N-HEPTANE

(CAS #142-82-5)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: September 15, 2019[a]

Expiration Date: September 15, 2024

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

[a] ToxServices incorporated January 2020 comments submitted by the Washington State Department of Ecology into this document.

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GreenScreen® Executive Summary for n-Heptane (CAS #142-82-5)

n-Heptane is a colorless liquid under standard temperature and pressure. It is highly volatile and flammable. It occurs in natural gas and crude oil at 0.1 - 1.9% and an n-heptane content of 2.5% has been reported in petroleum, 0.97% in gasoline, and 0.000107% in coal used by power plants. n-Heptane is also found as a volatile component of raw or cooked meat, seafood, and certain plants. n-Heptane is isolated from petroleum streams via fractional distillation of petroleum followed by purification via rectification and can be produced via hydrogenation of 1-heptene. It functions as a solvent, anesthetic, standard for octane rating determinations, and chemical intermediate. Use levels in these categories could not be identified.

n-Heptane was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Health Hazard (developmental toxicity-D)
- Benchmark 2f
  - Very High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA)
- Benchmark 2g
  - High Flammability-F.

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), n-heptane meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if n-heptane were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Hazard Summary Table for n-Heptane

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

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 n-Heptane (CAS #142-82-5)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment Prepared By:
Name: Mouna Zachary, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: June 01, 2014

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.R.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: June 17, 2014

GreenScreen® Assessment Updated By:
Name: Rachel Galante, M.P.H.
Title: Associate Toxicologist
Organization: ToxServices LLC
Date: July 31, 2018

Update Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 10, 2018

GreenScreen® Assessment Updated By:
Name: Zach Guerrette, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 23, 2019

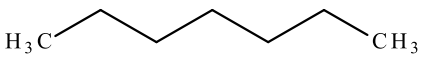
Update Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: September 15, 2019

Expiration Date: September 15, 2024[2]

Chemical Name: n-Heptane

CAS Number: 142-82-5

Chemical Structure(s):

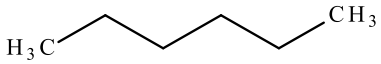


Also called:
Heptane; Dipropyl methane; Dipropylmethane; EC 205-563-8; Heptyl hydride; Heptanes; UN 1206 (ChemIDplus 2019).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
For the sensitization endpoint, hydrocarbons, C7-C9, n-alkanes, isoalkanes, cyclics (no CAS number provided), was used as a surrogate. In addition, commercial hexane containing ~50% n-hexane (CAS #110-54-3) is used to fill the data gaps in reproductive and developmental toxicities. These surrogates have been used to support the safety of n-heptane in ECHA's REACH registration dossier (ECHA

[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

2019a). As the composition of these substances are not fully characterized, ToxServices considered both of them to be weak surrogates.



Surrogate: n-Hexane, CAS #110-54-3

Identify Applications/Functional Uses (ECB 2000, HSDB 2014)**:**
1. Standard for octane rating determinations of fuels
2. Anesthetic
3. Solvent
4. Organic synthesis/Chemical intermediate
5. Preparation of laboratory reagents
6. Standard in testing knock of gasoline engines
7. Research/laboratory Chemical
8. Cleaning/washing agent

Known Impurities[3]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for n-Heptane[4,5 6,7]: n-Heptane was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Health Hazard (developmental toxicity-D).
- Benchmark 2f
  - Very High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA).
- Benchmark 2g
  - High Flammability-F.

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), n-heptane meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if n-heptane were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] 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.

Figure 1: GreenScreen® Hazard Summary Table for n-Heptane

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

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.

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), transformation products of chemicals that degrade rapidly and completely (i.e. meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates and are therefore not considered to be relevant because the products will not persist long enough to be encountered after use or release of the parent chemical. As n-heptane is readily biodegradable, it is not expected to have relevant transformation products. Furthermore, n-heptane exists solely as a vapor in the atmosphere and is readily degradable in water. Hydrolysis or photolysis of n-heptane is not expected to be an important environmental fate process. Based on its molecular formula, possible combustion products of n-heptane are CO and CO_2, which are naturally occurring, ambient substances and not relevant with respect to the GreenScreen Benchmark™ Score for n-heptane.

Introduction

n-Heptane is a colorless volatile liquid with gasoline-like odor. It occurs in natural gas and crude oil (0.1 - 1.9%). A content of 2.5% has been reported in petroleum, and this results in the major proportion of heptane found in the atmosphere. n-Heptane has been detected at 9,700 ppm in gasoline, and 1.07 ppm in coal used by power plants. n-Heptane is also found as a volatile component of raw or cooked meat, seafood, and certain plants. n-Heptane is produced via fractional distillation of petroleum followed by purification via rectification or hydrogenation of 1-heptene. n-Heptane is used as an industrial solvent (for adhesives, lacquers and inks in gravure printing), as an extraction solvent and in manufacture of plastic foams, and synthesis of toluene and alkylbenzenes (HSDB 2014).

ToxServices assessed n-heptane against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2016).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2018). 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).

n-Heptane is not listed on the SCP 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 2019) 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),[8] 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 n-heptane can be found in Appendix C.

- n-Heptane is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- n-Heptane is on the following lists for multiple endpoints:
  - Québec CSST - WHMIS 1988 - Class D2B - Toxic material causing other toxic effects.
  - EC - CEPA DSL - Inherently Toxic in the Environment (iTE).
  - German FEA - Substances Hazardous to Waters - Class 2 - Hazard to Waters.
  - EU - GHS (H-Statements) H410 - Very toxic to aquatic life with long lasting effects.
  - GHS – Japan Hazardous to the aquatic environment (chronic) - Category 1 [H410].
  - GHS – Australia H410 - Very toxic to aquatic life with long lasting effects.
  - GHS - New Zealand 9.1B (crustacean) - Very ecotoxic in the aquatic environment.
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

A harmonized EU classification is available for n-heptane (ECHA 2019b): it is classified as a GHS Category 2 flammable liquid (H225), a GHS Category 2 skin irritant (H315), a GHS Category 1 aspiration toxicant (H304), a GHS Category 3 specific target organ toxicant following single exposures for narcotic effects (H336), a GHS Category 1 acute aquatic toxicant (H400), and a GHS Category 1 chronic aquatic toxicant (H410). Details of the hazard statements are provided in Table 1 below. Recommended personal protective equipment and occupation exposure limits identified for n-heptane are presented in Table 2, below.

Table 1: H Statements for n-Heptane (CAS #142-82-5) (ECHA 2019b)

H Statement	H Statement Details
H225	Highly flammable liquid and vapor
H315	Causes skin irritation
H304	May be fatal if swallowed and enters airways
H336	May cause drowsiness or dizziness
H400	Very toxic to aquatic life
H401	Very toxic to aquatic life with long lasting effects

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for n-Heptane (CAS #142-82-5)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Appropriate personal protective clothing to prevent skin contact	HSDB 2014	ACGIH 2019 TLV: 400 ppm (8-hour TWA), 500 ppm (STEL)	ICSC 2015, OSHA 2019

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

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for n-Heptane (CAS #142-82-5)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
		Cal/OSHA PEL: 400 ppm (8-hour TWA), 500 ppm (STEL)	
Appropriate eye protection to prevent eye contact		EU OEL: 500 ppm, 2,085 mg/m^3 as TWA	
Respirator		NIOSH REL: 85 ppm (350 mg/m^3) TWA, 440 ppm (1,800 mg/m^3) 15-minute STEL, 759 ppm (IDLH)	
		OSHA PEL: 500 ppm (2,000 mg/m^3) TWA	

ACGIH: American Conference of Governmental Industrial Hygienists
EU: European Union
IDLH: Immediately dangerous to life or health
NIOSH: National Institute for Occupational Safety and Health
OEL: Occupational exposure limit
OSHA: Occupational Safety and Health Administration
PEL: Permissible exposure limit
REL: Recommended exposure limit
STEL: Short term exposure limit
TLV: Threshold limit values
TWA: Time weighted average

Physicochemical Properties of n-Heptane

n-Heptane is a colorless volatile liquid with gasoline-like odor. Due to its high vapor pressure, inhalation is the most probable route of human exposure to n-heptane. n-Heptane has a partition coefficient greater than 4 indicating that it is hydrophobic and may have bioaccumulation potential.

Table 3: Physical and Chemical Properties of n-Heptane (CAS #142-82-5)		
Property	**Value**	**Reference**
Molecular formula	C_7H_{16}	ChemIDplus 2019
SMILES Notation	C(CCC)CCC	ChemIDplus 2019
Molecular weight	100.203 g/mol	ChemIDplus 2019
Physical state	Liquid	ECHA 2019a
Appearance	Colorless	HSDB 2014
Melting point	-90.549ºC	HSDB 2014
Boiling point	98.2-98.4°C (ASTM D 1078)	ECHA 2019a
Vapor pressure	48 hPa (36 mm Hg) at 20ºC 6.09 kPa (45.7 mm Hg) at 25°C	ECB 2000 ECHA 2019a
Water solubility	2.4 mg/L at 20ºC	ECHA 2019a
Dissociation constant	Does not dissociate	ECHA 2019a
Density/specific gravity	0.69 g/cm^3 at 15ºC	ECHA 2019a
Partition coefficient	Log K_{ow} = 4.66 Log K_{ow} = 4.5	HSDB 2014 ECHA 2019a

Toxicokinetics

- ECHA 2019a
    - *Absorption*: Male F344/N rats (n=10) were administered nose-only inhalation exposures to escalating concentrations of heptane vapor (>99% purity). The concentrations were 1, 10, 100, 1,000, and 5,000 ppm on days 1, 2, 3, 4, and 5, respectively. Each exposure lasted 80 minutes with the rat confined to the exposure tube connected to the second sampling loop of a dual column gas chromatograph. The amount of n-heptane absorbed "was calculated from the output of the gas chromatograph and the flow rate past the rat's nose. During the exposure to 100 ppm, the uptake of heptane was 4.5 ± 0.3 nmol/kg/min/ppm during minutes 60-70. No other data were provided. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as only basic data were provided.
    - *Absorption*: The dermal absorption of n-heptane (purity not specified) was evaluated using an *in vitro* human skin model at three different laboratories. Human cadaver skin was exposed to 20 µL n-heptane for 10 or 60 minutes. After 10 and 60 minutes, the flux values were 113 µg/cm^2/h and 22.1 µg/cm^2/h, respectively. The barrier properties of the skin were 0.90 and 0.88 for the 10- and 60-minute exposures, indicating that the longer duration exposure compromised the barrier function of the skin.
    - *Distribution*: Male Sprague-Dawley rats (4/exposure duration) were administered whole body inhalation exposures to n-heptane vapor (>99% purity) at 100 ppm (equivalent to 0.52 mg/L) 12 hours/day for one, two, or three consecutive days. The animals were sacrificed immediately after the end of the exposure period or 12 hours after exposure on day 3. The brain, blood, kidney, liver, and perirenal fat were collected and evaluated for n-heptane content. Perirenal fat had the highest concentration of n-heptane, followed by kidney, brain, blood, and liver. The concentration of perirenal fat decreased with increasing number of exposures. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as it meets generally accepted scientific principles.
    - *Distribution*: Homogenized human tissues were exposed to 10-20 µg n-heptane (>98% purity) for 12 hours. The mean partition coefficients were 1.9 for blood, 10.8 for liver, 8.9 for kidney, 12.4 for brain, 385 for fat, 12.5 for muscle, 6.1 for heart, and 2.5 for lung. In contrast, the mean olive oil partition coefficient was 452. The study authors suggest that the low partition coefficient of 1.9 in blood suggests that n-heptane has low respiratory absorption. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the original study was well documented and met basic scientific principles.
    - *Distribution and Metabolism*: Male Sprague-Dawley rats (n=10) were administered whole body inhalation exposures to n-heptane (>90% purity) at 1,800 ppm (equivalent to 7.4 mg/L) for 7 hours. Blood, urine, and tissues (liver, muscle, kidney, nervous tissue) were collected at the end of the exposure period and 24 hours after exposure. At the end of the exposure period, 2-heptanol, 3-heptanol, 2-heptanone, 3-heptanone, 4-heptanone, gamma-valerolactone, and 2,5-heptanedione were detected in the urine. Twenty-four hours after the end of the exposure period, 2-heptanol and 3-heptanol accounted for 80% of the urinary metabolites, with gamma-valerolactone accounting for an additional 11% of the metabolites. At the end of the exposure period, 2-heptanol was detected in kidney, liver, muscle, and nervous tissue at 0.2-2 mg/L, while the mean n-heptane concentrations were 25.6 mg/L in liver, 10.1 mg/L in kidney, 22.9 mg/L in muscle, 5.7 mg/L in blood, and 18.4 mg/L in nervous tissue. n-Heptane and 2-heptanol were not detected in blood or tissues 24 hours after the end of the exposure period. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as only basic data were provided.

