REPUBLIC OF SLOVENIA
MINISTRY OF HEALTH
CHEMICALS OFFICE OF THE REPUBLIC OF SLOVENIA

Justification Document for the Selection of a CoRAP Substance

Substance Name (public name): 3-methyl-1,5-pentanediyl diacrylate

EC Number: 264-727-7

CAS Number: 64194-22-5

Authority: Chemical Office of the Republic of Slovenia

Date: 19/03/2019

Cover Note

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

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1 IDENTITY OF THE SUBSTANCE

1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	3-methyl-1,5-pentanediyl diacrylate
IUPAC name (public):	3-methyl-1,5-pentanediyl diacrylate
Index number in Annex VI of the CLP Regulation:	/
Molecular formula:	C12H18O4
Molecular weight or molecular weight range:	226.27
Synonyms:	3-methyl-5-(prop-2-enoyloxy)pentyl prop-2-enoate 3-methylpentane-1,5-diyl bisacrylate

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:

1.2 Similar substances/grouping possibilities

Has read-across been used by the registrant for the concern related endpoints? ☒ Yes ☐ No

A read-across has been used with hexane-1,6-diylbisacrylate (CAS No 13048-33)-4 for human health endpoints.

Is the substance a member of a category? ☐ Yes ☒ No

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

No ongoing process.

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

Human health hazard assessment

Manual screening took into consideration the data submitted by the registrant for the fulfillment of standard REACH information requirements for the tonnage band 100 tonnes or more (Annex IX) as well as other available sources.

Relevant findings of the Manual screening:

Findings on toxicological endpoints submitted by the registrant:

There is **no data on the carcinogenicity** due to the tonnage band.

Findings on other toxicological endpoints:

8.3. Skin sensitisation

8.3.2. Skin sensitisation, in vivo:

An OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay) was submitted with the test material (EC: 264-727-7, CAS: 64194-22-5). Compound meets the classification criteria for Category 1A (GHS) i.e. **EC3: 0.9%**

8.6. Repeated dose toxicity:

A short term repeated dose toxicity study i.e. OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) with another test material i.e. hexane-1,6-diylbisacrylate CAS No 13048-33-4.

In the registration dossier the read-across of repeated dose toxicity data is not supported by justification

8.6.2. Sub-chronic toxicity study (90-day):

NOT submitted. Instead TESTING PROPOSAL ON VERTEBRATE ANIMALS (December 2017 - June 2018) is mentioned for the substance of interest (EC: 264-727-7, CAS: 64194-22-5)

8.7. Reproductive toxicity

For the assessment of reproductive toxicity an OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) and an OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) were submitted with the test material CAS No: 13048-33-4.

In the registration dossier the read-across of reproductive toxicity data is not supported by justification.

8.7.2. Pre-natal developmental toxicity study

NOT submitted. Instead TESTING PROPOSAL ON VERTEBRATE ANIMALS (January 2018-August 2018) is mentioned for the substance of interest (EC: 264-727-7, CAS: 64194-22-5).

8.7.3. Extended One- Generation Reproductive Toxicity Study

No study submitted.

8.8. Toxicokinetics:

No experimental toxicokinetic study was provided instead ADME properties are discussed based on toxicological data and on physicochemical properties of the substance.

Concluding remark:

To address the standard REACH information requirements - 100 tonnes or more (Annex IX) for Repeated dose toxicity and Reproductive toxicity the registrant submitted screening study on another testing material with the CAS No: 13048-33. The registrant did not provide a justification study for the application of Read-across to assess both toxicities.

So far the registrant hasn't updated the dossier according to the testing proposals mentioned.

Additionally, screening methods usually cannot be used to replace the REACH requirement for a 90 days subchronic study, neither they provide evidence for definite claims of no reproduction/developmental effects.

A subchronic 90 day repeated dose study is not expected to provide conclusive evidence for acrylates related carcinogenicity.

