk (i.e., low, moderate, or high) using criteria modified from (Howe et al. 2006). Table B-1 in Appendix B describes the criteria used in this categorization, though the relative proportions of each substance were also factored into the final assessment. In addition, classification through the Globally Harmonized System (GHS) is also included for many of the compounds presented in this assessment (Occupational Safety and Health Administration (OSHA) 2012) (See Appendix B Tables B-2 – B-5).

7 RESULTS

7.1 Physical and Chemical Properties

Appendix C Table C-1 summarizes the physical and chemical properties. When data were not found, "ND" (no data) is inserted. In some cases, the property named is not applicable ("n/a") to the substance being described. For example, if the compound is a nonvolatile solid or an inorganic salt, vapor pressure, K_{ow} , K_{oc} , and K_H are typically negligible. Figures 1-14 show the chemical structures for each constituent.

7.2 Summaries

Summaries of mammalian toxicity data are collected in Appendix C Table C-2. Assessments of human health and environmental toxicity for each of the formula constituents are presented in Appendix C Tables C-3 and C-4, respectively. Each characterization is generally based on the criteria set forth in Appendix B.

7.3 DIPSOL 523-SC

7.3.1 Potassium Hydroxide (KOH) [CASRN 1310-58-3]

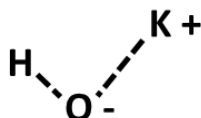


Figure 1. Potassium Hydroxide

7.3.1.1 General Information

KOH is a white or slightly yellow solid, usually forming lumps, rods, or pellets. It is highly corrosive due to its basic pH and is used industrially in many applications, including fungicide, herbicide, and anti-microbial (PubChem 2021h). The solid is hygroscopic and rapidly absorbs moisture from the atmosphere to the point of deliquescence. KOH dissociates completely in water into the potassium ion (K^+) and hydroxyl ion (OH^-), causing a vigorous exothermic reaction (ECHA 2021I). Synonyms include caustic potash and lye (O'Neil et al. 2006).

7.3.1.2 Toxicology Data

KOH causes direct local effects on the skin, eyes, and gastrointestinal tract after direct exposure. If KOH aerosols/mists are formed, they will cause direct local effects on the respiratory tract. Solutions with concentrations greater than 2% are corrosive, while concentrations of 0.5 to 2.0% are irritating. The irritant effects are reported as coughing,

wheezing, conjunctivitis, tearing, and irritation. Ingestion of KOH has also been noted to cause damage to the inner ear and subsequent permanent hearing loss (PubChem 2021h).

7.3.1.2.1 Oral

The oral LD₅₀ in rats is between 273 and 1,230 mg/kg (PubChem 2021h).

KOH is classified as GHS Category 4 for acute toxicity (PubChem 2021h).

Oral ingestion of KOH causes gastrointestinal burns (Organisation for Economic Co-operation and Development (OECD) 2001). Alkali burns in the trachea and esophagus are potentially fatal. Some camera batteries contain 45 % potassium hydroxide electrolyte, which can leak and cause liquefaction necrosis upon tissue contact (Blatnik et al. 1977).

7.3.1.2.2 Inhalation

No quantitative data were found.

If KOH aerosols/mists are formed, they will cause direct local effects on the respiratory tract. Solutions with concentrations greater than 0.5% are respiratory irritants and are corrosive above 2%. The reported effects of irritation include coughing, wheezing, conjunctivitis, and tearing of eyes (ECHA 2021l).

Aspiration of alkali into the airway can result in life-threatening injuries to the larynx, the tracheobronchial passages, and the lungs (OECD 2001).

7.3.1.2.3 Dermal

KOH is classified as GHS Category 1A for skin corrosion (PubChem 2021h).

Draize skin tests in rabbits, with gauze covering and application of 0.1 mL for 24 hours, qualified a 5% KOH solution as mildly irritating on intact skin and highly irritating on abraded skin. A 10% KOH solution was qualified as corrosive on both intact and abraded skin due to a Draize occlusive test on rabbits with 4 hours exposure to 0.5 mL of the solution (PubChem 2021h, WISER 2021).

7.3.1.2.4 Ocular

KOH is classified in Category 1 of the GHS (PubChem 2021h).

Eye damage by alkali burns is most significant around pH 11–11.5. Alkali penetrates quickly, saponifies plasma membranes, denatures collagen, and causes vascular thrombosis in the conjunctiva, episclera, and even the anterior uvea. The sequelae of corneal burns include scarring and opacification of the cornea with resultant loss of visual acuity, corneal neovascularization, ulcer formation, and perforation. Other sequelae of untreated or very severe alkali burns include epithelial erosions, secondary glaucoma, and progressive cicatrization (contraction of fibrous tissue formed at a wound site). Cicatrization reduces the size of the

wound while distorting tissue which occludes the ducts of primary and accessory lachrymal glands. This occlusion destroys conjunctival goblet cells to cause dry eyes, cicatricial entropion (an inversion resulting from scar tissue on the inner surface of the lid), and trichiasis (inversion of the eyelashes irritating the eye) (OECD 2001).

7.3.1.2.5 Development and Reproduction

KOH is not known to be a developmental or reproductive toxicant in the absence of injury to the mother (PubChem 2021h).

7.3.1.2.6 Genotoxicity

An Ames assay using *Salmonella typhimurium* strains TA97 and TA102 with and without metabolic activation and up to 1 mg KOH/plate were negative (OECD 2001).

KOH's clastogenic activity was studied in an *in vitro* chromosomal aberration test using Chinese hamster ovary K1 cells. No clastogenic activity was found at KOH concentrations of 0, 8, and 12 mM, corresponding to initial pH values of 7.3, 9.8, and 10.4, respectively. In the presence of microsomal activation (S9), a clastogenic activity was found at 12 mM (OECD 2001).

7.3.1.2.7 Carcinogenicity

There are no recent long term dosing studies in animals to investigate potential carcinogenic effects of KOH. Narat (1925) reported that long term application of a 3–6% solution of KOH to the backs of mice for up to 46 weeks lead to the formation of tumors which appeared to be carcinogenic. Rats as well as some strains of mice did not show these same effects. It is hard to interpret these results since the neither various animal strains nor the test compounds were clearly identified. The author did note that repeated application of the test solution did lead to inflammation and ulcerated lesions and it is likely that any type of prolonged irritation can cause the same type of result. Overall, there are no data to suggest KOH is carcinogenic in humans (OECD 2001).

7.3.1.2.8 Neurotoxicity

No information on the neurotoxicity of KOH was found.

7.3.1.2.9 Mechanism

As potassium hydroxide is dissociated in the body fluids, its systemic toxicity is discussed separately as potassium and hydroxyl ions.

Potassium is essential for the nervous and muscular cell's function and several metabolic activities, including protein synthesis (ECHA 2021l). Its average plasmatic concentration is approximately 140–200 mg/L. Moderate toxicity causes fatigue and weakness. Severe toxic doses (hyperkalemia) leads to neuromuscular paralysis and death by cardiac arrest due to intraventricular conduction defects, depolarizing cardiac muscle, and subsequent increase in cardiac muscle excitability (PubChem 2021h).

7.3.1.3 Ecological Data

7.3.1.3.1 Fate and Transport

Solubilized KOH is expected to be readily transported in aqueous systems until neutralized.

Aerosols of KOH are unstable. They are rapidly (within seconds) transformed by uptake of carbon dioxide from the atmosphere to potassium bicarbonate and potassium carbonate (OECD 2001).

7.3.1.3.2 Ecotoxicity

KOH is classified in the GHS as Category 3 for acute aquatic toxicity (PubChem 2021h).

The 96-hour LC₅₀ in mosquitofish (*Gambusia affinis*) was reported to be 80 mg/L (OECD 2001). Zebra mussels (*Dreissena polymorpha*) exhibit mortality at concentrations greater than 10 mg/L (Matisoff et al. 1996). Pond snails (*Lymnaea spp.*) exhibit mortality at a concentration of 100 mg/L; freshwater snails (*Biomphalaria alexandrina*) at 500 mg/L (ECHA 2021i). Lettuce (*Lactuca sativa*) showed effects at 42 mM KOH; a LOAEL for enchytraeid worms (*Cognettia spagnetorum*) was found at 3 g/L (ECOTOX 2021).

7.3.1.3.3 Degradation and Treatment

KOH can be neutralized by treatment with acid, resulting in the release of large amounts of heat, depending upon the concentration. Atmospheric releases will degrade rapidly due to reaction with carbon dioxide (OECD 2001).

KOH is expected to be poorly degraded by wastewater treatment plants and will likely result in damage to microbial communities that are part of those plants.

7.3.2 Surfactants

7.3.2.1 General Information

The TMR-19-01 Electroplating solution includes DIPSOL 523-SC which is composed of potassium hydroxide (10–20%) and 80–90% water +surfactants. DIPSOL provided the following information on the surfactant solution:

- Aliphatic 3%
- Alcohol ethoxylates 4%
- Sulfonates 3%
- Chelates 2%

Surfactant molecules typically have a hydrophilic structure at one end and are hydrophobic at the other end and this structure helps reduce water surface tension. Surfactants are used in many consumer products including soaps, shampoos and cosmetics (Fox and Boyes 2019) as

well as industrial and agricultural applications as emulsifiers, antifoaming agents, flocculants and in metalworking and electroplating (ECHA C12-C14 summary). The hydrophilic portion of the surfactant molecule can be anionic, cationic, or neutral. In terms of toxicity, cationic compounds are stronger irritants than the anionic or neutral compounds (Fox and Boyes 2019).

The components listed above are generic classes of surfactants and insufficient for performing an assessment of health and environmental concerns. Subsequently DIPSOL identified the surfactants as C12-C14 ethoxylated alcohol (CASRN 84133-50-6) and sodium lignosulfonate (CASRN 8061-51-6). Searches of the primary online databases for these two compounds yielded virtually no toxicity or environmental information. PubChem provided basic chemical structures and synonyms for the compounds and the European database had similar information as well as the GHS scores for use in labelling and handling for the ethoxy compound and the lignosulfonate (ECHA 2021f, 2021j; PubChem 2005, 2008).

7.3.2.2 Toxicology Data

Aliphatic surfactants are a large class of compounds that could include alpha olefin sulfonates, alkane sulfonates, and primary and secondary alkyl sulfates (Kumagai 1969). Searches of standard chemistry and toxicity databases yielded very little information and no toxicity or environmental data. Without more specific identification of this surfactant it is not feasible to make an assessment for this group.

Chelating agents are typically organic molecules used to bind and remove metallic ions. They are used medicinally to bind and remove toxic metals from the body (Ufelle 2019). Chelators are also used in agricultural products, consumer products, textiles and printing (Asemave 2018). DIPSOL did not identify a chelating agent for the TMR 19-01 electroplating solution. Common chelators include ethylenediamine tetracetic acid (EDTA) and nitrilotriacetic acid (NTA) (Asemave 2018). The GHS scores for these compounds are shown below (ECHA 2021e, 2021h). Without knowledge of the specific chelators used in the TMR 19-01 solution, we are unable to make any definitive assessment or conclusions regarding health and environmental effects of the chelator component.

7.4 DIPSOL F-0529

7.4.1 Tartaric Acid [CASRN 87-69-4]

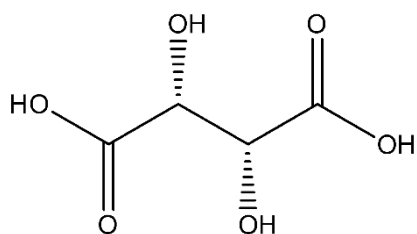


Figure 2. L-tartaric Acid

7.4.1.1 General Information

Tartaric acid is a crystalline organic acid that occurs naturally in plants, such as grapes, and is one of the primary acids found in wine (Regueiro 2014). Tartaric acid belongs to the class of organic compounds known as sugar acids and derivatives containing a saccharide unit and is the dihydroyl derivative of the 4 carbon succinic acid. Tartaric acid is added to other foods to give a sour taste and is used as an antioxidant (Lord et al. 2005). The naturally occurring form of the acid is L-(+)-tartaric acid or dextrotartaric acid (Lord et al. 2005). Synonyms include (2R,3R)-2,3-dihydroxysuccinic acid, L-threarcic acid, and 2,3-dihydroxybutanedioic acid, among others (PubChem 2021e).

7.4.1.2 Toxicology Data

Since it is widely present in nature and plant substances ingested, L-tartaric acid, at least at levels found naturally, is not thought to be toxic when ingested. The minimum recorded fatal dose is 12 g (ECHA 2021p). Potential acute health effects include skin contact (irritant), eye contact (irritant), ingestion, or inhalation (lung irritant).

7.4.1.2.1 Oral

The acute oral LD₅₀ in rats is reported to be >7,500 mg/kg (LD_{LO}); the LD_{LO} in both dogs and rabbit is 5,000 mg/kg (limit dose) (PubChem 2021e). Another study looking at female rats reported a LD₅₀ range of 2,000–5,000 mg/kg bw (ECHA 2021p).

7.4.1.2.2 Inhalation

No experimental data were found describing systemic toxicity from inhalation exposure and this end point is not classifiable in the GHS. Inhalation is reported to cause respiratory tract irritation (PubChem 2021e).

7.4.1.2.3 Dermal

Tartaric acid is a Category 2 skin irritant in the GHS, and a Category 1 sensitizer (PubChem 2021e). The dermal LD₅₀ in rats is reported to be >2,000 mg/kg (Sigma-Aldrich 2021).

7.4.1.2.4 Ocular

Tartaric acid is classified as GHS Category 1 and 2 for serious eye damage/irritation – depending on use (PubChem 2021e).

7.4.1.2.5 Development and Reproduction

Summarized reproduction studies of tartaric acid in different species such as mouse, rat, hamster, and rabbit, found that administrations of the highest dosage, 274 mg/kg bw in mice, 181 mg/kg bw in rats, 225 mg/kg bw in hamsters and 215 mg/kg bw in rabbits, did not cause any reproductive or developmental effects on tested animals (ECHA 2021p). The NOAEL in rats was 181 mg/kg bw/day.

7.4.1.2.6 Genotoxicity

Four *in vitro* studies and two mammalian bone marrow chromosome aberration tests were reported in the literature. No genetic toxicity was found in those tests, so it can be concluded that L-(+)-tartaric acid is non-mutagenic (PubChem 2021e).

7.4.1.2.7 Carcinogenicity

TA is not considered carcinogenic by the IARC, ACGIH, National Toxicology Program (NTP), and OSHA (Sigma-Aldrich 2021). However, some studies link it with lung cancer (Chen et al. 2015, Wishart et al. 2009).

7.4.1.2.8 Neurotoxicity

No data were found.

7.4.1.2.9 Mechanism

High doses of tartaric acid can interfere with malic acid production in the Krebs cycle, causing paralysis and death (Shaw et al. 1995). Tartaric acid is used as an antioxidant and is chiral, making it a valuable raw material in organic chemistry to synthesize other chiral molecules. Tartarate plays a role in inhibiting kidney stone formation; additionally, bacteria metabolize most tartarate consumed by humans in the gastrointestinal tract (Sreekumar et al. 2009).

7.4.1.3 Ecological Data

7.4.1.3.1 Fate and Transport

If released to soil, tartaric acid is expected to be highly mobile in groundwater and may pose a hazard to surface and drinking water. Based upon a predicted Henry's Law constant value of 1.32×10^{-10} atm-m³/mol and vapor pressure of 9.68×10^{-8} mmHg, tartaric acid will not partition to the atmosphere from water or wet or dry surfaces and is expected to exist in the atmosphere only in particulate form. Tartaric acid is not expected to bioaccumulate (Sigma-Aldrich 2021).

7.4.1.3.2 Ecotoxicity

The EC₅₀ of tartaric acid in green algae is reported to be 51.4 mg/L for 72-hour exposure. The EC₅₀ in *Daphnia* for a 48-hour exposure is 93.31 mg/L (Sigma-Aldrich 2021).

According to a supplier safety data sheet (SDS), tartaric acid is classified in GHS Category 3 for acute aquatic toxicity, indicating it is harmful to aquatic life (Sigma-Aldrich 2021).

7.4.1.3.3 Degradation and Treatment

Tartaric acid is readily biodegradable, with 85% degradation in an aerobic environment after 28 days (Sigma-Aldrich 2021), and has a low log K_{ow} (ECHA 2021p).

7.4.2 Water [CASRN 7732-18-5]

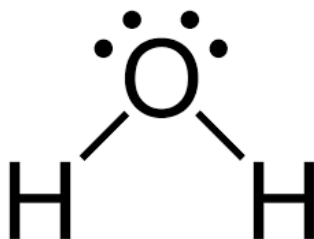


Figure 1. Water

7.4.2.1 General Information

Water appears as a clear, nontoxic liquid composed of hydrogen and oxygen, it is essential for life and the most widely used solvent. Due to its role as an amphiprotic solvent, it is utilized in several of the products reviewed. However, water's nontoxic designation and the low relative volumes used, it lacks relevance in this situation and will not be reviewed in this toxicity assessment.

