LATVIJAS VIDES, ĢEOLOĢIJAS UN METEOROLOĢIJAS CENTRS

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Oxydiethylene dibenzoate

EC No 204-407-6

CAS No 120-55-8

Evaluating Member State(s): Latvia

Dated: 3 August 2020

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Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2019

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Oxydiethylene dibenzoate (DEGDB) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected Reprotoxic,
- Consumer use,
- Exposure of environment and workers,
- High (aggregated) tonnage,
- Wide dispersive use.

During the evaluation additional concerns were not identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A Compliance check was performed by ECHA on the dossier for evaluation for DEGDB in 2016 (concluded). Amongst others, a pre-natal developmental toxicity study in rabbits was requested.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	x

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

No need for follow-up regulatory action at EU-level.

4.1.1. Harmonised Classification and Labelling

Not applicable.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	x
Actions by the registrants to ensure safety, as reflected in the registration dossiers	

Taking into account the information available in the registration dossier, the evaluating Member State was able to conclude on every concern endpoint and found no potential, inadequately controlled risks. The exposure concern could be clarified with the conclusion that due to the use information provided in the registration dossier the exposure data did not suggest indications for a high risk for the environment, workers and consumers. Hence, it is concluded that the initial concerns can be removed and there is no need for follow-up action at EU level.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

DEGDB was originally selected for substance evaluation in order to clarify concerns about:

- Reprotoxic properties;
- Wide dispersive use;
- Exposure of environment and workers;
- High RCR;
- Consumer use;
- High (aggregated) tonnage.

During the evaluation additional concerns were not identified.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Reprotoxic properties	Concern not substantiated. No further action.
Exposure/Wide dispersive use (environment/ workers/ consumer use), high RCR, high (aggregated) tonnage	Concern not substantiated. No further action.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, DEGDB was included in the Community rolling action plan (CoRAP) for evaluation in 2019. The Competent authority of Latvia (eMSCA) was appointed to carry out the evaluation.

The evaluation of Oxydiethylene dibenzoate was targeted at human health endpoints and focused on the grounds for concern that were included in the justification document for the inclusion of the substance in the CoRAP. Taking into account all information provided by the Registrant in IUCLID dossier, the evaluation Member State was able to conclude on every concerned endpoints and found no potential risks, which was controlled inadequately.

7.3. Identity of the substance

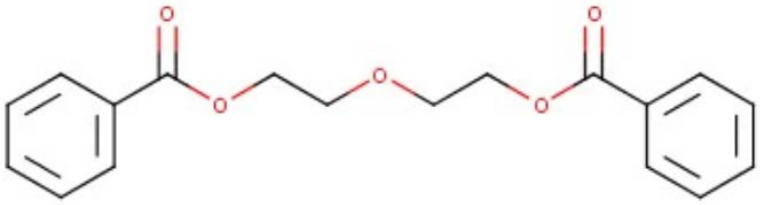
Table 4

SUBSTANCE IDENTITY	
Public name:	Oxydiethylene dibenzoate
EC number:	204-407-6

CAS number:	120-55-8
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C18H18O5
Molecular weight range:	314,3325
Synonyms:	Diethylene glycol, dibenzoate Ethanol, 2,2'-oxybis-, dibenzoate Ethanol, 2,2'-oxybis-, dibenzoate

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

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid (100%)
Melting/freezing point	24°C at 101 325 Pa
Boiling point	No boiling point to decomposition temperature, >230°C at 101 325 Pa
Relative density	1.2 at 20°C
Vapour pressure	0,000018 Pa at 25°C
Surface tension	60 nM/m at 20°C
Water solubility	38,3 mg/L at 20°C
Partition coefficient n-octanol/water (Log Kow)	3.2 at 30°C
Flash point	199 °C at 1013 hPa
Flammability	-
Explosive properties	Non explosive (100%)
Oxidising properties	Non oxidising (100%)
Viscosity	83mPa · s (dynamic) at 20°C