Table: Overview of toxicological data as submitted by the registrant

Toxicological endpoints	***Substance 3-methyl-1,5-pentanediyl diacrylate CAS No 64194-22-5***	***Additional information***
Oral acute toxicity, LD50 (mg/kg bw) in rats	>2000 mg/kg (OECD 423)	n.a.
Inhalation acute toxicity, LC50 (mg/L)	≥1050 - ≤ 5140 g/m3 (≥1.05 - ≤ 5.14 mg/L) (OECD 436)	Acuet Tox 4 H332: Harmful if inhaled.
Dermal acute toxicity, LD50 (mg/kg bw)	> 2000 mg/kg rat (OECD 402)	n.a.
Skin irritation	Irritant (OECD 439)	Skin Irrit. 2 H315: Causes skin irritation.
Eye irritation	Irritant (OECD 405)	Eye Irrit. 2 H319: Causes serious eye irritation.
Skin sensitisation	Skin sensitizer (OECD 429)	Skin Sens. 1A H317: May cause an allergic skin reaction.
Lowest Oral repeated dose toxicity, NOAEL (mg/kg bw/d)	Read-across Test material: CAS No: 13048-33-4 Doses tested: 75, 250 and 750 mg/kg/day (OECD 422)	NOAEL 250 mg/kg based on increased liver weight and clinical chemistry changes (Additonally at dose 250 mg/kg bw/day: squamous epithelial hyperplasia and hyperkeratosis in the non-glandular stomach
	Testing proposal for Sub-chronic toxicity study (90-day) Test material CAS No 64194-22-5 (OECD 408)	Planned study period (December 2017 - June 2018)

Toxicological endpoints		***Substance 3-methyl-1,5-pentanediyl diacrylate CAS No 64194-22-5***	***Additional information***
Mutagenicity *in vitro*		Negative (OECD 471)	n.a.
		Negative (OECD 487)	
		Negative (OECD 476)	
Mutagenicity *in vivo*		--	--
Carcinogenicity, NOAEL (mg/kg bw), in rats		--	--
Toxicity to reproduction, NOAEL/NOEL (mg/kg bw/d)	**F+ D**	Read-across Test material: CAS No: 13048-33-4 Doses tested: 75, 250 and 750 mg/kg/day (OECD 422)	(P0) NOAEL = 250 mg/kg Systemic toxicity: body weight, liver weight and clinical chemistry (P0) NOAEL = 750 mg/kg Toxicity to reporduction (F1) NOAEL≥ 750 mg/kg Based on the absence of adverse effects
	F	Read-across Test material: CAS No: 13048-33-4 (OECD 421)	(P0) NOAEL > 750 mg/kg Based on the absence of adverse effects
	F	Testing proposal Extended One-Generation Reproductive Toxicity Study (OECD 443) will be made if effects on reproductive organs will be observed in the Sub-chronic toxicity study (90-day)	--
	D	Testing proposal Prenatal developmental toxicity study Test material CAS No 64194-22-5 (OECD 414)	Planned study period (January 2018-August 2018)

Relevant information from other sources:

The substance is an acrylate. Acrylates have been associated with human health **concerns related to their potential for carcinogenicity**. Concern about cancer in humans can be traced to an early report of an excess of colon cancer in workers engaged in acrylic sheet manufacture (Maher and DeFonso, 1984).

TSCA (Toxic Substances Control Act): Based on SAR analysis of test data on analogous acrylates, EPA **identified concerns for carcinogenicity** and sensitization. Further to this EPA recommends testing that would help to characterize the human health effects of the substance and suggests carcinogenicity test (OPPTS Test Guideline 870.4200) (OECD 451).

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

There is no classification of the substance in table 3.1 in Annex VI of CLP Regulation (Regulation (EC) 1272/2008).

3.1.2 Self classification

- In the registration:

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
		264-727-7	64194-22-5	Acute Tox. 4	H332: Harmful if inhaled		
				Skin Irrit. 2	H315: Causes skin irritation.		
				Eye Irrit. 2	H319: Causes serious eye irritation.		
				Skin Sens. 1A	H317: May cause an allergic skin reaction.		
				STOT Single Exp. 3	H335: May cause respiratory irritation.		
				Acquatic Chronic 3	H412: harmful to acquatic life with long lasting effects.		

- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:

  There is no additional hazard classes for 3-methyl-1,5-pentanediyl diacrylate.

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

Not applicable.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[1]

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site *		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☒ 100 – 1000 tpa
☐ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential
***the total tonnage band has been calculated by excluding the intermediate uses, for details see the Manual for Dissemination and Confidentiality under REACH Regulation (section 2.6.11): https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0		

[1] *The dissemination site was accessed September 2018.*

4.2 Overview of uses

Table: Uses

Part 1:

☒ Manufacture	☒ Formulation	☒ Industrial use	☒ Professional use	☐ Consumer use	☐ Article service life	☐ Closed system

Part 2:

	Use(s)
Manufacture	**Manufacture** PROC 1,3,4,8a,8b, 9, 15,28 **ERC 1**
Formulation	– **Industrial formulation, blending, re-packing into coatings/inks** – Technical function of the substance : intermediate (precursor) PROC: 1,2,3,5,8a,8b, 9, 15,28 **ERC 2**
Uses at industrial sites	– **Industrial formulation, blending, re-packing into coatings/inks** – Technical function of the substance: intermediate (precursor) PROC 1,2,3,5,8a,8b, 9, 10,15,28 **ERC 5** – **Industrial use as a cross-linking agents/monomer in polymerisation** – Technical function of the substance: intermediate (precursor) PROC 1,3,4,8a,8b, 9, 15,28 **ERC 6c** **ERC 6d**
Professional use	– **Widespreading printing with ink cartridges** – Technical function of the substance: intermediate (precursor) PC 18; ink and toners PROC 1,3,10 **ERC 8c**

Part 3: There is high potential for exposure of

☒ Humans	☐ Environment

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

☒ Article 44(2) (refined prioritisation criteria for substance evaluation)

☐ Article 45(5) (Member State priority)

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

☒ Fulfils criteria as CMR/ Suspected CMR

☐ Fulfils criteria as Sensitiser/ Suspected sensitiser

☐ Fulfils criteria as potential endocrine disrupter

☐ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☐ Fulfils criteria high (aggregated) tonnage (*tpa > 1000*)

☒ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

5.3 Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐ C ☐ M ☐ R	Suspected CMR[1] ☒ C ☐ M ☐ R	☐ Potential endocrine disruptor
☐ Sensitiser	☐ Suspected Sensitiser[2]	
☐ PBT/vPvB	☐ Suspected PBT/vPvB[1]	☐ Other (please specify below)
Exposure/risk based concerns		
☒ Wide dispersive use	☐ Consumer use	☐ Exposure of sensitive populations
☐ Exposure of environment	☒ Exposure of workers	☐ Cumulative exposure
☐ High RCR	☐ High (aggregated) tonnage	☐ Other (please specify below)

[2] CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-classification)
Suspected PBT: Potentially Persistent, Bioaccumulative and Toxic

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

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☐ Information on exposure
☐ Information on ecotoxicological properties	☐ Information on uses
☐ Information ED potential	☐ Other (provide further details below)

Following the assessment of the available toxicological information, it is concluded that there is no reliable data on carcinogenicity, since these data are not standard information requirements 100 - 1000 tonnes (Annex IX). Even if a sub-chronic 90 day repeated dose study, would be submitted according to the standard information requirements, it is expected, that no definitive conclusions could be drawn regarding carcinogenicity. Therefore, the carcinogenicity study would have to be requested anyway for a definitive evaluation of carcinogenic toxicity of the substance.

In conclusion, to clarify suspected carcinogenicity the substance evaluation is proposed in order to get available data.

5.5 Potential follow-up and link to risk management

☒ Harmonised C&L	☐ Restriction	☐ Authorisation	☐ Other (provide further details)

A combined approach would be appropriate: TP for a 90d-study needs to be processed first. Thereafter, SEV and DEV combination may get the information needed. At the same time, the coordination with other evaluation MSCAs who evaluate acrylates would be needed.

Possible further risk management action is CLH.