

Justification Document for the Selection of a CoRAP Substance

Substance Name (public name): 1,3-diethyl-2-thiourea (DETU)

EC Number: 203-308-5

CAS Number: 105-55-5

Authority: Bureau for Chemical Substances,
Poland

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Cover Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

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1 IDENTITY OF THE SUBSTANCE

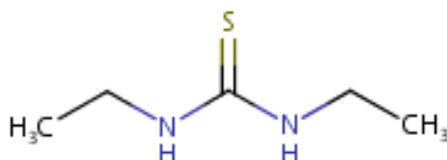
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	1,3-diethyl-2-thiourea
IUPAC name (public):	1,3-diethyl-2-thiourea
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C ₅ H ₁₂ N ₂ S
Molecular weight or molecular weight range:	132.23
Synonyms:	1,3-DIETHYL-2-THIOUREA 1,3-diethyl-thiourea N,N'-DIETHYLTHIOCARBAMIDE N,N'-Diethylthiourea NCI-C03816 PENNZONE E THIATE H THIOUREA, N,N'-DIETHYL- Urea, 1,3-diethyl-2-thio USAF EK-1803 DETU DIETHYLTHIOUREA N,N'-Diethylthioharnstoff urea, 1,3-diethyl-2-thio-

Type of substance Mono-constituent Multi-constituent UVCB

Structural formula of 1,3-diethyl-2-thiourea (DETU):



1.2 Similar substances/grouping possibilities

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2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

RMOA	<input type="checkbox"/> Risk Management Option Analysis (RMOA)	
REACH Processes	Evaluation	<input type="checkbox"/> Compliance check
		<input checked="" type="checkbox"/> Testing proposal
		<input type="checkbox"/> CoRAP and Substance Evaluation
	Authorisation	<input type="checkbox"/> Candidate List
		<input type="checkbox"/> Annex XIV
Restriction	<input type="checkbox"/> Annex XVII ¹	
CLH	<input type="checkbox"/> Annex VI (CLP) (see section 3.1)	
Processes under other EU legislation	<input type="checkbox"/> Plant Protection Products Regulation Regulation (EC) No 1107/2009	
	<input type="checkbox"/> Biocidal Product Regulation Regulation (EU) 528/2012 and amendments	
Previous legislation	<input type="checkbox"/> Dangerous substances Directive 67/548/EEC (NONS)	
	<input type="checkbox"/> Existing Substances Regulation 793/93/EEC (RAR/RRS)	
(UNEP) Stockholm convention (POPs Protocol)	<input type="checkbox"/> Assessment	
	<input type="checkbox"/> In relevant Annex	
Other processes/ EU legislation	<input type="checkbox"/> Other (provide further details below)	
Further details		

¹ Please specify the relevant entry.

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

- Not classified

3.1.2 Self classification

- In the registration:
 - Acute Tox. 4, H302: Harmful if swallowed.
 - Acute Tox. 4, H312: Harmful in contact with skin.
 - Eye Dam. 1, H318: Causes serious eye damage.
 - Skin Sens. 1B, H317: May cause an allergic skin reaction.
 - Carc. 2, H351: Suspected of causing cancer.
 - Aquatic Chronic 3, H412: Harmful to aquatic life with long lasting effects.
- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:
 - STOT RE 1, H372: Causes damage to organs (thyroid).
 - STOT SE 3, H335: May cause respiratory irritation.
 - Acute Tox. 3, H301: Toxic if swallowed.
 - Skin Irrit. 2, H315: Causes skin irritation.
 - Eye Irrit. 2, H319: Causes serious eye irritation.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES²

4.1 Tonnage and registration status

Table: Tonnage and registration status*

<input checked="" type="checkbox"/> Full registration(s) (Art. 10)		<input type="checkbox"/> Intermediate registration(s) (Art. 17 and/or 18)
Tonnage band (as per dissemination site)		
<input type="checkbox"/> 1 - 10 tpa	<input checked="" type="checkbox"/> 10 - 100 tpa	<input type="checkbox"/> 100 - 1000 tpa
<input type="checkbox"/> 1000 - 10,000 tpa	<input type="checkbox"/> 10,000 - 100,000 tpa	<input type="checkbox"/> 100,000 - 1,000,000 tpa
<input type="checkbox"/> 1,000,000 - 10,000,000 tpa	<input type="checkbox"/> 10,000,000 - 100,000,000 tpa	<input type="checkbox"/> > 100,000,000 tpa
<input type="checkbox"/> <1 >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		<input type="checkbox"/> Confidential
This substance has 2 active registrations		

*the total tonnage band has been calculated from information on the ECHA dissemination site by excluding the intermediate uses, for details see the Manual for Dissemination and Confidentiality under REACH Regulation (section 2.6.11): https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0