- U.S. EPA 2016
    - *Absorption*: Pulmonary retention after inhalation exposure is 25-29% in rats and humans, and the blood-air partition coefficients for n-heptane are 4.75-5.4 for rats and 1.9-2.85 for humans.
    - *Distribution*: Organ/air distribution coefficients identified *in vitro* for rats and humans indicate that n-heptane is distributed readily throughout the body, but accumulates the most in adipose tissue.
    - *Distribution and elimination*: Following inhalation exposures to concentrations < 35 ppm, the body clearance half-lives are 1.88 hours in humans and 0.174 hours in rats. At concentrations ≥ 100 ppm, n-heptane accumulated in the perirenal fat and brain of rats exposed for 1-2 weeks, but was no longer detectable after a 2-week recovery period.
    - *Metabolism*: n-Heptane is metabolized via the cytochrome P450 enzymes to alcohols, mostly 2-heptanol and 3-heptanol, and then further metabolized via hydroxylation and dehydrogenation to produce monohydroxy, dihydroxy, diketo, and hydroxyketo metabolites. Following acute or prolonged inhalation exposure in rats, the most abundant urinary metabolites were 2-heptanol, 3-heptanol, γ-valerolactone, and 6-hydroxy-2-heptanone. Heptanol metabolites are conjugated by sulfates or glucuronates prior to excretion.

In summary, n-heptane is absorbed via the inhalation and dermal routes of exposure. Following absorption, it distributes predominantly to fat tissues. n-Heptane is primarily metabolized via cytochrome P-450-mediated oxidation reactions to 2-heptanol and 3-heptanol, which may undergo further metabolism via hydroxylation and dehydrogenation reactions. The metabolites are eliminated in the urine.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
n-Heptane was assigned a score of Low for carcinogenicity based on negative modeling results. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on modeling.

- Authoritative and Screening Lists
    - *Authoritative:*
        - US EPA - IRIS Carcinogens - (1986) Group D - Not classifiable as to human carcinogenicity.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2013
    - The OncoLogic computer program, a structure-activity relationship program developed by the United States Environmental Protection Agency, was used to evaluate the carcinogenic potential of n-heptane. n-Heptane was evaluated as an aliphatic hydrocarbon type compound as a saturated alkane. With a few exceptions, there is no evidence that members of the saturated aliphatic hydrocarbons (i.e., alkanes) class may be of any significant cancer concern. Therefore, virtually all alkanes can be assigned a low concern (Appendix D).
- OECD 2019a
    - No structural alerts for genotoxic or nongenotoxic carcinogenicity were identified by the OECD QSAR Toolbox (Appendix E).

- Toxtree 2018
    - n-Heptane does not have structural alerts for genotoxic or non-genotoxic carcinogenicity by Toxtree (Appendix F).
- VEGA 2019
    - The CAESAR model predicted n-heptane as carcinogen with low confidence as n-heptane was outside the applicability domain of the model (Appendix G).
    - The ISS model predicted n-heptane as a non-carcinogen with low confidence as n-heptane was outside of the applicability domain for the model (Appendix G).
    - The IRFMN/Antares model predicted n-heptane as a possible non-carcinogen with moderate confidence. Only moderately similar compounds with known experimental value in the training set have been found, the accuracy of prediction for similar molecules found in the training set is not optimal, similar molecules found in the training set have experimental values that disagree with the predicted value, and the predicted compound could be outside of the applicability domain (Appendix G).
    - The IRFMN/ISSCAN-CGX model predicted n-heptane as a possible non-carcinogen with low confidence as n-heptane was outside of the applicability domain for the model (Appendix G).
    - The IRFMN oral carcinogenicity classification model predicted n-heptane to be a non-carcinogen with good reliability, based on unspecified experimental data (Appendix G).
    - The IRFMN inhalation carcinogenicity classification model predicted n-heptane to be a non-carcinogen with good reliability, based on unspecified experimental data (Appendix G).
- Based on the weight of evidence, a score of Low was assigned. OncoLogic predicted the compound to be of low concern for carcinogenicity, and neither OECD Toolbox nor Toxtree identified any structural alerts for genotoxic or non-genotoxic carcinogenicity. Three models in VEGA predicted that n-heptane is a non-carcinogen; but the reliability was reduced in all of the three models due to the compound being out of the applicability domain of the models. However, two models predicted it to be a non-carcinogen with good reliability. Only one model in VEGA predicted that n-heptane is a carcinogen; however, the reliability in this model is also reduced due to the chemical being outside of the applicability domain. Therefore, in the absence of data for the target chemical, a score of Low was assigned based negative predictions in all four modeling programs (i.e. OncoLogic, OECD Toolbox, Toxtree and VEGA models that produced results with good reliability).

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

n-Heptane was assigned a score of Low for mutagenicity/genotoxicity based on negative data for gene mutations and chromosome aberrations. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and negative for both mutagenicity and clastogenicity and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on measured data from well-conducted studies.

- 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 2019a
    - *In vitro:* n-Heptane was negative in a bacterial reverse gene mutation assay conducted similar to OECD Guideline 471. *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537 and TA1538 and *Escherichia coli* tester strains WP_2 and WP_2 *uvr*A were exposed to heptane (100% commercial product) in Tween80/ethanol at 3.91-250 µg/mL with and without metabolic activation. There were no increases in the frequency of mutation observed in any strain at any concentration with or without metabolic activation. The

REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on limited documentation.

- *In vitro*: n-Heptane was negative in a mammalian chromosome aberration test similar to OECD Guideline 473. Rat liver RL4 hepatocytes were exposed to heptane (100% commercial product) in Tween 80/ethanol at concentrations of 2.5, 5, or 10 µg/mL. The addition of exogenous metabolic activation was not necessary as hepatocytes have intrinsic metabolic capacity in cell culture. A statistically significant increase in the frequency of chromatid gaps was detected at the highest concentration (0.027) compared to the solvent control (0.013). However, a dose response was not observed for chromatid gaps and there were no increases in the incidence of other aberrations (e.g. polyploidy or chromatid). Therefore, the study authors did not consider the increased frequency of chromatid gaps in the high concentration group to be treatment-related. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on deviations from the Guideline (only 100 cells from each culture analyzed instead of the 300 cells recommended[9]).
- *In vitro:* n-Heptane was negative in a mitotic recombination assay conducted similar to OECD Guideline 481. *Saccharomyces cerevisiae* JD1 was exposed to heptane (100% pure commercial product) in Tween 80/ethanol at concentrations of 0.01, 0.1, 0.5, 1.0, or 5.0 mg/mL both with and without metabolic activation for 3 days. There was an increase in the ratio of prototrophs per plate in *S. cerevisiae* at the 5 mg/mL concentration. However, this reflected the decrease in cell viability at this concentration as there was no increase in the number of prototrophs per plate. No other significant increase in the ratio of mutations over controls was seen and under the conditions of this study the authors concluded that heptane was not mutagenic in either the presence or absence of metabolic activation. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on limited documentation.

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

n-Heptane was assigned a score of Low for reproductive toxicity based on lack of reproductive effects in a two-generation study in rats with commercial hexane. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on measured data from a weak surrogate.

- 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 2019a
  - *Surrogate: Commercial hexane*: In a GLP-compliant two-generation study in male and female Sprague-Dawley rats conducted according to OECD Guideline 416, animals (25/sex/dose) were exposed to commercial hexane vapor (52% hexane, no details provided on remainder) at 0, 900, 3,000, or 9,000 ppm via whole body inhalation 6 hours/day, 5 days/week, for 10 weeks before breeding, 3 weeks during mating, and post-natal days 4 – 28. F2 generation animals were exposed for 8 weeks before breeding. The parental animals were evaluated for clinical signs of toxicity, body weight, food consumption, gross pathology, histopathology, and reproductive indices (mating index, fertility index, gestational index, and live birth index). The offspring were evaluated for number, sex, stillbirths, live births, postnatal mortality, weight gain, presence of gross anomalies, physical abnormalities, and viability indices (4-, 7-, 14-, and 21-day survival indices and lactation

[9] https://www.oecd-ilibrary.org/environment/test-no-473-in-vitro-mammalian-chromosomal-aberration-test_9789264264649-en.

index). Reduced body weights were found at the highest concentration in both generations in adults and offspring. Therefore, a NOAEC of 3,000 ppm and LOAEL of 9,000 ppm (reported in ECHA as 10,560 and 31,680 mg/m^3, respectively) were identified for general toxicity. There were no effects on reproductive parameters and the ECHA record established the NOAEC for reproduction at 9,000 ppm (reported in the REACH dossier as 31,680 mg/m^3). The REACH dossier authors assigned a Klimisch score of 1 (reliable without restriction).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
n-Heptane was assigned a score of Moderate for developmental toxicity based on possible specific developmental toxicities observed at maternally toxic concentrations in mice but not in rats for the surrogate, classifying the chemical to GHS Category 2 (suspected). GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity in animals and a GHS Category 2 classification is warranted (CPA 2018b). The confidence in the score is low as skeletal abnormalities were found in mice but not rats, and it is likely that these effects were non-specific effects due to maternal toxicity.

- Authoritative and Screening Lists
  - *Authoritative:*
    - MAK - Pregnancy Risk Group D - "Either there are no data for an assessment of damage to the embryo or foetus or the currently available data are not sufficient for classification in one of the groups A–C".
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2019a
  - <u>*Surrogate: Commercial hexane:*</u> A GLP-compliant developmental study was conducted in a manner similar to OECD Guideline 414. Pregnant female CD-1 mice (30/group) were administered whole body inhalation exposures to commercial hexane (52.19% n-hexane) vapor at 0, 914, 3,026, or 9,107 ppm for 6 hours/day during gestational days 6-15. Maternal evaluations included clinical signs of toxicity, body weight, food and water consumption, and ovarian and uterine content. Fetal evaluations included examinations of external, visceral, and skeletal variations and malformations. Brown foci and tissues color changes were identified in the lungs of parental animals exposed to 3,000 and 9,000 ppm. A statistically significant increase in some skeletal abnormalities was detected in fetuses at 9,000 ppm. Therefore, the ECHA record identified the maternal toxicity NOAEL and LOAEL at 900 and 3,000 ppm (reported in the REACH dossier as 3,168 and 10,560 mg/m^3, respectively) and the developmental NOAEL and LOAEL at 3,000 and 9,000 ppm (reported in the REACH dossier as 10,560 and 31,680 mg/m^3, respectively). The REACH dossier authors assigned a Klimisch score of 1 (reliable without restriction).
  - <u>*Surrogate: Commercial hexane:*</u> A GLP-compliant developmental study was conducted according to OECD Guideline 414. Pregnant female Sprague-Dawley rats (25/group) were administered whole body inhalation exposures to commercial hexane (52.19% n-hexane) at 0, 914, 3,026, or 9,107 ppm for 6 hours/day during gestational days 6-15. Maternal evaluations included clinical signs of toxicity, body weight, food and water consumption, and ovarian and uterine content. Fetal evaluations included examinations of external, visceral, and skeletal variations and malformations. There were color changes in the lungs of parental animals exposed to 9,000 ppm and these animals also showed reduced body weight gain and food consumption. No treatment-related abnormalities were found in the fetuses. Therefore, the ECHA record identified the NOAEL and LOAEL at 3,000 and 9,000 ppm, respectively, for maternal toxicity (reported in ECHA as 10,560 and 31,680 mg/m^3,

respectively) and developmental NOAEL at 9,000 ppm (reported in ECHA as 31,680 mg/m^3). The REACH dossier authors assigned a Klimisch score of 1 (reliable without restriction).

- The weight of evidence indicates that developmental toxicity consisted of skeletal abnormalities in mice but not rats at a maternally toxic concentration. It is likely that these effects were non-specific effects due to maternal toxicity. However, the possibility of specific developmental effects cannot be ruled out. Therefore, ToxServices conservatively classified the compound to GHS Category 2 (suspected) for developmental toxicity based on limited or marginal evidence in animals. Confidence level is reduced due to the likelihood that the developmental effects are secondary to maternal toxicity.