7.1.2.2 Toxicology Data

Water itself is nontoxic and is in fact essential for life. Solutes dissolved in water may be toxic, but those interactions are covered by the reactive groups that the solute belongs to. Water has been verified to be of low concern by the EPA based on experimental and modeled data. Additionally, No hazards have been classified by majority groups or information sources.

7.5 DIPSOL IZ-264 c

7.5.1 Cobalt (II) Nitrate [CASRN 10141-05-6]

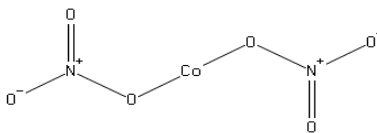


Figure 4. Cobalt (II) Nitrate

7.5.1.1 General Information

Cobalt is a metallic element with the atomic number 27 (PubChem 2021c). It is found naturally in rocks, soil, water, plants, and animals. Cobalt (II) nitrate is a high solubility common source of cobalt in metalorganic frameworks and polymers. Cobalt is an essential element for life, as it is part of vitamin B12; however, overexposure has toxic effects (ECHA 2021c, PubChem 2021c). Nitrite is known to cause methemoglobinemia at high exposures and causes red blood cell lysis (anemia) at prolonged exposures. Synonyms include Cobalt bis(nitrate), Cobalt dinitrate, cobalt nitrate, cobalt (2+) nitrate, cobalt (II) nitric acid, cobaltous nitrate. (ECHA 2021c, PubChem 2021c).

7.5.1.2 Toxicology Data

Cobalt (II) nitrate is used to manufacture cobalt pigments, decorate stoneware, prepare catalysts, produce vitamin B12 supplements, and electronics-related industries (PubChem 2021c). In humans, repeated or prolonged contact may cause skin sensitization and asthma. Ingestion may cause effects on the bone marrow, heart, and thyroid (PubChem 2021c). Animal studies conducted on guinea pigs demonstrated endocrine effects, while rat studies reported metabolic and kidney effects (ECHA 2021c, IMAP 2014b).

7.5.1.2.1 Oral

Cobalt (II) nitrate has moderate acute toxicity in rats following oral gavage exposure with reported oral LD₅₀ in rats between 434 mg/kg (Speijers et al. 1982) and LD₅₀ of 978 mg/kg body weight (IMAP 2014b).

No data are available for oral repeated dose toxicity for chemicals in this group. However, available data on an analog chemical, cobalt chloride hexahydrate (CASRN 7791-13-1), found no observable adverse effect (NOAEL) at 2.5 mg/kg bw/day and the lowest observable adverse effect level (LOAEL) at 10 mg/kg bw/day based upon increases in hemoglobin content and numbers of erythrocytes (ATSDR 2004).

7.5.1.2.2 Inhalation

The GHS classifies cobalt (II) nitrate as a respiratory sensitizer Category 1 (Safe Work Australia (SWA) 2021, ECHA 2021c).

There is limited information on cobalt nitrate's respiratory effects; however, chemicals in this group cause severe health damage by prolonged exposure through inhalation. The lowest observable adverse effect concentration (LOAEC) is 0.3 mg/m³ of the analog chemical cobalt sulfate heptahydrate (CASRN 10026-24-1) was identified as having local effects on the larynx. The available data on an analog chemical, cobalt sulfate heptahydrate (CASRN 10026-24-1), cobalt chloride (CASRN 7646-79-9) aerosols can produce an asthmatic response in sensitized individuals (ATSDR 2004, 2017).

7.5.1.2.3 Dermal

Cobalt (II) nitrate is listed as a skin sensitizer GHS Category 1 (ECHA 2021c, SWA 2021) and is considered to be corrosive to the skin (ATSDR 2004). However, based on the toxicokinetic data cobalt (II) nitrate may have low dermal absorption (ATSDR 2004).

7.5.1.2.4 Ocular

Cobalt (II) nitrate is listed as causing severe eye damage/irritation (PubChem 2021c).

7.5.1.2.5 Development and Reproduction

Cobalt (II) nitrate is classified as Category 1B by the GHS and Europe (ECHA 2021c, SWA 2021). Additionally, in Australia, cobalt (II) nitrate is classified as hazardous: Category 2 substance toxic to reproduction, with the risk phrase 'May impair fertility' (IMAP 2014b).

Animal tests show that this substance possibly causes toxicity to human reproduction or development (PubChem 2021c). Other reproductive animal studies in males at a dose of 14.6 µg/kg found paternal effects on the testes, epididymis, and sperm duct (NIOSH 2021).

While several studies on developmental toxicity are reported, it is challenging to confirm toxicity due to various methodological differences and interpretations.

7.5.1.2.6 Genotoxicity

Most of the data for cobalt metal particles and soluble cobalt (II) salts show these materials to be genotoxic *in vitro*. However, a human occupational study of 35 workers in a cobalt refinery did not indicate increased DNA strand breaks or other genotoxicity markers when compared with 27 unexposed workers (Environment and Climate Change Canada (ECCC) 2011, OECD 2014).

Cobalt (II) nitrate is listed as a GHS Category 1 germ cell mutagen (ECHA 2021c, IMAP 2014b).

7.5.1.2.7 Carcinogenicity

The GHS and European classification for cobalt (II) nitrate is Category 1B (ECHA 2021c, SWA 2021).

It is also noted that ingested nitrate or nitrite under conditions resulting in endogenous nitrosation is probably carcinogenic to humans; additionally, soluble cobalt (II) salts are possibly carcinogenic to humans (IMAP 2014b, OECD 2014).

7.5.1.2.8 Neurotoxicity

No information or data were found.

7.5.1.2.9 Mechanism

No mechanism for cobalt nitrate was found; however, with the known dissociation of cobalt ions, assumptions can be made based on cobalt toxicity. Cobalt is believed to exhibit its toxicity through oxidant-based and free radical-based processes. It produces oxygen radicals causing increased lipid peroxidation, DNA damage, and cell apoptosis. Cobalt may inhibit DNA repair by interacting with zinc finger DNA repair proteins and has also been shown to inhibit heme synthesis and glucose metabolism (ATSDR 2004). Nitrate's toxicity is a result of its conversion to nitrite once in the body. Nitrite causes the autocatalytic oxidation of oxyhemoglobin to hydrogen peroxide and methemoglobin which has reduced capacity to bind oxygen and potentially causing hypoxia. (ATSDR 2017, Keszler et al. 2008).

7.5.1.3 Ecological Data

7.5.1.3.1 Fate and Transport

Several lines of evidence suggest that the bioaccumulation potential of cobalt in natural ecosystems is relatively low. Inorganic cobalt compounds are nonvolatile and released into the atmosphere in particulate form. Cobalt compounds dissociate in water and release cobalt ions (Co^{2+}). Elemental cobalt powders may also release cobalt ions in a solution if discharged to surface waters (PubChem 2021c). Cobalt has been detected in atmospheric deposition and rain-snow precipitation (ECHA 2021c). A proportion of dissolved forms end up in sediments.

7.5.1.3.2 Ecotoxicity

Cobalt (II) nitrate is classified as "Hazardous to the aquatic environment (acute/chronic)" and placed in the GHS Category 1 (ECHA 2021c, SWA 2021). Freshwater aquatic data were recently collected to be used for developing cobalt water quality standards (Stubblefield et al. 2020). Algae, duckweed, invertebrates and fish species were tested for adverse chronic effects. Invertebrates ($\text{EC}_{20}=11.1 \mu\text{g/L}$) and algae/plant species ($\text{EC}_{10}=4.9 \mu\text{g/L}$) were found to be more sensitive to chronic cobalt than fish ($\text{EC}_{10}=2.17 \text{ mg/L}$; $\text{EC}_{20}=2.45 \text{ mg/L}$). Based on the EC_{10} values and species sensitivity distributions, an aquatic $\text{EC}_5=1.80 \mu\text{g/L}$ was derived.

Cobalt is a trace micronutrient in plants and animals but is toxic at higher concentrations (Mahey 2020). Cobalt toxicity is dependent on species sensitivity, co-occurring metals in soil, soil type and pH. Generally, plant growth is unaffected up to 0.5 ppm cobalt; however, some plant species can grow in soil containing upwards of 10,000 ppm cobalt.

7.5.1.3.3 Degradation and Treatment

Evaporation of cobaltous nitrate at 20 °C is negligible (PubChem 2021c). However, elemental cobalt is considered persistent since the ions released into solution when dissolved cannot be irreversibly degraded (PubChem 2021c).

7.5.2 Water

See section 7.4.2 for information on water.

7.6 DIPSOL IZ-264 T

7.6.1 Chromic Chloride [CASRN 10060-12-5]

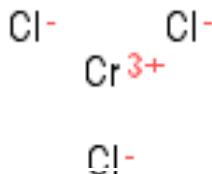


Figure 5. Chromic Chloride

7.6.1.1 General Information

Chromium (III) chloride is used in organic synthesis and reactions. Chromium is a chemical element that has the symbol Cr and atomic number 24. It is naturally occurring in rocks, animals, plants, and soil and is usually mined as chromite ore. The anhydrous compound with the formula CrCl_3 is a violet solid. The most common form is the dark green hexahydrate, $\text{CrCl}_3 \cdot 6 \text{H}_2\text{O}$. Chromium chlorides find use as catalysts and as precursors to dyes for wool. Chromium is most toxic in its +6 oxidation state (Cr(VI)) due to its cell permeability and higher redox potential. Trivalent chromium (Cr(III)) is biologically necessary for sugar and lipid metabolism in humans. (PubChem 2021b). Synonyms include chromic chloride, chromic chloride hexahydrate, chromium chloride, chromium trichloride, CrCl_3 , puratronic chromium chloride, trichlorochromium (ECHA 2021b).

7.6.1.2 Toxicology Data

Chromium is most toxic in its hexavalent (+6) oxidation state (Cr(VI)) due to its cell permeability and higher redox potential. Hexavalent chromium's similarity to sulfate and chromate is transported into cells through a sulfate transport mechanisms. In the cell, hexavalent chromium is reduced to trivalent chromium by ascorbate, glutathione, nicotinamide, and adenine dinucleotide (ATSDR 2012). Trivalent chromium (Cr(III)) is biologically necessary for sugar and lipid metabolism in humans. (PubChem 2021b). Chromium is absorbed by oral, inhalation, or dermal exposure and distributes to nearly all tissues, with the highest concentrations found in the kidney and liver. Bone is also a significant storage site and may contribute to long-term retention, yet it is excreted with the urine (ATSDR 2012, Salnikow 2008).

7.6.1.2.1 Oral

Chromium (III) chloride has a hazard category for acute toxicity of 4, with a hazard statement "Harmful if swallowed" (ECHA 2021b).

The oral LD₅₀ in rats was reported at 1,870 mg/kg; however, chromium's (III) toxicity increases with water solubility (PubChem 2021b). Thus, the acute oral LD₅₀ of chromium trichloride may also be estimated on an analogous compound like chromium trinitrate nonahydrate (ECHA 2021b). Vernot et al. (1977) found an LD₅₀ value of 1,465 mg/kg (equivalent to 190 mg Cr/kg bw) for chromium trinitrate. The rat LD₅₀ for chromic trinitrate nonahydrate is reported as 3,250 mg/kg (ChemIDplus 2022). The acute toxicity of chromous chloride CrCl₂, which readily oxidizes to chromium (III) in aqueous solvents, was reported as LD₅₀ = 1,870 mg/kg (ECHA 2021b).

7.6.1.2.2 Inhalation

Chromium (III) chloride induces coughing upon exposure. A mouse inhalation LC₅₀ of 31,500 µg/m³/2 hr (ChemIDplus 2021b) or 31.5 mg/kg (Izmerov et al. 1982) was reported.

A 90-day inhalation study of chromium (III) hydroxy sulfate, a soluble chromium (III) compound, found no systemic toxicity, but local effects in the respiratory tract were observed (Derelanko et al. 1999). Similar effects can be expected for chromium trichloride hexahydrate upon inhalation exposure (ECHA 2021b).

7.6.1.2.3 Dermal

Chromium (III) chloride is a GHS skin sensitizer Category 1, with a hazard statement "May cause an allergic skin reaction" (ECHA 2021b).

No acute dermal studies for chromium (III) chloride are available (PubChem 2021b). However, a dermal study with chromium (III) nicotinate found no mortality and no adverse symptoms in rats at 2000 mg/kg bw. (ECHA 2021b, PubChem 2021b). Based on those results, acute dermal toxicity for chromium (III) chloride is not expected. The acute dermal finding for chromium (III) nicotinate is considered representative of chromium trichloride. Although chromium trichloride is acidic, the skin barrier remains intact and no enhanced skin penetration is expected upon exposure to chromium trichloride (ECHA 2021b).

7.6.1.2.4 Ocular

The potential of chromium trichloride to cause damage to the conjunctiva, iris or cornea was assessed on White New Zealand rabbits. The ocular reactions were assessed 1, 24, 48, and 72 hours after application. Slight conjunctival redness and slight discharge were observed in the animals during the study (ECHA 2021b). The described ocular reaction for chromium trichloride has a low potential for ocular damage (ECHA 2021b); however, it is noted that it can cause Redness (PubChem 2021b).

7.6.1.2.5 Development and Reproduction

In a study reported in ECHA, mated female mice were administered chromium (III), and no maternal toxicity was observed (ECHA 2021b). A two-generation reproductive toxicity study using chromium (III) tri(pyridine-3-carboxylate) reported a no-observed-adverse-effect level (NOAEL) exceed 60 ppm in the diet (ECHA 2021b). Also, no effects on fertility were seen in a 90-day inhalation study and 90-day rat diet of insoluble and soluble chromium (III) sources

(Derelanko et al. 1999) (Ivankovic and Preussman 1975). Additionally, an *in vitro* study using mouse embryonic stem cells did not show any embryotoxic effects towards chromium trichloride, while potassium chromate (chromium VI) showed apparent embryonic effects (Stummann et al. 2007). Chromium (III) compounds are considered unlikely to show reproductive toxicity when evaluated in rats and mice.

7.6.1.2.6 Genotoxicity

Chromic chloride was not found to be genotoxic in four Salmonella strains tested with or without metabolic activation (PubChem 2021b). However, chromium (VI) reduction to chromium (III) induces highly reactive hydroxyl radicals and other reactive radicals which have genotoxic effects (Cohen et al. 1993).

7.6.1.2.7 Carcinogenicity

Chromic chloride was not classifiable as a human carcinogen (PubChem 2021b).

Occupational exposure to trivalent chromium and other chromium compounds by inhalation has been studied in the chromate manufacturing and ferrochromium industries exposures; all include mixed exposures to both chromium (III) and chromium (VI) (ECHA 2021b).

Epidemiological studies carried out in Germany, Italy, Japan, the U.K., and the USA of workers in the chromate production industry have consistently shown excess risks for lung cancer. The workers may be exposed to a variety of forms of chromium, including chromium (VI) and chromium (III) compounds (INCHEM 2021b). Chromium (VI) species are the etiological agents for increased cancer risk in chromium workers. Data addressing exposures to chromium (III) alone are not available, and the number/focus of the studies is inadequate to evaluate human carcinogenic potential (PubChem 2021b).

The data from oral and inhalation exposures of animals to chromium (III) do not report cancer. IARC concluded that animal data available are insufficient for evaluating the carcinogenicity of chromium (III) compounds (IARC 1990).

7.6.1.2.8 Neurotoxicity

No data were found for the toxicity of chromium chloride. However, a study of workers exposed to chromium (III) ranges from 0.005 to 0.06 mg/m³ suggests that chromium may directly affect the olfactory nerve (Kitamura et al. 2003). Another cohort study found no evidence of central nervous system lesions or changes (Rosenman and Stanbury 1996). No information was located regarding neurological effects in humans or animals after inhalation exposure to chromium (III) compounds or in animals after inhalation exposure to chromium (VI) compounds.

7.6.1.2.9 Mechanism

The mechanism for toxicity of chromium chloride is not reported. However, trivalent chromium may form complexes with peptides, proteins, and DNA, resulting in DNA-protein crosslinks, DNA strand breaks, chromium-DNA adducts, chromosomal aberrations, and alterations in cellular signaling pathways. It can induce carcinogenesis by overstimulating cellular regulatory

pathways and increasing peroxide levels by activating specific mitogen-activated protein kinases. It may also cause transcriptional repression by crosslinking histone deacetylase 1-DNA methyltransferase 1 complex to CYP1A1 promoter chromatin, inhibiting histone modification. Chromium may increase its toxicity by modifying metal regulatory transcription factor 1, causing the inhibition of zinc-induced metallothionein transcription (ATSDR 2012, Kim 1996, Salnikow 2008).