4.2 Overview of uses

Table: Uses

Part 1:

<input checked="" type="checkbox"/> Manufacture	<input checked="" type="checkbox"/> Formulation	<input checked="" type="checkbox"/> Industrial use	<input checked="" type="checkbox"/> Professional use	<input checked="" type="checkbox"/> Consumer use	<input type="checkbox"/> Article service life	<input type="checkbox"/> Closed system
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Part 2:

	Use(s) base on the ECHA's Website information
Uses as intermediate	use resulting in manufacture of another substance
Formulation	metal surface treatment products, polymers, water treatment chemicals and laboratory chemicals
Uses at industrial sites	laboratory chemicals and polymers, formulation of mixtures and/or re-packaging, transfer of substance into small containers, roller or brushing applications, mixing in open batch processes, production of mixtures or articles by tableting, compression, extrusion or pelletisation and transfer of chemicals
Manufacture	transfer of chemicals at dedicated facilities, closed batch processing in synthesis or formulation, transfer of substance into small containers,

² The dissemination site was accessed August 2018.

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	laboratory work and lubrication at high energy conditions and in partly open process
Uses by professional workers	laboratory chemicals
Consumer Uses	ECHA has no public registered data indicating whether or in which chemical products the substance might be used.
Article service life	ECHA has no public registered data on the use of this substance in activities or processes at the workplace.

The additional information based on the SPIN Database (Substances in Preparations in Nordic Countries):

Industrial use: manufacture of food products, fabricated metal products, motor vehicles, trailers and semi-trailers, other transport equipment, paper and paper products, computers, electronic and optical products, pulp, radio, television and communication equipment services to buildings and landscape activities, wholesale trade and commission trade.

Consumer uses: cleaning, washing and electroplating agents, surface treatment, corrosion inhibitors, solvents

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

- Article 44(2) (refined prioritisation criteria for substance evaluation)
- Article 45(5) (Member State priority)

5.2. Selection criteria met (why the substance qualifies for being in CoRAP)

- Fulfils criteria as CMR/ Suspected CMR
- Fulfils criteria as Sensitiser/ Suspected sensitiser
- Fulfils criteria as potential endocrine disrupter
- Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB
- Fulfils criteria high (aggregated) tonnage (*tpa* > 1000)
- Fulfils exposure criteria
- Fulfils MS's (national) priorities

5.3. Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR <input type="checkbox"/> C <input type="checkbox"/> M <input type="checkbox"/> R	Suspected CMR ¹ <input checked="" type="checkbox"/> C <input type="checkbox"/> M <input type="checkbox"/> R	<input type="checkbox"/> Potential endocrine disruptor
<input type="checkbox"/> Sensitiser	<input checked="" type="checkbox"/> Suspected Sensitiser ³	
<input type="checkbox"/> PBT/vPvB	<input type="checkbox"/> Suspected PBT/vPvB ¹	<input type="checkbox"/> Other (please specify below)
Exposure/risk based concerns		
<input checked="" type="checkbox"/> Wide dispersive use	<input checked="" type="checkbox"/> Consumer use	<input type="checkbox"/> Exposure of sensitive populations
<input checked="" type="checkbox"/> Exposure of environment	<input checked="" type="checkbox"/> Exposure of workers	<input type="checkbox"/> Cumulative exposure
<input type="checkbox"/> High RCR	<input type="checkbox"/> High (aggregated) tonnage	<input type="checkbox"/> Other (please specify below)
<u>Skin sensitisation</u>		
<p>The following studies on skin sensitization were reported in the registration dossier:</p> <ul style="list-style-type: none"> - key study: Magnusson and Kligman comparable study - according to the guinea pig test, DETU is a skin sensitizer, - supporting study: LLNA comparable study - based on the LLNA performed with DETU, no potential of skin sensitisation was showed in mice, - supporting study: SLNA comparable study - based on the SLNA performed with DETU, skin sensitisation potential was showed in mice. <p>In the registration dossier three reliable studies are available: a guinea pig maximalisation test, a mouse local lymph node assay (LLNA) and a sensitive local node assay on mice (SLNA). The results of these studies are conflicting: DETU showed a sensitisation potential on guinea pigs (GPMT test) and in SLNA test, but not in LLNA test.</p>		

According to the publication (1994), SLNA test is more sensitive than LLNA test.