Endocrine Activity (E) Score (H, M, or L): DG

n-Heptane 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:*
    - TEDX - Potential Endocrine Disruptors - Potential Endocrine Disruptor
- TEDX 2019
  - n-Heptane was place on the TEDX list of potential endocrine disruptors in March 2017. The study was reviewed and is summarized below:
    - Zorad et al. (1987) investigated insulin binding and degradation in isolated human erythrocytes following the addition of n-heptane *in vitro*. The addition of increasing amounts of n-heptane to human erythrocyte suspension resulted in a dose-dependent enhancement of specific insulin binding; non-specific insulin binding remained unchanged over the range of the concentrations tested. Stimulation of insulin degradation as measured in the extracellular medium following the addition of n-heptane showed a similar dose-dependent pattern.
- U.S. EPA 2020
  - The following is a summary of the Tox21 assays performed with n-heptane:
    - n-Heptane was active in 0/12 estrogen receptor assays.
    - n-Heptane was active in 2/10 androgen receptor assays.
    - n-Heptane was active in 0/6 thyroid receptor or thyroid stimulation hormone receptor assays.
    - n-Heptane was active in 0/2 steroidogenesis (aromatase) assays.
- Based on the weight of evidence, a score of Data Gap was assigned. n-Heptane is present on the TEDX - Potential Endocrine Disruptors screening list, which corresponds to a score of Moderate to High. The reason provided for classification appears to be based on effects to insulin binding and degradation observed in an *in vitro* study. However, it was not clear from the Zorad et al. (1987) study that n-heptane-related toxicity was causally related to endocrine disruption. Additionally, the available results from Tox21 assays indicate that n-heptane does not have significant androgen activity and is not active in estrogen receptor or thyroid receptor assays. According to GreenScreen® guidance, a chemical should be assigned a preliminary Moderate hazard classification if there is an indication of endocrine activity in the scientific literature, and it may remain a Moderate or be modified to a High score when there is a plausible related adverse effect corresponding to a Moderate or High, respectively. As the TEDX classification is based only on limited evidence of systemic effects, with no evidence of endocrine activity, and the Tox21 results

do not support endocrine activity for n-heptane, ToxServices did not consider the available data to be sufficient to assign a preliminary score of Moderate 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) Score (vH, H, M, or L): L

n-Heptane was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values being > 2,000 mg/kg, and inhalation LC_{50} values being > 20 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} are greater than 2,000 mg/kg and inhalation LC_{50} are greater than 20 mg/L for a gas or vapor (CPA 2018b). The confidence in the score is high as it is based on experimental data for all three routes of exposure.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS - New Zealand 6.1E (oral) - Acutely toxic
- ECHA 2019a
  - *Inhalation):* 4-hour vapor LC_{50} (male and female Sprague-Dawley rats) >29.29 mg/L (nominal), >73.5 mg/L (analytical) (non-GLP-compliant, similar to OECD Guideline 403)
    - Test substance was 100% pure commercial product.
    - The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on limited documentation.
- HSDB 2014 (no Klimisch scores assigned)
  - *Inhalation:* 2-hour LC_{50} (mouse) = 75 g/m^3, or 75 mg/L.
  - *Inhalation:* 4-hour LC_{50} (rat) = 103 mg/m^3, or 0.103 mg/L.
    - According to ChemIDplus (2019), this value is 103 g/m^3 (or 103 mg/L), not 103 mg/m^3.
- ECB 2000 (no Klimisch scores assigned)
  - *Oral:* LD_{50} (rats) = 17,000 mg/kg.
  - *Oral:* LD_{50} (mice) = 5,000 mg/kg.
  - *Dermal:* LD_{50} (rabbits) = 3,000 mg/kg.
  - *Inhalation:* 4-hour LC_{50} (species not specified) = 60 mg/L.

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

n-Heptane was assigned a score of High for systemic toxicity (single dose) based on the EU classifying it as a GHS Category 1 aspiration hazard (H304). GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (single dose) when they are classified as GHS Category 1 aspiration hazards (H304) by the EU (CPA 2018b). The confidence in the score is high as it is based on an authoritative list.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU - GHS (H-Statements) - H304 - May be fatal if swallowed and enters airways.
  - *Screening:*
    - GHS - Japan - Specific target organs/systemic toxicity following single exposure - Category 3 (H335)
      - Based on irritation to the respiratory tract in mice and humans (NITE 2009,

2014).
    - GHS - Australia - H304 - May be fatal if swallowed and enters airways.
    - GHS – Japan - H304 - May be fatal if swallowed and enters airways.
        - Based on n-heptane being a hydrocarbon with a kinematic viscosity of 20.5 mm^2/s or less at 40°C (NITE 2009, 2014).
    - GHS - New Zealand - 6.1E (oral) - Acutely toxic
        - Based on EU Risk Phrase R65 (may cause lung damage if swallowed) in the IUCLID dataset (CCID 2019).
- ECHA 2019a
    - *Inhalation (vapor):* In an acute inhalation toxicity study, male and female Sprague-Dawley rats (n=10) were exposed to n-heptane vapor (100% pure commercial product) at a nominal concentration of 29.29 mg/L (analytical concentration of 73.5 mg/L) for 4 hours. No mortality occurred and there were no clinical signs of toxicity. There was a slight reduction in body weight in males on day 2 of the observation period; however, this effect reversed by day 4. All animals appeared normal at terminal necropsy with the exception of one female with enlarged mandibular lymph nodes on the right side. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on limited documentation.

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

n-Heptane was assigned a score of Low for systemic toxicity (repeated dose) based on a NOAEC of 8.82 mg/L in a 26-week inhalation (vapor) study in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when LOAEC values are greater than 1.0 mg/L for 90-day inhalation (vapor) studies in animals (CPA 2018b). The confidence in the score is high as it was based on a well-conducted study.

- 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 2016, ECHA 2019a
    - *Inhalation (vapor):* Male Wistar rats (n=7) were administered whole body inhalation exposures to n-heptane vapor (>99% purity) at 3,000 ppm (equivalent to 12,470 mg/m^3 (12.47 mg/L) as calculated by ECHA) n-heptane 12 hours/day, 7 days/week for 16 weeks. The animals were evaluated for clinical signs of toxicity and body weights (see the neurotoxicity section below for a discussion of the neurophysiologic and histopathological findings). No clinical signs of toxicity were identified following treatment. The mean body weight of animals exposed to heptane was not significantly different from those of control animals except at week 8. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on the inclusion of only one concentration in the study design and information lacking regarding statistical methods.
    - *Inhalation:* Male Sprague-Dawley rats (6-9/concentration) were administered inhalation exposures (type not specified) to n-heptane (form and purity not specified) at 1,500 ppm 9 hours/day, 5 days/week, for 7, 14 or 30 weeks. The animals were evaluated for urinary metabolites and the appearance of polyneuropathy. The study authors identified a NOAEC of 1,500 ppm based on the lack of adverse effects identified following exposure to the single concentration tests. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on the inclusion of only one concentration and only males in the study design.

- *Inhalation (vapor):* In a non-GLP-compliant repeated inhalation exposure toxicity study conducted in a manner similar to OECD Guideline 413, male and female Sprague-Dawley rats (15/sex/concentration) were administered whole body inhalation exposures to n-heptane vapor (≥ 98.5% purity) at concentrations of 0, 1.65, or 12.35 mg/L 6 hours/day, 5 days/week for 26 weeks. The equivalent concentrations for a 7-day/week exposure frequency were 0, 1.18, and 8.82 mg/L, respectively. Following the exposure period, the animals were maintained for a 2-week recovery period. Animals were evaluated for mortality, clinical signs, body weight, hematology, clinical chemistry, urinalysis, gross pathology and histopathology. Clinical signs included labored or rapid breathing and slight prostration during the first week of the study during exposure only, and anogenital fur and dry rales during weekly observations. There were no treatment related effects to body weight, hematology, or urinalysis. Only female rats at 12.35 mg/L ppm showed a significant increase in serum alkaline phosphatase levels, but no liver, hematological, or renal abnormalities were found. The effects observed were consistent with acute central nervous system (CNS) depression and generally abated by the second week of study. The authors established a systemic NOAEC of 12.35 mg/L (equivalent to 8.82 mg/L for a 7 day/week exposure frequency) based on the lack of effects at the highest concentration tested. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on deviations from the OECD Guideline (26-week exposure period and only 15 animals/sex/group).
- *Inhalation (vapor):* Male Long-Evans rats (10-11 in treatment group, 9 controls) were administered whole body inhalation exposures to n-heptane (99.5% purity) at 0, 3.3, or 16.6 mg/L n-heptane 6 hours/day, 7 days/week for 28 days. The animals were evaluated for clinical signs of toxicity and body weight. There were no differences in mean body weight gain until after cessation of exposure. From the termination of exposure over the remaining 8 weeks of the study, the body weight gain was statistically significantly lower in rats exposed to 16.6 mg/L. No other visually observable indicators of toxicity were detected. The REACH dossier authors assigned a Klimisch score of 1 (reliable without restriction).

- U.S. EPA 2016 (no Klimisch scores assigned)
  - *Oral:* In a range-finding study, male Charles River CD cesarean-obtained barrier-sustained (COBS) rats (3/dose) were administered gavage doses of undiluted n-heptane (95.7% purity) at 1,000, 2,000, or 4,000 mg/kg/day 5 days/week for 3 weeks (adjusted to daily doses of 714, 1,430, and 2,860 mg/kg/day, respectively). There were no treatment-related mortalities and no adverse clinical signs. There were no effects to body weight or food consumption. Treated rats had an increase in serum LDH, increased liver and kidney weights and hyperplasia of the gastric non-glandular epithelium. However, the authors concluded small group sizes and inadequate reporting of any measure of variability within treatment groups or statistical analyses preclude the determination of a critical effect or a LOAEL for this study.
  - *Oral:* In a subchronic study, male Charles River CD COBS rats (8/dose) were administered gavage doses of undiluted n-heptane (95.7% purity) at 4,000 mg/kg/day 5 days/week for 13 weeks (adjusted to a daily dose of 2,860 mg/kg/day). Five of the eight rats died from acute chemically induced pneumonitis. Treated rats had significantly reduced food consumption in the first week only, and decreased body weight throughout most of the study. A slight, but statistically significant 20% reduction in serum glucose levels was observed in the three surviving rats. A statistically significant reduction in absolute heart weight and significant increase in relative liver weight, relative kidney weight and relative adrenal weight were reported. Grossly enlarged livers were found in all treated animals that died.

Histopathological examination of exposed rats revealed local irritative effects on the forestomach mucosa. Low incidences of several hepatic (hepatocyte vacuolation, serosal adhesions, congestion) and renal (hyaline droplets, increased incidence of tubular dilation with casts, increased incidence of regenerating renal tubular epithelium, hemorrhage, congestion, focal nephritis) lesions were seen in treated rats. However, the authors concluded high mortality due to gavage error (5/8 treated rats) precludes the determination of a critical effect or LOAEL for this study. Potential treatment-related effects include persistent body-weight depression, gross liver enlargement, organ-weight changes, and histopathology of the forestomach, liver, kidney, and adrenal glands.

- HSDB 2014, ECHA 2019a
    - *Inhalation (vapor):* Biochemical effects were seen in male Wistar rats (15/group, 5 sacrificed after one week, 5 sacrificed after two weeks, and 5 sacrificed after a two-week recovery period) exposed to heptane vapors (purity not specified) at concentrations of 100, 500, or 1,500 ppm 6 hours/day, 5 days/week for 2 weeks. These included increased brain RNA concentration, acid proteinase activity, decreased glutathione levels and increased NADPH-diaphorase activity. However, the effects were reversible and returned to normal 2 weeks after exposure was terminated. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on the inclusion of only males in the study design and limited statistical methods.
- Based on a weight of evidence a score of Low was assigned. Oral studies in rats were not adequate for determining effect levels, due to deficiencies in study design and reporting. A majority of inhalation studies investigate neurotoxic effects of n-heptane and are discussed in the neurotoxicity section below. The 26-week study in rats provides the most adequate data for assigning a score for this endpoint. As the NOAEC in this study was 8.82 mg/L, which is greater than the GHS guidance value of 1.0 mg/L for a gas or vapor (UN 2017), a score of Low was assigned.