7.6.1.3 Ecological Data

7.6.1.3.1 Fate and Transport

Chromium (III) chloride is very soluble; for risk assessment, a K_{OC} value of 1 (as a worst-case) is used (NzEPA 2021a). As an inorganic salt, it is mobile in an aqueous environment and expected to have a low potential for adsorption. Chromium (III) chloride fully dissociates in aqueous media and has virtually no potential for adsorption to soil or sediment (ECHA 2021b). Exposure to air is considered negligible as inorganic salts do have no vapor pressure. Chromium is removed from the atmosphere by fallout and precipitation (ATSDR 2012).

7.6.1.3.2 Ecotoxicity

Hazard statements: Hazardous to the aquatic environment (long-term), GHS Category: Aquatic Chronic 2; toxic to aquatic life with long-lasting effects (ECHA 2021b, PubChem 2021b).

Chromium trichloride (anhydrous) is insoluble in cold water and assessed by testing chromium trichloride hexahydrate, which is very well soluble in water (585 g/L). All aquatic toxicity data are established with chromium (III) chloride hexahydrate and other chromium (III) that can be used as alternative chromium (III) source to assess aquatic toxicity of chromium (III) chloride. As chromium trichloride and trichloride hexahydrate are acidic in water, pH effects play a specific role when these substances are tested (ECHA 2021b).

Toxicity data for chromium trichloride hexahydrate (chromium (III) chloride hexahydrate) were reported for rainbow trout (*Oncorhynchus mykiss*): 96 hour LD_{50} 57.4 mg/L and saltwater fish (mummichog, *Fundulus heteroclitus*) 161 mg/L. Additionally, the long-term toxicity NOEC in freshwater fish (*Salmo gairdneri*) was 0.246 mg/L (ECHA 2021b, I. INCHEM 2021b).

Short-term toxicity reported as the IC_{50} for freshwater invertebrates (*Daphnia magna*) was 63.3 mg/L, marine invertebrates: 34.7 mg/L, Protozoa (*Tetrahymena pyriformis*): 256 mg/L, and freshwater green algae 2.0 mg/L. Additionally long-term toxicity NOECs for freshwater invertebrates (*Daphnia magna*) was 3.4 mg/L, a marine invertebrate (*Neanthes arenaceodentata*): 258 mg/L, and a freshwater green algae: 0.41 mg/L (ECHA 2021b).

7.6.1.3.3 Degradation and Treatment

When heated to decomposition, chromium (III) chloride emits toxic fumes of chlorine-containing compounds. It can violently react with lithium and nitrogen and is incompatible with strong oxidizers placing it in the Non-Redox-Active Inorganic Compounds group (ATSDR 2012,

PubChem 2021b). These reactions can be classified as fire and health hazards (INCHEM 2021b, PubChem 2021b).

7.6.2 Sodium Hydroxide [CASRN 7647-14-5]

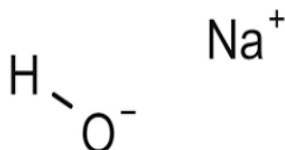


Figure 6. Sodium Hydroxide

7.6.2.1 General Information

Sodium hydroxide is an odorless, white crystalline compound with powerful alkaline properties. Synonyms include caustic sodium, ascarite, and soda lye. It is also hygroscopic.

7.6.2.2 Toxicology Data

Sodium hydroxide is corrosive and irritating and causes direct local effects to the skin, eyes, and gastrointestinal tract following exposure. Inhalation of particulates can cause similar direct local effects on the respiratory tract (OECD 2002a).

7.6.2.2.1 Oral

A study in rabbits determined an LD₅₀ of 325 mg/kg-bw (von Fazekas 1936). In rabbits, an oral LD_{Lo} of 500 mg/kg-bw was found (ChemIDplus 2021a). The type of injury sustained following oral exposure to NaOH depends on the physical form. Ingestion of solid NaOH will injure the mouth and pharynx, while a liquid formulation will damage the esophagus and stomach (Cello et al. 1980, Gumaste and Dave 1992).

7.6.2.2.2 Inhalation

Animal studies on inhalation of NaOH were not found; however, in humans, exposure to a 5% solution of NaOH resulted in irreversible lung damage after one day of exposure to poor ventilation (Hansen and Isager 1991). Exposure to NaOH mists can cause worker-related wheezing and rhinitis but with no effect on lung function (ECHA 2021o).

7.6.2.2.3 Dermal

Application of a 50% solution of NaOH to mice resulted in mortality (20%) if the application was not removed within 30 minutes of exposure (Bromberg et al. 1965). No mortality occurred if the application was immediately removed. Side effects included severe burns.

Irritation studies in pigs showed large blisters within 15 minutes of skin application at concentrations as low as 8% (Srikrishna and Monteiro-Riviere 1991). Application of 8% and 16% resulted in necrosis of all exposed epidermal layers. A 24% exposure leads to necrosis in the subcutaneous tissue.

In humans, the NaOH is irritating at exposures as low as 0.5% (OECD 2002a).

Human patch tests have found no evidence of sensitization by exposure to NaOH (OECD 2002a).

7.6.2.2.4 Ocular

In rabbits, corrosion occurs as low as 1.2%; in some cases, irritation did occur below 1% (OECD 2002a). The corrosive effects were irreversible.

7.6.2.2.5 Development and Reproduction

No data were found.

7.6.2.2.6 Genotoxicity

Sodium hydroxide was negative in the Ames assay (De Flora et al. 1984). There was also no clastogenic effect in the Chinese Hamster Ovary cell chromosomal aberration test without an S9 liver fraction (Morita et al. 1989). Incubation of the cells in the presence of S9 did increase clastogenic activity, but more than likely due to exposure at non-physiological pH levels than the compound itself.

In the mouse micronucleus assay, no increase in the incidence of micronuclei were found (Aaron et al. 1989).

7.6.2.2.7 Carcinogenicity

No data were found.

7.6.2.2.8 Neurotoxicity

No data were found.

7.6.2.2.9 Mechanism

Sodium hydroxide in an aqueous solution breaks protein bonds such as disulfide salt bridges. The bond breaks lead to severe necrosis at the application site and dissolve hair/fingernails after 20 hours of direct contact at pH values higher than 9.2 (PubChem 2021j).

7.6.2.3 Ecological Data

7.6.2.3.1 Fate and Transport

Sodium hydroxide dissociates in water to sodium and hydroxyl ions. It is highly water-soluble and has a low vapor pressure, so it is expected primarily in aqueous environments. As it is present in solution in sodium and hydroxyl ions, it will not adsorb on particulate matter, so, therefore, it is very mobile. It is not expected to bioaccumulate. Depending on the amount of NaOH spilled, the buffering capacity of the soil may neutralize any accumulation in the soil. The compound will be quickly neutralized by carbon dioxide and other acids in the air. Salts will be washed out by rain, but may have at least local aquatic effects.

7.6.2.3.2 Ecotoxicity

Consideration of aquatic toxicity is limited to the sodium and hydroxyl ions and the buffering capacity of the medium. A highly buffered test medium will neutralize the hydroxyl ions, while poorly buffered test media will rapidly increase pH.

The LC₅₀ in a 24-h test in *Carassius auratus* was 160 mg/L (OECD 2002a). At a dose of 100 mg/L, the pH was equivalent to 9.8, and there was no mortality at this level. In *Idis* (*Leuciscus idus melanotus*), the LC₅₀ was 189 mg/L, while the 96-h test in *Gambusia affinis* resulted in an LC₅₀ of 125 mg/L. In pond water, fry of pike perch (*Lucioperca lucioperca* L.) were susceptible to NaOH exposure at 35 mg/L. In *Lebistes reticulatus*, a chronic exposure found decreased survival, growth, and fecundity at concentrations as low as 25 mg/L.

In *Daphnia magna*, a threshold of toxicity was found at 40 mg/L, while in *Ceriodaphnia* cf. *dubia*, the LC₅₀ was 40 mg/L following a 48-h exposure (OECD 2002a). The LC₅₀ in *Ophryotrocha diadema* after a 48-h exposure was between 33 and 100 mg/L.

In the Microtox assay, the 15-min EC₅₀ was 22 mg/L in a non-buffered medium.

7.6.2.3.3 Degradation and Treatment

Sodium hydroxide is a highly alkaline substance that will dissociate completely in water and soil. It will not be environmentally persistent (OECD 2002a).

7.6.3 Oxalic Acid [CASRN 144-62-7]

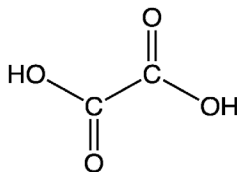


Figure 7. Oxalic Acid

7.6.3.1 General Information

Oxalic acid is a colorless crystalline solid that dissolves in water to give colorless, dicarboxylic acidic solutions. Oxalic acid is used in dyeing processes and bleaches, including cleaning, and removing rust and acting as a chelating agent for metal cations. It is found in everyday foods, such as spinach, beet leaves, parsley, chives, and cassava, all exceptionally high in oxalates (ECHA 2021i). Oxalic acid can be generated from the dehydrogenation of glycolic acid produced by the metabolism of ethylene glycol. Oxalate is a competitive inhibitor of lactate dehydrogenase (LDH) and a well-known uremic toxin. Synonyms include ammonium oxalate, ethane-1,2-dioate, ethane-1,2-dioic acid, ethanedioate, ethanedioic acid, ethanedioic acid dihydrate, and others (PubChem 2021g).

7.6.3.2 Toxicology Data

The toxicity of oxalic acid is due to kidney failure caused by precipitation of calcium oxalate that form kidney stones (PubChem 2021g). In some patients with renal insufficiency, oxalate deposits in cardiac tissue has led to congestive heart failure (Salyer and Hutchins 1974). Oxalic acid can also cause joint pain due to similar precipitates in the joints. In humans, ingested oxalic acid has an oral lowest published lethal dose of 600 mg/kg (PubChem 2021g).

7.6.3.2.1 Oral

Oxalic acid is classified as harmful if swallowed – GHS Category 4 for acute oral toxicity (PubChem 2021g).

In humans, the probable oral lethal dose has been estimated between 50–500 mg/kg (EPA 1992), and fatal doses have been reported between 3–30 g in people (EMEA 2003, PubChem 2021g).

The oral LD₅₀ in rats was reported to be between 375 mg/kg (Vernot et al. 1977) and LD₅₀ of 7,500 mg/kg body weight (EPA 2005). The lowest observed adverse effect level (LOAEL) was determined to be 1250 mg/kg/day (EPA 2005). At the highest dose, the animals had reduced thyroid weights, changes in hormone levels, renal toxicity, and reduced thyroid function (PubChem 2021g, EPA 1992).

7.6.3.2.2 Inhalation

After inhalation exposure, irritation and ulceration of the respiratory tract's mucous membrane have been reported (PubChem 2021g). Burning and corrosion of the mouth, esophagus, and stomach have been reported following oral exposure (PubChem 2021g).

Oxalic acid is classified in Category 1B of the GHS as corrosive to the respiratory tract (ECHA 2021i).

7.6.3.2.3 Dermal

Oxalic acid is classified as harmful if in contact with skin - Category 4 in the GHS for acute toxicity (PubChem 2021g).

The rabbit dermal LD₅₀ was 20 g/kg (EMEA 2003). A study conducted on rabbits used a 1:10 dermal solution of oxalic acid and observed redness, hardening, and "bloodshot" of the skin. Oxalic acid is classified as hazardous with the risk phrase "Harmful in contact with skin" (SWA 2021).

7.6.3.2.4 Ocular

Oxalic acid is classified in Category 1B of the GHS as corrosive to the eyes (PubChem 2021g). Oxalic acid was reported to cause burns, conjunctivitis, and corneal damage when a solution came in contact with the eyes (ECHA 2021i, PubChem 2021g).

7.6.3.2.5 Development and Reproduction

Oxalic acid does not show specific reproductive or developmental toxicity. Any reproductive and developmental effects are considered secondary to parental toxicity (ECHA 2021i, PubChem 2021g, EPA 2005).

7.6.3.2.6 Genotoxicity

Oxalic acid is not considered genotoxic based on available studies. Reverse mutation assays using *Salmonella typhimurium* were negative (EPA 2005). Additionally, a chromosome aberration test in Chinese hamster lung fibroblasts was negative (EMEA 2003).

7.6.3.2.7 Carcinogenicity

Oxalic acid is not listed by IARC (IARC 2021). Further, a study found no evidence of carcinogenicity in rats at doses of approximately 50–600 mg/kg bw/day (EMEA 2003).

7.6.3.2.8 Neurotoxicity

No data were found.

7.6.3.2.9 Mechanism

May cause damage to organs (kidney) through prolonged or repeated exposure - Cat. 2 GHS (PubChem 2021g).

Oxalic acid combines with metal ions such as Ca^{2+} , Fe^{2+} , and Mg^{2+} to deposit corresponding oxalates' crystals, which irritate the gut and kidneys. The toxicity of oxalic acid is due to kidney failure caused by solid calcium oxalate precipitation, the kidney stones' main component (ECHA 2021i). Oxalic acid can also cause joint pain due to the formation of similar precipitates in the joints and perturb the calcium-potassium ratio in critical tissues (PubChem 2021g). Ingestion of ethylene glycol results in oxalic acid as a metabolite that can also cause acute kidney failure (EMEA 2003).

7.6.3.3 Ecological Data

7.6.3.3.1 Fate and Transport

7.6.3.3.2 Ecotoxicity

Oxalic acid is used as an inert ingredient in pesticide formulations and is toxic to terrestrial vertebrates such as rats with LD_{50} of 375 mg/kg (PubChem 2021g).

Oxalic acid's quick aerobic and anaerobic biodegradability reduces the risk and poses a low risk of toxicity to all aquatic organisms, with effects exceeding 1000 ppm across all taxa (ECHA 2021i).

7.6.3.3.3 Degradation and Treatment

Oxalic acid is used in pesticide formulations as an inert ingredient; rapid biodegradation of oxalic acid limits its presence in drinking water; therefore, exposure through this route is expected to be minimal (PubChem 2021g). The primary route of exposure expected for the inert ingredient use of oxalic acid is through the food portion of the diet. The dietary exposure assessment for the inert ingredient use of oxalic acid was conducted by the EPA using the generic screening model to estimate oxalic acid dietary exposure (EPA 2005).

7.7 DIPSOL IZ-C17+B

7.7.1 Polyamine-1, Ethyleneimine

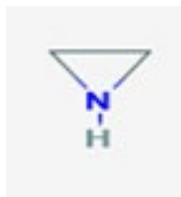


Figure 8. Ethyleneimine (C₂H₅N)

7.7.1.1 General Information

A search in PubChem and ECHA databases for CASRN 9002-98-6 yielded an entry for aziridine and ethyleneimine (EI) which appear to be associated with CASRN 151-56-4 (PubChem 2021a). This compound is a monomer with the physical and chemical characteristics presented in Appendix C. The compound with CASRN 9002-98-6 is a linear polymer of ethyleneimine and is typically referred to as polyethyleneimine (PEI) or aziridine, homopolymer (ECHA 2021a).

EI is a clear, colorless liquid. It is strongly alkaline and has an ammonia-like odor. EI and polymerization products are used in a wide range of industries, including paper manufacturing, textiles, adhesives, coatings, cosmetics and chemical processing and it is also an indirect food additive in food contact products (PubChem 2021a).

7.7.1.2 Toxicology Data

There is a reasonably extensive toxicity database for the EI monomer. It is very toxic acutely and there have been reports of fatalities from vapor exposures (Gresham and West 1975). It is a severe skin and eye irritant (NIOSH 1973). EI is a potent alkylating agent and is mutagenic in several *in vitro* and *in vivo* test systems (Verschaeve 1990). The ACGIH has established an 8-hour TLV[®] of 0.05 ppm based on irritation to the upper airways and damage to the liver and kidney, and they consider it to be a confirmed animal carcinogen (ACGIH 2019).

In contrast to the EI monomer, there is very little toxicity information specific to polymerized ethyleneimine (PEI). The ECHA database does provide GHS criteria, and they include GHS scores, but there are no supporting references provided (ECHA 2021a).

7.7.1.2.1 Oral

The oral LD₅₀ in rats ranges between 2,000 and 8,000 mg/kg and may depend on the size of the polymer, with the larger polymers showing lower acute toxicity (INCHEM 2021a). In repeated dosing studies in rats, doses as high as 1,000 mg/kg-day for 8.5 months produced no clinical signs or pathological changes in the test animals. In a similar study in dogs, animals dosed at

250, 500, and 1,000 mg/kg-day for 9 months exhibited dose-related degenerative changes in the kidney (INCHEM 2021a).