Moreover several cases of allergic contact dermatitis were observed and described in humans:

- Grant W.M. Diethylthiourea has been shown to be potent skin sensitizer, but whether this has any relationship to possible keratitis remains to be determined. In Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 337.
- Ramzy A.G, Pei M.N., Samuellsen K., Nilsson U. Investigation of diethylthiourea and ethyl isothiocyanate as potent skin allergens in Chloroprene rubber. Contact Dermatitis 72 (3):139-146, 2015.
- Fisher U., Duus J., Krongard T. Torkil M. Quantitative assessment of diethylthiourea exposure in two cases of occupational allergic contact dermatitis. Contact Dermatitis, 64, 110–120, 2011.
- Martinez-Gonzales M.C., Goday-Bujan J.J., Almagro M., Fonseca E. Allergic Contact Dermatitis to Diethylthiourea in a Neoprene Wader. Actas Dermosifiliogr. 2009;100:317-20.
- Uter W., Werfel T., White I., Johansen D. Contact Allergy: A Review of Current Problems from a Clinical Perspective. Int. J. Environ. Res. Public Health 2018, 15, 1108.

Carcinogenicity

Under the conditions of the bioassay presented in the registration dossier, DETU was carcinogenic in Fischer 344 rats (oral administration), inducing thyroid neoplasms and hyperplasia.

Other available information:

- Final prioritized candidate chemicals under consideration for carcinogenicity evaluation. Office of Environmental Health Hazard Assessment California Environmental Protection Agency (1999): There is a high level of carcinogenicity concern over N,N'-diethylthiourea because it significantly increased in the incidences of malignant thyroid tumors in male rats, and of combined malignant and benign thyroid tumors in female rats.
- Bioassay of n,n'-diethylthiourea for possible carcinogenicity (National Cancer Institute Carcinogenesis Technical Report Series No. 149, 1979): DETU was carcinogenic to rats, causing follicular-cell carcinomas of the thyroid in males and follicular-cell neoplasms of the thyroid females.

IARC classified the substance as carcinogen 3 – not classifiable as to its carcinogenicity to humans and with sufficient evidence for animal carcinogenicity (Detailed review paper on cell transformation assays for detection of chemical carcinogens. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 31, 2006).

Exposure of environment

As the substance is widely used, a potential environmental release represents a concern. The release to the environment of this substance is likely to occur from: indoor use (processing aid), industrial use (formulation of mixtures and formulation in materials, in processing aids at industrial sites, as an intermediate step in further manufacturing of another substance). Therefore an exposure assessment and, if then indicated, an environmental risk assessment is recommended.

³ CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-

5.4. Preliminary indication of information that may need to be requested to clarify the concern

<input checked="" type="checkbox"/> Information on toxicological properties	<input type="checkbox"/> Information on physico-chemical properties
<input type="checkbox"/> Information on fate and behaviour	<input checked="" type="checkbox"/> Information on exposure
<input checked="" type="checkbox"/> Information on ecotoxicological properties	<input type="checkbox"/> Information on uses
<input type="checkbox"/> Information ED potential	<input type="checkbox"/> Other (provide further details below)

5.5. Potential follow-up and link to risk management

<input type="checkbox"/> Harmonised C&L	<input type="checkbox"/> Restriction	<input type="checkbox"/> Authorisation	<input type="checkbox"/> Other (provide further details)
Depends on the substance evaluation results.			

References:

1. Registration dossier available at: <https://echa.europa.eu/pl/registration-dossier/-/registered-dossier/12736/7/8https://monographs.iarc.fr/list-of-classifications-volumes>.
2. Grant W.M. Diethylthiourea has been shown to be potent skin sensitizer, but whether this has any relationship to possible keratitis remains to be determined. In Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 337.
3. Ramzy A.G, Pei M.N., Samuellsen K., Nilsson U. Investigation of diethylthiourea and ethyl isothiocyanate as potent skin allergens in Chloroprene rubber. Contact Dermatitis 72 (3):139-146, 2015.
4. Fisher U., Duus J., Krongard T. Torkil M. Quantitative assessment of diethylthiourea exposure in two cases of occupational allergic contact dermatitis. Contact Dermatitis, 64, 110–120, 2011.
5. Martinez-Gonzales M.C., Goday-Bujan J.J., Almagro M., Fonseca E. Allergic Contact Dermatitis to Diethylthiourea in a Neoprene Wader. Actas Dermosifiliogr. 2009;100:317-20.
6. Uter W., Werfel T., White I., Johansen D. Contact Allergy: A Review of Current Problems from a Clinical Perspective. Int. J. Environ. Res. Public Health 2018, 15, 1108.
7. Final prioritized candidate chemicals under consideration for carcinogenicity evaluation. Office of Environmental Health Hazard Assessment California Environmental Protection Agency, 1999.
8. Bioassay of n,n'-diethylthiourea for possible carcinogenicity. National Cancer Institute Carcinogenesis Technical Report Series No. 149, 1979.
9. Detailed review paper on cell transformation assays for detection of chemical carcinogens. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 31, 2006.