Neurotoxicity (single dose, N-single) Score (vH, H, M, or L): M

n-Heptane was assigned a score of Moderate for neurotoxicity (single dose) based on association with the hazard statement H336 and on being listed as neurotoxic by Boyes, supported by animal and human data. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when associated with H336 and a Category 3 classification is warranted (CPA 2018b). The confidence in the score is high as it is based on an authoritative list with support from animal and human data.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU - GHS (H-Statements) - H336 - May cause drowsiness or dizziness.
    - *Screening:*
        - GHS - Australia - H336 - May cause drowsiness or dizziness.
        - Boyes - Neurotoxicants – Neurotoxic.
        - GHS - Japan - Specific target organs/systemic toxicity following single exposure - Category 3 (H336)
            - Based on acute central nervous system depression in human volunteers and narcosis in exposed mice (NITE 2009, 2014).
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- HSDB 2014 (no Klimisch scores assigned)
    - Inhalation exposures of 10,000-15,000 ppm heptane in mice produced CNS depression within 30-60 min. At higher concentrations (<20,000 ppm), 30-60 min exposures elicited convulsions and death in mice. Inhalation exposures to 48,000 ppm produced respiratory arrest in 3/4 exposed mice in 3 min. Righting reflexes of mice were affected at an inhalation

concentration of 40 mg/L, and inhalation exposures to 70 mg/L were lethal.
- Inhalation exposure of mice to heptane (form not specified) at 13,000-19,000 ppm elicited convulsions and deaths within 15-40 min. Prior to death, the mice typically exhibited prostration and loss of reflexes.
- Human volunteers exposed to 0.1% heptane experienced slight vertigo within 6 min; those exposed to 0.2% heptane experienced vertigo in 4 min; and those exposed to 0.5% heptane exhibited clinical signs of CNS depression in 7 min.
- In humans, concentrations of 4.8% heptane produced respiratory arrest within 3 minutes. Survivors exhibited marked vertigo and incoordination requiring 30 min for recovery as well as mucous membrane irritation, slight nausea, and lassitude.
- Workers exposed to solvent mixtures containing pentane, hexane, and heptane (concentration not specified) exhibited polyneuropathy characterized as asthenia (decreased muscle strength), signs of anorexia, paresthesia (tingling or prickling feeling in extremities), fatigue, and bilateral symmetrical muscle paralysis of the legs.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
n-Heptane was assigned a score of Low for neurotoxicity (repeated dose) based on an inhalation LOAEC of 16.6 mg/L for a 28-day study in rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when inhalation LOAEC values for a gas or vapor are greater than 1.0 mg/L for 90 days studies (3.25 mg/L for a 28-day study) (CPA 2018b). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - Boyes - Neurotoxicants – Neurotoxic.
    - GHS - Japan - Specific target organs/systemic toxicity following repeated exposure - Category 1 (H372 – nervous system).
      - No rationale provided (NITE 2014). Not classified with H372 during previous assessments (NITE 2006, 2009).
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- HSDB 2014, ECHA 2019a
  - *Inhalation*: In a subchronic study, male Wistar rats (n=7) were administered whole body inhalation exposures to n-heptane vapor (>99% purity) at 3,000 ppm (equivalent to 12,470 mg/m³ (12.47 mg/L) as calculated in the REACH dossier) 12 hours/day, 7 days/week for 16 weeks. No abnormal behavioral changes were observed. Peripheral nerves, muscles and neuromass junctions, examined microscopically, were normal. There were no statistically significant differences in motor nerve conduction velocity, distal latency or mixed nerve conduction velocity in any region of the tail. Authors concluded n-heptane was not a neurotoxicant in this study and established a NOAEC of 12,470 mg/m^3. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on the inclusion of only one concentration in the study design and information lacking regarding statistical methods.
  - *Inhalation*: Male Sprague-Dawley rats (6-9/concentration) were administered inhalation exposures (type not specified) to n-heptane (form and purity not specified) at a concentration of 1,500 ppm 9 hours/day, 5 days/week for 7, 14 or 30 weeks did not develop any signs of neuropathy. Histopathological examination of nerve tissues obtained from n-heptane dosed rats showed no signs of morphological "giant axonal degeneration" in the peripheral and central nervous systems. The REACH dossier authors assigned a Klimisch score of 2

(reliable with restrictions) based on the inclusion of only one concentration and only males in the study design.
    - *Inhalation*: In a non-GLP-compliant repeated inhalation exposures study conducted in a manner similar to OECD Guideline 413, 26-week study, male and female Sprague-Dawley rats (15/sex/concentration) were administered whole body inhalation exposures to n-heptane vapor (≥ 98.5% purity) at 0, 1.65 and 12.35 mg/L 6 hours/day, 5 days/week for 26 weeks. The equivalent concentrations for a 7-day/week exposure frequency were 0, 1.18, and 8.82 mg/L, respectively. Following the exposure period, the animals were maintained for a 2-week recovery period. Acute CNS depression was observed and generally abated by the second week of the study. No additional evidence of neurological disturbances or organ toxicity was reported. A LOAEC of 1,650 mg/m^3 (1.65 mg/L) for acute CNS depression was reported. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on deviations from the OECD Guideline (26-week exposure period and only 15 animals/sex/group).
    - *Inhalation*: The effects of whole body inhalation exposures to n-heptane vapor (99.5% purity) at 800 or 4,000 ppm for 6 hours/day, 7 days/week for 28 days on the function of the auditory system were examined by measurements of auditory brain stem response (ABR) in male Long Evans rats (9 controls, 10-11 in treatment groups). Decreased auditory sensitivity was seen in rats at 4,000 ppm (16.6 mg/L), but not at 800 ppm (3.3 mg/L). ToxServices identified a NOAEC of 3.3 mg/L and a LOAEC of 16.6 mg/L for this study. The REACH dossier authors assigned a Klimisch score of 1 (reliable without restriction).
- HSDB 2014, ECHA 2019a
    - *Inhalation*: Male Wistar rats (15/groups) were exposed to n-heptane via inhalation at 4.2, 21 and 62 µM 6 hours/day, 5 days/week for two weeks. Levels of n-heptane increased in brain and perirenal fat during the 2 weeks of exposure. None of the rats showed clinical signs of neurotoxicity. Neurochemical changes seen at week 2, including increased proteolysis and higher brain RNA content, were at control levels after 2 weeks recovery. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) based on the inclusion of only males in the study design and limited statistical methods.
- Based on the above data, repeated exposure of animals to n-heptane vapor has been shown to depress the CNS and Japan classified n-heptane as a GHS Category 1 specific target organ toxicant following repeated exposures based on effects to the nervous system (no justification provided). However, the effects are transient. Transient narcotic effects have been evaluated in the single dose neurotoxicity section above. No other adverse neurological effects were observed in repeated dose toxicity studies that warrant GHS classification. Therefore, a score of Low was assigned.

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

n-Heptane was assigned a score of Low for skin sensitization based on negative results identified in a guinea pig maximization test with the surrogate. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as the percentage of n-heptane in the mixture was not characterized.

- 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 2019a
    - *Surrogate: Hydrocarbons, C7-C9, n-alkanes, isoalkanes, cyclics*: The skin sensitization potential of hydrocarbons, C7-C9, n-alkanes, isoalkanes, cyclics (100% pure commercial

product[10]) was evaluated in a non-GLP-compliant guinea pig maximization test conducted in a manner similar to OECD 406. p-Strain guinea pigs (10/sex in treatment group, 5/sex in control group) were administered induction doses as intradermal injections of the test material at 1% w/v in corn oil and topical applications of 50% w/v test material in corn oil (coverage not specified). The challenge dose was applied as a topical application of 25% w/v test material in corn oil under occlusive dressing. No positive reactions were identified at readings 24 or 48 hours after the challenge dose. The study authors concluded that the test substance was not sensitizing to the skin under the tested conditions. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as only basic data were provided.

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

n-Heptane was assigned a score of Low for respiratory sensitization based on the lack of dermal sensitization potential according to the ECHA guidance (2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when they are not GHS classified (CPA 2018b). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2019a
  - n-Heptane does not contain any structural alerts for respiratory sensitization (Appendix H).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As n-heptane is not expected to be sensitizing to the skin (see skin sensitization section above), a literature search did not find any human evidence of respiratory sensitization by n-heptane, and n-heptane does not contain any structural alerts for respiratory sensitization (OECD 2019a), n-heptane is not expected to be a respiratory sensitizer.

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

n-Heptane was assigned a score of High for skin irritation/corrosivity based on the EU classifying it as a GHS Category 2 skin irritant (H315). GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when they are classified as GHS Category 2 skin irritants (H315) by the EU (CPA 2018b). The confidence in the score is high as it is based on an authoritative list.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU - GHS (H-Statements) - H315 - Causes skin irritation.
  - *Screening:*
    - GHS - Japan - Skin corrosion / irritation - Category 2
      - Based on irritation and dermatitis in humans after 1-hour exposure and the

[10] Consisted of 35% C7, 50% C8, 15% C9 saturated hydrocarbon isomers, 65% n and isoparaffins, and 35% naphthenes. The percentage of n-heptane in this mixture is not characterized.

EU harmonized classification (NITE 2009, 2014).
- GHS - Australia - H315 - Causes skin irritation.
- GHS - New Zealand - 6.3B - Mildly irritating to the skin
  - Based on the EU Risk Phrase R38 (irritating to skin) identified in the IUCLID dataset (CCID 2019).

- HSDB 2014
  - n-Heptane causes dry skin and irritates the skin.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): *H*
n-Heptane was assigned a score of High for eye irritation/corrosivity based on classification to GHS category 2 by GHS-country (screening list) supported by limited data. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when a GHS Category 2A (moderately irritating) classification is warranted (CPA 2018b). The confidence in the score is low due to limited experimental data and as it is based on a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS - Japan - Serious eye damage / eye irritation - Category 2
      - Based on slight irritation detected in rabbit studies (NITE 2006, 2014).
- HSDB 2014
  - n-Heptane causes redness and pain in the eyes.
- ECB 2000 (no Klimisch scores assigned)
  - n-Heptane was reported to be slightly irritating to the rabbit eye. No further details were provided.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): vH
n-Heptane was assigned a score of Very High for acute aquatic toxicity based on the EU classifying it as a GHS Category 1 acute aquatic toxicant (H400) and measured acute aquatic toxicity values as low as 0.1 mg/L in aquatic invertebrates. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when acute aquatic toxicity values are no greater than 1 mg/L and they are classified as GHS Category 1 acute aquatic toxicants (H400) by the EU (CPA 2018b). The confidence in the score is high as it is based on experimental data and an authoritative listing.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU - GHS (H-Statements) - H400 - Very toxic to aquatic life.
  - *Screening:*
    - GHS - Japan - Hazardous to the aquatic environment (acute) - Category 1
      - Based on a 96-hour LC_{50} of 0.1 mg/L in mysid shrimp (NITE 2009, 2014).
    - EC - CEPA DSL - Inherently Toxic in the Environment (iTE)
      - Based on a 96-hour LC_{50} of 0.1 mg/L in mysid shrimp (OECD 2019b).
- HSDB 2014
  - LC_{50} = 4 mg/L in *Carassius auratus* (fish, 24 hours).
  - LC_{50} = 2,940 mg/L in *Leuciscus idus melanotus* (fish, 48 hours)
    - Assigned a Klimisch score of 3 (note reliable) in ECHA (2019a) due to significant methodological deficiencies.
  - LC_{50} = 4,924 mg/L in *Gambusia affinis* (fish, 24, 48 and 96 hours)

        - Assigned a Klimisch score of 3 (note reliable) in ECHA (2019a) due to significant methodological deficiencies.
    - LC_{50} = 375 mg/L in *Tilapia mossambica* (fish, 96 hours).
    - EC_{50} = 82.5 mg/L in *Daphnia magn*a (invertebrates, 96 hours).
    - EC_{50} > 10 mg/L in *D. magn*a (invertebrates, 24 hours)
        - Assigned a Klimisch score of 3 (note reliable) in ECHA (2019a) due to insufficient documentation of testing procedure test concentrations.
- HSDB 2014, ECHA 2019a
    - LC_{50} = 0.2 mg/L in C*haetogammarus marinus* (invertebrates, 96 hours)
        - The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as a non-standard organism was used and the LC_{50} was derived from a 96-hour exposure rather than a 48-hour exposure typically performed for invertebrates.
    - LC_{50} = 0.1 mg/L in *Americamysis bahia* (invertebrates, 96 hours)
        - The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as a non-standard organism was used and the LC_{50} was derived from a 96-hour exposure rather than a 48-hour exposure typically performed for invertebrates.
- ECHA 2019a
    - Estimated LL_{50} (median lethal loading rate) = 5.738 mg/L (freshwater fish, 96 hours)
        - Calculated "using the Petrotox computer model (v. 3.04), which combines a partitioning model used to calculate the aqueous concentration of hydrocarbon components as a function of substance loading with the Target Lipid Model used to calculate acute and chronic toxicity of non-polar narcotic chemicals."
        - The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the result was obtained via an appropriate model.
    - Mobility EC_{50} = 1.5 mg/L in *D. magna* (invertebrates, 48 hours)
        - The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as it was performed according to a method that was comparable to acceptable guidelines.
    - Several additional acute aquatic toxicity tests were presented in the REACH dossier. However, they were assigned Klimisch scores of 3 (not reliable) due to "significant methodological deficiencies" or "insufficient documentation." Therefore, they are not discussed in this assessment.