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

DEGDB is used by consumers, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

Table 7

USES	Use(s)
Formulation	- Formulation of preparations; - Formulation in materials; - Distribution and storage (technical function of the substance during formulation: process regulators, used in vulcanisation or polymerisation processes; softeners; stabilisers)
Uses at industrial sites	- Industrial manufacture of adhesives and sealants; - Industrial manufacture of coatings and inks; - Industrial manufacture of lubricant additives; - Chemical processes for peroxide carrier; - Plasticizer for PVC
Uses by professional workers	- Professional use of adhesives and sealants; - Professional use of coatings and inks; - Professional use as a carrier for agricultural chemicals; - Professional use of lubricant additives; - Laboratory use.
Consumer Uses	- Consumer use of adhesives and sealants; - Consumer use of coatings and inks; - Consumer use of cosmetics and personal care products; - Consumer use as a carrier for agrochemicals; - Consumer use of plasticizer for PVC.
Article service life	- Adhesives and sealants; - Coatings and inks; - Cosmetics and personal care products; - Lubricant additives; - Plasticizer for PVC.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

DEGDB is not classified according to CLP Regulation.

7.6.2. Self-classification

- In the registration(s):

Not classified.

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

Acuatic Chronic 2, H411;
Eye Irrit. 2 H319.

7.7. Environmental fate properties

7.7.1. Degradation

In a modified Sturm test DEGDB was found to be degraded by 17% after 2 days, 71% after 10 days, and by 93% at the end of the 28 -day biotic phase of the test. The positive control substance, sodium benzoate, which was analysed contemporaneously degraded rapidly (65% degradationafter 6 days), and confirmed that the inoculum was viable and that the test was valid. Substances are considered to be readily degradable in this test if CO2 production is equal to or greater than 60% of the theoretical value within ten days of the level achieving 10%. In the modified Sturm test, DEGDB met these criteria, so it is considered to be readily biodegradable.

7.7.2. Environmental distribution

Organic carbon-water partition co-efficient Koc for DEGDB was found to be Koc=1500 at 20° indicating that the substance is rather strongly adsorbed onto soil and its organic matter and does not move easily throughout the soil (low mobility according to McCall`s soil mobility classification scheme).

7.7.3. Bioaccumulation

Evidence of a low bioaccumulation potential of DEGDB is provided by Quantitative structure–activity relationship (QSAR) model estimates showing Bioconcentration Factor (BCF) values <100 L/kg using a regression method based upon the experimental octanol-water partition coefficient log Kow value of 3.2, and using the Arnot-Gobas QSAR method the BCF or Bioaccumulation factor (BAF) values for all trophic levels are < 10 L/kg when biotransformation rates are utilized and ~ 200 L/kg when biotransformation is not included in the estimation. A substance with a BCF<2000 L/kg is regarded as non-bioaccumulative. For these reasons and taking into account animal welfare considerations a bioconcentration study was not proposed. In addition, the bioconcentration in aquatic species studies can be waived if direct and indirect exposure to the aquatic environment is unlikely. This substance has no defined uses where direct application to the aquatic environment would occur, and because the substance is readily biodegradable, wastewater treatment will not cause indirect exposure to the aquatic environment as well.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

Short-term acute toxicity of fish caused by the DEGDB was determined in the studies with freshwater fish rainbow trout and fathead minnows. The studies were conducted according to EC, OECD, and US EPA test guidelines and in compliance with GLP. The 96 h LC50 value for DEGDB with fathead minnow was 3.9 mg/L. The no observed effect concentration (NOEC) for DEGDB with fathead minnow was 1.5 mg/L). In addition, the 96 h LC50 value for DEGDB with rainbow trout was 2.9 mg/L. The NOEC for DEGDB with rainbow trout was 0.06 mg/L.

Long term toxicity to fish study was proposed to be waived based on the short-term testing results and the rapid biodegradability of the substance.

According to CLP criteria, substances are classified as Acute aquatic toxicity Cat. 1 if 96 h LC50 value is ≤ 1 mg/l, therefore the DEGDB is not classified for acute aquatic toxicity. In absence of adequate chronic toxicity data, two types of information are combined, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data). As the criteria for BCF ≥500 and Kow ≥4 are not fulfilled, the DPGDB shall not be classiefied in any of chronic aquatic toxicity categories.