7.7.1.2.2 Inhalation

No data were available for the polymer form. In the monomer form the chemical aziridine has a reported median lethal concentration (LC₅₀) of 15 ppm (0.03 mg/L) in rats following an eight-hour exposure (IMAP 2014a). Signs and symptoms include cough, dizziness, headache, labored breathing, nausea and vomiting (PubChem 2021a).

7.7.1.2.3 Dermal

PEI can cause skin irritation and may cause allergic skin reactions (ECHA 2021a).

7.7.1.2.4 Ocular

PEI can cause severe eye damage (BASF 2020, ECHA 2021a).

7.7.1.2.5 Development and Reproduction

No information was found on developmental or reproductive effects.

7.7.1.2.6 Genotoxicity

No data available for polymer. The monomer (Aziridine), is classified as hazardous Category 2 mutagenic substance (PubChem 2021a).

7.7.1.2.7 Carcinogenicity

No data were available for the polymer form. In the monomer form no epidemiological data relevant to the carcinogenicity were available. There is limited evidence in experimental animals for the carcinogenicity; however, the monomer is classified as possibly carcinogenic to humans (Group 2B) (PubChem 2021a).

7.7.1.2.8 Neurotoxicity

No data available.

7.7.1.2.9 Mechanism

No data available.

7.7.1.3 Ecological Data

7.7.1.3.1 Fate and Transport

The BASF PEI was completely soluble in water (BASF 2020). The monomer has a reported solubility in water of 23.3 mg/L (CompTox 2022).

The vapor pressure was reported to be 18 mmHg at 20 °C (BASF 2020). The vapor pressure of the monomer is 213 mmHg at 25° C (CompTox 2022).

7.7.1.3.2 Ecotoxicity

In the orfe (*Leuciscus idus*), the 96hour LC₅₀ ranged from 1–102.4 mg/L (BASF 2020).

No data were available for aquatic invertebrates or aquatic algae.

7.7.1.3.3 Degradation and Treatment

PEI was found to be poorly biodegraded but would adsorb to activated sludge (BASF 2020).

7.7.2 Diethylenetriamine (DETA) [CASRN 111-40-0]

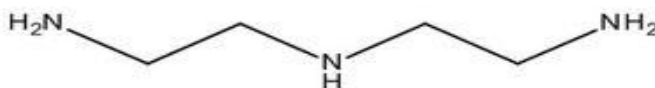


Figure 9. Diethylenetriamine (C₄H₁₃N₃)

7.7.2.1 General Information

DETA is a clear to slightly yellow liquid. Industrial uses include an epoxy curing agent in polyurethane manufacture, ion exchange resins in the food industry, and the oil industry as a solvent (ECHA 2021d). Synonyms include 2,2'-iminodi(ethylene), bis(2-aminoethyl)amine (ECHA 2021d, PubChem 2021d).

7.7.2.2 Toxicology Data

There is a reasonably robust toxicity database for DETA. Unfortunately, most of the references consist of very old citations or unpublished contractor reports that are unavailable. Much of the

information presented here is from European and U.S. databases, which provide summary information.

7.7.2.2.1 Oral

The oral LD₅₀ in rats was reported to be 1,553 mg/kg. Toxic signs included seizures and convulsions. Gross pathological findings included petechial hemorrhage of the lungs and effects on the liver and kidneys (ECHA 2021d).

7.7.2.2.2 Inhalation

In a 4-hour nose-only exposure to aerosolized DETA using F344 rats, the LD₅₀ was found to be between 70 and 300 mg/m³ (ECHA 2021d).

7.7.2.2.3 Dermal

The dermal LD₅₀ in rabbits was reported to be 1045 mg/kg (ECHA 2021d).

In a human study, undiluted DETA was highly caustic, causing severe burns to the skin. (Savitt 1955). In another human skin test, a single drop of DETA caused a mild to a moderate skin reaction in 9 out of 50 volunteers (Kydd 1960).

DETA was tested for sensitization using the guinea pig maximization test and elicited a strongly positive result (Leung 1997).

7.7.2.2.4 Ocular

DETA was corrosive when instilled into rabbit eyes. Washing the eyes following compound installation reduced the severity of the effects (ECHA 2021d).

7.7.2.2.5 Development and Reproduction

In a developmental toxicity study, male and female Wistar rats were dosed (oral gavage) with DETA at 30, 100, and 300 mg/kg-d. The animals were dosed for 2 weeks prior to mating and during mating, gestation, and 4 days postpartum. The authors found post-implantation losses in the two high dose groups due to maternal toxicity. There were no developmental effects seen in the offspring (ECHA 2021d).

7.7.2.2.6 Genotoxicity

DETA was negative when tested in the Ames mutagenicity test. DETA was tested at concentrations up to 10,000 µg/plate in four tester strains of Salmonella both with and without activation (Zeiger 1987). DETA also tested negative in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations (PubChem 2021d).

7.7.2.2.7 Carcinogenicity

DETA was applied to the skin of male C3H/HeJ mice 3 times per week for nearly 2 years to evaluate its potential carcinogenic effects. There were no treatment-related tumors found on the skin or any internal organs or systems (ECHA 2021d).

7.7.2.2.8 Neurotoxicity

DETA is reported as a weak partial agonist of N-methyl-D-aspartic acid (NMDA) receptor and has been explored as a potential polyamine neuroprotective agent (PubChem 2021d).

7.7.2.2.9 Mechanism

DETA was screened in 471 *in vitro* tests and is active in 9 tests to include nuclear receptor activation (estrogen receptor alpha), cell cycle and DNA binding activity (PubChem 2021d).

7.7.2.3 Ecological Data

7.7.2.3.1 Fate and Transport

Diethylenetriamine is miscible in water, has a relatively low vapor pressure and a low K_{OW} , and for these reasons, it is not likely to bioaccumulate. It is not susceptible to hydrolysis or photolysis, and biodegradation is thought to be the primary process for environmental degradation (ECHA 2021d).

7.7.2.3.2 Ecotoxicity

The 96-hour LC_{50} in guppies (*Poecilia reticulata*) was 430 mg/L (ECHA 2021d). In a chronic test, eggs from three-spined stickleback were exposed to DETA for 28 days. At the highest concentration tested (10 mg/L), there were no effects on hatching, mortality, or growth (ECHA 2021d), and the NOEC was >10 mg/L (Millipore-Sigma 2017). A static toxicity study in *Daphnia* reported the 48-hour LC_{50} to be 16 mg/L (Millipore-Sigma 2017), and the 21-day chronic test found a NOEC of 5.6 mg/L (ECHA 2021d).

In a long-term (8-week) chronic study in earthworms, DETA caused a significant decrease in reproduction at a 1000 mg/kg soil concentration. The NOEC was 500 mg/kg soil (ECHA 2021d).

There was no information available on the effects of DETA on terrestrial plants.

7.7.2.3.3 Degradation and Treatment

Biodegradation is likely the primary process for environmental degradation (ECHA 2021d).

7.8 DIPSOL IZ-C17+Ni

7.8.1 Nickel (II) Sulfate (NiSO₄) [CASRN 7786-81-4]

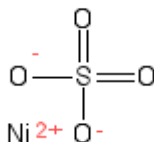


Figure 10. Nickel (II) Sulfate

7.8.1.1 General Information

Nickel sulfate is a compound commonly used for electroplating and as a chemical intermediate to produce other nickel compounds. Nickel is found abundantly in nature in laterite ore minerals, such as limonite, garnierite, and pentlandite (ATSDR 2005b). Nickel Sulfate is a yellow, green, or blue-colored crystalline inorganic compound that produces toxic gases upon heating (PubChem 2021f). Nickel has a biological role and is found in certain enzymes, including urease, hydrogenase, methyl coenzyme M reductase, and carbon monoxide dehydrogenase (ATSDR 2005b).

7.8.1.2 Toxicology Data

The toxicity of nickel sulfate is linked to the toxicity of nickel itself. Nickel is absorbed mainly through the lungs and gastrointestinal tract and accumulates in the lungs, thyroid, kidney, heart, and liver. Absorbed nickel is excreted in the urine, and unabsorbed nickel is excreted in the feces (ATSDR 2005b). Exposure can cause skin and asthma-like allergies, severe dermatitis, lungs, kidneys, gastrointestinal tract, and neurological system effects (ECHA 2021g, PubChem 2021f). Nickel sulfate is a known carcinogen and is associated with an increased risk of developing lung and nasal cancers (PubChem 2021f). The primary hazard is the threat to the environment (ECHA 2021g, NzEPA 2021b). Immediate steps should be taken to limit its spread to the environment.

7.8.1.2.1 Oral

Nickel sulfate is labeled as Category 4 for acute toxicity. One acute oral rat study found the LD₅₀ at 264 mg/kg for nickel sulfate hexahydrate (CASRN 10101-97-0) (ChemIDplus 2021c). Sigma's SDS reports an oral LD₅₀ of 325 mg/kg in male rats based on OECD Test Guideline 401 (Sigma-Aldrich 2015).

In a 2-year oral gavage study, male and female rats were administered 10–50 mg/kg bw/day of nickel sulfate hexahydrate (CASRN 10101-97-0) with effects on body weight (ECHA 2021g). There were also behavioral changes such as somnolence and changes to fluid intake (ChemIDplus 2021c). Additionally, gastrointestinal changes in structure or function of salivary glands, hypermotility, and diarrhea have been reported (IMAP 2014c).

In humans, oral exposure to nickel sulfate is associated with abdominal pain, dizziness, headache, nausea, and vomiting (PubChem 2021f). One reported accidental ingestion of nickel sulfate crystals (approximately 570 mg Ni/Kg) by a 2-year-old child resulted in cardiac arrest and death within 8 hours of ingestion (ATSDR 2005b).

7.8.1.2.2 Inhalation

Nickel sulfate is categorized as a respiratory sensitizer 1 (ECHA 2021g, PubChem 2021f) and is reported to cause cough and sore throat (PubChem 2021f). Nickel sulfate is classified as hazardous with the risk phrase "Harmful by inhalation." The LC₅₀ value was calculated to be 2.48 mg/L in male and female rats exposed to nickel sulfate hexahydrate (ECHA 2021g).

Nickel sulfate was evaluated for repeated-dose inhalation toxicity in rats. Exposures were associated with rapid breathing, reduced mean terminal body weights, lethargy, and increased mortality. Females exposed to levels of 7.0 mg/cu m exhibited lesions in the liver, lung, thymus, nose, and bronchial lymph nodes with testicle lesions in males (NzEPA 2021b, IMAP 2014c).

Pulmonary lesions were characterized by edema and hemorrhage, with epithelial degeneration of the alveoli caused by vacuolization and necrosis of isolated cells and hypertrophy of goblet cells (PubChem 2021f).

In humans, a man exposed to nanosized particles (50 nm) was reported to have urinary nickel concentrations of 700 mg/L compared with < 0.1–13.3 mg/L to the non-exposed individuals; and died 13 days after exposure due to respiratory distress. Histological examination reported alveolar damage and edema in the lungs and tubular necrosis in the kidneys (ATSDR 2005b).

A repeat exposure study in 14 male and 12 female workers exposed to nickel compounds (nickel sulfate and nickel chloride, concentrations exceeding (4–26 times TLV of 0.05 mg/m³) in a chemical plant for 25 and 15 years, respectively investigated biochemical markers of kidney damage. After analysis, it was concluded that exposure to high soluble nickel compounds has adverse effects on renal tubular function (Tyle 2008).

7.8.1.2.3 Dermal

Nickel sulfate is categorized as a skin irritant 2 and a skin sensitizer 1 (PubChem 2021f)

In a 30-day study where male rats were dermally exposed to nickel sulfate, the NOAEL was defined as 40 mg Ni/kg bw/day (Tyle 2008). This study suggests that animals may have been orally exposed to the chemical by grooming or licking the chemical paste applied onto animals' backs (ECHA 2021g). Another study on rabbits reported that dermal exposure was mildly irritating, producing mild erythema, which was reversible within 48 hours (ECHA 2021g).

Further studies using other exposure methods such as intraperitoneal (i.p.) injections, intramuscular (i.m.) injections have been conducted with nickel sulfate. Those values are reported as rat LD₅₀ 500 mg/kg via intraperitoneal injection and mouse LD₅₀ intraperitoneal 20894 µg/kg (PubChem 2021f). While some of these studies have reported the development of tumors at the injection site, the route of administration is not considered relevant as humans are likely to be exposed via inhalation, oral intake, or dermal contact (Tyle 2008). Reports on the analogous nickel sulfate hexahydrate (ATSDR 2005b, Tyle 2008) indicate that dermal absorption is expected to be very limited (ATSDR 2005b).

7.8.1.2.4 Ocular

The chemicals of this group are mild eye irritants. Nickel sulfate is reported to be a slight eye irritant in animal studies (ECHA 2021g), with redness reported in humans (PubChem 2021f). Data available on a rabbit study indicate that 0.1 g of nickel sulfate hexahydrate (CASRN 10101-97-0) produced iritis and conjunctivitis (ECHA 2021g). Observation in human volunteers exposed to nickel sulfate reported mild irritation at 0.13% concentration. In comparison, the threshold to produce a skin reaction on intact skin was 20% (Tyle 2008).

7.8.1.2.5 Development and Reproduction

Nickel sulfate is labeled as reproductive toxicity Category 2 (ECHA 2021g) or GHS reproductive toxicity Category 1B (PubChem 2021f).

An oral mouse study conducted on males at a dose of 250 mg/kg reported paternal effects on spermatogenesis, including genetic material, sperm morphology, motility, and count (PubChem 2021f). In male rats, 23 mg NiSO₄/kg reduced spermatogenesis and sperm motility; it was also noted that treated rats had smaller testes weights than the control rats (ECHA 2021g).

A cohort study of 356 women who worked in a nickel hydrometallurgy plant exposed to nickel sulfate (0.08–0.196 Ni/m³) and a control group of 342 local female construction workers arctic region of Russia primarily. The study reported that the spontaneous abortion rate was higher in the women exposed to nickel sulfate (15.9%) versus the female construction workers (8.5%). However, the study's authors note that the nickel hydrometallurgy workers may also have been exposed to high chlorine concentrations along with other confounding factors not controlled for (ATSDR 2005b, Tyle 2008).

At the Severonikel nickel refinery in the town of Moncegor'sk, pregnant workers were exposed to nickel at concentrations as high as 0.33 mg Ni/m³. In 1994, it was reported that there were increased spontaneous abortions, congenital defects and other health effects in these refinery workers (Chashschin 1994). A registry for the workers was established; however, epidemiological studies conducted thus far with the Kola registry have not identified a causal link between exposure and reproductive/developmental effects (Vaktskjold et al. 2004; Vaktskjold et al. 2006; Vaktskjold et al. 2007, 2008a, 2008b).

7.8.1.2.6 Genotoxicity

Nickel sulfate is classified as a positive mutagenic substance in GSH Category 2 (PubChem 2021f). Under the Australian Hazardous Substances Information System (HSIS), nickel sulfate is labeled a hazardous Category 3 mutagenic substance with the risk phrase "Possible risk of irreversible effects" (IMAP 2014c).

Studies conducted with human and mammalian cells show that nickel sulfate induces chromosomal effects in a dose-dependent manner (Tyle 2008).

7.8.1.2.7 Carcinogenicity

Nickel sulfate is classified as hazardous Category 1A carcinogenic substances with the risk phrase "May cause cancer by inhalation" (PubChem 2021f). The International Agency for Research on Cancer (IARC) has classified soluble nickel compounds as "Carcinogenic to humans" (Group 1) (IARC 2012). The NTP (2021) identifies all nickel compounds as a known human carcinogen.

Epidemiological data from nickel refineries demonstrate a positive dose-dependent association between exposure to nickel sulfate and an increased risk of respiratory cancers (Tyle 2008). A cohort study conducted on refinery workers in South Wales confirmed that nickel sulfate was a significant risk factor in developing lung and nasal cancers. Another study conducted on Harjavalta (Finland) workers reported that the majority of the exposure to soluble nickel compounds between 1960 and 1985 was nickel sulfate with an inhalable aerosol fraction of 0.1–0.4 mg Ni/m³ had an increased risk of lung and nasal cancers (Tyle 2008).

7.8.1.2.8 Neurotoxicity

No studies were located regarding neurological effects in humans after inhalation exposure to Nickel. However, animal studies on male mice at doses > 0.1 mg/kg bw-day produced a dose- and time-dependent reduction in the thickness of turbinate olfactory epithelium (ECHA 2021g).

7.8.1.2.9 Mechanism

Nickel is known to substitute for other essential elements in certain enzymes, such as calcineurin. It is genotoxic, and some nickel compounds promote cell proliferation. Nickel has a high affinity for chromatin proteins, particularly histones and protamines (ATSDR 2005b). The complexing of nickel ions with heterochromatin results in disturbed gene expression alterations via DNA hypermethylation, gene silencing, and inhibition of histone acetylation. Nickel has also been shown to alter several transcription factors, including NF-KB (ATSDR 2005b, ECHA 2021g). There is also evidence that nickel ions inhibit DNA repair by inhibiting repair enzymes or competing with zinc ions for binding to zinc-finger, resulting in structural changes in DNA. Nickel ions can also complex with several cellular ligands resulting in oxygen radicals, which induce base damage, DNA strand breaks, and DNA protein crosslinks (ATSDR 2005b, ChemIDplus 2021c).

7.8.1.3 Ecological Data

7.8.1.2.1 Fate and Transport

Nickel sulfate dissolves in water and can be easily transported via waterways (Arun 2011).

Nickel is released to the atmosphere in particulate matter, dispersed by wind, removed by sedimentation, dry deposition, washout by rain, and rainout (Schroeder et al.1987). The removal rate and distance traveled from the source depend on source characteristics, particle size and density, and meteorological conditions (ATSDR 2005b).

Adsorption of nickel onto suspended particles in water is one of the removal mechanisms of Nickel from the water column. The water-borne particulate matter competes with adsorption onto dissolved organic matter, limiting the amount of Nickel that can be removed from the water column through the settling of suspended particles (Martino 2003).

7.8.1.3.2 Ecotoxicity

Nickel sulfate is classified as both Aquatic Acute and Aquatic Chronic Category 1 for toxicity (PubChem 2021f).

The substance is very toxic to aquatic organisms and may cause long-term effects in the aquatic environment. It is strongly advised not to let the chemical enter the environment (ECHA 2021g).

Nickel sulfate is classified as having toxicity to fathead minnow LC_{50} 2.9–17.6 mg/L, toxicity to *Daphnia magna* and other aquatic invertebrates (ChemIDplus 2021c), EC_{50} 2 mg/L, toxicity to *Scenedesmus quadricauda* (green algae) EC_{50} 0.58 mg/L (Sigma-Aldrich 2015).

7.8.1.3.3 Degradation and Treatment

In water, nickel primarily exists in the hexahydrate form. While nickel forms strong, soluble complexes with hydroxide ion, sulfate ion, and hydrogen carbonate, these species are minor compared with hydrated nickel (II) ion in surface water and groundwater with pH (Arun 2011).

Precipitation can remove soluble nickel from water. In aerobic waters, nickel ferrite is the most stable compound (ATSDR 2005b). Nickel may also be removed by coprecipitation with hydrous iron and manganese oxides. Nickel removed by precipitation and coprecipitation settles into the sediment.

7.8.2 Polyamine-2, 2(-chloromethyl)oxirane [CASRN 25988-97-0]



Figure 2. 2(-chloromethyl)oxirane

7.8.2.1 General Information

Synonyms for this constituent include dimethylamine-epichlorhydrin copolymer, methanamine, N-methylmethanamine.

7.8.2.2 Toxicology Data

Methanamine (CASRN 25988-97-0) is one of a group of polymers screened for health and environmental effects by Health Canada (ECCC 2020). They included methanamine in a group of polymers referred to as poly-(EDMA) polymers. The poly-(EDMA) polymers were evaluated as part of a more extensive study that screened nine polyamines. The poly-(EDMA) compounds were formed by reacting epichlorhydrin with dimethylamine. They occur as liquids and are typically used in wastewater treatment, pulp and paper manufacturing, food packaging, and electroplating.

Unfortunately, there was no mammalian toxicity information available and only limited data from ecological receptor species. The GHS scores and descriptor information are presented here, but no supporting data or rationale for these scores were found except for the limited aquatic toxicity data.

7.8.2.2.1 Oral

Methanamine was classified as harmful if swallowed (ECHA 2021k).

7.8.2.2.2 Inhalation

Methanamine was classified as harmful if inhaled (ECHA 2021k).

7.8.2.2.3 Dermal

No information was available.

7.8.2.2.4 Ocular

Methanamine can cause serious eye injury (ECHA 2021k).

7.8.2.2.5 Development and Reproduction

No information was available.

7.8.2.2.6 Genotoxicity

No information was available.

7.8.2.2.7 Carcinogenicity

No information was available.

7.8.2.2.8 Neurotoxicity

No information was available.

7.8.2.2.9 Mechanism

No information was available.

7.8.2.3 Ecological Data

7.8.2.3.1 Fate and Transport

Poly-2 is water soluble with a high molecular weight. If released into the environment, it is expected to be adsorbed and be retained in the soil and sediment. Due to its high molecular weight, it is not likely to volatilize (ECCC 2020).

7.8.2.3.2 Ecotoxicity

Cary et al. (1987) has tested the acute toxicity of poly-2 in *Daphnia* and found a 48-hour EC₅₀ of 0.08 mg/L. In fish (*Lepomis macrochirus*), the 96-hour LC₅₀ was 0.18 mg/L and in *Pimphales promelas*, the LC₅₀ was 0.25 mg/L. Goodrich et al. (Goodrich 1991) found that the 96-hour LC₅₀ in rainbow trout (*Onchorhynchus mykiss*) ranged from 0.042 mg/L to 0.156 mg/L depending on the size of the polymer. Additionally, the addition of as little as 50 µg humic acid or other organic compounds markedly reduced toxicity (Cary 1987, Goodrich 1991).

There were no data on terrestrial plants or animals and no avian data.

7.8.2.3.3 Degradation and Treatment

There are no data on biodegradation but based on the structure, the poly (EDMA) polymers are expected to show a low biodegradation potential (ECCC 2020).

7.9 Caustic Soda

7.9.1 Sodium Hydroxide [CASRN 1310-73-2]

See section 7.6.2 for information sodium hydroxide.

7.9.2 Sodium Chloride [CASRN 7647-14-5]

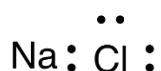


Figure 12. Sodium Chloride

7.9.2.1 General Information

Synonyms include halite, salt, table salt, rock salt, common salt. Sodium chloride is an inorganic salt of sodium and chloride. It is a white crystalline solid. It is well known in cooking and seasoning food, but there are thousands of commercial uses for sodium chloride, including de-icing roadways, agriculture, chemical manufacturing, and water conditioning (ECHA 2021n).

7.9.2.2 Toxicology Data

Sodium chloride dissociates into Na^+ and Cl^- ions. Sodium ions are essential for life and help maintain proper blood pressure and water balance in the body. The primary source of sodium intake is food. The DFA reported that the daily sodium intake through the diet is 4,000–6,000 mg/day (EPA 2003).

7.9.2.2.1 Oral

In animal studies, Wistar rats were gavaged with a 25% solution of NaCl in water at 2,150, 3,160, 4,640, and 6,810 mg/kg. All rats in the two high-dose groups died; the LD_{50} was 3,550 mg/kg (ECHA 2021n). In humans, high levels of exposure can cause nausea, vomiting, muscle twitching, convulsions and death (EPA 2003). Campbell and Train (2017) surveyed the literature describing human fatalities resulting from accidental and deliberate salt ingestion. They found that about 10 g of sodium or 5 teaspoons of salt was lethal in children, while in adults, the lethal dose was about 4 tablespoons of salt (25 g). In some cases, the salt was taken as an emetic and in some cases, it was mistaken for sugar. In one case report, a six-year-old boy consumed an estimated 4 tablespoons of rock salt. The resulting serum sodium levels were 234 mEq/L. Normal serum sodium levels are 140 mEq/L and levels of 160 mEq/L are generally lethal, yet the patient survived (Kupiec 2004).

In chronic feeding studies with sodium chloride in rodents, toxic effects included hypertension, edema, and nephrotoxicity and kidney failure. Male SD rats were fed diets with elevated sodium chloride. Concentrations of NaCl in the test diets ranged from 0.15% in the control diet and 2.8,

5.6, 7.0, 8.4 and 9.8% elevated salt test groups. All rats in the high sodium diets showed elevations in mean systolic blood pressure. Approximately 20% of the rats in the three highest dose groups developed severe and generally fatal edema and extreme damage to the kidneys (Meneely 1953a, 1953b). Dahl and Heine (1961) reported similar effects on blood pressure in rats fed diets supplemented with sea salt. Long-term epidemiology studies confirm the hypertensive effects of high salt diets in humans (Barttarbee et al. 1978).

In drinking water, the threshold for taste is 30–60 mg/L and the EPA has established a threshold of 20 mg/L for people on a 500 mg/day sodium-restricted diet (EPA 2018).

7.9.2.2.2 Inhalation

There is limited information on the inhalation hazard from NaCl. In a poorly documented study, the acute LC₅₀ of sodium chloride was greater than 42 mg/L. This is based on a 1-hour exposure to an aerosol of 20% sodium chloride (ECHA 2021n).

7.9.2.2.3 Dermal

Undiluted or dilute solutions of sodium chloride did not irritate intact rabbit skin (ECHA 2021n). Herouet et al. (1999) used Langerhans cells to investigate the sensitizing potential of four chemicals. In this assay, sodium chloride was used as a neutral control chemical and did not demonstrate the biomarker changes seen in the sensitizing chemicals.

7.9.2.2.4 Ocular

There is little direct information on eye irritation. Normal saline (0.9%) has been used to treat eye irritation from contact lens wear (Barabino 2005). Eye irritancy data with 100% NaCl in animal studies are inconclusive (ECHA 2021n), but anecdotal evidence from seawater exposures (about 35,000 mg/L NaCl) suggests that it is an irritant.

7.9.2.2.5 Development and Reproduction

There were no data on potential reproductive toxicity from sodium chloride.

Grollman and Grollman (1962) investigated the effects of administering 1% and 2% sodium chloride in drinking water to pregnant rats at various times in the gestation cycle. Offspring from animals treated with 2% NaCl starting 7 days before pregnancy or day 5 of gestation were hypertensive even at 1 year of age. The low dose (1% NaCl) had no noticeable effect on blood pressure in the offspring.

7.9.2.2.6 Genotoxicity

Moore and Brock (1988) tested sodium chloride in a mouse lymphoma cell bioassay. They found a positive dose-response in both mutant frequency and number. The sodium chloride concentrations required to produce these effects were extremely high and represented non-physiological exposure conditions. Fujie et al. (1990) also reported chromosomal aberrations with soy sauce (18% NaCl) and 40 mM NaCl/kg body weight.

7.9.2.2.7 Carcinogenicity

There are no animal studies to show that sodium chloride is carcinogenic. Based on the widespread use of salt in cooking and everyday life and the U.S. Food and Drug Administration classification as Generally Recognized as Safe (GRAS), the European Union concluded that that sodium chloride should not be classified as a carcinogen (ECHA 2021m).

There have been animal studies (Chamely 1985, Nishikawa 1995, Fox 1999) as well as human epidemiology studies (Nogan 2002, Strumylaite 2006, Peleterio 2011) linking a higher incidence of stomach cancer to salt intake. More recent evidence suggests a complex association between stomach cancer and salt intake and may involve a synergistic response with *Helicobacter pylori* infection (Wang 2009).

7.9.2.2.8 Neurotoxicity

No data were available. Since nerve transmission depends upon a balance of sodium and potassium ions across the axon membrane, it is likely that very high sodium ion levels would tend to make propagation of action potentials more difficult.

7.9.2.2.9 Mechanism

The EPA (2003) summarized many epidemiology studies that showed a significant correlation between sodium intake and elevated systolic and diastolic blood pressure. Hypertension is linked to a greater risk of strokes and cardiovascular and renal effects. Despite the convincing association between salt exposure and hypertension, there was no clear evidence that reduced salt intake reversed the risk of cardiovascular disease (EPA 2003).

7.9.2.3 Ecological Data

7.9.2.3.1 Fate and Transport

Sodium chloride is highly soluble in water and dissociates into Na⁺ and Cl⁻ ions. These ions are very mobile in the environment and are not expected to partition to sediments or bioaccumulate (ECHA 2021n).

7.9.2.3.2 Ecotoxicity

In goldfish (*Lepomis machrochirus*), the acute 96-hour LC₅₀ as reported in a standardized test using a flow-through methodology ranged from 5840 mg/L (ECHA 2021) to 12,900 mg/L (Trama 1954). In a chronic (33 days) study with fathead minnows (*Pimphles promelas*), the no-effect concentration was 252 mg/L (ECHA 2021n).

Sodium chloride toxicity to freshwater invertebrates ranges from 1,022–2,100 mg/L in water fleas (*Daphnia magna*) based on short term, 48-hour toxicity tests (Warne 1999, Guilhermino 2000). In an endangered Unionid mussel (*Lampsilis siliquoidea*), the 24-hour EC₅₀ for juvenile mussels ranged from 911–3,092 mg/L chloride depending on water hardness (N. Wang et al. 2018). Birds are susceptible to NaCl toxicity due to consuming salt crystals mistaken for food

(New Hampshire Department of Environmental Services 2007). The 12-hour LD₅₀ for house sparrows was 3,000–3,500 mg/kg (Bollinger T. 2005).

In a terrestrial plant (red fescue), the short-term (7 days) EC₅₀ for seed germination was 500.8 mg/kg soil (ECHA 2021n).

7.9.2.3.3 Degradation and Treatment

As an inorganic salt, NaCl does not degrade. PubMed lists over 500 references on NaCl removal from water, including adsorption (Shanmugasundaram and Sudalaimani 2012), ion exchange (Popper 1963) and reverse osmosis (Henmi 2010).

7.9.3 Sodium Carbonate [CASRN 497-19-8]

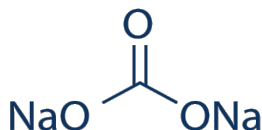


Figure 13. Sodium Carbonate

7.9.3.1 General Information

Sodium carbonate is a white or colorless, odorless crystalline powder (PubChem 2021i). Synonyms include disodium carbonate, soda ash, washing soda, and carbonic acid disodium salt. Aqueous solutions are alkaline. Sodium carbonate is used in several industrial processes, including a food additive, cleaners and bleaches, photography, and pharmaceuticals (PubChem 2021i).

7.9.3.2 Toxicology Data

Sodium carbonate is an alkaline solution. A 0.1 M aqueous solution has a pH of 11.6, which can be irritating and cause direct local effects to the skin, eyes, and gastrointestinal tracts. Inhalation of particulates can cause similar direct local effects on the respiratory tract (OECD 2002b).

7.9.3.2.1 Oral

In rodents, the sodium carbonate LD₅₀ was 4,090 mg/kg (rat) and 6,000 mg/kg (mouse). (PubChem 2021). An LD_{Lo} in humans was reported to be 714 mg/kg. Toxic signs included bleeding and ulceration in the small intestine (PubChem 2021i).

7.9.3.2.2 Inhalation

There were only limited data describing the toxicity of sodium carbonate by inhalation. Busch et al. (1983) reported inhalation LC₅₀ values for rats (2,300 mg/m³, 2 hr), mice (1,200 mg/m³, 2 hr) and guinea pigs (800 mg/m³). Toxic signs included lesions in the pharynx and larynx as well as tracheal edema and pulmonary hemorrhage.

7.9.3.2.3 Dermal

An acute dermal toxicity study in rabbits was conducted and it was reported that the dermal LD₅₀ was greater than 2,000 mg/kg, indicating lack of toxicity (OECD 2002b).

In a dermal irritancy study, a 50% aqueous solution of sodium carbonate was applied to intact and abraded rabbit skin and occluded for 4 hours. The site was then washed and examined at 1, 4, 24, and 72 hours post-application, and no signs of erythema or edema were reported (HERA 2005). York et al. (1996) performed an irritancy test with sodium carbonate on human volunteers. Tests were performed by administering 0.2 g of solid sodium carbonate on a moistened patch for up to 4 hours. Test sites were evaluated at 24, 48, and 72 hours. Sodium carbonate did not irritate the 26 test subjects and was not classified as a skin irritant.

Overall, sodium carbonate is considered a low risk for skin irritation (OECD 2002b); however, concentrated sodium carbonate is a strongly alkaline solution, and long-term dermal exposures are likely to produce skin irritation (AICIS 2014). Sodium carbonate has not been reported as a skin sensitizer.

7.9.3.2.4 Ocular

Murphy et al. (1982) instilled Na₂CO₃ into rabbit eyes, and in half of the animals, the exposed eyes were rinsed with tap water 30 seconds after exposure. The eyes were scored using the Draize criteria at 1 hour, 24 hours, day 2, day 3, and day 7. In both washed and unwashed eyes, the irritancy scores were moderate to severe at 1 hour. The washed eyes were normal by day 3, while the unwashed eyes still showed moderate irritation on day 7. Overall, sodium carbonate is considered to be an eye irritant (OECD 2002b).

7.9.3.2.5 Development and Reproduction

No data were found to describe the potential reproductive effects of sodium carbonate.

Developmental toxicity was tested in pregnant mice by gavage of aqueous sodium carbonate solutions at doses ranging from 3.4 to 340 mg/kg-day on gestation days 6–15. There were no effects on implantation and no increase in soft tissue and skeletal abnormalities compared to the control groups. Similar results were seen in rats and rabbits (FDA 1987).

7.9.3.2.6 Genotoxicity

Sodium chloride was tested for mutagenicity in the *E. coli* Chromotest. Doses ranged from 0.1 to 11,000 µg/mL. Toxicity was noted at 1,100 µg/mL, but mutagenicity was negative (Olivier 1987).

7.9.3.2.7 Carcinogenicity

Sodium carbonate is not expected to be a carcinogen.

7.9.3.2.8 Neurotoxicity

No neurotoxicity data were found.

7.9.3.2.9 Mechanism

Aqueous sodium carbonate solutions are alkaline and depending upon concentration may pose a primary irritancy hazard to the skin and mucous membranes in the eyes and respiratory tract. On ingestion, sodium carbonate dissociates into sodium and carbonate. The carbonate is neutralized by stomach acid forming bicarbonate and CO₂. The sodium is taken up by the body, which already contains a large sodium pool, and any excess would be excreted through normal processes (HERA 2005).

7.9.3.3 Ecological Data

7.9.3.3.1 Fate and Transport

Sodium carbonate is readily soluble in water; it is an inorganic salt and has low vapor pressure. Sodium carbonate has a melting point of 851 °C and decomposes when heated so no boiling point can be determined (OECD 2002b). In water, it dissociates into sodium and carbonate ions, which will remain in the water and not adsorbed to particulate matter (OECD 2002b).

7.9.3.3.2 Ecotoxicity

A 96-hour LC₅₀ in bluegill (*Lepomis macrochirus*) was 300 mg/L (HERA 2005). In mosquito fish (*Gambusia affinis*) the 96-hour LC₅₀ was 740 mg/L (HERA 2005).

Warne et al. (1999) reported the effects of sodium carbonate on the freshwater water flea, *Ceriodaphnia*. The 48-hour EC₅₀ was 200–227 mg/L.

7.9.3.3.3 Degradation and Treatment

Sodium carbonate dissociates entirely in water and soil and will not be environmentally persistent (OECD 2002b).

7.10 DIPSOL N-777

7.10.1 Zinc Oxide [CASRN 1314-13-2]



Figure 14. Zinc Oxide

7.10.1.1 General Information

Zinc oxide is an odorless white or yellowish-white crystalline powder with a bitter taste. It is used in pesticides (fungicide, herbicide, bacteriostat), as a pigment in white paints, in cosmetics (diaper cream, sunblock), as a flame retardant and dental cements. Synonyms include pigment white 4 and nogenol.

7.10.1.2 Toxicology Data

Zinc oxide is associated with metal fume fever, which includes fever, chills, dry or sore throat, chest tightness and headache (HSDB 2014). Symptoms are alleviated within 24 hours after exposure has ended.

7.10.1.2.1 Oral

Mice exposed orally to a single bolus of zinc oxide (1,000 mg/kg-bw) showed increased blood hemoglobin and altered motor activity (HSDB 2014). Additionally, there were observations of gastroenteritis following gavage. The LD_{50} in rats was >2,000 mg/kg-bw (ECHA 2019).

Chronic exposure of rats to 5 mg/kg-d for 6 months showed mild effects in the kidneys and hyperplasia in the spleen (HSDB 2014). A NOAEL for rats fed zinc monoglycerolate was 31.52 mg/kg bodyweight (ECHA 2019).

7.10.1.2.2 Inhalation

Zinc oxide fumes can cause mild chills, flushing, fatigue, muscle and stomach aches, dyspnea, and nausea upon first exposure. Subsequent exposures showed decreased symptomology (HSDB 2014). Guinea pigs exposed to upwards of 2,600 mg/m³ zinc oxide fumes for no more than an hour exhibited similar symptoms as in humans, with temperature drops quickly following exposure, recovering over the subsequent 18 hours. Guinea pigs exposed to 2,500 mg/m³ zinc oxide fumes for 3–4 hours died shortly after exposure. Similar responses were seen in rabbits exposed to 110–600 mg/m³ zinc oxide fumes for an hour. An LC_{50} in rats was found to be 5,700 mg/m³ (ECHA 2019).

Repeated exposure in guinea pigs (7 mg/m³) for 5-days showed decreased total lung capacity and vital capacity throughout exposure. Lungs showed signs of edema (HSDB 2014). The NOAEL is 0.5 mg/m³ for a 28-day exposure in rats (ECHA 2019).

7.10.1.2.3 Dermal

Human patch tests and the guinea pig maximization test are negative for a sensitizing reaction to zinc oxide (HSDB 2014). There is no evidence that the compound is an irritant or is corrosive. The LD₅₀ in rats is > 2,000 mg/kg-bw (ECHA 2019).

7.10.1.2.4 Ocular

Ocular tests in rabbits are negative for irritation and corrosion (HSDB 2014).

7.10.1.2.5 Development and Reproduction

Several studies in rats, mice, rabbits, and hamsters assessed the incidence of developmental or reproductive toxicity with dietary exposure levels up to 200 mg/kg-d via diet, 50 mg/kg-d via gavage, or 7.5 mg/m³ (ECHA 2019). No effects on development were observed in any of these studies, with NOAELs established at the top end dose for all studies.

7.10.1.2.6 Genotoxicity

Rats exposed by inhalation to zinc oxide showed a slight increase in chromosomal aberrations, but it was non-significant (HSDB 2014). A mouse gavage study also found no increase in chromosomal aberrations measured by the micronucleus assay (ECHA 2019). ZnO is also negative in the Ames test and the comet assay.

7.10.1.2.7 Carcinogenicity

No data were found; zinc oxide is not anticipated to be carcinogenic.

7.10.1.2.8 Neurotoxicity

Rats exposed to 600 mg/kg-d zinc oxide for 10 days were examined for morphological and histoenzymatic changes in brain structures. Changes included degeneration of neurocytes, the proliferation of the oligodendroglia and glial proliferation in the white matter. Decreases in acid phosphatase activity, adenosinetriphosphatase, acetylcholine esterase, and butyrylthiocholineesterase were found to increase in thiamine pyrophosphatase and non-specific esterase (HSDB 2014).

7.10.1.2.9 Mechanism

Unbalanced copper and zinc binding to Cu, Zn-superoxide dismutase are linked to amyotrophic lateral sclerosis (ALS) (Vonk and Klomp 2008). Additionally, metal fume fever is thought to be an immune response to inhaled zinc. (ATSDR 2005a).

The gastrointestinal system's excessive absorption of zinc suppresses copper and iron absorption resulting in anemia, most likely from the through competitive binding of intestinal mucosal cells. Also, stomach acid dissolves metallic zinc to give corrosive zinc chloride, which can cause damage to the stomach lining (ATSDR 2005c).

7.10.1.3 Ecological Data

7.10.1.3.1 Fate and Transport

Zinc oxide is relatively insoluble; however, as particle size decreases, solubility does increase. Solubility is also dependent on pH, temperature and the presence of organic matter, such as decreasing pH, increasing temperature, or increasing salinity, allowing for higher solubility (ECHA 2019). Upon release into the environment, Zn^{+} ions will adsorb onto soil and sediments and remain bound to soil or sediment instead of partitioning into the water. It can bioaccumulate as Zn^{+} in fish and other organisms, but due to homeostatic processes, Zn^{+} poisoning is unlikely (ATSDR 2005a).

In the air, zinc oxide is expected to be present in a particulate form as a fume (HSDB 2014). It will not volatilize.

7.10.1.3.2 Ecotoxicity

Zinc oxide (as Zn^{+2}) is a GHS Category 1 acute aquatic hazard. Established LC_{50} values for fish range from 0.33 mg/L (neutral/high pH, *Pimephales promelas*) to 0.169 mg/L (neutral/high pH, *Oncorhynchus mykiss*) (ECHA 2019). The LC_{50} for *P. promelas* at low pH was 0.780 mg/L. *Danio rerio* has been assessed for nanoparticulate toxicity of ZnO , with an LC_{50} of 1.79 mg/L. for chronic exposures to ZnO , NOECs were determined for seven freshwater species, with a range of 0.044–0.530 mg/L. The following families were represented: Cyprinodontidae, Cyprinidae, Salmonidae, and Cottidae. *Clupea harengus* is a saltwater species, and the NOEC was determined to be 0.025 mg/L.

The LC_{50} for *Ceriodaphnia dubia* ranged from 0.147mg/L to >0.53 mg/L depending on pH and water hardness (neutral/high pH and low hardness to low pH and high hardness) (ECHA 2019). In freshwater invertebrates, NOECs ranged between 0.014–0.4 mg/L for 13 species, including poriferans, molluscs, crustaceans, rotifers, and insects. In marine species, 26 were assessed with NOECs ranging from 0.0056-0.9 mg/L. Species included annelids, cnidarians, crustaceans, echinoderms, mollusca, and nematodes.

The IC_{50} for *Selenastrum carpirocnutum* (algae) was 0.0136 mg/L, while the chronic NOEC for the same species was 0.019 mg/L (ECHA 2019). In marine algae, the NOECs ranged from 0.0078-0.67 mg/L for 12 species.

The EC_{10} in *Enchyraeus albidus* (worm species) was 35.7 mg/kg dry weight and 1,634 mg/kg dry weight for *Lumbricus terrestris*. The NOEC/ EC_{10} for *Folsomia candida* (soil arthropod) ranged from 14.6–1,000 mg/kg dry weight.

In terrestrial plants, the NOEC/EC₁₀ range is 32 mg/kg dry weight for *Trifolium pratense* and *Vicia sativa*, while for *Triticum aestivum*, it is 5,855 mg/kg dry weight.

7.10.1.3.3 Degradation and Treatment

As an inorganic compound, it is not expected to be readily susceptible to degradation. It will be environmentally persistent.

7.10.2 Water

See section 7.4.2 for information on water.

8 DISCUSSION

8.1 Formulation Summaries

8.1.1 DIPSOL 523-SC

DIPSOL 523-SC is a pretreatment product designed to tolerate large amounts of emulsified oil without losing its effectiveness. DIPSOL 523-SC is a concentrated liquid heavy-duty soak cleaner formulated for removal of heavy grease, oil, and shop dirt from steel, copper, and brass. The manufacturer's SDS (523SC SDS) is the primary source of information on this product. The overall product is classified in GHS Category 1 for both skin corrosion/irritation, serious eye damage/eye irritation, and corrosive if ingested. These classifications are likely due to the fact this product is 10–20% potassium hydroxide, which is a strong base. It is also stated that DIPSOL 523-SC thermal decomposition may yield carbon monoxide and/or carbon dioxide.

8.1.2 DIPSOL F-0529

DIPSOL F-0529 is a metal corrosion treatment comprised of 10–45% tartaric acid. The manufacturer's SDS (F-0529 SDS) is the primary source of the information on this product. The product is classified in GHS Category 1 for serious eye damage, Category 3 for specific target organ toxicity, and Category 1A for respiratory tract irritation and skin corrosion/irritation. DIPSOL F-0529 is harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

8.1.3 DIPSOL IZ-264

DIPSOL IZ-264 is a trivalent chrome conversion coating for DIPSOL IZ-C17 (zinc-nickel alloy deposit). It produces a blue bright coating similar to that obtained from hexavalent chrome formulations for corrosion resistance. It is comprised of 5–20% cobalt (II) nitrate. It has the GHS classification of Category 1 for respiratory and skin sensitization, and Category 2 for skin corrosion and eye irritation. This product also has a genetic affect with GHS classification of Category 2 for germ cell mutagenicity and carcinogenicity. Environmental effects of chronic aquatic hazard Category 2 are likely due to the concentration of cobalt (II) nitrate since it can dissociate in water to cobalt and nitrate ions.

8.1.4 DIPSOL IZ-264 T

DIPSOL IZ-264 T is a trivalent chrome conversion coating for corrosion resistance. It is comprised of 5-25% chromic chloride. It has the GHS classification of Category 1 for respiratory and skin sensitization, skin corrosion and eye damage. DIPSOL IZ-264 T has a GHS classification of Category 2 for germ cell mutagenicity and reproductive toxicity, but how this classification was determined is unknown since trivalent chromate is not reported to have a genetic effect. Additionally, this product is reported to be an acute aquatic hazard GHS Category 3.

8.1.5 DIPSOL IZ-C17+B

DIPSOL IZ-C17+ is an alkaline type, cyanide free, zinc nickel alloy for electroplating process, and has excellent heat and corrosion resistance especially in high atmospheric temperature applications. It is predominantly comprised of 60–99% polyamine-2, and 1–3% diethylenetriamine with the remainder being water. According to the manufacturers SDS DIPSOL IZ-C17+B is a GHS Category 1 respiratory/skin sensitizer, eye damage, and skin irritant. The formulation is labeled as reproductive toxicity Category 2, and an aquatic hazard Category 1. The sources of these categorization is not unknown since the information that is available for polyamine-2 in the governmental and commercial databases are limited.

8.1.6 DIPSOL IZ-C17+Ni

DIPSOL IZ-C17+Ni is used in zinc alloy processes with a combination of 5-10% polyamine-1 and 20-30% nickel (II) sulfate, designed to accept clear and black trivalent conversion coatings. According of the manufactures SDS this formulation has a GHS classification of Category of 1 for respiratory and skin sensitization. It is classified as Category 1A for reproductive toxicity and carcinogenicity, and germ cell mutagenicity Category 2. Theses categorizations must be based on nickel (II) sulfate since there is limited information on polyamine-1.

8.1.7 Caustic Soda

The categorization of caustic soda is based on Duda Diesel LLC SDS for caustic soda beads provided by DIPSOL. Caustic soda is one of the common names for sodium hydroxide (NaOH) and is used for metal finishing. The formulation is 98% sodium hydroxide, at concentrations below 20% Sodium hydroxide is corrosive and irritating to the skin, eyes, and gastrointestinal tract following exposure.

8.1.8 DIPSOL N-777

DIPSOL NZ-777 is a zinc concentration solution that is 30-40% sodium hydroxide and 5-15% zinc oxide, and has been formulated to avoid the dangerous works which may occur at the make-up of the solution and the replenishment for zinc oxide in the operation of alkaline non-cyanide zinc plating. According to the manufactures SDS, DIPSOL NZ-777 is serious GHS Category 1 for eye damage and skin corrosion/irritation.

8.2 Individual Constituent Summaries

Tables of individual constituents' toxicity and ecological toxicity are located in Appendix C.

8.2.1 Chromic Chloride

Chromium is most toxic in its hexavalent oxidation state due to its cell permeability and higher redox potential. Trivalent chromium is biologically necessary for sugar and lipid metabolism in humans. Chromium is absorbed by oral, inhalation, or dermal exposure and distributes to nearly all tissues, with the highest concentrations found in the kidney and liver. Bone is also a significant storage site and may contribute to long-term retention. Aquatic toxicity data are established with chromium chloride hexahydrate. Chromium trichloride and hexahydrate are acidic in water, pH effects play a specific role when these substances are tested.

8.2.2 Cobalt (II) Nitrate

Cobalt nitrate is used to manufacture cobalt pigments, decorate stoneware, prepare catalysts, produce vitamin B12 supplements, and electronics-related industries. In humans, repeated or prolonged contact may cause skin sensitization and asthma. Ingestion may cause effects on the bone marrow, heart, and thyroid. Animal studies conducted on Guinea pigs demonstrated endocrine effects, while rat studies reported metabolic and kidney effects. Cobalt nitrate has moderate acute toxicity in rats following oral gavage exposure. Cobalt compounds dissociate and release cobalt ions. Elemental cobalt may release cobalt ions in a solution if discharged to surface waters. Cobalt has been detected in atmospheric deposition and rain-snow precipitation. Elemental cobalt is considered persistent since the ions released into solution when dissolved cannot be irreversibly degraded.

8.2.3 Diethylenetriamine

There is a reasonably robust toxicity database for DETA. Unfortunately, most of the references consist of very old citations or unpublished contractor reports that are unavailable. Much of the information presented is from European and U.S. databases, which provide summary information. Toxic signs included seizures and convulsions. Gross pathological findings included petechial hemorrhage of the lungs and effects on the liver and kidneys. In a human study, undiluted DETA was highly caustic, causing severe burns to the skin. In another human skin test, a single drop of DETA caused a mild to a moderate skin reaction in 9 out of 50 volunteers.

8.2.4 Nickel (II) Sulfate

The toxicity of nickel sulfate is linked to the toxicity of nickel, Nickel is absorbed through the lungs and gastrointestinal tract. Exposure can cause skin and asthma-like allergies, severe dermatitis and neurological system effects. Nickel sulfate is a known carcinogen and is associated with an increased risk of developing lung and nasal cancers. The primary hazard is the ecotoxicity, and immediate steps should be taken to limit its spread to the environment.

8.2.5 Oxalic Acid

The toxicity of oxalic acid is due to kidney failure caused by solid calcium oxalate precipitation, the kidney stones' main component, while some deaths have been attributed to cardiac arrest. Oxalic acid can also cause joint pain due to similar precipitates in the joints. In humans, ingested oxalic acid has an oral lowest published lethal dose of 600 mg/kg, with other lethal doses reported between 3–30 g in people. Oxalic acid's quick aerobic and anaerobic biodegradability poses a low risk of toxicity to all aquatic organisms, with effects exceeding 1,000 ppm across all taxa.

8.2.6 Polyamine-1

There are two forms of polyamine-1 that were found with the specific CASRN. The monomer has a reasonably extensive toxicity database. It is very toxic acutely and there have been reports of fatalities from vapor exposures, the monomer is also a severe skin and eye irritant. The monomer is a potent alkylating agent and is mutagenic in several in vitro and in vivo test systems. The ACGIH has established an 8-hour TLV of 0.05 ppm based on irritation to the upper airways and damage to the liver and kidney, and they consider it to be a confirmed animal carcinogen. In contrast to the monomer, there is very little toxicity information specific for the polymer. The ECHA database does provide GHS criteria, and they include GHS scores, but there are no supporting references provided. The oral LD₅₀ in rats ranges between 2,000 and 8,000 mg/kg and may depend on the size of the polymer, with the larger polymers showing lower acute toxicity.

8.2.7 Polyamine-2

Polyamine-2 is one of a group of polymers screened for health and environmental effects by Health Canada. They included it in a group of polymers referred to as poly(EDMA) polymers. The poly(EDMA) polymers occur as liquids and are typically used in wastewater treatment, pulp and paper manufacturing, food packaging, and electroplating. Unfortunately, there was no mammalian toxicity information available and only limited data from ecological receptor species. The GHS scores and descriptor information are presented here, but no supporting data or rationale for these scores were found except for the limited aquatic toxicity.

8.2.8 Potassium Hydroxide

When present at concentrations above 2%, or when inhaled, KOH represents an extreme hazard to the gastrointestinal tract, respiratory tract, eyes, and skin. Effects are due to the pH of solutions containing KOH, rather than the presence of potassium. KOH does not appear to cause developmental or reproductive effects at concentrations which do not impact the mother. Mutagenic potential and likelihood of developing cancer due to exposure are low. Like its effects on human health, the ecotoxicological hazards of KOH stem primarily from the effects of its alkaline pH.

8.2.9 Sodium Carbonate

Sodium carbonate is an alkaline solution, a 0.1 M aqueous solution has a pH of 11.6, which can be irritating and cause direct local effects to the skin, eyes, and gastrointestinal tracts. Inhalation of particulates can cause similar direct local effects on the respiratory tract. Toxic signs included bleeding and ulceration in the small intestine. There were only limited data describing the toxicity of sodium carbonate by inhalation. Toxic signs included lesions in the pharynx and larynx as well as tracheal edema and pulmonary hemorrhage.

8.2.10 Sodium Chloride

Sodium chloride dissociates into Na^+ and Cl^- ions. The primary source of sodium intake is food. The U.S. Food and Drug Administration reported that the daily sodium intake through the diet is 4,000–6,000 mg/day. In animal studies, Wistar rats were gavaged with a 25% solution of NaCl in water and all rats in the two high-dose groups died; the LD_{50} was 3,550 mg/kg. In humans, high levels of exposure can cause nausea, vomiting, muscle twitching, convulsions and death. It is reported that about 10 g of sodium or 5 teaspoons of salt was lethal in children, while in adults, the lethal dose was about 4 tablespoons of salt.

8.2.11 Sodium Hydroxide

Sodium hydroxide is corrosive, irritating and causes direct local effects to the skin, eyes, and gastrointestinal tract following exposure. Inhalation of particulates can cause similar direct local effects on the respiratory tract. The type of injury sustained following oral exposure to NaOH depends on the physical form. Ingestion of solid NaOH will injure the mouth and pharynx, while a liquid formulation will damage the esophagus and stomach. At low concentrations, systemic effects of NaOH are not expected to be an issue due to the dissociation of NaOH to sodium and hydroxyl ions and the body's ability to maintain homeostasis with regards to pH and sodium ions. Animal studies on inhalation of NaOH were not found; however, in humans, exposure to a 5% solution of NaOH resulted in irreversible lung damage after one day of exposure in poor ventilation.

8.2.12 Surfactants

The components listed are generic classes of surfactants and insufficient for performing an assessment of health and environmental concerns. Searches of the primary online databases for these compounds yielded virtually no toxicity or environmental information. Aliphatic surfactants are a large class of compounds that could include alpha olefin sulfonates, alkane sulfonates, and primary and secondary alkyl sulfates. Searches of standard chemistry and toxicity databases yielded very little information and no toxicity or environmental data. DIPSOL did not identify a chelating agent, we are unable to make any definitive assessment or conclusions regarding health and environmental effects of the chelator component.

8.2.13 Tartaric Acid

L-tartaric acid, at least at levels found naturally, is not thought to be toxic when ingested. Reproduction studies did not find any reproductive or developmental effects on tested animals.

High doses of tartaric are capable of causing severe eye damage. Based upon a predicted Henry's Law constant value of $1.32\text{E-}10 \text{ atm-m}^3/\text{mol}$ and vapor pressure of $9.68\text{E-}08 \text{ mmHg}$, Tartaric acid will not partition to the atmosphere from water or dry surfaces and is expected to exist in the atmosphere only in particulate form.

8.2.14 Zinc Oxide

Zinc oxide is associated with metal fume fever, which includes fever, chills, dry or sore throat, chest tightness and headache. Mice exposed orally to a single bolus zinc oxide showed increased blood hemoglobin and altered motor activity. Chronic exposure of rats to 5 mg/kg-d for 6 months showed mild effects in the kidneys and hyperplasia in the spleen. A NOAEL for rats fed zinc monoglycerolate was $31.52 \text{ mg/kg bodyweight}$. Zinc oxide fumes can cause mild chills, flushing, fatigue, muscle and stomach aches, dyspnea, and nausea upon first exposure. Subsequent exposures showed decreased symptomology. In the air, zinc oxide is expected to be present in a particulate form as a fume.

8.3 Regulations and Standards

Polyamine 2 (CASRN 25988-97-0) was approved by the FDA as a secondary food additive (FDA 2020).

Diethylenetriamine (CASRN 111-40-0) has an occupational exposure level (OEL) TLV of 1 ppm recommended by the ACGIH (ACGIH, 2019). This TLV also includes a skin notation indicating potential systemic effects from dermal exposure.

Sodium carbonate (CASRN 497-19-8) has an Australian OEL of 7.5 mg/m^3 as a TWA and a STEL of 15 mg/m^3 (AICIS 2014). The U.S. Department of Energy has published Protective Action Criteria (PACs) for sodium carbonate. The PAC values are 1-hour exposure criteria and the severity of the effects are indicated by numerical categories or levels. Level 1 represents minimal but noticeable effects from exposure, level 2 effects are more severe, potentially irreversible and level 3 effects are very serious, potentially life threatening. For sodium carbonate, the PAC 1 = 7.6 mg/m^3 , PAC 2 = 80 mg/m^3 , and PAC 3 = 500 mg/m^3 (DOE 2021).

Zinc oxide has an OEL of 2 mg/m^3 as a TLV recommended by the ACGIH (ACGIH 2019). OSHA occupational permissible exposure limit (PEL) for fumes is 5 mg/m^3 and 15 m/m^3 for dusts (Department of Labor 2011). NIOSH recommends Immediately Dangerous to Life and Health (IDLH) level is 500 mg/m^3 and the Recommended Exposure Limit (REL) is 5 mg/m^3 (NIOSH 2016b).

For cobalt metal dust, OSHA has designated a workplace as PEL of 0.1 mg/m^3 as an 8 hour TWA (ATSDR 2004, NIOSH 2021). The NIOSH REL is 0.05 mg/m^3 (NIOSH 2021). Tartaric acid is listed under the Right to Know regulations of Pennsylvania and New Jersey (Sigma-Aldrich 2021). No exposure limit values have been established for this product; it is advisable not to exceed the generic exposure limits of inhalable dust: 10 mg/m^3 and respirable dust: 5 mg/m^3 based on 8 hours (ECHA 2021p, Sigma-Aldrich 2021).

For nickel sulfate, the ACGIH has recommended a TLV of 0.1 mg/m³ for soluble inorganic compounds and a cancer notation of A4, carcinogenic in animals (ACGIH 2019). The NIOSH REL is 0.015 mg/m³ as an 8 hour TWA (NIOSH 2016a).

Potassium hydroxide has an ACGIH TLV of 2 mg/m³; the NIOSH REL is also 2 mg/m³ (HSDB 2015). Potassium hydroxide is used as a general purpose food additive in animal drugs, feeds, and related products as is Generally Recognized As Safe when used in accordance with good manufacturing or feeding practice (21 CFR 582).

Sodium hydroxide has an ACGIH (2019) recommended TLV and an OSHA PEL of 2 mg/m³ (PubChem, 2021j).

9. RECOMMENDATIONS

These preparations are commercially available and designed to replace more toxic formulations, but information on some of the components were not uniformly accessible for this review. Specifically, little toxicity information exists for polyamine-1 and polyamine-2 which are approved for use by the FDA, and the manufacturer failed to provide specific compound information for the surfactants used in DIPSOL 523-SC. All products can cause severe eye and skin irritation in their concentrated form; see Table 2. Dipsol IZ-C17-+Ni appears to be the most toxic across all endpoints, to include cancer and developmental toxicity hazards. Caustic soda has the least toxicity across all endpoints. Ultimate product selection should consider the hazards depicted in Table 2 as well as industrial hygiene requirements and disposal of the materials. All local, state, and national environmental regulations must be observed and these products should not enter surface waters or be released to municipal waste water.

Table 2. Formulation Toxicity Assessment

Product	Skin Irritation ¹	Eye Irritation ²	Skin Sensitization ³	Carcinogen ⁴	Spec. Organ Tox. Single ⁵	Spec. Organ Tox. Repeated ⁶	Reproductive toxicity ⁷	Germ Cell Mutagenicity ⁸	Acute Oral Toxicity ⁹	Acute Inhal. Toxicity ¹⁰	Acute dermal toxicity ¹¹	Respiratory Sensitization ¹²	Ecological toxicity ¹³
7.3 Dipsol 523-SC	1A	1	1	NL	1	1	NL	NL	3	1	NL	NL	1
7.4 Dipsol F-0529	1A	1	1	NL	3	NL	NL	NL	4	1A	1A	3	3
7.5 Dipsol IZ-264	1B	1	1	1B	2	1	1B	2	4	NL	NL	1	1
7.6 Dipsol IZ-264 T	1A	1	1	NL	1	1	2	2	4	1	4	1	3
7.7 Dipsol IZ-C17+B	1B	1	1	NL	3	2	1B	NL	4	2	4	1	1
7.8 Dipsol IZ-C17+Ni	1B	1	1	1A	NL	1	1A	1B	2	1	1	1	1
7.9 Caustic Soda	1A	1	NL	NL	3	NL	NL	NL	4	4	4	NL	3
7.10 Dipsol N-777	1A	1	NL	NL	1	2	2	NL	4	NL	4	NL	1
Notes: ¹ 1A=Corrosion <3 minutes; 1B=Corrosion <1hour; ² 1=irreversible eye damage ³ 1=sensitization; NL=not listed ⁴ 1A=known human carcinogen; 1B=presumed human carcinogen; NL=not listed ⁵ 1=high hazard, 2=moderate hazard; 3=low hazard; NL=not listed (negligible hazard) ⁶ 1=high hazard, 2=moderate hazard; NL=not listed (negligible hazard) ⁷ 1A=may damage fertility or fetus; 1B=may damage fetus; 2=suspected of damaging fertility or fetus; NL=not listed ⁸ 1B=may cause genetic defects; 2=suspected of causing genetic defects; NL=not listed ⁹ 2=fatal if swallowed, 3=toxic if swallowed, 4=harmful if swallowed ¹⁰ 1=fatal if inhaled; 1A=respirator sensitizer; 2=fatal if inhaled; 4=harmful if inhaled; NL=not listed ¹¹ 1A=Corrosion <3 minutes; 1=fatal in contact with skin, 4=harmful in contact with skin; NL=not listed ¹² 1=sensitizer; 3=respiratory irritant; NL=not listed ¹³ 1=very toxic to aquatic life; 3=harmful to aquatic life													
Hazard Color Key based on GHS scheme; see Appendix B.													
Very High	High	Moderate-High	Low-Moderate	Low-Negligible									

10. POINT OF CONTACT

The point of contact for this assessment is Dr. Blas Guigni. He may be reached by telephone 410-436-3980, DSN: 584-3980; e-mail: usarmy.apg.medcom-phc.mbx.tox-info@mail.mil.

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APPENDIX A

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APPENDIX B

ENVIRONMENTAL SAFETY AND OCCUPATIONAL HEALTH SEVERITY CATEGORIZATION

Table B-1. Categorization Criteria used in the Development of Environmental Safety and Occupational Health Severity

	Low	Moderate	High	Unknown
PERSISTENCE	Readily biodegrades water <28 days soil <28 days	Degradation ½ life: water <40 days soil <120 days	Degradation ½ life: water >40 days soil >120 days	Data are unavailable, insufficient, or unreliable
TRANSPORT	Water sol. < 10 mg/L log K _{oc} > 2.0	Water sol. 10-1000 mg/L log K _{oc} 1.0-2.0	Water sol. > 1,000 mg/L log K _{oc} <1.0	
BIO- ACCUMULATION	log K _{ow} <3.0	log K _{ow} 3.0-4.5	log K _{ow} >4.5	
TOXICITY	No evidence of carcinogenicity/ mutagenicity (IARC group 3 & 4); Subchronic LOAEL > 200 mg/kg-d	Mixed evidence for carcinogenicity/ mutagenicity (IARC group 2B); Subchronic LOAEL 5-200 mg/kg-d	Positive corroborative evidence for carcinogenicity/ mutagenicity (IARC group 1 & 2A); Subchronic LOAEL < 5 mg/kg-d	
ECOTOXICITY	Acute LC ₅₀ >1 mg/L or LD ₅₀ 1,500 mg/kg; Subchronic EC ₅₀ >100 µg/L or LOAEL >100 mg/kg-d	Acute LC ₅₀ 1-0.1 mg/L or LD ₅₀ 1,500-150 mg/kg; Subchronic EC ₅₀ 100-10 µg/L or LOAEL 100-10 mg/kg-d	Acute LC ₅₀ <100 µg/L or LD ₅₀ <150 mg/kg; Subchronic EC ₅₀ <10 µg/L or LOAEL <10 mg/kg-d	

Source: modified from Howe et al. 2007

Legend:

mg/L = milligrams per liter

log K_{oc} = Organic carbon partition coefficient

Log K_{ow} = Octanol-water partition coefficient

IARC = International Agency for Research on Cancer

LOAEL = lowest-observed adverse effect level

LC₅₀ = concentration expected to result in 50% lethality to a population of test animals

LD₅₀ = Dose resulting in 50% mortality

mg/kg-d = milligrams per kilogram per day

µg/L = micrograms per liter

Globally Harmonized System (GHS)

GHS is the acronym for the Globally Harmonized System of Classification and Labeling of Chemicals. The GHS attempts to establish international consensus for defining health, physical, and environmental hazards of chemicals; creating a classification process for comparison with defined hazard criteria; and communicating hazard information and protective measures on labels and Safety Data Sheets (SDS) (formerly known as Material Safety Data Sheets (MSDS)). The GHS attempts to reduce differences among levels of protection for workers established by the different countries and reduce regulatory burden and barriers to commerce while establishing consistent standards for classification. The GHS is the result of an international mandate adopted in the 1992 United Conference on Environment and Development, often called the "Earth Summit." The harmonization and classification of chemicals was one of six program areas endorsed by the United Nations General Assembly to strengthen international efforts in the environmentally sound management of chemicals.

While several aspects of the GHS, the one most important area for our purposes is classification of chemicals into various hazard categories based upon their effects and the route of exposure. Tabular extracts of the criteria for acute toxicity (oral and inhalation), dermal, and ocular effects are included in Table B-2.

Table B-2. GHS Acute Toxicity

	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg)	≤5	>5 ≤50	>50 ≤300	>300 ≤2,000	Criteria: -Anticipated LD ₅₀ between 2,000 and 5,000 mg/kg. -Indication of significant effects in humans. -Any mortality in Category 4. -Significant clinical signs in Category 4. -Indications from other studies.
Dermal (mg/kg)	≤50	>50 ≤200	>200 ≤1,000	>1,000 ≤2,000	
Gases (ppm)	≤100	>100 ≤500	>500 ≤2,500	>2,500 ≤5,000	
Vapors (mg/L)	≤0.5	>0.5 ≤2.0	>2.0 ≤10	>10 ≤20	
Dusts & Mists (mg/L or g/m ³)	≤0.05	>0.05 ≤0.5	>0.5 ≤1.0	>1.0 ≤5	*If assignment to a more hazardous class is not warranted.

Legend:

mg/kg = milligrams per kilogram

ppm = parts per million

mg/L = milligrams per liter

LD₅₀ = Dose resulting in 50% mortality

Table B-3. GHS Skin Corrosion/Irritation

Category 1A	Category 1B	Category 1C	Category 2	Category 3	Not Categorized
Corrosion < 3 minutes Observation < 1 hour	Corrosion < 1 hour Observation < 14 days	Corrosion < 4 hours Observation < 14 days	Irritation Reversible adverse effects in dermal tissue Draize score: ≥ 2.3, <4.0, or persistent inflammation	Mild Irritation Reversible adverse effects in dermal tissue Draize score: ≥ 1.5, <2.3	Corrosion and irritation not observed
Destruction of dermal tissue; visible necrosis in at least one animal.					

Table B-4. GHS Eye Effects

Category 1	Category 2A	Category 2B	Not categorized
Irreversible damage 21 days after exposure	Irritant Reversible in 21 days	Mild irritant Reversible in 7 days	Non-irritating

Table B-5. GHS Acute and Chronic Aquatic Toxicity

Table 2.0: GHS Acute and Chronic Aquatic Toxicity				
Acute Aquatic Toxicity				
Category I	Category II	Category III		Not Categorized
Acute toxicity ≤ 1.00 mg/L	Acute toxicity > 1.00 but ≤10.0 mg/L	Acute toxicity > 10.0 but < 100 mg/L		Acute toxicity > 100 mg/L
Chronic Aquatic Toxicity when biodegradation ½ life is > 7 days				
Category I	Category II	Category III	Category IV	Not Categorized
Acute Cat I and log K _{OW} ≥ 4, unless BCF < 500; Or chronic toxicity ≤ 0.01 mg/L	Acute Cat II and log K _{OW} ≥ 4, unless BCF < 500; Or chronic toxicity 0.01-0.1 mg/L.	Acute Cat III and log K _{OW} ≥ 4, unless BCF < 500; Or chronic toxicity 0.1-1.0 mg/L	Acute toxicity > 100.0 mg/L, biodegradation ½ life >7 days, and log K _{OW} ≥ 4, unless BCF < 500; Or chronic toxicity > 1.0 mg/L	Acute toxicity >100 mg/L, Log K _{OW} < 4, BCF< 500 and chronic toxicity > 1.0 mg/L

Legend:

mg/L = milligrams per liter

K_{OW} = octanol-water partition coefficient

BCF = bioconcentration factor

Table B – 6. GHS Carcinogenicity

GHS Carcinogenicity			
Category 1A	Category 1B	Category 2	Not categorized
Known to have carcinogenetic potential for humans (human evidence)	Presumed human carcinogens (animal evidence)	Suspected human carcinogen (human or animal evidence but not sufficiently convincing to place in Category 1)	Non-carcinogenic

APPENDIX C

DATA TABLES

Table C-1. Individual Constituent Physical and Chemical Properties

Compound/ Formulation	Molar Mass (g/mol)	Melting Point (°C)	Boiling Point (°C)	Aqueous solubility (mg/L) @ 25°C	log K _{ow}	log K _{oc}	Henry's Law Constant (K _H) (atm- m ³ /mol) @ 25°C	Vapor Pressure (mmHg) @ 25°C
Chromic chloride	158.35 ^a	~1,150 ^c	1,300 ^c	2.87E+06 ^c	N/A	N/A	N/A	N/A
Cobalt (II) nitrate	182.94 ^b	55-56 ^b	decomposes at 100-105 ^b	1.3E+06 ^b	N/A	N/A	N/A	N/A
Diethylenetriamine	103.17 ^d	-39 ^d	207.0 ^d	1E+06 ^d	-1.65 ^d	0.606 _c	1E-14 ^e	0.23 ^e
Ethoxylated alcohol	595 ^d	ND	300 ^c	1.1 ^c	ND	ND	ND	9.7E-5 ^c
Lignosulfonate	534.51 ^d	993 ^c	1704 ^c	Soluble ^e	ND	ND	ND	ND
Nickel (II) sulfate	154.76 ^d	decomposes at 848 ^e	N/A ^c	293 g/L ^c	N/A	N/A	N/A	N/A
Oxalic acid	90.03 ^d	decomposes 189.5 ^d	ND	2.20E+03 ^f	-2.22 ^f	5 ^d	1.43E-10 ^{df}	2.34E-04 ^{df}
Polyamine-1 (*as the monomer)	*43.07 ^d	*-76 ^b	~100 ^g *56.3 ^b	Miscible ^g ^d	*- 0.474 ^b	*0.78 ^b	*3.91E-06 ^b	18 (20 °C) ^g *213 ^b
Polyamine-2	137.61 ^d	ND	ND	>1,000 ^d	ND	ND	ND	ND
Potassium hydroxide	56.11 ^h	380 ^h	1323 ⁱ	1210 ^j	N/A	N/A	N/A	N/A
Sodium carbonate	105.99 ^d	851 ^d	Decomposes ^d	3.07E+05 ^d	N/A	N/A	N/A	N/A
Sodium chloride	58.44 ^d	800.7 ^d	1,465 ^d	3.57E+05 ^d	N/A	N/A	N/A	N/A
Sodium hydroxide	39.997 ^d	323 ^d	1,388 ^d	3.6E+05 ^d	N/A	N/A	N/A	1.82E-21 ^e
Tartaric Acid	150.09 ^e	179.1 ^d	between 168-170 _c	150 g/L (20 °C) ^c	-1.91 at 20 °C	1.22 ^c	1.32 ^c	< 3.7E-04 (20 °C) ^c
Zinc Oxide	81.4 ^e	1974 to 1975 ^j	ND	Insoluble ^d	N/A	N/A	N/A	N/A

Notes:

^a ATSDR 2012 ^b Williams 2017 ^c ECHA 2021
^d PubChem 2021 ^e ChemIDPlus 2021 ^f EPA 2005
^g BASF 2020 ^h O'Neil 2006 ⁱ Dean 1992
^j HSDB 2015

Table C-2. Individual Constituent Toxicity Data

Compound/ Formulation	Acute Oral LD ₅₀ (mg/kg)	Chronic Oral LOAEL (mg/kg-d)	Inhalation LC ₅₀ (g/m ³ -h)	Dermal	Ocular	Genotoxicity	Carcinogenicity
Chromic chloride	440 ^e	ND	31.5 ^e	Negative ^b	Negative ^b	ND	Likely ^b
Cobalt(II) nitrate	190 ^a	10 ^a	ND	Mild irritant ^c	Irritant ^b	Possible irreversible effects ^d	Suspected
Diethylenetriamine	1553 ^a	530 ^a	0.28-1.2 ^a	Irritant/ Sensitizer ^k	Severe irritant ^g	Negative ^a	Neg – Dermal ^a
Ethoxylated alcohol	GHS 4 ^a	ND	ND	GHS 2 ^a	GHS 1 ^a	ND	ND
Lignosulfonate	>40,000 ^b	ND	ND	ND	GHS 2 ^a	ND	ND
Nickel(II) sulfate	264 ^b	0.012 ^a	2.48 ^a	Irritant/Sensitizer ^l	Irritant ^l	Positive ^b	Likely ^a
Oxalic acid	375-475 ^a	1,250 ^o (70-day)	ND	Corrosive ^b	Corrosive ^b	Negative ⁱ	Negative ^a
Polyamine-1	2000-8000 ^j	<250 ^j	ND	Irritant/Sensitizer ^a	Severe irritant ^a	Negative ^a	ND
Polyamine-2	GHS 4 ^a	ND	ND	ND	GHS 2 ^a	ND	ND
Potassium hydroxide	273-1,230 ^b	ND	ND	Corrosive ^b	Corrosive ^b	Negative ^b	Negative ^b
Sodium carbonate	4,090-6,600 ^m	ND	0.8-2.3 ^{i m}	Mild irritant ^a	Severe irritant ^a	Negative ⁿ	Negative
Sodium chloride	3,550 ^b	ND	>42 ^a	Negative ^a	Inconclusive ^a	Negative ^a	Negative ^a
Sodium hydroxide	500 (LDLo) ^f	ND	ND	Corrosive, Non-sensitizer ^g	Corrosive ^g	Negative ^h	Negative
Tartaric acid	>2,000 ^a	270.8 ^a	0.874 ^a	Corrosive/ Neg sens ^a	Strong irritant ^a	Negative ^a	Negative ^a
Zinc oxide	7,950 ^b	ND	>5.7 ^b	Neg irr/ Neg sens ^{l o}	Negative ^b	Negative ^b	Negative ^b

Notes:

^a ECHA 2022^b PubChem 2022^c INCHEM 2021^d IMAP 2014^e ATSDR 2012^f Fazekas 1936^g OECD 2002a^h De Flora et al. 1984ⁱ EMEA 2003^j INCHEM 2021^k Leung 1997^l Sigma-Aldrich 2015^m PubChem 2018ⁿ Oliver 1987^o EPA 1992

Table C-3. Individual Constituent Toxicity Assessment

Compound/Formulation	Oral	Inhalation	Dermal	Ocular	Carcinogenicity	Comments
Chromic chloride	Mod	Mod	High	High	Low	5-25% formulation
Cobalt (II) nitrate	Mod	High	High	High	Mod	5-20% formulation, GHS Labelling of Chemicals
Diethylenetriamine	Mod	Mod	High	High	Low	
Nickel (II) sulfate	High	Mod	Mod	Unk	Mod	
Oxalic acid	High	Mod	High	High	Low	
Polyamine-1	High	High	High	High	Mod	Avoid all contact in all cases consult a doctor!
Polyamine-2	Mod	Mod	Unk	Mod	Unk	GHS Labelling of Chemicals
Potassium hydroxide	Mod	High	High	High	Low	10-20% formulation
Sodium carbonate	Low	Mod	Mod	Mod	Unk	
Sodium chloride	Low	Low	Unk	Unk	Unk	
Sodium hydroxide	Mod	Unk	High	High	Unk	High corrosive
Surfactant	Unk	Unk	Unk	Unk	Unk	
Tartaric acid	Low	Low	Low	Mod	Low	10-45% formulation
Zinc oxide	High	Mod	High	High	Low	
Ethoxylated alcohol	Low	Unk	Unk	Mod	Unk	Limited studies, used by industry
Lignosulfonate	Low	Unk	Unk	Mod	Unk	Common industrial use

Table C-4. Individual Constituent Ecotoxicity Assessment

Compound/Formulation	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
Chromic chloride	High	High	Low	High	Mod	Discharge to environment not recommended hexavalent and trivalent chromium considered
Cobalt(II) nitrate	High (I)	Mod	Low	Mod	Mod	Based on the toxicity of Cobalt
Diethylenetriamine	Mod	Unk	Unk	Low	Unk	
Ethoxylated alcohol	High	Unk	Unk	Mod	Unk	
Lignosulfonate	Low	Unk	Unk	Low	Unk	
Nickel(II) sulfate	High	Mod	Mod	Mod	Low	Discharge to environment not recommended
Oxalic acid	Low	Mod	Mod	High	Unk	No bird studies
Polyamine-1	Mod	Unk	Unk	Low	Unk	
Polyamine-2	High	Unk	Unk	Unk	Unk	
Potassium hydroxide	Low	Low	Low	Low	Unk	
Sodium carbonate	Low	Low	Low	Low	Unk	
Sodium chloride	Low	Low	Low	Low	Low	
Sodium hydroxide	Low	Low	Low	Low	Unk	
Tartaric acid	Low	Low	Low	Mod	Unk	
Zinc oxide	High	High	Low	Low	Low	

Table C-5. Formulation Toxicity Assessment

Product	Skin Irritation	Eye Irritation	Skin Sensitization	Carcinogenicity	Spec. Organ Tox. Single	Spec. Organ Tox. Repeated	Reproductive toxicity	Germ Cell Mutagenicity	Acute Oral Toxicity	Acute Inhal. Toxicity	Acute dermal toxicity	Respiratory Sensitization	Ecological toxicity
7.3 Dipsol 523-SC	1A	1	1	NL	1	1	NL	NL	3	1	NL	NL	1
7.4 Dipsol F-0529	1A	1	1	NL	3	NL	NL	NL	4	1A	1A	3	3
7.5 Dipsol IZ-264	1B	1	1	1B	2	1	1B	2	4	NL	NL	1	1
7.6 Dipsol IZ-264 T	1A	1	1	NL	1	1	2	2	4	1	4	1	3
7.7 Dipsol IZ-C17+B	1B	1	1	NL	3	2	1B	NL	4	2	4	1	1
7.8 Dipsol IZ-C17+Ni	1B	1	1	1A	NL	1	1A	1B	2	1	1	1	1
7.9 Caustic Soda	1A	1	NL	NL	3	NL	NL	NL	4	4	4	NL	3
7.10 Dipsol N-777	1A	1	NL	NL	1	2	2	NL	4	NL	4	NL	1

Legend:

NL = not listed

GLOSSARY

°C	degrees Celsius
ACGIH	American Conference of Governmental Industrial Hygienists
APHC	U.S. Army Public Health Center
AR	Army Regulation
atm-m³/mol	cubic meters of atmosphere per mole
logBCF	bioconcentration factor
bp	boiling point
CASRN	Chemical Abstracts Service Registry Number
DOD	Department of Defense
EC₅₀	effective concentration to achieve 50% effect
ECOSAR	Ecological Structure Activity Relationships
ECOTOX	EPA Ecotoxicology Database System
EPA	U.S. Environmental Protection Agency
EPI Suite	The Estimation Programs Interface Suite
EQT	Environmental Quality Technology
ESOH	environment, safety, and occupational health
EU	ethoxylated undecanol
g/L	grams per liter
g/m³-h	grams per cubic meter per hour
g/mol	grams per mole
GD	gestation day
GHS	Globally Harmonized System
HF	hydrofluoric acid
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
K_H	Henry's law constant
KOH	potassium hydroxide
LC₅₀	concentration expected to result in 50% lethality
LD₅₀	dose expected to result in 50% lethality
LOAEL	Lowest Observed Adverse Effect Level
log K_{oc}	organic carbon partition coefficient
log K_{ow}	octanol-water partition coefficient
µg/L	micrograms per liter
µg/m³	micrograms per cubic meters
µL/L	microliters per liter
µmol/L	micromoles per liter
mg/kg	milligrams per kilogram

mg/kg-day	milligrams per kilogram per day
mg/L	milligrams per liter
mg/m³	milligrams per cubic meter
mL	milliliter
mL/kg	milliliter per kilogram
mM	millimole
mmHg	millimeters of mercury
N/A	not applicable
Na₂SiO₃	sodium silicate
NaH₂PO₄	sodium dihydrogen phosphate
ND	no data
NIOSH	U.S. National Institute for Occupational Safety and Health
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NzEPA	New Zealand Environmental Protection Authority
OECD	Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration
PC	Permissible Concentration
ppm	parts per million
QSAR	Quantitative Structure-Activity Relationship
RDT&E	Research, Development, Testing, and Evaluation
REL	Recommended Exposure Limit
SDS	safety data sheet
STEL	Short Term Exposure Limit
TLV	Threshold Limit Value
TMN-6	Poly(oxy-1,2-ethanediyl), α-[3,5-dimethyl-1-(2-methylpropyl)hexyl]-ω-hydroxy
TOPKAT	Toxicity Prediction by Komputer Assisted Technology
TOXNET	U.S. National Library of Medicine's Toxicology Data Network
TWA	Time-Weighted Average
Unk	Unknown
vp	vapor pressure
WHO	World Health Organization