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

n-Heptane was assigned a score of Very High for chronic aquatic toxicity based on predicted ChV values of 0.04 mg/L in fish, 0.05 mg/L in daphnia and 0.23 mg/L. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are less than 0.1 mg/L (CPA 2018b). The confidence in the score is low as it is based on modeled data.

- 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 96-hour LC_{50} of 0.1 mg/L in mysid shrimp (OECD 2019b).
    - *Other*
        - EU - GHS (H-Statements) - H410 - Very toxic to aquatic life with long lasting effects.

        - GHS - Australia - H410 - Very toxic to aquatic life with long lasting effects.
        - GHS - Japan - Hazardous to the aquatic environment (chronic) - Category 1
            - Based on the acute aquatic toxicity classification and a high bioaccumulative potential based on a log K_{ow} = 4.66 (NITE 2009, 2014).
        - GHS - New Zealand - 9.1B (crustacean) - Very ecotoxic in the aquatic environment
            - Based on a 48-hour EC_{50} of 1.5 mg/L in daphnia and its bioaccumulation potential (log K_{ow} = 4.66) (CCID 2019).
- ECHA 2019a
    - Estimated growth NOELR (no observed effect loading rate) = 1.284 mg/L (freshwater fish, 28-day)
        - Calculated "using the Petrotox computer model (v. 3.04), which combines a partitioning model used to calculate the aqueous concentration of hydrocarbon components as a function of substance loading with the Target Lipid Model used to calculate acute and chronic toxicity of non-polar narcotic chemicals."
        - The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the result was obtained via an appropriate model.
- U.S. EPA 2017a
    - n-Heptane was assigned to the neutral organics ECOSAR chemical class. The most conservative chronic aquatic toxicity values were 0.04 mg/L in fish, 0.05 mg/L in daphnia, and 0.23 mg/L in green algae (Appendix I).

Environmental Fate (Fate)

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

n-Heptane was assigned a score of Very Low for persistence based on experimental data that indicates this chemical is readily biodegradable and meets the 10-day window. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when they are readily biodegradable and meet the 10-day window (CPA 2018b). The confidence in the score is high as it is based on data from experimental studies.

- 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 2019a
    - In a non-GLP-compliant biodegradation test conducted according to an American Public Health Association guideline, aerobic, natural soil was exposed to heptane (>99% purity) at 3.3 mg/L for 20 days. The test substance degraded 28.2% in 2 days, 63.2% in 5 days, and 70% in 10 days. Although the test guideline was not a ready biodegradation test, the overall results suggest that it would meet the criteria for ready biodegradation. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the method used was comparable to an acceptable guideline.
    - In a biodegradation test, 400 mL of gasoline containing 150 mg/L of n-heptane was exposed to non-adapted, activated domestic sludge for 25 days. About 20% degradation was reached on day 2 and more than 60% degradation was reached prior to day 10; 100% degradation was measured after 25 days. Although the test guideline was not a ready biodegradation test, the overall results suggest that it would meet the criteria for ready biodegradation. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the method used was comparable to an acceptable guideline.

  - In a biodegradation test, adapted soil was exposed to n-heptane (99% purity) at an unspecified concentration for 4 days. At the end of the exposure period, 100% degradation was measured. The n-heptane degradation rate was reported as 87 µg/day. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the original source was not available and was not reviewed.
  - n-Heptane (99% purity) biodegraded to an extent of 23.4% after 3 days incubation with an inoculum acclimated to gasoline, which contains n-heptane. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the original source was not available and was not reviewed.
- U.S. EPA 2017b
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that n-heptane is expected to be readily biodegradable (Appendix J). The Level III Fugacity Model (MCI Method) predicts 62.6% will partition to water with a half-life of 8.54 days, 35.7% will partition to air with a half-life of 38 hours (1.58 days), and 1.17% will partition to soil with a half-life of 17.3 days (Appendix J).
- Based on the weight of evidence, a score of Very Low was assigned. n-Heptane met the 10-day window in several biodegradation tests. The Level III Fugacity Model predicts n-heptane will mainly partition to water. It is ToxServices internal policy to assign the hazard score for persistence based on the dominant environmental compartment(s) identified via fugacity modeling (ToxServices 2016). Therefore, ToxServices assigned a Very Low score for this endpoint as it met the 10-day window in biodegradation tests.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *M*
n-Heptane was assigned a score of Moderate for bioaccumulation based on estimated BCF values of 552-681.8. GreenScreen® criteria classify chemicals as a Moderate hazard for bioaccumulation when BCF values are >500-1,000 (CPA 2018b). The confidence in the score is low as it is based on modeling.

- 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 2019a
  - An estimated BCF of 552 was calculated in fish for n-heptane, using a log K_{ow} of 4.66 and a regression-derived equation. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the study used an acceptable calculation method and was peer-reviewed.
- U.S. EPA 2017b
  - An estimated BCF of 681.8 and BAF of 687.7 were calculated based on a log K_{ow} of 4.66 (Appendix J).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
n-Heptane 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 lists.

- 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 2019a
    - n-Heptane does not contain any chemical groups associated with explosive properties.
    - Based on chemical structure, n-heptane is not capable of reacting exothermically with combustible materials.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of n-heptane. These procedures are listed in the GHS (UN 2017).
    - Based on its structure, n-heptane is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix K).
    - Based on its structure, n-heptane is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.
- Based on the above information and assessment, ToxServices did not classify n-heptane as a reactive chemical under GHS criteria (UN 2017).

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

n-Heptane was assigned a score of High for flammability based on the EU classifying it as a GHS Category 2 flammable liquid (H225). GreenScreen® criteria classify chemicals as a High hazard for flammability when they are classified as GHS Category 2 flammable liquids (H225) by the EU (CPA 2018b). The confidence in the score was high as it is based on authoritative lists supported by measured data.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU - GHS (H-Statements) - H225 - Highly flammable liquid and vapour.
        - Québec CSST - WHMIS 1988 - Class B2 - Flammable liquids.
    - *Screening:*
        - GHS - Australia - H225 - Highly flammable liquid and vapour.
        - GHS - Japan - Flammable liquids - Category 2
            - Based on a flash point of -4°C and an initial boiling point of 98.4°C (NITE 2009, 2014).
        - GHS - New Zealand - 3.1B - Flammable Liquids: high hazard
            - Based on a flash point of -3.9°C and an initial boiling point of 98°C (CCID 2019).
- ECHA 2019a
    - n-Heptane has a flash point of -4°C as identified in a non-GLP-compliant test of unspecified type. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the study was peer reviewed with limited details.
    - n-Heptane has a boiling point of 98.2-98.4°C as identified in a non-GLP-complaint ASTM D 1078 test. The REACH dossier authors assigned a Klimisch score of 2 (reliable with restrictions) as the study was not performed according to GLP but a standard test procedure was followed.
- U.S. DOT 2008a
    - n-Heptane is classified to hazard class or division 3 (flammable liquid) and packaging group II.
- Based on the available data, n-heptane is classified to GHS Category 2 for flammable liquids (liquids which have a flash point < 23ºC and initial boiling point > 35ºC) (UN 2017).

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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 n-Heptane (CAS #142-82-5)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

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	n-Heptane	142-82-5	*L*	**L**	*L*	*M*	DG	**L**	**H**	**L**	**M**	**L**	**L**	*L*	**H**	*H*	**vH**	*vH*	**vL**	*M*	*L*	**H**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
n-Heptane	2

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
n-Heptane	2

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												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for n-Heptane (CAS #142-82-5)

142-82-5
N-HEPTANE
ALSO CALLED [44607-13-8] Heptane (primary CASRN is 142-82-5), [8031-33-2] Heptane (primary CASRN is 142-82-5), 2...
View all synonyms (33)

Share Profile

Hazards | Properties | Functional Uses | Process Chemistry | Resources

Pharos Hazards View

Download Lists

ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LISTS
Endocrine	Medium	TEDX - Potential Endocrine Disruptors	Potential Endocrine Disruptor	
Mammalian	High	EU - GHS (H-Statements)	H304 - May be fatal if swallowed and enters airways	+6
	Low	GHS - New Zealand	6.1E (oral) - Acutely toxic	
	High	GHS - Australia	H304 - May be fatal if swallowed and enters airways	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H301 - Toxic if swallowed (unverified)	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H312 - Harmful in contact with skin (unverified)	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H330 - Fatal if inhaled (unverified)	
	Potential Concern	GHS - Japan	Aspiration hazard - Category 1 [H304]	
Organ toxicant	High	GHS - Japan	Specific target organs/systemic toxicity following repeated exposure - Category 1 [H372]	+4
	Medium	GHS - Japan	Specific target organs/systemic toxicity following single exposure - Category 3 [H335 or H336]	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified)	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H371 - May cause damage to organs (unverified)	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H372 - Causes damage to organs through prolonged or repeated exposure (unverified)	
Acute aquatic	Very High	EU - GHS (H-Statements)	H400 - Very toxic to aquatic life	+1
	Very High	GHS - Japan	Hazardous to the aquatic environment (acute) - Category 1 [H400]	
Chron aquatic	High	EU - GHS (H-Statements)	H410 - Very toxic to aquatic life with long lasting effects	+3
	High	GHS - Australia	H410 - Very toxic to aquatic life with long lasting effects	
	Very High	GHS - Japan	Hazardous to the aquatic environment (chronic) - Category 1 [H410]	
	High	GHS - New Zealand	9.1B (crustacean) - Very ecotoxic in the aquatic environment	
Flammable	High	EU - GHS (H-Statements)	H225 - Highly flammable liquid and vapour	+4
	High	GHS - Australia	H225 - Highly flammable liquid and vapour	
	High	GHS - Japan	Flammable liquids - Category 2 [H225]	
	High	GHS - New Zealand	3.1B - Flammable Liquids: high hazard	
	Potential Concern	Québec CSST - WHMIS 1988	Class B2 - Flammable liquids	
Neurotoxicity	Medium	EU - GHS (H-Statements)	H336 - May cause drowsiness or dizziness	+2
	Medium	GHS - Australia	H336 - May cause drowsiness or dizziness	
	Potential Concern	Boyes - Neurotoxicants	Neurotoxic	

Eye irritation	Medium	GHS - Japan	Serious eye damage / eye irritation - Category 2 [H319]	
Skin irritation	High	EU - GHS (H-Statements)	H315 - Causes skin irritation	+4
	High	GHS - Japan	Skin corrosion / irritation - Category 2 [H315]	
	High	GHS - Australia	H315 - Causes skin irritation	
	Medium	GHS - New Zealand	6.3B - Mildly irritating to the skin	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H314 - Causes severe skin burns and eye damage (unverified)	
Multiple	Medium	Québec CSST - WHMIS 1988	Class D2B - Toxic material causing other toxic effects	+2
	Potential Concern	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)	
	Potential Concern	German FEA - Substances Hazardous to Waters	Class 2 - Hazard to Waters	
Restricted list	Potential Concern	CA SCP - Candidate Chemicals	Candidate Chemical List	
Cancer	Potential Concern	US EPA - IRIS Carcinogens	(1986) Group D - Not classifiable as to human carcinogenicity	+1
	Potential Concern	EU - Manufacturer REACH hazard submissions	H350 - May cause cancer (unverified)	
Developmental	Potential Concern	MAK	Pregnancy Risk Group D	
Reproductive	Potential Concern	EU - Manufacturer REACH hazard submissions	H360 - Suspected of / May damage fertility and/or the unborn child (unverified)	
Gene mutation	Potential Concern	EU - Manufacturer REACH hazard submissions	H340 - May cause genetic defects (unverified)	
Respiratory	Potential Concern	EU - Manufacturer REACH hazard submissions	H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled (unverified)	
Skin sensitize	Potential Concern	EU - Manufacturer REACH hazard submissions	H317 - May cause an allergic skin reaction (unverified)	