7.8.1.2. Aquatic invertebrates

An acute Daphnia magma immobilisation study was performed to determine the acute toxicity of the DEGDB. The study was conducted according to EC, OECD, and US EPA test guidelines and in compliance with GLP. The 48 h EL50 (immobilisation value for DEGDB with Daphnia magna) was determined to be 6.7 mg/L. The no observed effect loading rate (NOELR) was 1.0 mg/L.

Long term toxicity to invertebrates study was proposed to be waived based on the short-term testing results and the rapid biodegradability of the substance.

According to CLP criteria, DEGDB shall not be classified for acute toxicity and chronic toxicity.

7.8.1.3. Algae and aquatic plants

An algal growth inhibition test was conducted to determine the effect of the DEGDB on the growth of algae Pseudokirchneriella subcapitata (previously - Selenastrum capricornutum). The study was conducted according to EC, OECD, and US EPA test guidelines and in compliance with GLP. The EL50 (Area under the curve 72 h) was 5.2 mg/L and the EL50 (Growth rate 0 - 72 h) was 11 mg/L, while the EL50 (Area under the curve 96 h) was 5.9 mg/L and the EL50 (Growth rate 0 - 96 h) was 15 mg/L.

According to CLP criteria, DEGDB shall not be classified for acute toxicity and chronic toxicity.

7.8.1.4. Sediment organisms

No relevant information is available. The substance is readily biodegradable and exposure to sediment organisms is unlikely.The substance is not a PBT or vPvB substance and does not meet the criteria for classification as dangerous to aquatic environment. According to Annex IX of REACH, testing on sediment organisms can be waived.

7.8.1.5. Other aquatic organisms

No relevant information is available.

7.8.2. Terrestrial compartment

There are no defined uses where direct exposure of this substance to the soil compartment is likely. Also, as this substance is readily biodegradable, it can be assumed that it will be biodegraded within the STP process and as a consequence indirect transfer to the soil compartment from sludge is not expected. According to Annex IX of REACH, testing on terrestrial organisms can be waived in such case.

Nevertheless, the results from an earthworm (Eisenia fetida) study have been used to assess the hazard to terrestrial organisms. No mortalities were seen during the study, and all worms were normal in appearance on days 7 and 14 of the test. Under the conditions of this study, the LC50 value of DEGDB to the earthworm was found to be in excess of 1000 ppm (1000 mg/kg). The no observed effect level (NOEL) was considered to be 1000 ppm (1000 mg/kg).

7.8.3. Microbiological activity in sewage treatment systems

An activated sludge respiration inhibition test was conducted to determine the effect of DEGDB on sewage micro-organisms. The study was conducted in accordance with EC, OECD and US EPA test guidelines and in compliance with GLP. DEGDB had no significant inhibitory effect on the respiration rate of activated sludge at any of the concentrations employed in the tests. The NOEC was determined to be ≥ 100 mg/L, the highest concentration tested. A second study that supports this result was performed to assess the effect of DEGDB on the growth of the bacteria Pseudomonas putida. Exposure of Pseudomonas putida to DEGDB gave EC10 and EC50 values greater than 10 mg/L. The NOEC was determined to be ≥ 10 mg/L.

7.8.4. PNEC derivation and other hazard conclusions

Table 8

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks / Justification**
Freshwater	PNEC freshwater: 2.9 µg/L	Assessment factor: 1000 Extrapolation method: assessment factor PNEC freshwater Lowest short-term L(E)C50 from each of three trophic levels fish, invertebrates (daphnia) and algae. The LC50 from acute toxicity to rainbow trout: 2.9 mg/l.
Marine water	PNEC marine water: 0.29 µg/L	Assessment factor: 10000 Extrapolation method: assessment factor PNEC marine water

