NICKEL DIBUTYLDITHIOCARBAMATE

(CAS #13927-77-0)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 8, 2021

ToxServices Review Date: November 8, 2026[1]

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[1] Although CPA's Assessment Expiration Policy (CPA 2018a) indicates that Benchmark 1 assessments have no expiration date, ToxServices strives to review BM-1s in a five-year period to ensure currency of data presented in the BM-1 GreenScreen® assessments.

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GreenScreen® Executive Summary for Nickel Dibutyldithiocarbamate (CAS #13927-77-0)

Nickel bis(dibutyldithiocarbamate) (NBC) is an organometalloid produced by the reaction of aqueous solutions of sodium dibutyldithiocarbamate with nickel chloride, acetate, or sulfate. Nickel bis(dibutyldithiocarbamate) is used as an antioxidant in synthetic rubber manufacturing.

Nickel dibutyldithiocarbamate is a dark green, fine-powder. Nickel dibutyldithiocarbamate has low solubility in water, 8.93×10^{-3} mg/L at 20°C and is estimated to be more soluble in octanol than in water (log K_{ow} >0). Its estimated boiling point of 521.96°C and low vapor pressure of 3.075×10^{-4} mmHg, indicate that it is not volatile. Nickel dibutyldithiocarbamate is a high melting point solid and does not ignite or propagate combustion, and it not a flammable chemical.

Nickel dibutyldithiocarbamate was assigned a **GreenScreen Benchmark™ Score of 1** ("Avoid—Chemical of High Concern"). This score is based on the following hazard score combinations:

- Benchmark 1c
  - Very High Persistence-P + High Group I Human Health Hazard (carcinogenicity-C)
  - Very High P + High Group II* Human Health Hazard (repeated dose systemic toxicity-STr*)
- Benchmark 1e
  - High Group I Human Health Hazard (C)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), nickel dibutyldithiocarbamate meets requirements for a GreenScreen Benchmark™ Score of 1 despite the hazard data gap. In a worst-case scenario, if nickel dibutyldithiocarbamate were assigned a High score for the data gaps E, it would still be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* genotoxicity and endocrine activity testing, *in silico* modeling for endocrine activity and respiratory sensitization, and OECD Guideline 301 B ready biodegradation test for persistence. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

Type I (input data) uncertainties in nickel dibutyldithiocarbamate's NAMs dataset include lack of experimental data for respiratory sensitization along with a lack of validated test method for respiratory sensitization. Nickel dibutyldithiocarbamate's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of OECD Toolbox in identifying structural alerts without defining the applicability domain, the uncertain relevance of the EDSP Tox 21 screening assays and *in silico* modeling of endocrine receptor binding due to lack of consideration of toxicokinetic factors including metabolism, the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization, and the inability of EPI Suite™ to model the fate of organometallic compounds. Some of nickel dibutyldithiocarbamate's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data

GreenScreen® Hazard Summary Table for Nickel Dibutyldithiocarbamate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
H	**L**	*M*	*L*	DG	**L**	**L**	**H**	*M*	*L*	**L**	*M*	**L**	*H*	**L**	*L*	*vH*	*L*	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for Nickel Dibutyldithiocarbamate (CAS #13927-77-0)

Method Version: GreenScreen® Version 1.4
Assessment Type[2]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v1.4) Prepared By:
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Organization: ToxServices LLC
Date: October 15, 2021, October 31, 2021

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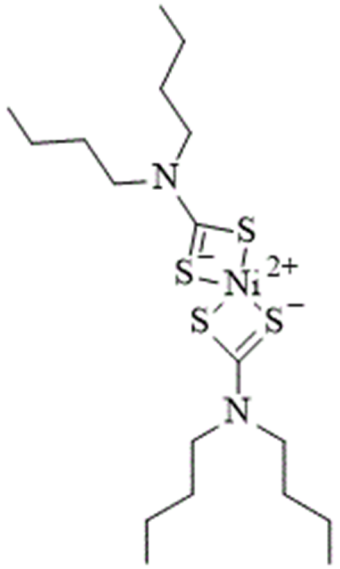
Organization: ToxServices LLC
Date: October 18, 2021, November 8, 2021

ToxServices Review Date: November 8, 2026[3]

Chemical Name: Nickel dibutyldithiocarbamate

CAS Number: 13927-77-0

Chemical Structure(s):



(ChemIDplus 2021)

Also called: (Dibutyldithiocarbamato)nickel(II); AI3-26152; Bis(dibutyldithiocarbamato)nickel; Carbamic acid, dibutyldithio-, nickel salt; Carbamic acid, dibutyldithio-, nickel(II) salt; Carbamodithioic acid, dibutyl-, nickel(2+) salt; Dibutyldithiocarbamic acid, nickel salt; EINECS 237-696-2; HSDB 2950; NBC; Nickel bis(dibutyldithiocarbamate); Nickel dibutyldithiocarbamate; Nickel(II)

[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[3] Although CPA's Assessment Expiration Policy (CPA 2018a) indicates that Benchmark 1 assessments have no expiration date, ToxServices strives to review BM-1s in a five-year period to ensure currency of data presented in the BM-1 GreenScreen® assessments.

dibutyldithiocarbamate; Nickel, bis(dibutylcarbamodithioato-S,S')-, (SP-4-1)-; Nocrac NBC; NSC 4797; Rylex NBC; UNII-99D240X626; UV Chek AM 104; Vanguard N (ChemIDplus 2021).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s): ToxServices identified a sufficiently complete toxicological dataset to assign nickel dibutyldithiocarbamate a Benchmark Score. Therefore, no surrogates were used in the current assessment.

Identify Applications/Functional Uses:
Antioxidant for rubber vulcanization and synthetic rubber manufacturing (HSDB 2010).

Known Impurities[4]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Nickel Dibutyldithiocarbamate[5,6 7,8]: Nickel dibutyldithiocarbamate was assigned a **GreenScreen Benchmark™ Score of 1** ("Avoid—Chemical of High Concern"). This score is based on the following hazard score combinations:

- Benchmark 1c
  - Very High Persistence-P + High Group I Human Health Hazard (carcinogenicity-C)
  - Very High P + High Group II* Human Health Hazard (repeated dose systemic toxicity-STr*)
- Benchmark 1e
  - High Group I Human Health Hazard (C)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), nickel dibutyldithiocarbamate meets requirements for a GreenScreen Benchmark™ Score of 1 despite the hazard data gap. In a worst-case scenario, if nickel dibutyldithiocarbamate were assigned a High score for the data gaps E, it would still be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for Nickel Dibutyldithiocarbamate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
H	**L**	*M*	*L*	DG	**L**	**L**	**H**	*M*	*L*	**L**	*M*	**L**	*H*	**L**	*L*	*vH*	*L*	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of

[4] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[5] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[6] See Appendix A for a glossary of hazard endpoint acronyms.
[7] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[8] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

Nickel dibutyldithiocarbamate is not readily biodegradable; it is highly insoluble in water and not likely to breakdown via hydrolysis. No hydrolysis products are expected under acidic, basic, and neutral conditions (OECD 2021, Appendix G). Therefore, no feasible or relevant environmental transformation products were identified.

Introduction

Nickel bis(dibutyldithiocarbamate) is an organometalloid produced by the reaction of aqueous solutions of sodium dibutyldithiocarbamate combined with nickel chloride, acetate, or sulfate (HSDB 2010). Nickel bis(dibutyldithiocarbamate) is used as an antioxidant in synthetic rubber manufacturing (HSDB 2010).

ToxServices assessed nickel dibutyldithiocarbamate against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2021a). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

Nickel bis(dibutyldithiocarbamate) is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[9] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for nickel dibutyldithiocarbamate can be found in Appendix C.

- Nickel dibutyldithiocarbamate is an LT-1 chemical when screened using Pharos due to hazards associated nickel metal, and therefore a full GreenScreen® is required to confirm this score.
- Nickel dibutyldithiocarbamate is not listed on the U.S. DOT list.
- Nickel dibutyldithiocarbamate is on the following lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - Quebec CSST – WHMIS 1988 – Class D2A – Very toxic material causing other toxic effects.

[9] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

Hazard Statement and Occupational Control

Nickel dibutyldithiocarbamate does not have a harmonized European Union (EU) Globally Harmonized System of Classification and Labeling (GHS) classification; however, GHS H statements are listed in the European Chemicals Agency (ECHA) dossier, as indicated in Table 1. General personal protective equipment (PPE) recommendations and occupational exposure limits (OELs) were identified and presented in Table 2, below.

Table 1: GHS H Statements for Nickel Dibutyldithiocarbamate (CAS #13927-77-0) (ECHA 2021)

H Statement	H Statement Details
H319	Causes serious eye irritation.
H351	Suspected of causing cancer.
H413	May cause long lasting harmful effects to aquatic life.
No harmonized GHS H statements are reported by ECHA.	