APPENDIX D: OncoLogic Carcinogenicity Results for n-Heptane (CAS #142-82-5)

OncoLogic Justification Report

CODE NUMBER: 142825

SUBSTANCE ID:

User Inputs :

Select the Hydrocarbon type? : Saturated Hydrocarbons (Alkanes)

Select Saturated Hydrocarbon type? : All Other Alkanes

ALIPHATIC HYDROCARBONS, SATURATED (i.e., ALKANES)
Level of Concern: LOW

JUSTIFICATION:

With a few exceptions, there is no evidence that members of the saturated aliphatic hydrocarbon (i.e., alkane) class may be of any significant cancer concern.* Therefore, virtually ALL alkanes can be assigned a LOW concern with the following exceptions:

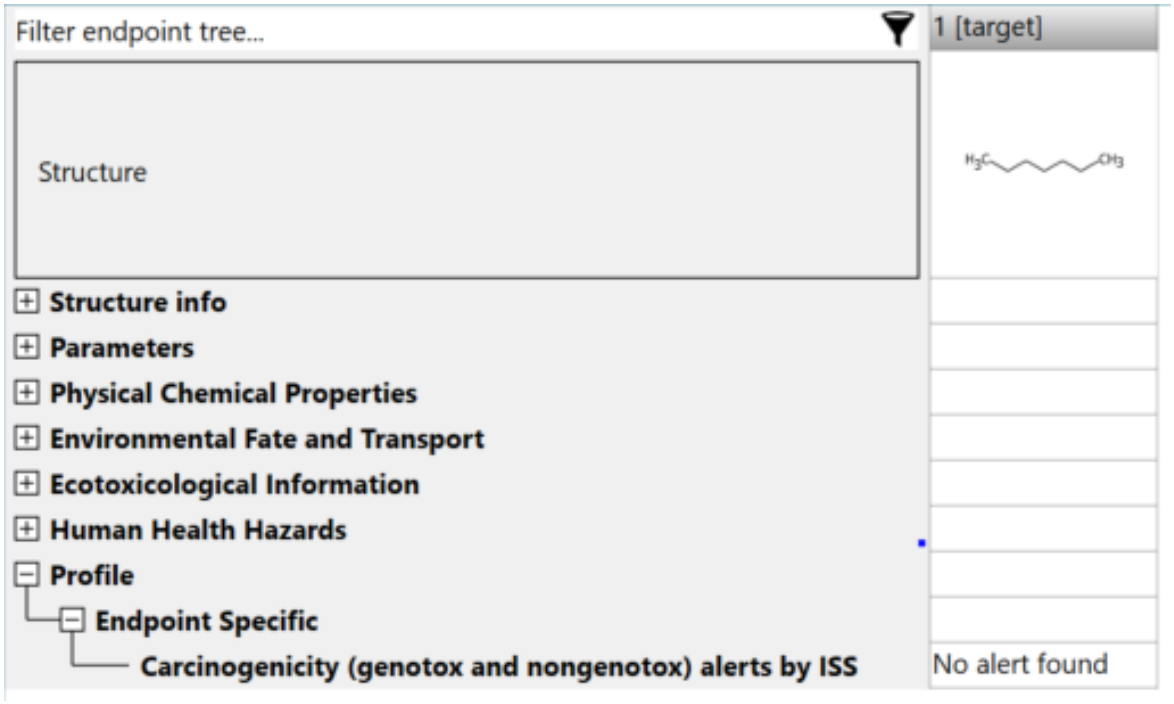
Marginal cancer concern may be assigned for the following cases:
[See other menu selections for additional information]

1. Medium sized (7 to 10 carbons) branched alkanes with at least one secondary carbon.

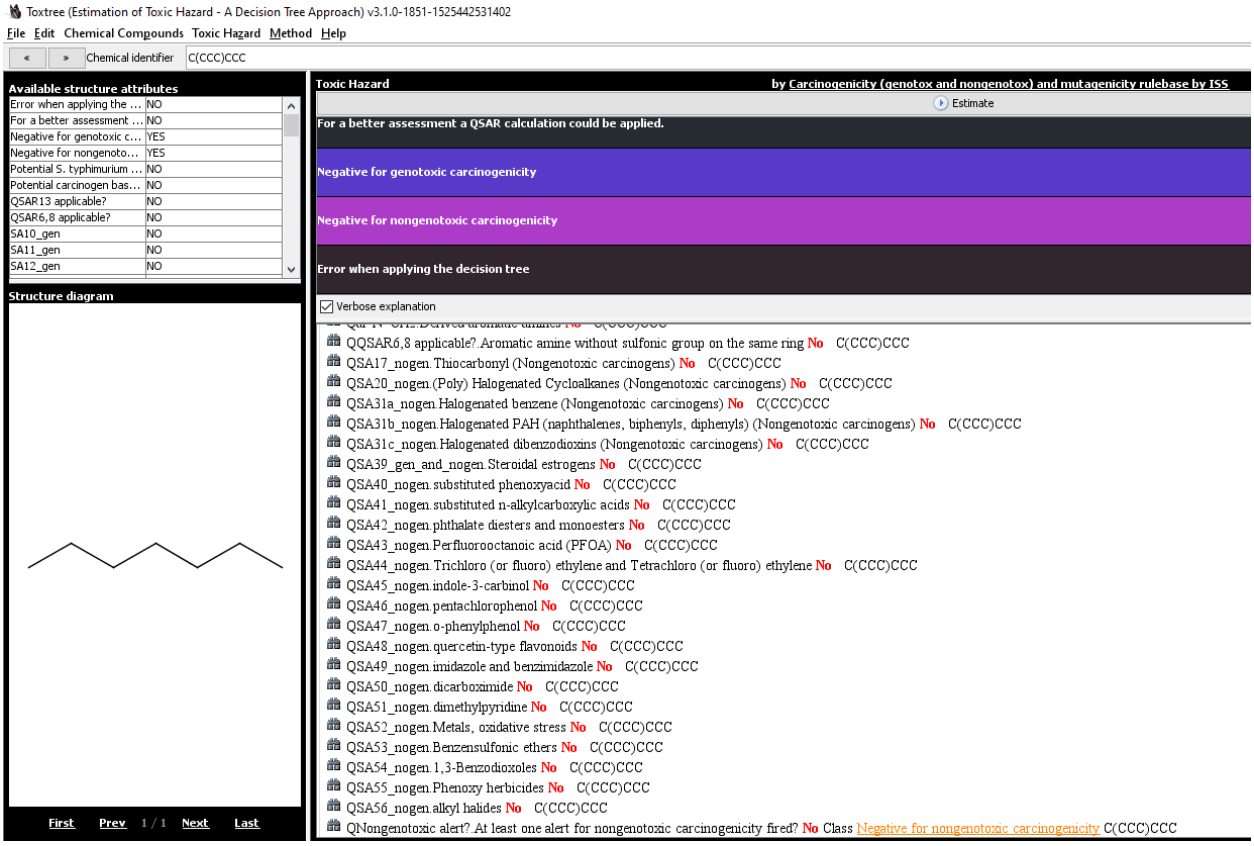
2. Medium sized (10 to 14 carbon) straight chain alkanes.

*It should be cautioned that the list of exceptional cases may not be exhaustive. If short-term predictive data are available, the Functional Arm of the OncoLogic system should also be used to assess the carcinogenic potential of your chemical.

APPENDIX E: OECD Toolbox Carcinogenicity Results for n-Heptane (CAS #142-82-5)



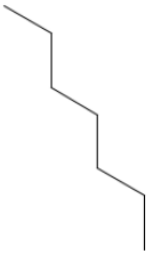
APPENDIX F: Toxtree Carcinogenicity Results for n-Heptane (CAS #142-82-5)



APPENDIX G: VEGA Carcinogenicity Results for n-Heptane (CAS #142-82-5)

1. Prediction Summary

Prediction for compound Molecule 0

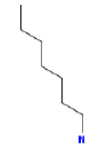


Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- only moderately similar compounds with known experimental value in the training set have been found
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: CCCCCCC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.817
P(NON-Carcinogen): 0.183
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

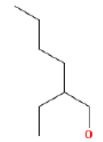
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 111-68-2
Dataset id: 357 (Test set)
SMILES: NCCCCCCC
Similarity: 0.782

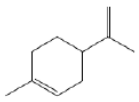
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #2

CAS: 104-76-7
Dataset id: 314 (Training set)
SMILES: OCC(CC)CCCC
Similarity: 0.757

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #3

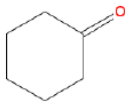
CAS: 5989-27-5
Dataset id: 412 (Training set)
SMILES: C=C(C)C1CC=C(C)CC1
Similarity: 0.748

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

Compound #4

CAS: 115-11-7
Dataset id: 399 (Test set)
SMILES: C=C(C)C
Similarity: 0.715

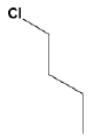
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 108-94-1
Dataset id: 187 (Test set)
SMILES: O=C1CCCCC1
Similarity: 0.7

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 109-69-3
Dataset id: 110 (Training set)
SMILES: CCCCCl
Similarity: 0.687

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

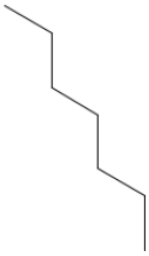
✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.769 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.
✔	**Model class assignment reliability** Pos/Non-Pos difference = 0.633 Explanation: model class assignment is well defined.
✔	**Neural map neurons concordance** Neurons concordance = 1 Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron.

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.
⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.
✖ The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound Molecule 0

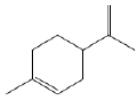


Prediction: Reliability:

Prediction is NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- only moderately similar compounds with known experimental value in the training set have been found
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: CCCCCCC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

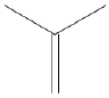
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 5989-27-5
Dataset id: 267 (Training set)
SMILES: C=C(C)C1CC=C(C)CC1
Similarity: 0.748

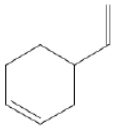
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 115-11-7
Dataset id: 597 (Training set)
SMILES: C=C(C)C
Similarity: 0.715

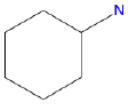
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 100-40-3
Dataset id: 238 (Training set)
SMILES: C=CC1CC=CCC1
Similarity: 0.704

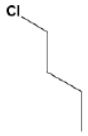
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 108-91-8
Dataset id: 834 (Training set)
SMILES: NC1CCCCC1
Similarity: 0.697

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

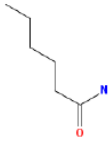


Compound #5

CAS: 109-69-3
Dataset id: 157 (Training set)
SMILES: CCCCCl
Similarity: 0.687

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA8 Aliphatic halogens



Compound #6

CAS: 628-02-4
Dataset id: 387 (Training set)
SMILES: O=C(N)CCCCC
Similarity: 0.665

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.731 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

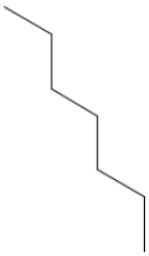
✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound Molecule 0

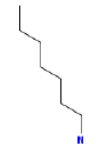
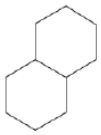
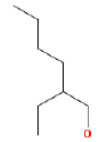
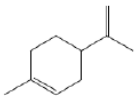
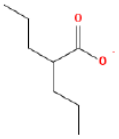


Prediction: Reliability:

Prediction is Possible NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- only moderately similar compounds with known experimental value in the training set have been found
- accuracy of prediction for similar molecules found in the training set is not optimal
- some similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: CCCCCCC
Experimental value: -
Predicted Mutagen activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

	Compound #1 CAS: N.A. Dataset id: 357 (Training set) SMILES: NCCCCCCC Similarity: 0.782 Experimental value: NON-Carcinogen Predicted value: Possible NON-Carcinogen
	Compound #2 CAS: N.A. Dataset id: 1202 (Training set) SMILES: C1CCC2CCCCC2(C1) Similarity: 0.776 Experimental value: Carcinogen Predicted value: Possible NON-Carcinogen
	Compound #3 CAS: N.A. Dataset id: 314 (Training set) SMILES: OCC(CC)CCCC Similarity: 0.757 Experimental value: NON-Carcinogen Predicted value: Possible NON-Carcinogen
	Compound #4 CAS: N.A. Dataset id: 412 (Training set) SMILES: C=C(C)C1CC=C(C)CC1 Similarity: 0.748 Experimental value: Carcinogen Predicted value: Possible NON-Carcinogen
	Compound #5 CAS: N.A. Dataset id: 381 (Training set) SMILES: C=C(C)C Similarity: 0.715 Experimental value: Carcinogen Predicted value: Possible NON-Carcinogen
	Compound #6 CAS: N.A. Dataset id: 1216 (Training set) SMILES: O=C([O-])C(CCC)CCC Similarity: 0.707 Experimental value: Carcinogen Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