		Lowest short-term L(E)C50 from each of three trophic levels fish, invertebrates (daphnia) and algae. The LC50 from acute toxicity to rainbow trout:2.9 mg/l.
Intermittent releases to water	PNEC intermittent releases: 29 µg/L	PNEC intermittent release assessment factor: 100 PNEC intermittent release extrapolation method: assessment factor PNEC intermittent release Lowest short-term L(E)C50 from each of three trophic levels fish, invertebrates (daphnia) and algae. The LC50 from acute toxicity to rainbow trout:2.9 mg/l.
Sediments (freshwater)	PNEC sediment (freshwater): 0.474 mg/kg sediment dwt	Extrapolation method: equilibrium partitioning method The value has been calculated according to the equilibration partitioning coefficient method using EUSES 2.1.1
Sediments (marine water)	PNEC sediment (marine water): 0.047 mg/kg sediment dwt	Extrapolation method: equilibrium partitioning method The value has been calculated according to the equilibration partitioning coefficient method, using EUSES 2.1.1.
Sewage treatment plant	PNEC STP: 10 mg/L	Assessment factor: 10 Extrapolation method: assessment factor PNEC STP The NOEC >100 mg/l from an activated sludge respiration inhibition study was used.
Soil	PNEC soil: 1 mg/kg soil dw	Assessment factor: 1000 Extrapolation method: assessment factor NOEL soil The NOEL from an earthworm study 1000 ppm (mg/kg) was used.
Air	Not applicable – no hazard	-
Secondary poisoning	PNEC oral: 333 mg/kg food	Assessment factor: 30 (AF for chronic rat study)/20 (food consumption factor for rat > 6 weeks of age - daily food intake in g per bw in g) = 1.5 Reproductive (developmental) and 2-generation dietary study in rat: NOAEL = 500 mg/kg bw/day.

7.8.5. Conclusions for classification and labelling

According to CLP criteria, DEGDB shall not be classified for acute toxicity and chronic toxicity based on acute toxicity studies on fish, invertebrates and algae and taking into account BCF and Kow values of the substance.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

To investigate the metabolism of DEGDB (diethylene glycol dibenzoate CAS no.: 120-55-8) the substance was radiolabelled with the 14C and the study was performed when orally dosed was administered to male and female Sprague Dawley (CD) rats (Registration dossier, study report, 2000). The study was conducted to EU and to OECD test guidelines and to GLP. Virtually all of single oral doses of 50 and 750 mg/kg of ring [U-14C phenyl] DEGDB administered to the rats were absorbed metabolised and excreted in the urine within 24 hours of administration. No measurable radioactivity was detected in expired air.

DEGDB is metabolised via hydrolysis of the ester bonds to benzoic acid; this free acid is then conjugated with either glycine (major pathway) or glucuronic acid (minor pathway) prior to excretion.

A radiolabelled study of the metabolism of DEGDB in the rat by oral gavage demonstrated that DEGDB does not have a tendency to bioaccumulate

7.9.2. Acute toxicity and Corrosion / Irritation

In key experimental studies using rats (Sprague-Dawley), the oral LD50 values obtained were 4843 mg/kg bw (male) and 3535 mg/kg bw (female) and 4190 mg/kg bodyweight (both sexes) (Registration dossier, study report, 1998) The study was conducted according to EPA OTS 798.1175 and OECD 401 test guidelines, and in compliance with GLP. In similar studies conducted earlier, the LD50 was determined to be >3000 mg/kg bodyweight for both sexes. Therefore, the oral LD50 in the rat (both sexes) is determined as higher than 3000 mg/kg bodyweight.

Acute inhalation toxicity

Rats (male & female) were exposed to an atmosphere of DEGDB (calculated to be 200 mg/L) over a four hour period and observed over 14 days, no deaths were seen (Registration dossier, study report, 1974). On this basis, DEGDB would not be considered a toxic material by the inhalation route of administration.

Acute dermal toxicity

Male and female rats (Sprague-Dawley) were exposed to a 2000 mg/kg dose of DEGDB by the dermal route for 24 hours, then observed for 14 days following test material removal. No rats died during the observation period, and no clinical or pathological signs were observed. The study was conducted according to EPA OTS 798.1100 and OECD 402 test guidelines. (Registration dossier, study report, 1998). On the basis of these results, LD50: >2000 mg/kg bw (male/female).