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Nickel Dibutyldithiocarbamate (CAS #13927-77-0)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Eye/Face Protection: Safety glasses with side shields; dust goggles; splash goggles – dependent on specific scenario. **Skin Protection:** Chemical-resistant, impervious gloves complying with an approved standard should be worn at all times. **Body protection:** Lab coat **Respiratory Protection:** Dust respirator.	Vanderbilt Chemicals, LLC 2019	**ACGIH TLV (United States, 4/2014).** TWA: 0.2 mg/m³, (as Ni) 8 hours. Form: Inhalable fraction **OSHA PEL 1989 (United States, 3/1989).** TWA: 1 mg/m³, (as Ni) 8 hours. **NIOSH REL (United States, 10/2013).** TWA: 0.015 mg/m³, (as Ni) 10 hours. **OSHA PEL (United States, 2/2013).** TWA: 1 mg/m³, (as Ni) 8 hours.	Vanderbilt Chemicals, LLC 2019

ACGIH: American Conference of Governmental Industrial Hygienists
NIOSH: National Institute for Occupational Safety and Health
OSHA: Occupational Safety and Health Administration
PEL: Permissible Exposure Limit
REL: Recommended Exposure Limits
TLV: Threshold Limit Value
TWA: Time Weighted Average

Physicochemical Properties of Nickel Dibutyldithiocarbamate

Nickel dibutyldithiocarbamate is a dark green fine powder. Nickel dibutyldithiocarbamate has low solubility in water at 8.93×10^{-3} mg/L at 20°C and is estimated to be more soluble in octanol than in water (log K_{ow} >0). Its estimated boiling point of 521.96°C, which is greater than 250°C, indicates that it is not a volatile organic compound (VOC).

Table 3: Physical and Chemical Properties of Nickel Dibutyldithiocarbamate (CAS #13927-77-0)

Property	Value	Reference
Molecular formula	$C_{18}H_{36}N_2NiS_4$	ChemIDplus 2021
SMILES Notation	CCCCN(CCCC)C1=[S-][Ni+2]2(SC(=[S-]2)N(CCCC)CCCC)S1	ChemIDplus 2021

Table 3: Physical and Chemical Properties of Nickel Dibutyldithiocarbamate (CAS #13927-77-0)		
Property	**Value**	**Reference**
Molecular weight	467.453 g/mol	ChemIDplus 2021
Physical state	Solid (EPA OPPTS 830.6303)	ECHA 2021
Appearance	Dark green powder (EPA OPPTS 830.6302)	ECHA 2021
Melting point	90.20°C (exp) (OECD 102)	ECHA 2021
Boiling point	521.96°C (est)	ECHA 2021
Vapor pressure	6.075×10^{-4} mmHg (0.081 Pa) at 25°C (est)	ECHA 2021
Water solubility	8.93×10^{-3} mg/L (8.93 µg/L) at 20°C (exp) (OECD 105, EPA OPPTS 830.7860)	ECHA 2021
Dissociation constant	Not identified	
Density/specific gravity	1.301 g/L at 20°C (exp) (OECD 109, EU Method A.3)	ECHA 2021
Partition coefficient	Log K_{ow} = 5.44 at 25°C (est/calculated)	ECHA 2021

Toxicokinetics

- *Absorption:*
  - No *in vivo* data is available on the toxicokinetic activity of nickel dibutyldithiocarbamate are available for any routes of exposure, oral, dermal, or inhalation for absorption. It is likely nickel dibutyldithiocarbamate will be absorbed via the inhalation and oral routes. It is a fine powder with experimental particle size distributions of D90 of 10.9 µm and D50 of 6 µm, which is favorable for absorption via the respiratory tract (ECHA 2021). Even though the substance has a high calculated log K_{ow} of 5.44 and poor water solubility suggesting poor absorption by passive diffusion, these properties favor micellular solubilization (ECHA 2021). In addition, substances that are absorbed via the gastrointestinal (GI) tract are likely to be absorbed when inhaled; therefore, oral absorption of the test substance is likely.
  - Dermal absorption through the stratum corneum is likely to be low based on poor water solubility of 0.0893 mg/L (ECHA 2021).
  - The authors of the REACH dossier adopted default absorption values of 100% for inhalation, 50% for oral, and a conservative 0.1% for dermal based on the physicochemical properties of the compound (ECHA 2021).
- *Distribution:*
  - No *in vivo* data is available on the distribution of nickel dibutyldithiocarbamate. The hydrophobic nature of the substance and its molecular weight of 467.453 g/mol do not favor passive diffusion which limits distribution; however, *in vivo* data support distribution throughout the body. The results of an OECD 422 oral repeated dose toxicity study in rats demonstrated changes in the heart, skeletal muscles, liver, alveoli, adrenal glands, and parathymic lymph nodes, that indicates the test substance is distributed throughout the body (ECHA 2021). In addition, the log K_{ow} of 5.44 indicates increased intracellular concentrations, especially in fatty tissues (ECHA 2021).
- *Metabolism:*
  - No *in vivo* data are available on the metabolism of nickel dibutyldithiocarbamate. Using the OECD QSAR toolbox, it was predicted that upon incubation with rat liver S9 mix, hydroxylation of the butyl groups would occur (OECD 2021, ECHA 2021). *In vivo* (rat) metabolic clearance of the substance is predicted to occur by oxidation of the butyl group

and N-dealkylation, both reactions that can be catalyzed by cytochrome P450 enzymes (ECHA 2021).

- *Excretion:*
    - No *in vivo* data are available on the excretion of nickel dibutyldithiocarbamate. Nickel dibutyldithiocarbamate is a hydrophobic solid with a molecular weight of 467.453 g/mol. Characteristics favoring urinary excretion include good water solubility and a low molecular weight (below 300 in the rats). Urinary excretion is therefore not expected for nickel dibutyldithiocarbamate but is likely for the metabolites (ECHA 2021).
- In summary, nickel dibutyldithiocarbamate is expected to be absorbed via oral and inhalation routes. Nickel dibutyldithiocarbamate absorbed distributes throughout the body and is hydrolyzed via oxidation of the butyl group and N-dealkylation, both reactions that can be catalyzed by cytochrome P450 enzymes. Elimination of nickel dibutyldithiocarbamate is not expected to occur via urinary excretion; however, elimination of metabolites via urinary excretion is likely.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *H*
Nickel dibutyldithiocarbamate was assigned a score of High for carcinogenicity based on ToxServices classifying it as a GHS Category 1 carcinogen due to authoritative listings for nickel compounds as a group. The existing negative 18-month study in mice is too limited to rule out carcinogenic potential. GreenScreen® criteria classify chemicals as a High hazard for carcinogenicity when they are classified as GHS Category 1 carcinogens (CPA 2018b). The confidence in the score is low as a limited 18-month study specifically on nickel dibutyldithiocarbamate is negative, and it is uncertain if nickel is bioavailable from the compound.

- Authoritative and Screening Lists
    - *Authoritative:*
        - CA – EPA – Prop 65 – Carcinogen – Hazard of nickel compounds.
        - IARC – Group 1 – Agent is carcinogenic to humans – Hazard of nickel compounds.
        - US NIH – Report on Carcinogens – known to be a human carcinogen – Hazard of nickel compounds.
    - *Screening:*
        - GHS – Japan – H350 – Category 1A – May cause cancer.
            - Japan declassified nickel dibutyldithiocarbamate for carcinogenicity later in 2008 (NITE 2008)
- ECHA 2021
    - In an 18-month carcinogenicity study, male and female of two mice strains: B6C3F1 and B6AKF1 (18/sex), were exposed to nickel dibutyldithiocarbamate at 0.1 mg/kg in 0.5% gelatin by gavage for the first 3 weeks followed by exposure via feed. In 3 male and 3 female B6AKF1 mice, pulmonary adenoma was observed. No other tumors were detected in this strain. One female B6C3F1 mouse also had a pulmonary adenoma. One male B6C3F1 mice had a Type A reticulum cell sarcoma, one male mouse had a pulmonary adenoma, and in 3 male mice had hepatoma. The observed tumors in exposed mice were not statistically different from the control animals. As this study has been performed prior to the implementations of official guidelines, several limitations exist in the design of this study, such as only mice were studied, only 18 animals per sex were tested instead of the required

50 per sex. Furthermore, animals were exposed for only 18 months instead of two years and finally only one dose level has been tested (Bionetics Research Laboratories 1968 as cited in ECHA Dossier).

- IARC 2012, ECHA 2021
    - Several international agencies have evaluated the evidence regarding the carcinogenic effects of nickel, including the (International Agency for Research on Cancer (IARC), Agency of Toxic Substances and Disease Registry (ATSDR), and National Toxicology Program (NTP). The most recent IARC (2012) evaluation considers nickel compounds to be carcinogenic to humans (Group 1). However, not all nickel substances are carcinogenic in the performed tests. Both water soluble and poorly water-soluble nickel species are taken up by cells. Soluble nickel compounds after inhalation exposure are rapidly absorbed through the lungs, and excreted in the urine. Insoluble nickel species are absorbed by phagocytosis and nickel ions are gradually released. According to IARC, the ultimate genotoxic agent is Ni(II). Direct reaction of Ni(II) with DNA does not seem to be relevant under realistic exposure conditions, but several indirect mechanisms have been identified, such as oxidative stress, inhibition of DNA repair, and epigenetic mechanisms.
- NTP 2016
    - Metallic nickel and certain nickel alloys are reasonably anticipated to be human carcinogens based on evidence of malignant tumor formation at multiple tissue sites in multiple species of experimental animals.
    - The content of nickel in the alloy has been positively correlated with tumor production.
    - Metallic nickel and nickel alloys probably are carcinogenic by dissolution and release of ionic nickel which is an active genotoxic and carcinogenic species.
    - Both soluble and insoluble nickel compounds are considered human carcinogens.
- In summary, IARC (2012) and NTP (2016) evaluated nickel compounds as carcinogenic or anticipated to be carcinogenic to humans due to containing the nickel entity. The nickel species found in the nickel dibutyldithiocarbamate is the Ni(II) form, the entire compound is not water soluble and is an inhalation risk; however, toxicokinetic information is limited for nickel dibutyldithiocarbamate. The REACH dossier authors classified nickel dibutyldithiocarbamate as a GHS Category 2 carcinogen given the uncertainty of the nickel entity to dissociate from the compound. ToxServices assigned a more conservative classification of GHS Category 1 to align with authoritative bodies. Therefore, the score of High was assigned.

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

Nickel dibutyldithiocarbamate was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity in bacterial mutagenicity assays and in an *in vitro* mammalian cell gene mutation assay, and for clastogenicity in an *in vitro* mammalian cell micronucleus test for the target chemical. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and are negative for both gene mutations and chromosomal aberrations (CPA 2018b). Confidence in the score is high because it is based on reliable data for the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
    - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant Ames test conducted according to OECD Guideline 471. *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP_2 *uvr* A were exposed to nickel

dibutyldithiocarbamate (purity not specified) in DMSO at concentrations up to 5,000 µg/plate with and without metabolic activation (S9 mix from Aroclor 1254 induced rat livers). Negative and positive controls were valid. Precipitation was observed at 556 µg/plate and above in all strains and considered not to affect the counting of the background lawn. No cytotoxicity was observed; however, the test substance was tested up to maximum concentration required by guideline (Klimisch 1, reliable without restriction) (Triskelion 2017 as cited in ECHA Dossier).

- *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant Ames test conducted similar to OECD Guideline 471. *S. typhimurium* tester strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to nickel dibutyldithiocarbamate (purity not specified) in DMSO at concentrations up to 5,000 µg/plate with and without metabolic activation (Aroclor 1254 induced rat liver S9 mix). Negative and positive controls (2-nitrofluorene, 9-aminoacridine, 2-aminoanthramine, and N-ethyl-N-nitro-N-nitrosoguanidine) were valid. No precipitation or cytotoxicity was observed; however, the test substance was tested up to maximum concentration required by guideline (Klimisch 2, reliable with restrictions) (HRC 1985 as cited in ECHA Dossier).
- *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant mammalian cell gene mutation test at the thymidine kinase locus conducted according to OECD Guideline 490. Mouse lymphoma L5178Y cells were exposed to nickel dibutyldithiocarbamate (>98% purity) in DMSO at 3.9, 7.8, 15.7, 31.3, 62.5, 125, 250 and 500 µg/mL for a 3 hour treatment (Exp. 1) and at 7.8, 15.7, 31.3, 62.5, 125, 180, 250, 320, 400 and 500 µg/mL for a 24 hour treatment (Exp. 2), with and without metabolic activation (S9 mix from Aroclor 1254 induced rats livers). The vehicle and positive controls (3-methylcholanthrene and methylmethanesulfonate) were valid. No precipitation was observed. Cytotoxicity was observed in Experiment 1, at the highest concentration of 500 µg/mL, with 95% and 99% viability, with and without metabolic activation, respectively. In Experiment 2, the viability of cells at the highest dose tested of 500 µg/mL was 96% without metabolic activation. Relative total growth (RTG) values in Experiment 1 at 500 µg/mL were 70% and 76% at 4 hours, without and without metabolic activation, respectively, and 43% after 24 hours without metabolic activation 500 µg/mL in Experiment 2. There was no evidence of induced mutant colonies over background (Klimisch 1, reliable without restriction) (Triskelion 2018 as cited in ECHA Dossier).
- *In vitro*: Negative results for clastogenicity were obtained in a GLP-compliant mammalian cell micronucleus test conducted according to OECD Guideline 487. Human peripheral blood lymphocytes were exposed to nickel dibutyldithiocarbamate (>98% purity) in DMSO at 1, 2, 3.9, 7.8, 15.6, 31.3, 62.5, 125, 250, and 500 µg/mL for a 4-hour exposure (Experiment I) with and without metabolic activation (S9 mix from Aroclor 1254 induced rat livers), and the same concentrations for a 24-hour exposure (Experiment II) without metabolic activation. The vehicle and positive controls (cyclophosphamide and vinblastine sulphate) were valid. Precipitation was observed in both Experiment I and II as a green cell pellet. Precipitation was observed during the fixation stage in Experiment I with metabolic activation at 62.5 µg/mL and above, and without metabolic activation at 500 µg/mL. Precipitation was observed in Experiment II without metabolic activation at 62.5 µg/mL and above. No cytotoxicity was observed. From the results obtained in this *in vitro* micronucleus test, it is concluded that the test substance was not clastogenic and/or aneugenic to cultured human lymphocytes, under the conditions used in this study (Klimisch 1, reliable without restriction) (Triskelion 2018 as cited in ECHA Dossier).

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

Nickel dibutyldithiocarbamate was assigned a score of Moderate for reproductive toxicity based on ToxServices classifying it as a GHS Category 2 reproductive toxicant. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when they are classified as GHS Category 2 reproductive toxicants (CPA 2018b). Confidence in the score is low due to lack of details reported on the dystocia effects observed in the high dose females, which may be secondary to severe maternal toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* In a GLP-compliant combined repeated dose toxicity with reproductive and developmental toxicity screening test that was conducted according to OECD Guideline 422, male and female Wistar IGS rats (12/sex/dose) were administered nickel dibutyldithiocarbamate (purity not specified) in corn oil at concentrations of 0.2, 2, and 10 mg/kg/day via gavage daily. Males were treated for a 14-day pre-mating period, 14-day mating period, and until sacrifice after a total of 31 days, while females were treated for a 14-day pre-mating period, 14-day mating period, through gestation, and until postnatal day 14 for a total of up to 63 days. Mean body weights and body weight gain were reduced in high-dose males and in high-dose females during gestation. Reductions in food consumption were noted in the high-dose group in both sexes. There were no relevant effects on reproductive organs or on reproductive performance parameters in the low-dose (0.2 mg/kg/day) and mid-dose groups (2 mg/kg/day). There were no treatment-related clinical signs in males or, until parturition, in females. At parturition, dystocia occurred in the high-dose group, one female was found dead, and eight females were humanely killed because of conditional decline. Signs noted prior to their death included respiratory distress, piloerection, and soiled fur/perineum. Two other pregnant high-dose rats delivered, but had litters with mainly dead pups, and showed paleness, piloerection, and a lower body temperature. Results of T4 hormone analysis in male adult animals and in male and female pups on PND 13 did not show any significant effects between the groups. Treatment did not adversely affect mating, fertility, or copulation/conception indices or the mean estrous cycle lengths. In the high-dose females that were humanely killed, the number of implantation sites and the number and appearance of the pups were not noticeably affected. In the remaining (low- and mid-dose) groups there were no adverse changes in the duration of gestation, the number of implantation sites, and the number of pups delivered. In these groups, there were no relevant or treatment-related changes in pup observations, pup sex and pup survival, pup anogenital distance, nipple retention, pup thyroid weight or macroscopy. Slight (≤ 8%) and not dose-related reductions in total pup weight in the low- and mid-dose groups on day 7 of lactation, and in female pup weight in the mid-dose group on day 13 of lactation were not considered to be adverse. The study authors identified a reproductive NOAEL of 10 mg/kg/day for males based on no adverse effects on reproductive organs or on reproductive performance parameters in any dose group. The study authors identified a female reproductive toxicity NOAEL of 2 mg/kg/day, the highest dose for which sufficient maternal survival was available to evaluate fertility (Klimisch 1, reliable without restriction) (Triskelion 2019 as cited in ECHA Dossier).
    - Due to the dystocia observed in the high dose females in the presence of systemic toxicity, ToxServices has conservatively assigned nickel dibutyldithiocarbamate as a GHS Category 2 reproductive toxicant.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Nickel dibutyldithiocarbamate was assigned a score of Low for developmental toxicity based on the lack of developmental effects observed up to 2 mg/kg/day (oral) in an OECD 422 study even in the presence of maternal toxicity. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate data are available, and they are not classified under GHS (CPA 2018b). Confidence in the score is low as it is based on the results of a screening study, in which the highest dose was too toxic to the maternal animals to be reliably evaluated.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* In the previously described GLP-compliant combined repeated dose toxicity with reproductive and developmental toxicity screening test that was conducted according to OECD Guideline 422, male and female Wistar IGS rats (12/sex/dose) were administered nickel dibutyldithiocarbamate (purity not specified) in corn oil at concentrations of 0.2, 2, and 10 mg/kg/day via gavage daily. Males were treated for a 14-day pre-mating period, 14-day mating period, and until sacrifice after a total of 31 days, while females were treated for a 14-day pre-mating period, 14-day mating period, through gestation, and until postnatal day 14 for a total of up to 63 days. Mean body weights and body weight gain were reduced in high-dose males and in high-dose females during gestation. Reductions in food consumption were noted in the high-dose group in both sexes. There were no relevant effects on reproductive organs or on reproductive performance parameters in the low- (0.2 mg/kg/day) and mid-dose groups (2 mg/kg/day). There were no treatment-related clinical signs in males or, until parturition, in females. At parturition, dystocia occurred in the high-dose group, one female was found dead, and eight females were humanely killed because of conditional decline. Signs noted prior to their death included respiratory distress, piloerection, and soiled fur/perineum. Two other pregnant high-dose rats delivered, but had litters with mainly dead pups, and showed paleness, piloerection, and a lower body temperature. Results of T4 hormone analysis in male adult animals and in male and female pups on PND 13 did not show any significant effects between the groups. Treatment did not adversely affect mating, fertility, or copulation/conception indices or the mean estrous cycle lengths. In the high-dose females that were humanely killed, the number of implantation sites and the number and appearance of the pups were not noticeably affected. In the remaining (low- and mid-dose) groups there were no adverse changes in the duration of gestation, the number of implantation sites, and the number of pups delivered. In these groups, there were no relevant or treatment-related changes in pup observations, pup sex and pup survival, pup anogenital distance, nipple retention, pup thyroid weight or macroscopy. Slight (≤ 8%) and not dose-related reductions in total pup weight in the low- and mid-dose groups on day 7 of lactation, and in female pup weight in the mid-dose group on day 13 of lactation were not considered to be adverse. The study authors identified a systemic toxicity NOAEL of 0.2 mg/kg/day based on non-neoplastic histopathology. The study authors identified a developmental toxicity NOAEL of 2 mg/kg/day, the highest dose for which sufficient maternal survival was available to evaluate prenatal development (Klimisch 1, reliable without restriction) (Triskelion 2019 as cited in ECHA Dossier).

Endocrine Activity (E) Score (H, M, or L): DG
Nickel dibutyldithiocarbamate was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
    - *Oral:* In the previously described GLP-compliant combined repeated dose toxicity with reproductive and developmental toxicity screening test that was conducted according to OECD Guideline 422, male and female Wistar IGS rats (12/sex/dose) were administered nickel dibutyldithiocarbamate (purity not specified) in corn oil at concentrations of 0.2, 2, and 10 mg/kg/day via gavage daily. Males were treated for a 14-day pre-mating period, 14-day mating period, and until sacrifice after a total of 31 days, while females were treated for a 14-day pre-mating period, 14-day mating period, through gestation, and until postnatal day 14 for a total of up to 63 days. The animals were evaluated for clinical signs of toxicity, body weights, estrous cyclicity, thyroid hormone levels (T4), organ weights, and histopathology (kidney, thyroid, ovary, and uterus). The absolute and relative weights of prostate and seminal vesicles were decreased in high-dose males. In addition, the absolute weight of the epididymides was decreased in high-dose males. Vacuolation occurred in the zona fasciculata of the adrenal gland in mid- and high-dose males. Results of T4 hormone analysis in male adult animals and in male and female pups on PND 13 did not show any significant effects between the groups. There were no treatment-related effects on estrous cyclicity during the pre-mating period, or in the number of pregnant females, pre-coital time or mating indices. There were no relevant or treatment-related changes in pup observations, pup sex and pup survival, pup anogenital distance, nipple retention, pup thyroid weight or macroscopy (Klimisch 1, reliable without restriction) (Triskelion 2019 as cited in ECHA Dossier).
- U.S. EPA 2021b
    - Nickel dibutyldithiocarbamate was active in 0/8 estrogen receptor (ER) assays, 0/9 androgen receptor (AR) assays, 0/2 steroidogenesis assays, and 0/8 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (Appendix D).
    - Nickel dibutyldithiocarbamate was predicted to be active (very weak) for estrogen receptor binding using the CERAPP Potency Level (from literature) model. It was predicted to be inactive for estrogen receptor agonism, antagonism, and binding using the CERAPP Potency Level (consensus) model. It was also predicted to be inactive for androgen receptor agonism, antagonism, and binding using the COMPARA (Consensus) model in ToxCast (Appendix E).
- VEGA 2021
    - ToxServices attempted to evaluate nickel dibutyldithiocarbamate using VEGA (v.1.2.8); however, results were outside of the applicability domains in the estrogen receptor relative binding affinity (IRFMN 1.0.1), estrogen receptor-mediated effect (IRFMN/CERAPP 1.0.0), androgen receptor-mediated effect (IRFMN/COMPARA 1.0.0), thyroid receptor alpha effect (NRMEA 1.0.0) and thyroid receptor beta effect (NRMEA 1.0.0) VEGA models (VEGA 2021, output not included).
- DTU 2021
    - ToxServices attempted to evaluate nickel dibutyldithiocarbamate using Danish QSAR; however, results for nickel dibutyldithiocarbamate were not available in the Danish QSAR database (DTU 2021, output not included).
- Based on the weight of evidence, a score of Data Gap was assigned. Nickel dibutyldithiocarbamate was reported to be inactive in the *in vitro* EDSP21 high throughput screening assays and mostly

negative or only weakly positive in ToxCast modeling. Additionally, in a subacute oral combined repeated dose study that evaluated endocrine parameters no adverse effects related to endocrine mechanisms were observed in rats. However, no *in vivo* assays for the hormone levels of the three endocrine pathways (estrogen, androgen, and thyroid) were identified, and *in silico* predictions along with *in vitro* data are not sufficient to assign a score of Low for this endpoint.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): L

Nickel dibutyldithiocarbamate was assigned a score of Low for acute mammalian toxicity based on oral values greater than 5,000 mg/kg in rats and dermal values greater and 2,000 mg/kg in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when acute oral and dermal LD_{50} values are greater than 2,000 mg/kg (CPA 2018b). Confidence in the score was high because it was based on a well-conducted studies on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral*: LD_{50} (Sprague-Dawley rats) > 5,000 mg/kg (males and females) (equiv. to Toxic Substances Control Act Health Effects Guidelines, EPA 1982) (Klimisch Score 2, reliable with restrictions) (Unnamed 1986 as cited in ECHA Dossier).
    - Corn oil was used as the vehicle, and test substance purity was unspecified.
  - *Oral*: LD_{50} (Wistar rats) > 5,000 mg/kg (males and females) (Klimisch Score 2, reliable with restrictions) (Unnamed 1978 as cited in ECHA Dossier).
    - DMSO was used as the vehicle, and test substance purity was unspecified.
  - *Dermal*: LD_{50} (New Zealand rabbits) > 2,000 mg/kg (males and females) (equiv. to OECD Guideline 402) (Klimisch Score 2, reliable with restrictions) (Unnamed 1986 as cited in ECHA Dossier).
    - No vehicle was used, and test substance purity was unspecified.
  - *Inhalation*: (whole body, dust) 4hr LC_{50} (Sprague-Dawley rats) > 0.416 mg/L (males and females) (GLP-compliant, equiv. to OECD Guideline 403) (Klimisch Score 2, reliable with restrictions) (Unnamed 1986 as cited in ECHA Dossier).
    - Test substance purity was unspecified.
  - Additional acute oral toxicity tests are presented in the REACH dossier for nickel dibutyldithiocarbamate. However, they were assigned Klimisch Scores of 3 (not reliable) or 4 (not assignable); therefore, ToxServices did not include the results of these studies in the current assessment.
- Based on weight of evidence, nickel dibutyldithiocarbamate was assigned Low based on oral and dermal acute toxicity. Oral LD_{50} values are > 5,000 mg/kg in rats and the dermal LD_{50} is > 2,000 mg/kg, which would both classify it to GHS Category 5 or Not Classified. The 4-hour dust inhalation LC_{50} value was > 0.416 mg/L in rats, which was the highest concentration that could be generated in the study. However, there was a low efficiency of dust generation (measured concentration was only 0.9 - 4% of the nominal concentration).

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

Nickel dibutyldithiocarbamate was assigned a score of Low for systemic toxicity (single dose) based on no signs of systemic toxicity up to 5,000 mg/kg/day in oral and up to 2,000 mg/kg/day in dermal acute studies in rats and rabbits, respectively. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and negative, and they are not GHS classified (CPA 2018b). Confidence in the score was high because it was based on a well-conducted studies on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral*: In the GLP-unspecified acute oral toxicity test conducted in a manner similar to Toxic Substances Control Act Health Effects Guidelines, EPA 1982 that identified an oral LD_{50} > 5,000 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included piloerection that resolved by day 3. Reduced body weights were identified for 3 surviving males (on day 3) and 4 surviving females (3 on day 3, 1 on day 11), while the remaining surviving animals exhibited body weight gains. All other observations and measurements were unremarkable (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).
  - *Oral*: In the GLP-unspecified acute oral toxicity test that identified an oral LD_{50} > 5,000 mg/kg in male and female Wistar rats, clinical signs of toxicity included sluggishness and signs of ataxia that disappeared after 24 hours. There were no mortalities and gross pathology was unremarkable (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).
  - *Dermal*: In the GLP-unspecified acute dermal toxicity test conducted in a manner similar to OECD 402 that identified a dermal LD_{50} > 2,000 mg/kg in male and female New Zealand rabbits, clinical signs of toxicity included decreased food consumption in two male rabbits on days 4 and 5, diarrhea on day 3 in one of these male rabbits, and no signs of systemic toxicity in remaining 3 out of 5 males and all five female rabbits. There were no dermal reactions at the site of application in any of the rabbits; however, some staining of the skin and adjacent fur by the test substance was observed. Reduced body weights were identified for 2 male and 3 female rabbits on day 2, 4 males and 3 females on day 3, one male on day 8, and one female on day 11. Poor weight gain was recorded on days 3 and 8 for one male and on day 15 of another male rabbit. An unchanged weight was recorded for one male on day 2 only, while the remaining surviving animals exhibited body weight gains. There were no mortalities and gross pathology was unremarkable (Unnamed Study 1986 as cited in ECHA Dossier).
  - *Inhalation*: In the GLP-compliant acute inhalation toxicity test conducted according to OECD 403 that identified a 4-hour inhalation LC_{50} > 0.416 mg/L in male and female Sprague-Dawley rats, clinical signs of toxicity included closing or partial closing of the eyes, abnormal breathing and abnormal body posture in all rats; however, these signs were considered to be consistent with a non-specific response to dust exposure. Reduced body weights were identified for some animals; however, specific numbers were not provided. There were no mortalities and gross pathology was unremarkable (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).

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

Nickel dibutyldithiocarbamate was assigned a score of High systemic toxicity (repeated dose) based on ToxServices classifying it as a Category 1 specific target organ toxicant following repeated oral doses under GHS criteria for effects on the heart and skeletal muscle system. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when they are classified as GHS Category 1 specific target organ toxicants following repeated oral doses (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* In the previously described GLP-compliant combined repeated dose toxicity with reproductive and developmental toxicity screening test that was conducted according to OECD Guideline 422, male and female Wistar IGS rats (12/sex/dose) were administered nickel dibutyldithiocarbamate (purity not specified) in corn oil at concentrations of 0.2, 2, and 10 mg/kg/day via gavage daily. Males were treated for a 14-day pre-mating period, 14-day mating period, and until sacrifice after a total of 31 days, while females were treated for a 14-day pre-mating period, 14-day mating period, through gestation, and until postnatal day 14 for a total of up to 63 days. There were no treatment-related clinical signs in males or, until parturition, in females. At parturition, dystocia occurred in the high-dose group, one female was found dead and eight females were humanely killed because of conditional decline. Signs noted prior to their death included respiratory distress, piloerection, and soiled fur/perineum. Two other pregnant high-dose rats delivered, but had litters with mainly dead pups, and showed paleness, piloerection, and a lower body temperature. Mean body weights and body weight gain were reduced in high-dose males and in high-dose females during gestation. Reductions in food consumption were noted in the high-dose group in both sexes. In mid- and high-dose males, red blood cell count, hemoglobin concentration, and packed cell volume were decreased, and reticulocytes were increased. Prothrombin time was increased in high-dose males. Total white blood cell, lymphocyte and eosinophil counts were decreased, and the percentage of monocytes was increased in high-dose males. In high-dose males, ASAT activity and urea, chloride and sodium concentrations were increased, while total protein, albumin, glucose, and calcium concentrations were decreased compared to controls. The absolute and relative weights of the heart were increased in mid- and high-dose males. The absolute and relative weights of the heart were also considerably increased in the two surviving high-dose dams. The absolute and relative weights of the liver were increased, and those of the prostate and seminal vesicles were decreased in high-dose males. In addition, the absolute weight of the epididymides was decreased in high-dose males. Macroscopic examination at scheduled necropsy showed enlarged parathymic lymph nodes in 5/12 high-dose males and in 2/3 remaining high-dose females. Enlarged parathymic lymph nodes were also noted in 6/9 high-dose females that died or were killed in moribund condition. A dose-dependent degeneration of the heart muscle was observed in mid- and high-dose males, characterized by the presence of fibrotic areas. Degeneration of the skeletal muscle accompanied by necrosis and mononuclear inflammation in high-dose males. In the mid-dose group, 1/5 males showed necrosis and mononuclear inflammation of the skeletal muscle. Hyperemia occurred in the liver of high-dose males and mid-dose females. Perivascular inflammation and accumulation of alveolar macrophages occurred in the lungs of mid- and high-dose

males and mid-dose females. In addition, the incidence of alveolitis was increased in high-dose males. Vacuolation occurred in the zona fasciculata of the adrenal gland in mid- and high-dose males. Increased incidence of histiocytosis in the parathymic lymph nodes were observed in males and females of the high-dose group. Results of T4 hormone analysis in male adult animals and in male and female pups on PND 13 did not show any significant effects between the groups. The study authors identified a systemic toxicity NOAEL of 0.2 mg/kg/day based on degeneration of heart and skeletal muscle observed at mid-dose and high-dose groups (Klimisch 1, reliable without restriction) (Triskelion 2019 as cited in ECHA Dossier).

- As the exposure duration was less than 90 days, ToxServices adjusted the GHS oral guidance values of 10 and 100 mg/kg/day (UN 2021) by a factor of 3 (31 days is approximately a third of 90 days) to 30 and 300 mg/kg/day, respectively. ToxServices classified nickel dibutyldithiocarbamate as a GHS Category 1 specific target organ toxicant following repeated oral dosing based on effects to the heart/skeletal muscle occurring at the LOAEL of 2 mg/kg/day.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *M*
Nickel dibutyldithiocarbamate was assigned a score of Moderate for neurotoxicity (single dose) based on ToxServices classifying it as a Category 3 specific target organ toxicant following single exposures for narcotic effects. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified as GHS Category 3 specific target organ toxicant following single exposures for narcotic effects (CPA 2018b). The confidence in the score is low as these signs were only found in one oral study in Wistar rats and may be reflective of general toxicity rather than specific neurotoxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral*: In the GLP-unspecified acute oral toxicity test conducted in a manner similar to Toxic Substances Control Act Health Effects Guidelines, EPA 1982 that identified an oral LD_{50} > 5,000 mg/kg in male and female Sprague-Dawley rats, clinical signs of toxicity included piloerection that resolved by day 3. All other observations and measurements were unremarkable (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).
  - *Oral*: In the GLP-unspecified acute oral toxicity test that identified an oral LD_{50} > 5,000 mg/kg in male and female Wistar rats, clinical signs of toxicity included sluggishness and signs of ataxia that disappeared after 24 hours. There were no mortalities and gross pathology was unremarkable (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).
  - *Dermal*: In the GLP-unspecified acute dermal toxicity test conducted in a manner similar to OECD 402 that identified a dermal LD_{50} > 2,000 mg/kg in male and female New Zealand rabbits, clinical signs of toxicity included decreased food consumption in two male rabbits on days 4 and 5, diarrhea on day 3 in one of these male rabbits, and no clinical signs indicating neurotoxicity in remaining 3 out of 5 males and all five female rabbits. There were no mortalities and gross pathology was unremarkable (Unnamed Study 1986 as cited in ECHA Dossier).
  - *Inhalation*: In the GLP-compliant acute inhalation toxicity test conducted according to OECD 403 that identified a 4-hour inhalation LC_{50} > 0.416 mg/L in male and female

Sprague-Dawley rats, clinical signs of toxicity included closing or partial closing of the eyes, abnormal breathing and abnormal body posture in all rats; however, these signs were considered to be consistent with a non-specific response to dust exposure. There were no mortalities and gross pathology was unremarkable (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).

- In summary, single oral and inhalation doses of nickel dibutyldithiocarbamate produced signs of transient narcotic effects, including sluggishness (decreased movement), ataxia, and abnormal gait. However, the single inhalation neurotoxic responses observed were not considered due to non-specific dust-response, and therefore not considered toward weight of evidence. Therefore, ToxServices classified it as a specific target organ toxicant following single exposures for narcotic effects under GHS criteria (UN 2021).

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

Nickel dibutyldithiocarbamate was assigned a score of Low for neurotoxicity (repeated dose) based on no systemic neurological effects seen up to the highest tested dose of 10 mg/kg/day conducted in a GLP-compliant OECD 422 oral combined repeated dose toxicity study in rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is reduced as the highest tested dose (10 mg/kg/day) is significantly below the duration-adjusted GHS guidance value of 300 mg/kg/day for a 30-day study for GHS Category 2, and severe toxicity/mortality occurred in the high dose group that may have obscured specific neurotoxicity effects.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* In the previously described combined GLP-compliant repeated dose toxicity with reproductive and developmental toxicity screening test that was conducted according to OECD Guideline 422, male and female Wistar IGS rats (12/sex/dose) were administered nickel dibutyldithiocarbamate (purity not specified) in corn oil at concentrations of 0.2, 2, and 10 mg/kg/day via gavage daily. Males were treated for a 14-day pre-mating period, 14-day mating period, and until sacrifice after a total of 31 days, while females were treated for a 14-day pre-mating period, 14-day mating period, through gestation, and until postnatal day 14 for a total of up to 63 days. There were no treatment-related clinical signs in males or, until parturition, in females. At parturition, dystocia occurred in the high-dose group, one female was found dead and eight females were humanely killed because of conditional decline. Signs noted prior to their death included respiratory distress, piloerection, and soiled fur/perineum. Two other pregnant high-dose rats delivered, but had litters with mainly dead pups, and showed paleness, piloerection, and a lower body temperature. The results of the neurobehavioral observations and motor activity assessment did not indicate any neurotoxic potential of the test substance in rats. Weak evidence of an effect of treatment on body temperature was, however, observed in the functional observation test: at the end of the treatment period, body temperature was statistically significantly decreased in the female high-dose group which included by then only two dams. Gross pathology and histopathology were performed on brain and no adverse effects were noted (Klimisch 1, reliable without restriction) (Triskelion 2019 as cited in ECHA Dossier).
    - ToxServices identified a neurotoxicity NOAEL of 10 mg/kg/day for this study.

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

Nickel dibutyldithiocarbamate was assigned a score of Low for skin sensitization based on negative results for sensitization in a Buehler test. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when they have negative data and are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - A GLP-unspecified Buehler test conducted in a manner similar to OECD 406 was performed with female Dunkin-Hartley guinea pigs (10/group) administered dermal doses of nickel dibutyldithiocarbamate (purity not specified). The induction doses were 0.5 mL (40%) in liquid paraffin for 6 hours and the challenge doses were 0.5 mL (40%) in liquid paraffin for 6 hours under occlusive coverage. Two weeks after the ninth induction application, the challenge applications were applied. At 24, 48, and 72 hours after the challenge dose, no animals in any dose group exhibited positive skin reactions. Therefore, the authors concluded that nickel dibutyldithiocarbamate was not sensitizing to the skin under the tested conditions (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).

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

Nickel dibutyldithiocarbamate was assigned a score of Moderate for respiratory sensitization based on ToxServices classifying it as a GHS Category 1B respiratory sensitizer. Nickel compounds are known respiratory sensitizers according to AOEC. However, insoluble nickel compounds may be less sensitizing. While nickel dibutyldithiocarbamate does not contain structural alerts for respiratory sensitization and was not a skin sensitizer in guinea pigs, which does not warrant GHS classification per ECHA guidance (ECHA 2017), the ECHA guidance also includes consideration of human data and other lines of evidence. GreenScreen® criteria classify chemicals as a Moderate hazard for respiratory sensitization when they are classified as GHS Category 1B respiratory sensitizers (CPA 2018b). The confidence in the score is low as no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:*
    - AOEC – Asthmagen (Rs) – sensitizer – induced – Hazard of nickel compounds.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2000
  - Chronic inhalation exposure to nickel in humans results in respiratory effects, including a type of asthma specific to nickel, decreased lung function, and bronchitis.
  - Animal studies have reported effects on the lungs and immune system from inhalation exposure to soluble and insoluble nickel compounds (nickel oxide, subsulfide, sulfate heptahydrate).
  - Soluble nickel compounds are more toxic to the respiratory tract than less soluble compounds.
- OECD 2021
  - Nickel dibutyldithiocarbamate does not contain any structural alerts for respiratory sensitization (Appendix F)
- Based on weight of evidence, ToxServices conservatively classified nickel dibutyldithiocarbamate as a GHS Category 1B respiratory sensitizer based the low to moderate frequency of occurrence

with insoluble nickel compounds, such as the target substance and lack of structural alerts for the target substance. Therefore, a score of Moderate was assigned for this endpoint.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L
Nickel dibutyldithiocarbamate was assigned a score of Low for skin irritation/corrosivity based on ToxServices not classifying it as a skin irritant under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - A GLP-unspecified dermal irritation test conducted in a manner similar to OECD Guideline 404 was performed with New Zealand White rabbits (6 total) administered topical applications of 0.5 g undiluted nickel dibutyldithiocarbamate (purity unspecified) to intact and abraded skin under semi-occlusive dressing for 24 hours. A 7-day observation period followed the exposure period. At 24, 48, and 72 hours, the mean overall irritation score was 0/8, and the authors concluded that nickel dibutyldithiocarbamate was not irritating under the tested conditions. None of the animals showed any observable responses to treatment throughout the observation period (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).
  - Nickel dibutyldithiocarbamate was not irritating in a GLP-unspecified dermal irritation test was performed with New Zealand White rabbits (12 total) administered topical applications of 0.5 g undiluted test substance (purity unspecified) to intact and abraded skin under semi-occlusive dressing for 24 hours. A 7-day observation period followed the exposure period. At 24 and 72 hours, animal #1 has an erythema score of ¼ that was not fully reversible at 72 hours; however, the rest of the 5 animals exhibited erythema scores of 0, and a mean erythema score of 0.167. At 24 and 72 hours, the mean edema score was 0/4, and the authors concluded that nickel dibutyldithiocarbamate was not irritating under the tested conditions. At the end of the 24-hour application period, very slight erythema was observed in one rabbit with application on intact skin and 3 rabbits with applications on abraded skin. After 72 hours, very slight scaliness was observed on the one rabbit treated on the intact skin, and two of the rabbits treated on abraded skin. (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1978 as cited in ECHA Dossier).
- GHS criteria define skin irritants as chemicals that produce mean scores ≥ 1.5 for erythema and/or edema in at least 2 of 3 animals following readings at 24, 48, and 72 hours (UN 2021). As the results of the two skin irritation tests do not indicate skin irritation above this threshold, ToxServices did not classify nickel dibutyldithiocarbamate as a dermal irritant under GHS criteria.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *H*
Nickel dibutyldithiocarbamate was assigned a score of High for eye irritation based on ToxServices classifying it as a GHS Category 2A eye irritant. GreenScreen® criteria classify chemicals as a High hazard for eye irritation when they are classified as GHS Category 2A eye irritants (CPA 2018b). The confidence in the score is low due to the critical study having a reduced observation period compared to OECD Guideline 405 to determine the full reversibility of effects observed.

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

  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - Nickel dibutyldithiocarbamate was not irritating in a GLP-unspecified dermal irritation test conducted in a manner similar to OECD Guideline 405 with New Zealand White rabbits (6 total) administered ocular instillations of 100 mg undiluted test substance (purity unspecified). A 7-day observation period followed the exposure period. The mean corneal opacity scores across 24, 48, and 72 hours were 1.67, 1.67, 1.67, 1.33, 0, and 0.67 in each of the 6 animals, and the effects were fully reversible in all but one animal by 7 days. The mean scores for iris were 1, 1, 1, 1, 0, and 0 for each of the six animals, with the effects fully reversible in all but one animal by 7 days. The mean scores for conjunctival redness were 1.33, 1.33, 1.67, 1.67, 1.67 and 2 in each of the six animals, with effects not fully reversible in 5 animals by 7 days. The mean chemosis scores were 1.33, 1.33, 1.67, 2, 2, and 1 for each of the 6 animals, with effects fully reversible in 7 days in all animals. The authors concluded that nickel dibutyldithiocarbamate was irritating (GHS Category 2) under the tested conditions. (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1978 as cited in ECHA Dossier).
  - Nickel dibutyldithiocarbamate was not irritating in a GLP-unspecified ocular irritation test conducted in a manner similar to OECD Guideline 405 with New Zealand White rabbits (9 total, 4 males, 5 females) administered ocular instillations of 65 mg undiluted test substance (purity unspecified) and rinsed after 20-30 seconds. A 7-day observation period followed the exposure period. Two animals gave a positive response. Conjunctivae redness was observed in two animals one day after instillation, and transient mild conjunctival reactions were seen in three animals. At 24, 48, and 72 hours, the mean cornea opacity score was 0. At 24, 48, and 72 hours, the mean iris score was 0. At 24, 48, and 72 hours, the reported conjunctivae scores were 0 for all animals except animal #2 (1/3), animal #6 (1/3), and animal #4 (0.33/3). At 24, 48, and 72 hours, the reported chemosis score were 0 for all animals except animal #2 (0.67/4), animal #6 (0.33/4). All eyes were normal one to three days after instillation. Under the conditions of the test, the test substance was not considered irritating to eyes (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1986 as cited in ECHA Dossier).
- In summary, under GHS criteria (UN 2021), a chemical is classified as irritating to the eyes if it produces mean scores ≥ 1 for corneal opacity, ≥ 1 for iritis, ≥ 2 for conjunctival redness, and/or ≥ 2 for chemosis in at least 2 of 3 animals following readings at 24, 48, and 72 hours, with reversibility of the irritation effects occurring within 21 days (Category 2A) or 7 days (Category 2B). Irritating effects of sufficient severity on the rabbit eye were reported in the Unnamed Study 1978 (corneal opacity score ≥ 1 and iritis score ≥ 1) above. The study was limited by a shorter observation period (7 days instead of 21 days), even though some effects were not fully reversed at day 7. Given that the Unnamed Study 1986 shows no indication of eye irritation in rabbits with a lower dose of 68 mg instead of 100 mg, ToxServices assumed that effects observed in the first study would have been fully reversed at 21 days after exposure. Therefore, ToxServices classified nickel dibutyldithiocarbamate as a Category 2A ocular irritant under GHS criteria (UN 2021).

Ecotoxicity (Ecotox)

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

Nickel dibutyldithiocarbamate was assigned a score of Low for acute aquatic toxicity based on lack of toxicity above water solubility. No details were identified for the critical study used by Canada to classify the compound as iTE, including solvents used, and the LC_{50} is also above the measured water

solubility of the compound. Therefore, ToxServices did not weigh this study heavily. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute L/EC_{50} values are > 100 mg/L or no toxicities are observed up to saturation in water (CPA 2018b). The confidence in the score is high as it is based on reliable measured data including all trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - EC - CEPA DSL - Inherently Toxic in the Environment (iTE).
      - Based on a 168-hour LC_{50} of 0.075 mg/L in *Hyallela Azteca* (aquatic invertebrate) (CCR 2021).
- ECHA 2021
  - Nickel dibutyldithiocarbamate has a measured water solubility of 8.93 µg/L in an OECD Guideline 105 test.
  - 96-hour LC_{50} (*Poecilia reticulata*, Guppy) > 16 mg/L (nominal, semi-static, saturated concentration) (equiv. to OECD Guideline 203) (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1991 as cited in ECHA Dossier).
    - Test substance purity was 97%, and acetone was used to solubilize the compound in the test medium.
  - 48-hour mobility EC_{50} (*Daphnia magna*) > 0.0063 mg/L (6.3 µg/L) (measured) (GLP-compliant, OECD Guideline 202, EPA OPPTS 850.1010) (Klimisch Score 1, reliable without restriction) (Unnamed Study 2018 as cited in ECHA Dossier).
    - Dimethylformamide (DMF) was used to solubilize the compound in the test medium.
  - 72-hour growth rate EC_{50} (*Pseudokirchneriella subcapitata*, freshwater algae) > 0.001 mg/L (10 µg/L) (nominal) (GLP-compliant, OECD Guideline 202, EU Method C.3 1992) (Klimisch Score 1, reliable without restriction) (Unnamed Study 2019 as cited in ECHA Dossier).
    - DMF was used to solubilize the compound in the test medium.

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

Nickel dibutyldithiocarbamate was assigned a score of Low for chronic aquatic toxicity based on a lack of toxic effects at saturation in water. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity data are > 10 mg/L or no toxicities are observed up to solubility limits in water (CPA 2018b). The confidence in the score is reduced as no data were identified for the daphnia trophic level.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
  - *Other:*
    - GHS – Japan – H413 – Category 4 - May cause long lasting harmful effects to aquatic life “Hazardous to the aquatic environment (chronic)”.
- ECHA 2021
  - Nickel dibutyldithiocarbamate has a measured water solubility of 8.93 µg/L in an OECD Guideline 105 test.
  - 10-day NOEC (*Danio rerio,* Zebrafish) = 10 mg/L, and LOEC = 32 mg/L (nominal, semi-static) (equiv. to OECD Guideline 212) (Klimisch Score 2, reliable with restrictions) (Unnamed Study 1991 as cited in ECHA Dossier).

        - Test substance purity was 97%, and acetone was used to solubilize the test compound.
    - 72-hour growth rate NOEC (*P. subcapitata*, freshwater algae) = 0.001 mg/L (10 µg/L) (highest concentration tested) (nominal) (GLP-compliant, OECD Guideline 202, EU Method C.3 1992) (Klimisch Score 1, reliable without restriction) (Unnamed Study 2019 as cited in ECHA Dossier).
        - DMF was used to solubilize the compound in the test medium.

Environmental Fate (Fate)

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

Nickel dibutyldithiocarbamate was assigned a score of Very High for persistence based on the nickel metal being expected to be recalcitrant in the environment, with support of no biodegradation observed in the OECD 301B study. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when they are recalcitrant in the environment (CPA 2018b). The confidence in the score is low as it is based on expert judgment. Modeling with EPI Suite™ was not used as organometallic compounds are outside the applicability domain of the model.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - EC - CEPA – DSL – Persistent.
- ECHA 2021
    - A GLP-compliant ready biodegradability test conducted according to OECD 301B: CO2 Evolution Test (1992) and EU Method C.4-C was performed with aerobic, domestic, non-adapted, activated sludge exposed to nickel dibutyldithiocarbamate (purity not specified) at 10 mg/L for 28 days. An average of 0% degradation (CO2 evolution) over 28 days. Nickel dibutyldithiocarbamate was not considered to be readily biodegradable in this test, and did not meet the 10-day window (Klimisch Score 1, reliable without restriction) (Unnamed Study 2018 as cited in ECHA Dossier).
- EC 1994, 2018
    - Nickel dibutyldithiocarbamate is on the CEPA – DSL due to the nickel entity.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *L*

Nickel dibutyldithiocarbamate was assigned a score of Low for bioaccumulation based on expert judgment for nickel by the ATSDR. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when BCFs are between 100 and 500 (CPA 2018b). The confidence in the score is low as it is based on expert judgment of the nickel moiety.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017
    - EPI Suite ™ could not evaluate nickel dibutyldithiocarbamate because its class of chemicals, organometalloids, is outside the applicability domain of EPI Suite ™.
- ATSDR 2005
    - There is some evidence that nickel can accumulate in plants, but it does not bioaccumulate in fish or small terrestrial animals.
        - Therefore, ToxServices concludes that nickel has a BCF < 500.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Nickel dibutyldithiocarbamate was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score was low as it is not based on measured data or authoritative listings.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - Nickel dibutyldithiocarbamate does not contain structural alerts for explosive or oxidizing properties.
  - Based on the chemical structure and experience handling the chemical, nickel dibutyldithiocarbamate is not pyrophoric and is not expected to be flammable in contact with water.
- Vanderbilt Chemicals LLC 2019
  - Vanox® NDBC has NFPA and HMIS reactivity ratings of 0, indicating that it is not reactive.
- Based on the above information, ToxServices did not classify nickel dibutyldithiocarbamate as a reactive chemical under GHS criteria (UN 2021).

Flammability (F) Score (vH, H, M, or L): L
Nickel dibutyldithiocarbamate was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is available (CPA 2018b). The confidence in the score was high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - Nickel dibutyldithiocarbamate is a high melting point solid, 90.2°C.
  - Nickel dibutyldithiocarbamate (purity unspecified) was investigated in s GLP-compliant Burning Rate Test for Solids according to EU method A.10 and UN Manual of Test and Criteria: Test N.1 (Test method for readily combustible solids). The test found that the test substance did not ignite or propagate combustion either by burning with flame or smoldering along 200 mm powder train within 2 minutes of the test period (Klimisch Score 1, reliable without restriction) (Unnamed Study 2018 as cited in ECHA 2021).
- Vanderbilt Chemicals LLC 2019
  - The material safety data sheet for nickel dibutyldithiocarbamate (purity unspecified) states that it has a flammability rating of 1 from NFPA ("Materials that require considerable preheating, under all ambient temperature conditions, before ignition and combustion can occur (e.g., mineral oil, ammonia). Includes some finely divided suspended solids that do not require heating before ignition can occur. Flash point at or above 93.3 °C (200 °F)")
  - The safety material data sheet identifies a hazard risk from combustible dusts and "May form combustible dust concentrations in air."

- As nickel dibutyldithiocarbamate is a high melting point solid and does not ignite or propagate combustion, ToxServices did not classify it as a flammable chemical under GHS criteria (UN 2021).

Use of New Approach Methodologies (NAMs)[10] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* genotoxicity and endocrine activity testing, *in silico* modeling for endocrine activity and respiratory sensitization, and OECD Guideline 301 B ready biodegradation test for persistence. NAMs are non-animal alternatives that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 2020). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

As shown in Table 5, Type I (input data) uncertainties in nickel dibutyldithiocarbamate's NAMs dataset include lack of experimental data for respiratory sensitization along with a lack of validated test method for respiratory sensitization. Nickel dibutyldithiocarbamate's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of OECD Toolbox in identifying structural alerts without defining the applicability domain, the uncertain relevance of the EDSP Tox 21 screening assays and *in silico* modeling of endocrine receptor binding due to lack of consideration of toxicokinetic factors including metabolism, the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization, and the inability of EPI Suite™ to model the fate of organometallic compounds. Some of nickel dibutyldithiocarbamate's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Respiratory sensitization**: No experimental data are available and there are no validated test methods. Very limited human evidence on nickel compounds are available under occupational scenarios.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[11]. The mammalian cell gene mutation assay (as defined in OECD Guideline 490) cannot reliably detect aneugens, and the exogenous

[10] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

[11] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

	metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells)[12]. **Endocrine activity:** ToxCast models don't define applicability domain; the *in vivo* relevance of EDSP Tox 21 screening assays and *in silico* modeling of receptor binding activities is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization. **Persistence and bioaccumulation**: Modeling could not be performed with EPI Suite™ as organometallic compounds are outside its applicability domain.

Endpoint	NAMs Data Available and Evaluated? (Y/N)	Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay / *in vitro* micronucleus assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays *In silico* modeling: ToxCast models/ VEGA / Danish QSAR
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	

[12] https://www.oecd-ilibrary.org/docserver/9789264264908-en.pdf?expires=1622037214&id=id&accname=guest&checksum=F0669770FC98B49A32E3AFBA1A4D86F5

Persistence	Y	Non-animal testing: OECD 301 B Biodegradation test
Bioaccumulation	N	

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Nickel Dibutyldithiocarbamate (CAS #13927-77-0)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	NBC	13927-77-0	*H*	L	*M*	*L*	DG	L	L	H	*M*	*L*	L	*M*	L	*H*	L	*L*	*vH*	*L*	*L*	L

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
NBC	1

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

Table 6

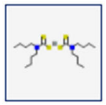
Chemical Name	Final GreenScreen® Benchmark Score
NBC	1

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

Table 5: Data Gap Assessment Table

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

APPENDIX C: Pharos Output for Nickel Dibutyldithiocarbamate (CAS #13927-77-0)



13927-77-0
Nickel, bis(dibutyldithiocarbamato)-
ALSO CALLED (Dibutyldithiocarbamato)nickel(II), 101239-20-7, 11140-03-7, 332343-04-1, 420849-75-8, 75178-20-0, 9...
View all synonyms (37)

Share Profile

Hazards | Properties | Functional Uses | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

		Group I Human					Group II and II* Human								Ecotox			Fate		Physical		Mult	Non-GSLT			
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
All Hazards	LT-1	H	-	-	-	-	H	-	-	-	-	-	H-M	-	-	-	M	-	vH-H	pC	-	-	U	-	-	-	R

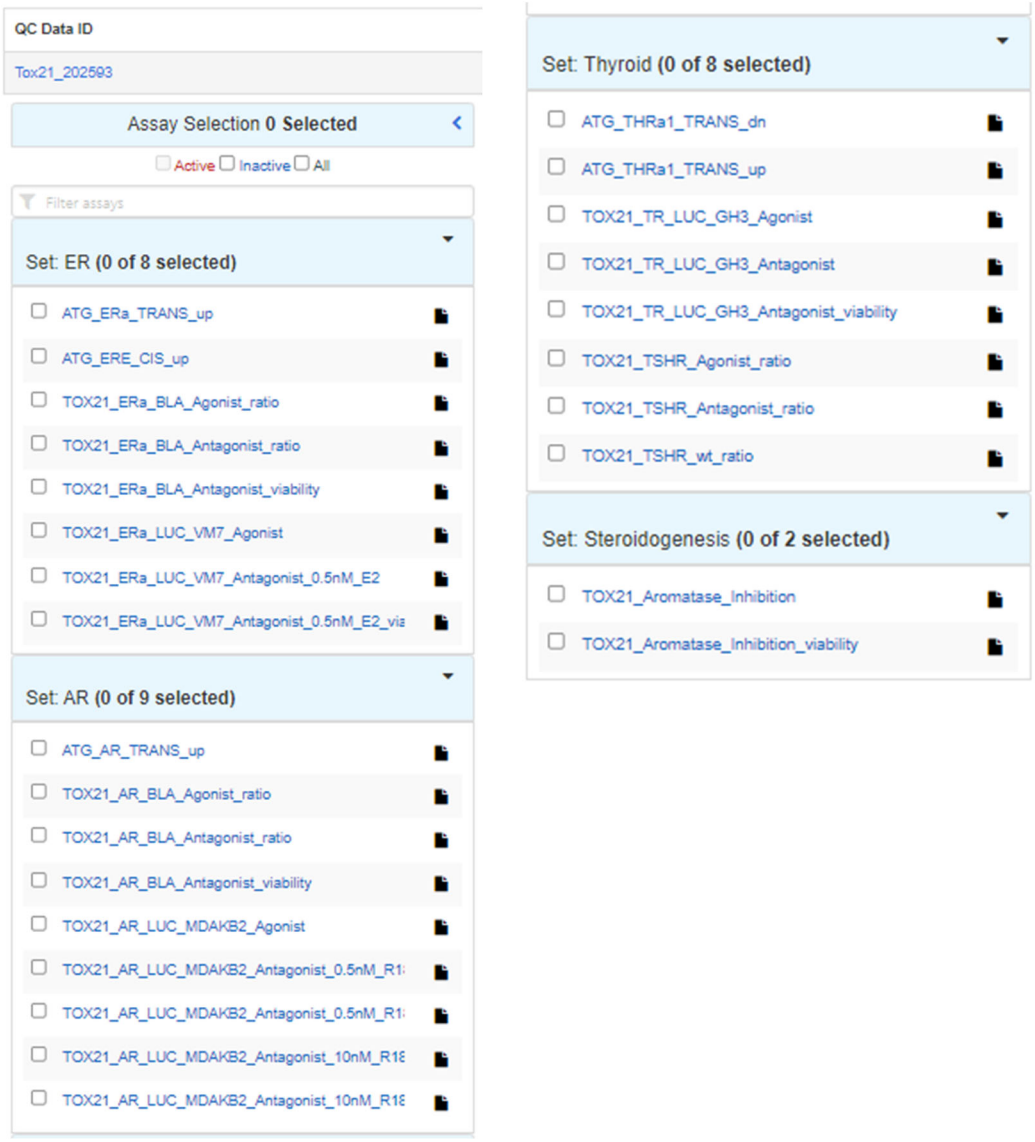
Hazard Lists

Download Lists

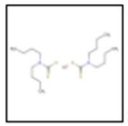
ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Carcinogenicity	H	LT-1	CA EPA - Prop 65	Carcinogen *	+4
	H	LT-1	IARC	Group 1 - Agent is Carcinogenic to humans *	
	H	LT-1	US NIH - Report on Carcinogens	Known to be a human Carcinogen *	
	H	LT-P1	GHS - Japan	H350 - May cause cancer [Carcinogenicity - Category 1A]	
	H	NoGS	US EPA - PPT Chemical Action Plans	Known human carcinogen - TSCA Criteria met *	
Acute Mammalian Toxicity	H	NoGS	US EPA - PPT Chemical Action Plans	Chronic toxicity from inhalation exposures - TSCA Criteria met *	+1
	M	NoGS	US EPA - PPT Chemical Action Plans	Acute toxicity from inhalation exposures - TSCA Criteria met *	
Respiratory Sensitization	H-M	LT-UNK	AOEC - Asthmagens	Asthmagen (Rs) - sensitizer-induced *	
Chronic Aquatic Toxicity	M	LT-UNK	GHS - Japan	H413 - May cause long lasting harmful effects to aquatic life [Hazardous to the aquatic environment (chronic) - Category 4]	

Persistence	vH-H	LT-UNK	EC - CEPA DSL	Persistent	+1
	pC	NoGS	US EPA - PPT Chemical Action Plans	High environmental persistence - TSCA Criteria met *	
Bioaccumulation	pC	NoGS	US EPA - PPT Chemical Action Plans	High bioaccumulation potential - TSCA Criteria met *	+1
	pC	NoGS	US EPA - PPT Chemical Action Plans	Low bioaccumulation potential - TSCA Criteria met *	
Carcinogenicity,Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	Québec CSST - WHMIS 1988	Class D2A - Very toxic material causing other toxic effects	
Acute aquatic toxicity; Chronic aquatic toxicity	U	LT-UNK	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)	

APPENDIX D: CompTox EDSP21 Results for Nickel Dibutyldithiocarbamate (CAS #13927-77-0)



APPENDIX E: ToxCast Model Predictions for Nickel Dibutyldithiocarbamate (CAS #13927-77-0)



Nickel bis(dibutyldithiocarbamate)
13927-77-0 | DTXSID2020927
Searched by CAS-RN.

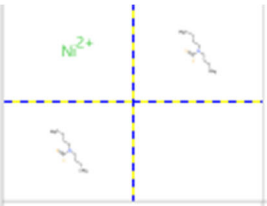
ToxCast: Models

ToxCast Model Predictions

Download ToxCast Model Predictions

Model	Receptor	Agonist	Antagonist	Binding
ToxCast Pathway Model (AUC)	Androgen	-	-	-
ToxCast Pathway Model (AUC)	Estrogen	-	-	-
COMPARA (Consensus)	Androgen	Inactive	Inactive	Inactive
CERAPP Potency Level (From Literature)	Estrogen	-	-	Active (Weak)
CERAPP Potency Level (Consensus)	Estrogen	Inactive (Inactive)	Inactive (Inactive)	Inactive (inactive)

APPENDIX F: OECD Toolbox Respiratory Sensitization Results for Nickel Dibutyldithiocarbamate (CAS #13927-77-0)

Structure		
Structure info		
Additional Ids	EC Number:2376962	EC Number:2376962
CAS Number	13927-77-0	13927-77-0
CAS-SMILES relation	High	Moderate
Chemical name(s)	(SP-4-1)-Bis(dibutylcar...	nickel bis(dibutyldithio...
Identity	Sources:6	Sources:7
Molecular formula	C18H36N2NiS4	C18H36N2NiS4
Predefined substance type	Mono constituent	Mono constituent
SMILES	[Ni+2].CCCCN(CCCC)C...	CCCCN(CCCC)C(=S)S[...
Parameters		
Physical Chemical Properties		
Environmental Fate and Transport		
Ecotoxicological Information		
Human Health Hazards		
Profiling		
Predefined		
Database Affiliation	ECOTOX	Biodegradation NITE
Inventory Affiliation	AIIC	Canada DSL
OECD HPV Chemical Categories	Tertiary Amines	Tertiary Amines
Substance type	Discrete chemical	Discrete chemical
US-EPA New Chemical Categories	Dithiocarbamates (Chr...	Dithiocarbamates (Chr...
Endpoint Specific		
Carcinogenicity (genotox and nongen...	No alert found	Structural alert for non...
Oncologic Primary Classification	Carbamate Type Com...	Carbamate Type Com...
Respiratory sensitisation	No alert found	No alert found
Metabolism/Transformation		
Hydrolysis simulator (acidic)	0 metabolite(s)	0 metabolite(s)
Hydrolysis simulator (basic)	0 metabolite(s)	0 metabolite(s)
Hydrolysis simulator (neutral)	0 metabolite(s)	0 metabolite(s)

APPENDIX G: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for nickel dibutyldithiocarbamate. This GreenScreen® assessment has undergone one round of minor updates that does not affect its benchmark score.

Table 5: Change in GreenScreen® Benchmark™ for Nickel Dibutyldithiocarbamate

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
October 18, 2021	BM-1	v. 1.4	New assessment
November 8, 2021	BM-1	v. 1.4	Minor updates in response to Ecology comments

Licensed GreenScreen® Profilers

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