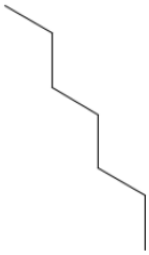
⚠	**Global AD Index** AD index = 0.716 Explanation: the predicted compound could be out of the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.771 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
⚠	**Accuracy of prediction for similar molecules** Accuracy index = 0.664 Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.
⚠	**Concordance for similar molecules** Concordance index = 0.664 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✓	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

✓ The feature has a good assessment, model is reliable regarding this aspect.
⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.
✗ The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound Molecule 0

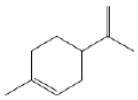


Prediction: Reliability:

Prediction is Possible NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- only moderately similar compounds with known experimental value in the training set have been found
- accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: CCCCCCC
Experimental value: -
Predicted Mutagen activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

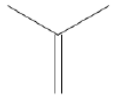


Compound #1

CAS: 5989-27-5
Dataset id: 218 (Training set)
SMILES: C=C(C)C1CC=C(C)CC1
Similarity: 0.748

Experimental value: Carcinogen
Predicted value: Carcinogen

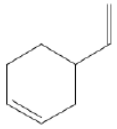
Alerts (not found in the target): Carcinogenity alert no. 39



Compound #2

CAS: 115-11-7
Dataset id: 682 (Training set)
SMILES: C=C(C)C
Similarity: 0.715

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

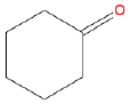


Compound #3

CAS: 100-40-3
Dataset id: 196 (Training set)
SMILES: C=CC1CC=CCC1
Similarity: 0.704

Experimental value: Carcinogen
Predicted value: Carcinogen

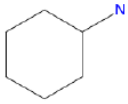
Alerts (not found in the target): Carcinogenity alert no. 39



Compound #4

CAS: 108-94-1
Dataset id: 934 (Training set)
SMILES: O=C1CCCCC1
Similarity: 0.7

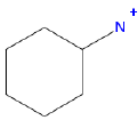
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #5

CAS: 108-91-8
Dataset id: 748 (Training set)
SMILES: NC1CCCCC1
Similarity: 0.697

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #6

CAS: 4998-76-9
Dataset id: 935 (Training set)
SMILES: [NH3+]C1CCCCC1
Similarity: 0.691

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.721
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.672
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

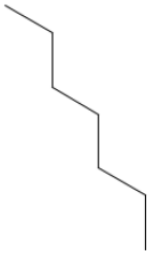
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound Molecule 0

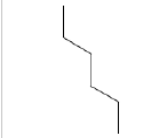


Prediction: Reliability:

Prediction is NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: CCCCCCC
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

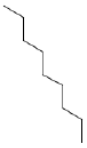
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 110-54-3
Dataset id: 540 (Training set)
SMILES: CCCCCC
Similarity: 0.957

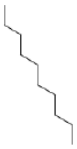
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 111-84-2
Dataset id: 610 (Training set)
SMILES: CCCCCCCCC
Similarity: 0.929

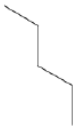
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 124-18-5
Dataset id: 425 (Training set)
SMILES: CCCCCCCCCC
Similarity: 0.908

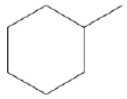
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 109-66-0
Dataset id: 626 (Training set)
SMILES: CCCCC
Similarity: 0.908

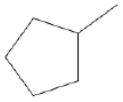
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 108-87-2
Dataset id: 587 (Training set)
SMILES: CC1CCCCC1
Similarity: 0.891

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 96-37-7
Dataset id: 588 (Training set)
SMILES: CC1CCCC1
Similarity: 0.856

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.971
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.942
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

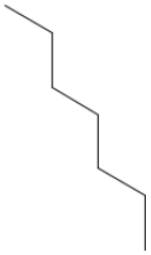
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

Prediction for compound Molecule 0

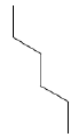


Prediction: Reliability:

Prediction is NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: CCCCCCC
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

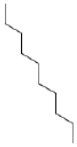
CAS: 110-54-3
Dataset id: 516 (Training set)
SMILES: CCCCCC
Similarity: 0.957

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

Compound #2

CAS: 111-84-2
Dataset id: 593 (Training set)
SMILES: CCCCCCCCC
Similarity: 0.929

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

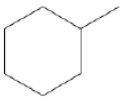
CAS: 124-18-5
Dataset id: 389 (Training set)
SMILES: CCCCCCCCCC
Similarity: 0.908

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

Compound #4

CAS: 109-66-0
Dataset id: 612 (Training set)
SMILES: CCCCC
Similarity: 0.908

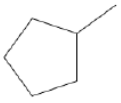
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 108-87-2
Dataset id: 567 (Training set)
SMILES: CC1CCCCC1
Similarity: 0.891

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 96-37-7
Dataset id: 568 (Training set)
SMILES: CC1CCCC1
Similarity: 0.856

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

	**Global AD Index** AD index = 0.971 Explanation: the predicted compound is into the Applicability Domain of the model.
	**Similar molecules with known experimental value** Similarity index = 0.942 Explanation: strongly similar compounds with known experimental value in the training set have been found.
	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
	**Concordance for similar molecules** Concordance index = 1 Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.
	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

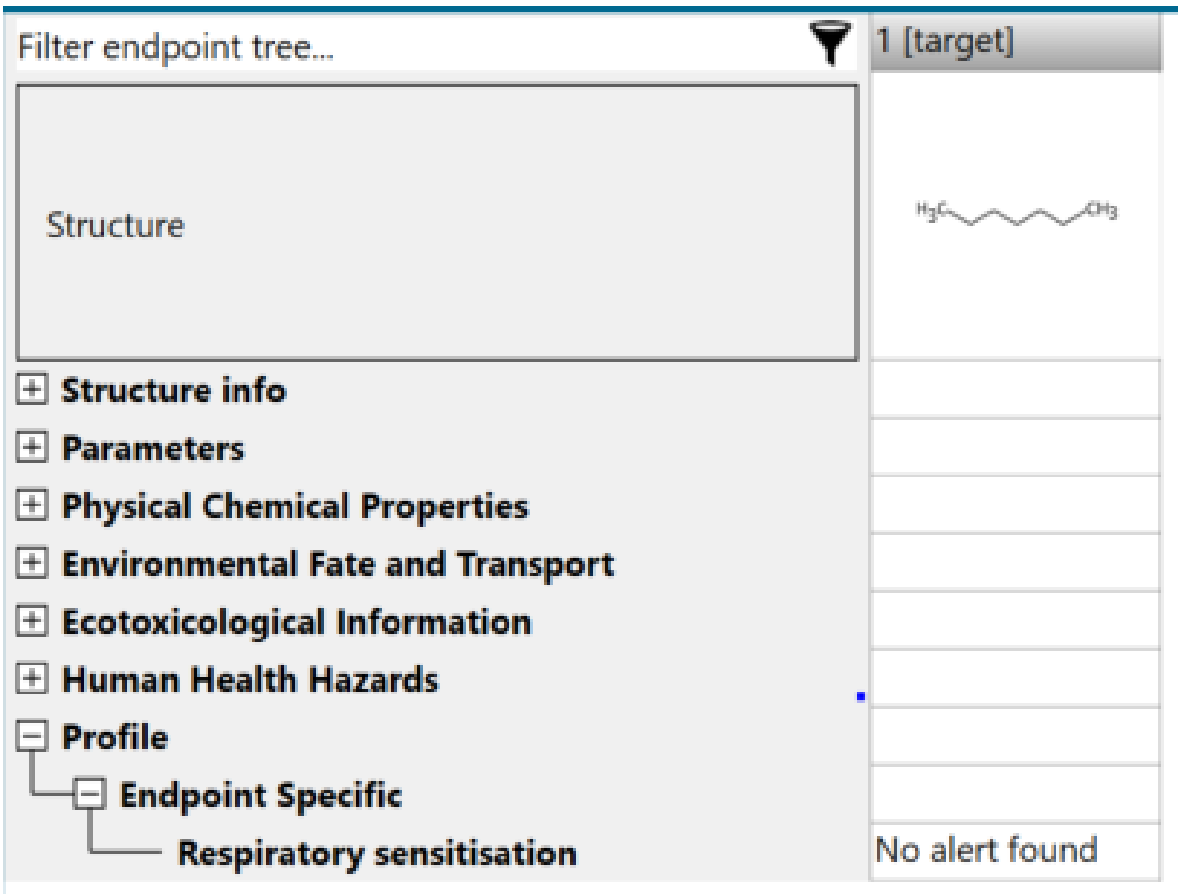
Symbols explanation:

 The feature has a good assessment, model is reliable regarding this aspect.

 The feature has a non optimal assessment, this aspect should be reviewed by an expert.

 The feature has a bad assessment, model is not reliable regarding this aspect.

APPENDIX H: OECD Toolbox Respiratory Sensitization Results for n-Heptane (CAS #142-82-5)



APPENDIX I: ECOSAR Modeling Results for n-Heptane (CAS #142-82-5)

Created on Jul 31, 2018 1:37:50 PM

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
142825	Heptane	C(CCCCC)C

Structure

Details	
Mol Wt	100.21
Selected LogKow	4.66
Selected Water Solubility (mg/L)	2.4
Selected Melting Point (°C)	-90.6
Estimated LogKow	3.78
Estimated Water Solubility (mg/L)	2.92
Measured LogKow	4.66
Measured Water Solubility (mg/L)	3.4
Measured Melting Point (°C)	-90.6

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	0.34	5	
Daphnid	48h	LC50	0.24	5	
Green Algae	96h	EC50	0.5	6.4	
Fish		ChV	0.04	8	
Daphnid		ChV	0.05	8	
Green Algae		ChV	0.23	8	
Fish (SW)	96h	LC50	0.43	5	
Mysid	96h	LC50	0.05	5	

1 / 2

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish (SW)		ChV	0.24	8	
Mysid (SW)		ChV	0	8	
Earthworm	14d	LC50	92.31	6	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

APPENDIX J: EPI Suite Modeling Results for n-Heptane (CAS #142-82-5)

CAS Number: 142-82-5
SMILES : C(CCCCC)C
CHEM : Heptane
MOL FOR: C7 H16
MOL WT : 100.21
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 4.66
Boiling Point (deg C) : 98.20
Melting Point (deg C) : -90.60
Vapor Pressure (mm Hg) : 36
Water Solubility (mg/L): 2.4
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 3.78
Log Kow (Exper. database match) = 4.66
Exper. Ref: MILLER,MM ET AL. (1985)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 96.16 (Adapted Stein & Brown method)
Melting Pt (deg C): -81.01 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 46.5 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 6.2E+003 (Mean VP of Antoine & Grain methods)
MP (exp database): -90.6 deg C
BP (exp database): 98.5 deg C
VP (exp database): 4.60E+01 mm Hg (6.13E+003 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 2.915
log Kow used: 4.66 (user entered)
melt pt used: -90.60 deg C
Water Sol (Exper. database match) = 3.4 mg/L (25 deg C)
Exper. Ref: YALKOWSKY,SH & DANNENFELSER,RM (1992)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 2.6374 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 2.27E+000 atm-m3/mole (2.30E+005 Pa-m3/mole)
Group Method: 2.39E+000 atm-m3/mole (2.42E+005 Pa-m3/mole)
Exper Database: 2.00E+00 atm-m3/mole (2.03E+005 Pa-m3/mole)
For Henry LC Comparison Purposes:

User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.978E+000 atm-m3/mole (2.004E+005 Pa-m3/mole)
VP: 36 mm Hg (source: User-Entered)
WS: 2.4 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 4.66 (user entered)
Log Kaw used: 1.913 (exp database)
Log Koa (KOAWIN v1.10 estimate): 2.747
Log Koa (experimental database): 2.950

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.8083
Biowin2 (Non-Linear Model) : 0.9686
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.2761 (days-weeks)
Biowin4 (Primary Survey Model) : 3.9722 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.6039
Biowin6 (MITI Non-Linear Model): 0.8280
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.4892
Ready Biodegradability Prediction: YES