According to the criteria laid down in CLP regulation the DEGDB is considered not acutely toxic by the oral, dermal and inhalation routes and needs not to be classified.

Irritation

In skin irritation study using rabbits (New Zealand White) no irritation (dermal reaction) was observed following a single semi-occlusive application to intact skin for four hours. (Registration dossier, study report, 1998). The study was conducted according to EPA OTS 798.4470 and OECD 404 test guidelines.

In eye irritation study using rabbits (New Zealand White) neat test material (0.1 ml) was instilled into one eye of six healthy adult rabbits, and the effects observed for three days (72h). Transient hyperaemia of blood vessels only was observed in all animals. These reactions had resolved in all instances by one or two days after instillation. No corneal damage or iridial inflammation was observed. (Registration dossier, study report, 1998). The study was conducted according to EPA OTS 798.4500 and OECD 405 test guidelines. As a single instillation of DEGDB into the rabbit eye did not elicit a positive response according to the established test criteria, it is therefore considered as non-irritant.

Based on available data, the eMSCA can support this conclusion.

7.9.3. Sensitisation

A study was performed to determine the potential for skin sensitization to guinea pigs (Dunkin-Hartley) of the test substance DEGDB. The study was conducted according to EPA OTS 798.4100, OECD 406 test guidelines, and in compliance with GLP. Evidence of skin sensitization was seen in all animals treated by the positive control substance, Hexyl cinnamic aldehyde, confirming the sensitivity of the method. DEGDB did not produce evidence of skin sensitization (delayed contact hypersensitivity) in any of the animals tested (Registration dossier, study report, 1998).

According to the criteria laid down in CLP regulation DEGDB is not considered a skin sensitizer.

Based on available data, the eMSCA can support this conclusion.

7.9.4. Repeated dose toxicity

A 13 -week repeated oral dose (dietary) study (according to OECD TG 408 and GLP) was conducted to determine the effects of prolonged exposure on rats of the test material DEGDB. Groups of ten rats (Crl:(IGS) CDBR) were dosed by dietary administration with DEGDB for a period of 13 weeks at levels 0 (untreated diet control), 250, 1000, 1750, and 2500 mg/kgbw/day. Additional rats were dosed at 0 and 2500 mg/kg bw/day to allow for an assessment of recovery from treatment for four weeks after dosing. No findings of toxicological importance were detected in this study at a dosage of 1000 mg/kg/day or below. Dosages of 1750 or 2500 mg/kg/day were tolerated (with one exception - a single mortality at 2500 mg/kg/day) but induced clinical findings changes in blood parameters, minor treatmentrelated pathology and/or adverse effects on bodyweight gain. When selected animals previously receiving 2500 mg/kg/day were maintained off dose for 4 weeks all treatment related changes showed evidence of or complete recovery (Registration dossier, study report, 1998).

The result of the subchronic test (90 day rat oral) revealed a NOAEL of 1000 mg/kg bw/day. Therefore, according to the criteria laid down in CLP regulation the test item DEGDB, is considered as posing no danger of serious health damage by prolonged oral exposure and is not classified.

Based on available data, the eMSCA can support this conclusion.

7.9.5. Mutagenicity

In the interest of completeness of the assessment, mutagenicity of DEGDB was assessed but not comprehensively. From the results of the four different in-vitro investigations (gene mutation in bacteria (according to OECD TG 471, OECD TG 472), chromosomal aberration

in-vitro (according to OECD TG 473) and gene mutation in mammalian cells (according to OECD TG 476)), substance did not express evidence of mutagenic activity in bacterial system (tested in four strains of Salmonella typhimurium and one strain of Escherichia coli), showed no evidence of clastogenic activity in-vitro cytogenetic test system (Chinese Hamster Lung (CHL)) and did not demonstrate mutagenic potential in vitro mammalian cell mutation assay, which are considered reliable and suitable for classification purposes under CLP Regulation.

Based on the available information, the eMSCA can agree that the substance needs not to be classified for genetic toxicity.

7.9.6. Carcinogenicity

Not evaluated.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Effects on fertility

In a vaginal cornification/uterine weight bioassay, DEGDB did not possess estrogenic activity up to and including the maximally tolerated dose (Registration dossier, study report, 1997).

A two generation study in in Sprague-Dawley rats was conducted to assess the effects on reproductive performance of the test material DEGDB (Registration dossier, study report, 2001). The study was conducted according to OECD and EPA test guidelines, and in compliance with GLP.

Dietary administration of DEGDB at concentrations of 1000, 3300 or 10000 ppm was generally well tolerated by the P(F0) and subsequent F1 animals and their respective progeny. Exposure to the test material was consistent with expectations throughout both generations. Organ weight assessment of the F0 and F1 parent animals did not suggest any adverse effects of DEGDB on any organs. Assessment of spermatogenesis and histopathology in both parental generations showed that there were no injurious effects on the testes or other reproductive organs. Furthermore, detailed histopathological examination of the tissues from both sexes in both generations did not reveal any adverse effects of treatment with DEGDB. The only possible effect of DEGDB treatment detected at assessment of organ weights: lower absolute and relative spleen weight among F2 males and females compared to controls. The toxicological significance of this finding is uncertain since it was not detected among F1 offspring or among P(F0) and F1 adult animals.

The evidence from this study suggested that a dietary concentration of DEGDB at 10000 ppm should be considered as the No Observed Adverse Effect Level (NOAEL) for P(F0) and F1 parent animals. The NOAEL for developing offspring is considered to be 3300 ppm. The No Observed Effect Level (NOEL) for reproductive parameters is considered to be 10000 ppm (equivalent to a minimum estimated daily achieved dosage of 500 mg/kg/d).

Developmental toxicity

A pre-natal developmental toxicity study in rats was conducted to determine the effect of the test material DEGDB when administered during and beyond the organogenesis phase of gestation (Registration dossier, study report, 2000). The study was conducted according to Japanese, US EPA, OECD, and EC test guidelines, and in compliance with GLP. Dose levels - 250, 500 and 1000 mg/kg/day.

Key findings:

Clinical signs related to treatment were limited to post-dosing salivation, adose-response effect was seen but was thought to be due to the palatability of the test material. A slight reduction in mean foetal weight in the 1000 mg/kg/d group was observed, however the

difference from control was small and was significant only in the female foetuses (3.5g vs 3.63g in control). An increased incidence in the number of foetuses with cervical ribs was seen in the 1000 mg/kg bw/day group (4/154 foetuses from 3/22 litters) when compared to the control (1/158 foetuses from 1/22 litters). Although the incidence of cervical rib in the 1000 mg/kg/d group was higher than the concurrent control in this study, the incidence of cervical rib in historical control groups from 12 studies conducted at HLS between 1997-99 ranged from 0-4 foetuses and 0-2 litters. Furthermore, historical control data (Registration dossier, study report, 2008) indicates that the background foetal and litter incidence of cervical rib in 2800 control litters of CrlCD SD rats ranges from 0-3.7% and 0-16.7%, respectively. Thus, the incidence of cervical ribs in this study is within the historical control background incidence for the SD rat and is not considered to be a treatment related effect. At 500 mg/kg bw/day a slight increase in the incidence of retarded ossification was seen, however when compared to the historical control data, a relationship to treatment was considered equivocal.

There were no indications of an adverse effect of treatment in dams or foetuses in the 250 mg/kg/day group. The no-effect-level for maternal toxicity was concluded to be 1000 mg/kg bw/day. The no-adverse-effect-level for foetal growth and development was 500 mg/kg bw/day and the no-observed-effect-level was 250 mg/kg bw/day.

The NOAEL for maternal toxicity in the pre-natal developmental toxicity study with DEGDB administered by oral gavage from gestation day 6-19, was considered to be 1000 mg/kg bw/day. The NOAEL for foetal growth and development was 500 mg/kg bw/day.

An OECD 414 developmental toxicity study in rabbits was conducted to determine the effect of the test material DEGDB when administered during and beyond the organogenesis phase of gestation (Study report, 2018). The study was conducted according to US EPA, OECD, and EC test guidelines, and in compliance with GLP.

Groups of 22 time-mated female New Zealand White rabbits were treated by oral gavage from days 6 to 28 post-coitum, inclusive, with DEGDB. According to preliminary results obtained in a rabbit dose range-finding (DRF) study, doses up to 375 mg/kg/day during gestation days 6 to 28 resulted in no toxicologically relevant effects on dams or foetuses. Selected dose levels for the main study were therefore 0 (vehicle control), 75, 200 and 500 mg/kg/day. The rabbits of the control group received the vehicle, arachis oil, alone.

In the main study, treatments at 200 and 500 mg/kg/day resulted in two and nine unscheduled maternal deaths, respectively. As this mortality rate showed a clear dose-related response and as no mortality was observed in the control and 75 mg/kg/day groups, this was considered as treatment-related. For the remaining females treated at 200 and 500 mg/kg/day surviving to scheduled necropsy, and for all females at 75 mg/kg/day, no treatment-related findings were noted. No toxicologically relevant changes in the number of pregnant females, corpora lutea and implementation sites, or pre- or post-implementaiton loss, litter size and sex ratio were noted by treatment up to 500 mg/kg/day. No treatment-related foetal external and visceral malformations and variations, and skeletal malformations were noted at the same dose levels. The evaluation of developmental effects at 500 mg/kg/day was slightly compromised by the low number of litters (n=13) available at scheduled necropsy, due to maternal mortality in the high dose group. As consistent results were observed in the available litters, sufficient data was available for a proper toxicological evaluation of developmental toxicity. Treatment at 500 mg/kg/day resulted in significant lower foetal body weights of both sexes, reaching statistical significance for the male foetal weights. In addition, a dose-dependent increased litter incidence of unossified metacarpals and/or metatarsals was noted at 200 and 500 mg/kg/day, reaching statistical significance at 500 mg/kg/day. The incidence at 200 mg/kg/day was higher than the available historical control data.

In conclusion, based on the results in this prenatal developmental toxicity study in New Zealand White rabbits, the maternal and developmental No Observed Adverse Effect Level (NOAEL) for DEGDB was established as 75 mg/kg/day.

On the basis of the findings in the OECD TG 414, OECD TG 416 and a vaginal cornification/uterine weight bioassay, DEGDB is not considered to meet the CLP criteria for classification based on reproductive or developmental effects.

Based on the available information, the eMSCA can conclude that the substance needs not to be classified as reprotoxic.

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Derivation and justification of respective DNELs for reproductive toxicity based on experimentally determined NOAELs both for fertility effects and developmental toxicity are reflected in the Table 9 below

Table 9

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/DMEL**	**Justification/Remarks**
Workers					
Reproductive toxicity (effects on fertility, developmental toxicity)	Long-term systemic effects (inhalation)	Two generation study on reproductive performance (Registration dossier, study report, 2001)). pre-natal developmental toxicity study on rats (Registration dossier, study report, 2000).	NOAEL: 500 mg/kg bw /day (rats, oral route)*	DNEL 5.8 mg/m^3	AF = 150 (allometric scaling “1” x inter-specific correction for metabolic rate “2.5” x intra-species, worker “5” x exposure duration extrapolation “6” x route to route extrapolation “2”
Reproductive toxicity (effects on fertility, developmental toxicity)	Long-term systemic effects (dermal)	Two generation study on reproductive performance (Registration dossier, study report, 2001)). pre-natal developmental toxicity study on rats (Registration dossier, study report, 2000).	NOAEL: 500 mg/kg bw /day (rats, oral route)	DNEL 1.7 mg/kg bw/day	AF = 300 (allometric scaling “4” x inter-specific correction for metabolic rate “2.5” x intra-species, worker “5” x exposure duration default “6”

General population					
Reproductive toxicity (effects on fertility, developmental toxicity)	Long-term systemic effects (inhalation)	Two generation study on reproductive performance (Registration dossier, study report, 2001)). pre-natal developmental toxicity study on rats (Registration dossier, study report, 2000).	NOAEL: 500 mg/kg bw /day (rats, oral route) **	DNEL 1.4 mg/m^3	AF = 300 (allometric scaling “1” x inter-specific correction for metabolic rate “2.5” x intra-species, general population “10” x exposure duration default, sub-acute to chronic “6” x assessment factor (route to route) “2”
Reproductive toxicity (effects on fertility, developmental toxicity)	Long-term systemic effects (dermal)	Two generation study on reproductive performance (Registration dossier, study report, 2001)). pre-natal developmental toxicity study on rats (Registration dossier, study report, 2000).	NOAEL: 500 mg/kg bw /day (rats, oral route)	DNEL 0.8 mg/kg bw/day	AF = 600 (allometric scaling from rat to human “4” x inter-specific correction for metabolic rate “2.5” x intra-species, general population “10” x exposure duration default, sub-acute to chronic “6”

* the dose descriptor starting point = 500 mg/kg bw/day x 1/(0.38 m^3/kg bw/d) x 6.7 m^3/10 m^3 = 881.05 mg/m^3, where:

- NOAEL for repeated dose toxicity through oral route “500 mg/kg bw/day”
- route-to-route extrapolation factor from oral to inhalation “1”
- a standard breathing volume for the rat 0.38 m^3/kg bw/d for 8 hours exposure
- correction factor for 8 hours exposure of workers – basic caloric demand 6.7 m^3
- correction factor for 8 hours exposure of workers – caloric demand under light activity 10 m^3

** the dose descriptor starting point = 500 mg/kg bw/day x 1/(1.15 m^3/kg bw/d) = 434.8 mg/m^3, where:

- NOAEL for repeated dose toxicity through oral route “500 mg/kg bw/day”
- route-to-route extrapolation factor from oral to inhalation “1”
- a standard breathing volume for the rat 1.15 m^3/kg bw/d for 24 hours exposure

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

According to the criteria laid down in the CLP regulation DEGDB is considered not acutely toxic by the oral, dermal and inhalation routes and needs not to be classified, it is non-irritant and not considered a skin sensitizer. For repeated dose toxicity and mutagenicity also no classification is proposed. The available information does not trigger any classification for toxicity to reproduction according to criteria outlined in the CLP chapter 3.7.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and vPvB assessment

On the basis of the available information, the eMSCA considers that the substance is readily biodegradable, not bioaccumulative, and not toxic. The eMSCA can conclude that the substance is not PBT/vPvB.

7.12. Exposure assessment

7.12.1. Human health

DEGDB does not meet criteria for being classified as a hazardous chemical. Therefore according to the REACH Guidance on Information Requirements and Chemical Safety Assessments, including Part A: Introduction to the Guidance Document an exposure assessment is not required and not performed by eMSCA.

7.12.1.1. Worker

No exposure assessment is carried out by eMSCA based on non-classification of the substance.

7.12.1.2. Consumer

No exposure assessment is carried out by eMSCA based on non-classification of the substance.

7.12.2. Environment

No environmental exposure assessment is carried out by eMSCA based on non-classification of the substance and taking into account that DEGDB is readily biodegradable and not bioaccumulative.

7.13. Risk characterisation

7.13.1. Human Health

DEGDB is not classified as a hazardous substance, therefore no risk characterisation assessment is performed by eMSCA.

7.13.2. Environment

No environmental risk characterization is carried out by eMSCA based on non-classification of the substance and taking into account that DEGDB is readily biodegradable and not bioaccumulative.

7.14. Abbreviations

AF - Assessment factor

eMSCA – evaluating Member State Competent Authority

CMR - Carcinogenic, mutagenic or toxic to reproduction

CSR - Chemical Safety Report

DNEL - Derived no-effect level

LEV - Local Exhaust Ventilation

NOAEC - No observed adverse effect concentration

NOEL - No observed effect level

OECD - Organisation for Economic Co-operation and Development

OC – Occupational conditions

PPE - Personal protective equipment

PROC – Process category

RCR – Risk Characterisation Ratio

RMM – Risk Management Measure