Hydrocarbon Biodegradation (BioHCwin v1.01):
LOG BioHC Half-Life (days) : 0.7385
BioHC Half-Life (days) : 5.4758

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 4.8E+003 Pa (36 mm Hg)
Log Koa (Exp database): 2.950
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 6.25E-010
Octanol/air (Koa) model: 2.19E-010
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 2.26E-008
Mackay model : 5E-008
Octanol/air (Koa) model: 1.75E-008

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 6.8713 E-12 cm3/molecule-sec
Half-Life = 1.557 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 18.679 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
3.63E-008 (Junge-Pankow, Mackay avg)

1.75E-008 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 239.7 L/kg (MCI method)
Log Koc: 2.380 (MCI method)
Koc : 1.107E+004 L/kg (Kow method)
Log Koc: 4.044 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 2.742 (BCF = 551.7 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.2835 days (HL = 1.921 days)
Log BCF Arnot-Gobas method (upper trophic) = 2.834 (BCF = 681.8)
Log BAF Arnot-Gobas method (upper trophic) = 2.837 (BAF = 687.7)
log Kow used: 4.66 (user entered)

Volatilization from Water:
Henry LC: 2 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 1.022 hours
Half-Life from Model Lake : 95.09 hours (3.962 days)

Removal In Wastewater Treatment (recommended maximum 95%):
Total removal: 99.91 percent
Total biodegradation: 0.12 percent
Total sludge adsorption: 38.71 percent
Total to Air: 61.08 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	35.7	38	1000
Water	62.6	208	1000
Soil	1.17	416	1000
Sediment	0.546	1.87e+003	0

Persistence Time: 78 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	35.7	38	1000
Water	62.6	208	1000
water	(62.4)		
biota	(0.143)		
suspended sediment	(0.0224)		
Soil	1.17	416	1000

Sediment 0.546 1.87e+003 0
Persistence Time: 78 hr

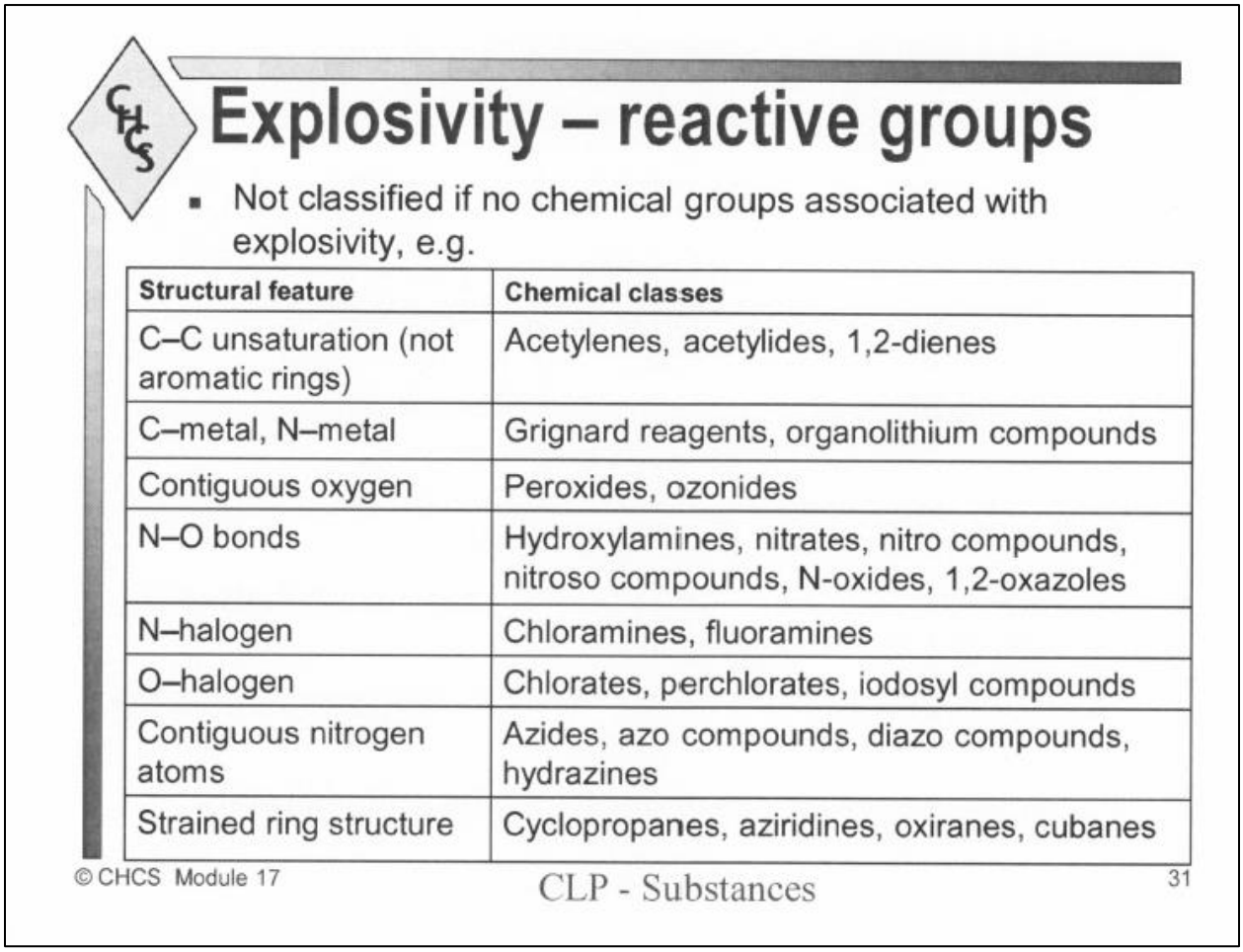
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	24.5	38	1000
Water	44.4	208	1000
water	(43.1)		
biota	(0.0985)		
suspended sediment	(1.21)		
Soil	16	416	1000
Sediment	15.1	1.87e+003	0

Persistence Time: 109 hr

APPENDIX K: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

- Not classified if no chemical groups associated with explosivity, e.g.

Structural feature	Chemical classes
C–C unsaturation (not aromatic rings)	Acetylenes, acetylides, 1,2-dienes
C–metal, N–metal	Grignard reagents, organolithium compounds
Contiguous oxygen	Peroxides, ozonides
N–O bonds	Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles
N–halogen	Chloramines, fluoramines
O–halogen	Chlorates, perchlorates, iodosyl compounds
Contiguous nitrogen atoms	Azides, azo compounds, diazo compounds, hydrazines
Strained ring structure	Cyclopropanes, aziridines, oxiranes, cubanes

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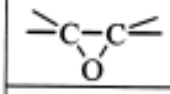
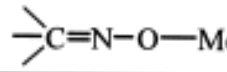
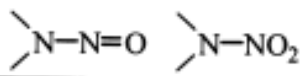
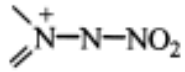
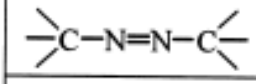
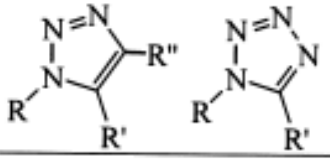
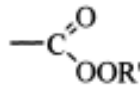
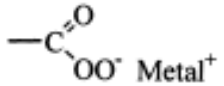
Explosivity – Full List

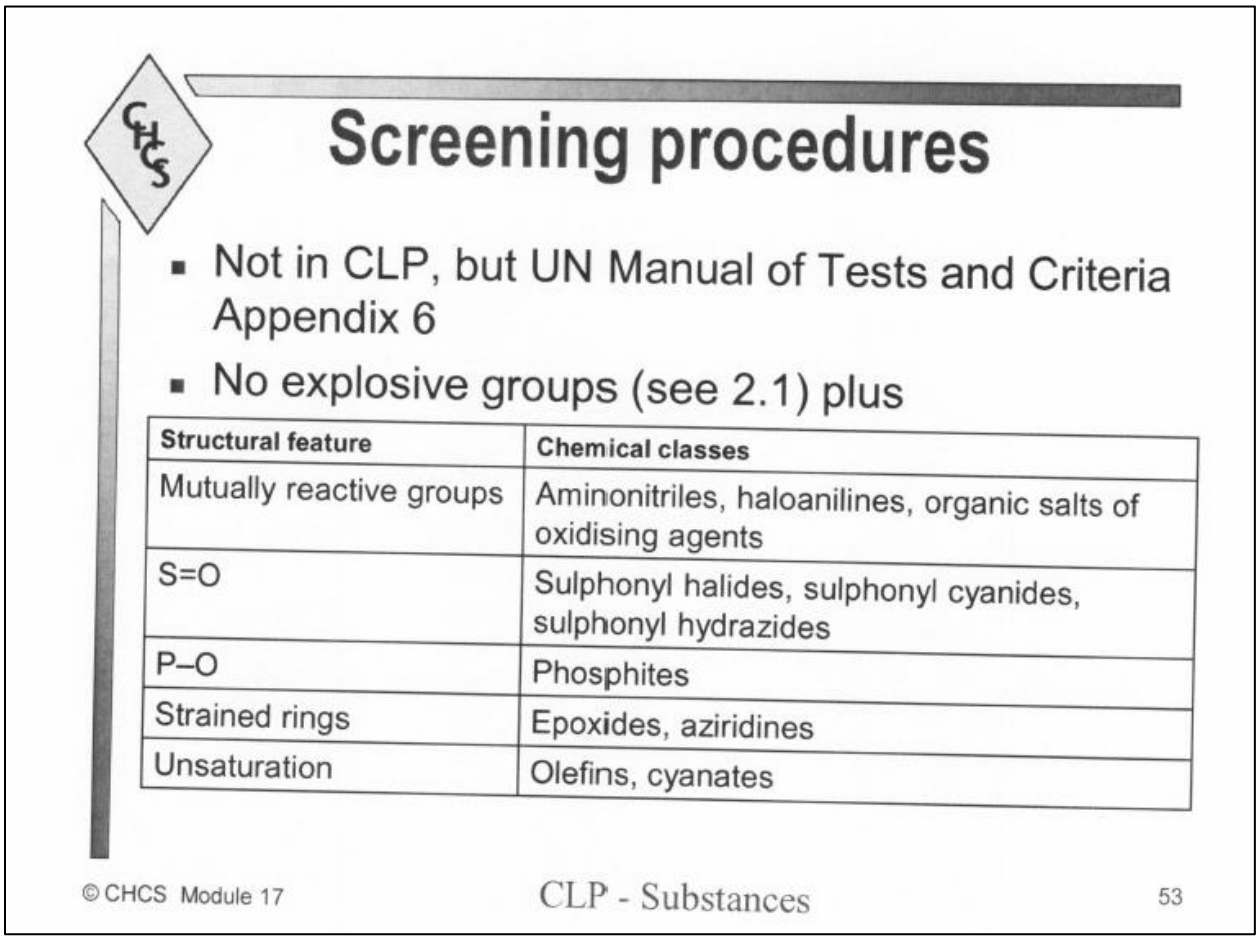
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or *aci*-Nitro Salts
	N-Metal Derivatives (especially heavy metals)
	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. $NC1_3$, $RNC1_2$	N-Halogen Compounds

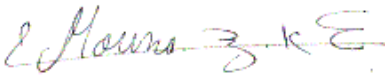
Adapted from Bretherick (Bretherick's Handbook of Reactive Chemical Hazards 6th Ed., 1999, Butterworths, London)

Self-Reactive Substances



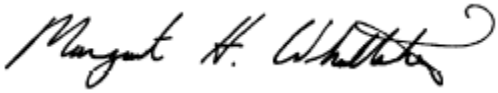
Licensed GreenScreen® Profilers

n-Heptane GreenScreen® Evaluation Prepared by:



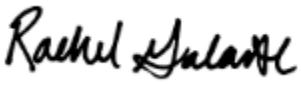
Mouna Zachary, Ph.D.
Toxicologist
ToxServices LLC

n-Heptane GreenScreen® Evaluation QC'd by:



Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC

n-Heptane GreenScreen® Evaluation Updated by:



Rachel Galante, M.P.H.
Associate Toxicologist
ToxServices LLC

n-Heptane GreenScreen® Evaluation Update QC'd by:

Bingxuan Wang, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC

n-Heptane GreenScreen® Evaluation Updated by:

Zach Guerrette, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC

n-Heptane GreenScreen® Evaluation Update QC'd by:

Bingxuan Wang, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC