LATVIJAS VIDES, ĢEOLOĢIJAS UN METEOROLOĢIJAS CENTRS

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Oxydipropyl dibenzoate

EC No 248-258-5

CAS No 27138-31-4

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

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

- Suspected Reprotoxic;

- Wide dispersive use;

- Exposure of environment and workers;

- High RCR;

- Consumer use;

- High (aggregated) tonnage.

During the evaluation additional concerns were not identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

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

- A Decision on a testing proposal was performed by ECHA on the dossier for evaluation for DPGDB in 2019 (ongoing) covering environment relevant endpoints.

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 and additional information provided by registrant on 28.07.2020, 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

DPGDB 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, DPGDB 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 Oxydipropyl 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 evaluating Member State was able to conclude on every concerned endpoints and found no potential risks, which were controlled inadequately.

7.3. Identity of the substance

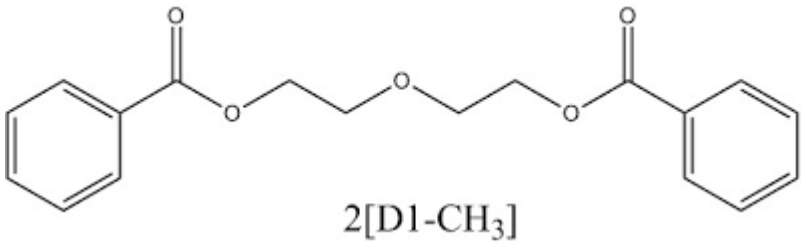
Table 4

SUBSTANCE IDENTITY	
Public name:	Oxydipropyl dibenzoate
EC number:	248-258-5

CAS number:	27138-31-4
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C60H66O15
Molecular weight range:	342.389
Synonyms:	Dipropylene glycol dibenzoate Propanol, 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	-20°C at 101 325 Pa
Boiling point	No boiling point to decomposition temperature, >270°C
Relative density	1.12 at 20°C
Vapour pressure	0,00016 Pa at 25°C
Surface tension	59 nM/m at 20°C
Water solubility	8.69 mg/L at 20°C
Partition coefficient n-octanol/water (Log Kow)	3.9 at 20°C
Flash point	192 °C at 1013 hPa
Flammability	Non flammable (100%)
Explosive properties	Non explosive (100%)
Oxidising properties	Non oxidising (100%)
Viscosity	111 mPa · 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

DPGDB 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)
Manufacture	- Manufacture and use as a process solvent/carrier
Formulation	- Formulation of preparations; - Formulation in materials.
Uses at industrial sites	- Industrial use of adhesives and sealants; - Industrial use of coatings and inks; - Industrial use of lubricants; - Industrial use of plasticizers.
Uses by professional workers	- Professional use of adhesives and sealants; - Professional use of coatings and inks; - Professional use as a carrier for agrochemicals; - Professional use of lubricants; - Laboratory use; - Professional use of plasticizer.
Consumer Uses	- 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.
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

DPGDB is not classified according to CLP Regulation.

7.6.2. Self-classification

- In the registration(s):

Aquatic Chronic 3, H412.

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

Acuatic Chronic 3, H412;
Aquatic Chronic 2 H411;
Eye Irrit. 2 H319;
Repr. 2 H361;
Acute Tox. 4 H302;
Skin Irrit. 2 H315;
Aquatic Chronic 1 H410.

7.7. Environmental fate properties

7.7.1. Degradation

DPGDB is considered to be readily biodegradable according to a Freshwater Modified Sturm Test (OECD 301B). DPGDB was found to have degraded by 6 % after 2 days, 62 % after 12 days, and by 85 % at the end of the 28-day biotic phase of the test. The positive control substance, sodium benzoate, which was analysed contemporaneously degraded rapidly (63% degradation after 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, DPGDB met these criteria, so may be considered to be readily biodegradable.

7.7.2. Environmental distribution

Organic carbon-water partition co-efficient Koc for DPGDB was found to be Koc=3981 at 20° indicating that the substance is rather strongly adsorbed onto soil and its organic matter and does not move easily throughout the soil (slighty mobile according to McCall`s soil mobility classification scheme).

7.7.3. Bioaccumulation

Evidence of a low bioaccumulation potential of DPGDB 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 DPGDB was determined in the studies with freshwater fish rainbow trout and fathead minnows. The substance was introduced using a water accommodated fraction (WAF) and by flow through. The studies were conducted according to EC, OECD, and US EPA test guidelines and in compliance with GLP. The WAF studies suffered from low concentrations of the test substance being measured in the initial WAF solution and subsequent losses of the test substance as well as were giving contradictory results. In its turn, the flow through studies were exhibiting constant exposure levels throughout the studies and the results from both species were similar and in line with QSAR estimations. The results from the flow through studies are being used for the hazard determination. The 96 h LC50 value for DPGDB with fathead minnow was 3.7 mg/L. The no observed effect concentration (NOEC) for DPGDB with fathead minnow was 1.2 mg/L). In addition, the 96 h LC50 value for DPGDB with rainbow trout was >3.0 mg/L. The NOEC for DPGDB with rainbow trout was 3.0 mg/L. These values are supported by the QSAR modelling indicating a value of 3.94mg/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 DPGDB 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 classified in any of the chronic aquatic toxicity categories.

7.8.1.2. Aquatic invertebrates

An acute Daphnia magna immobilisation study was performed to determine the acute toxicity of the DPGDB. 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 DPGDB with Daphnia magna) was determined to be 19.3 mg/L. The no observed effect loading rate (NOELR) was 2.2 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, DPGDB 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 DPGDB on the growth of algae 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 1.1 mg/L and the EL50 (Growth rate 0 - 72 h) was 4.9 mg/L, while the EL50 (Area under the curve 96 h) was 0.95 mg/L and the EL50 (Growth rate 0 - 96 h) was 3.6 mg/L.

According to CLP criteria, DPGDB 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 DPGDB 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 DPGDB on sewage micro-organisms. The study was conducted in accordance with EC, OECD and US EPA test guidelines and in compliance with GLP. DPGDB 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 DPGDB on the growth of the bacteria Pseudomonas putida. Exposure of Pseudomonas putida to DPGDB 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: 3.7 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 fathead minnow: 3.7 mg/l.

Marine water	PNEC marine water: 0.37 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 fathead minnow:3.7 mg/l.
Intermittent releases to water	PNEC intermittent releases: 37 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 fathead minnow:3.7 mg/l.
Sediments (freshwater)	PNEC sediment (freshwater): 1.49 mg/kg sediment dwt or 0.323 mg/kg wwt	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): 0.149 mg/kg sediment dwt or 0.0323 mg/kg wwt	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 wwt	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, DPGDB 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

Based on structural similarity and similar physicochemical properties, Oxydiethylene Dibenzoate (DEGDB CAS 120-55-8) and DPGDB, it is considered that the read-across from target (DPGDB) and source substance (DEGDB) for the endpoints related to basic toxicokinetics is scientifically justified and valid. The eMSCA can support this conclusion.

To investigate the metabolism of DEGDB 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.

An older study on the toxicokinetics of DPGDB (i.e., technical grade Benzoflex 9-88 plasticizer administered to rats) also reported that the substance is rapidly metabolized and excreted, with 70% of the dose excreted via urine (within 48 hours) as hippuric acid and 10% excreted via feces (Butz et al. 1982)

7.9.2. Acute toxicity and Corrosion / Irritation

In two separate studies using rats, the oral LD50 values obtained were 5072 mg/kg bw (male) and 3295 mg/kg bw (female) (Registration dossier, study report, 1998) and 5368 mg/kg bw (male) and 4068 mg/kg bw (female) (Registration dossier, study report, 1975). In study using mouse, the oral LD50 values obtained were 4894 mg/kg bw (male) and 4068 mg/kg bw (female) (Registration dossier, study report, 1975)

Inhalation toxicity testing in rats determined LC50 values of > 200 mg/L/4h (Registration dossier, study report, 1975). The groups of five female and five male rats were exposed to a whole-body aerosol atmosphere containing approximately 200 mg/L of DPGDB for four hours, then observed for 14 days post exposure. Clinical signs seen during the 4 hour exposure period included decreased motor activity, eye squint, erythema, clear nasal discharge, salivation, lacrimation, tachypnea and slight dyspnea. In addition, at the termination of the exposure period both ocular and nasal porphyrin discharge, flaccidity and ataxia were observed.

Lacrimation in a few rats at 7, 8 and 9 days and clear nasal discharge in a few rats at 9, 10, 11 and 14 days.

None of the rats exposed to the test material died during the course of the observation period. On this basis, DPGDB would not be considered a toxic substance by the inhalation route of administration.

A dermal LD50 value > 2000 mg/kg bw (male/female) was determined in a study using rats (Registration dossier, study report, 1998).

Human data on the acute toxicity of DPGDB are not available.

The results of the oral, dermal and inhalation studies indicate that DPGDB needs not to be classified for acute toxicity.

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

The corrosion / irritation property of DPGDB was not evaluated.

7.9.3. Sensitisation

A study, according to Magnusson & Kligman, was performed to determine the potential of DPGDB for skin sensitisation of guinea pigs. The study was conducted according to EPA OTS 7984100 and OECD 406 test guidelines, and in compliance with GLP. Evidence of skin sensitisation was seen in all animals treated by the positive control substance, Hexyl cinnamic aldehyde, confirming the sensitivity of the method. Guinea pigs were treated with stock DPGDB for the intradermal injection (as 50:50 in FCA) and topical induction phases, and stock and 50% in Alembicol D for the topical challenge phase. At the end of the challenge phase, no positive reactions were observed in the test article-treated animals (Registration dossier, study report, 1998h).

According to the criteria laid down in CLP Regulation DPGDB is not considered a skin sensitiser.

Human data on the sensitisation potential of DPGDB are not available.

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

7.9.4. Repeated dose toxicity

According to OECD Guideline 408, Repeated Dose 90-Day Oral Toxicity in Rodents study was performed (Registration dossier, study report, 1999b). Groups of ten rats ((Crl: (IGS) CD BR)) were dosed by dietary administration with DPGDB for a period of 13 weeks at levels 0 (untreated diet control), 250, 1000, 1750, and 2500 mg/kg bw/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 bw/day or below. Dosages of 1750 or 2500 mg/kg bw/day were tolerated but induced clinical findings which were limited to changes in blood parameters, minor treatment-related pathology and/or adverse effects on bodyweight gain. When selected animals previously receiving 2500 mg/kg bw/day were maintained off dose for 4 weeks all treatment related changes showed evidence of or complete recovery.

DPGDB was found to be non-toxic orally under the conditions of this repeated dose toxicity test. The NOAEL was determined at 1000 mg/kg bw/d. Target organs: cardiovascular / hematological: spleen; digestive: cecum.

Based on this data the registrants concluded: According to the criteria laid down in CLP regulation DPGDB is considered as posing no danger of serious health damage by prolonged oral exposure, consequently no classification and labelling is warranted for this endpoint.

Based on the available information, the eMSCA can can agree with this conclusion.

7.9.5. Mutagenicity

In the interest of completeness of the assessment, mutagenicity of DPGDB was assessed but not comprehensively. From the results of the three different in-vitro investigations (gene mutation in bacteria, chromosomal aberration in-vitro and gene mutation in

mammalian cells), 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, DPGDB did not possess estrogenic activity up to and including the maximally tolerated dose (Registration dossier, study report, 1997).

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

In the main study, dietary administration of DPGDB at concentrations of 1000, 3300 or 10000 ppm was generally well tolerated by the P (F0) and subsequent F1 animals and their respective progeny. Bodyweight change of F1 females before paring and F1 males were slightly but significantly lower than in controls.

No adverse effects were seen on overall parental food consumption; food conversion efficiency calculated during the 10 week pre-mating phase was considered similar to controls for both generations.

Oestrous cycle, mating performance, fertility and fecundity were similar in all groups. Gestation lengths and the parturition process were unaffected by treatment. Assessment of the terminal vaginal smears taken from F0 females revealed a higher incidence of females in oestrus in groups treated with DPGDB compared with controls. This finding was not apparent among F1 females and is considered to be of doubtful biological significance.

Litter parameters at birth of the F1 and F2 progeny and their survival to weaning showed no apparent detrimental effects of treatment with DPGDB. However, in both F1 and F2 offspring at 10000 ppm there was a slight reduction on weight gain during days 14-21 of age and this finding may be linked to the transition to direct exposure to the test material as the offspring weaned on to solid diet at the same dietary inclusion levels as their parents.

No treatment related findings were seen at microscopic examination of the F1 offspring not selected to form the next generation or the F2 offspring killed after weaning. Macropathology, histopathology assessment and sperm analysis for the F0 and F1 adults showed no adverse effects of treatment.

The only possible effect of treatment detected at assessment of organ weights from F1 and F2 offspring was significantly 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 F0/F1 adult animals.

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

Effects on development

A pre-natal development study in rats was performed to determine the effect of the DPGDB when administered during and beyond the organogenesis phase of gestation. The study

folloved Japanese, US EPA and OECD test guidelines, and in compliance with GLP (Registration dossier, study report, 2000).
Groups of 22 female rats (Sprague-Dawley) were selected after mating, and were dosed by oral gavage with corn oil fortified with the DPGDB between day 6 and day 19 of gestation. Dose levels examined were 0 (vehicle control), 250, 500, and 1000 mg/kg bw/day. According to preliminary results obtained in rats in a dose range-finding study (Registration dossier, study report, 2000), doses up to 1500 mg/kg/d during gestation days 6 to 19 gave no adverse effect on dams or foetuses, but maternal toxicity was observed at the highest dose. The highest dose used in the main study was therefore 1000 mg/kg/d. The key findings of the study were a) incomplete ossification of the 5th and or 6th sternebrae (considered to be transient in nature rather than representing permanent structural changes and therefore are considered to be of no long-term toxicological importance); b) increase in cervical ribs at 1000 mg/kg bw/day (10/155 foetuses) from 6/22 litters when compared with the controls.
However, cervical ribs are not regarded as a malformation, but as an anomaly that occurs relatively frequently in rats of this strain. The most common type of this anomaly is reversible, disappearing postnatally as cervical vertebral processes (Registration dossier, study report, 2004; Registration dossier, study report, 2018). The presence of a low incidence as in the present study at toxic dose levels of 1000 mg/kg bw/d is not normally regarded as any great toxicological significance.

A prenatal Developmental GLP Toxicity Study was conducted according to test guideline 414. The test substance, dipropyleneglycol dibenzoate (DPGDB), in the vehicle (0.5% carboxymethylcellulose in deionized water) was administered orally by gavage to 3 groups of 24 time-mated female New Zealand White [Hra:(NZW)SPF] rabbits once daily from Gestation Days 7–28 (Registration dossier, study report, 2018). Dosage levels were 100, 250, and 500 mg/kg/day administered at a dose volume of 5 mL/kg. No fetal malformations were attributed to the test substance. Other fetal developmental variations occurred infrequently or at a frequency similar to that in the control group, did not occur in a dose-related manner, and/or were within the Charles River Ashland historical control data ranges, and therefore were not attributed to the test substance. Adverse effects on maternal survival, mean body weight changes, and food consumption were noted in the 500 mg/kg/day group; therefore, a dosage level of 250 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL) for maternal toxicity. Based on lower mean fetal weights at 500 mg/kg/day, a dosage level of 250 mg/kg/day was considered to be the NOAEL for embryo/fetal developmental toxicity when dipropyleneglycol dibenzoate was administered orally by gavage to time-mated New Zealand White rabbits. Importantly, a 10.5% decrease in fetal body weight in the 500 mg/kg/day dosage group reflects the 17% decrease in feed consumption in the dams during the fetal period and therefore this reduced fetal body weight is related to the maternal toxicity that was observed at that dose level.

It can be concluded, these data are sufficient for an adequate hazard and risk assessment. Based on the available data, no classification for fertility and development is justified. No further studies are considered necessary.

Based on the available information, the eMSCA can agree with this conclusion.

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

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					
Repeated dose toxicity	Long-term systemic effects (inhalation)	90-Day repeated dose oral toxicity study on rats ((Registration dossier, study report, 1999b).	NOAEL: 1000 mg/kg bw /day*	DNEL 8.8 mg/m^3	AF = 100 (allometric scaling from rat to human “4” x inter-specific correction for metabolic rate “2.5” x intra-species, worker “5” x exposure duration default, sub-acute to chronic “2”
Repeated dose toxicity	Long-term systemic effects (dermal)	90-Day repeated dose oral toxicity study on rats (Registration dossier, study report, 1999b).	NOAEL: 1000 mg/kg bw /day	DNEL 10 mg/kg bw/day	AF = 100 (allometric scaling from rat to human “4” x inter-specific correction for metabolic rate “2.5” x intra-species, worker “5” x exposure duration default, sub-acute to chronic “2”
General population					
Repeated dose toxicity	Long-term systemic effects (inhalation)	90-Day repeated dose oral toxicity study on rats ((Registration dossier, study report, 1999b).	NOAEL: 1000 mg/kg bw /day**	DNEL 2.2 mg/m^3 ***	AF = 400 (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 “2” x assessment factor (route to route) “2”
Repeated dose toxicity	Long-term systemic effects (dermal)	90-Day repeated dose oral toxicity study on rats (Registration dossier, study report, 1999b).	NOAEL: 1000 mg/kg bw /day	DNEL 5 mg/kg bw/day ****	AF = 200 (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 “2”
Repeated dose toxicity	Long-term systemic effects (dermal)	90-Day repeated dose oral toxicity study on rats (Registration dossier, study report, 1999b).	NOAEL: 1000 mg/kg bw /day	DNEL 5 mg/kg bw/day ****	AF = 200 (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 “2”

* the dose descriptor starting point = 1000 mg/kg bw/day x 1/(0.38 m^3/kg bw/d) x 50%/100% x 6.7 m^3/10 m^3 = 881.1 mg/m^3, where:

- NOAEL for repeated dose toxicity through oral route “1000 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
- workers for inhalation route would be assuming 50% oral absorption and 100% inhalation absorption (instead of 100% absorption for oral route)
- 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 = 1000 mg/kg bw/day x 1/(1.15 m^3/kg bw/d) = 869.6 mg/m^3, where:

- NOAEL for repeated dose toxicity through oral route “1000 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

*** instead of 8.7 mg/m^3 wrongly calculated by registrants

**** instead of 0.22 mg/m^3 wrongly calculated by registrants

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 DPGDB is considered not acutely toxic by the oral, dermal and inhalation routes and needs not to be classified, it is not considered a skin sensitiser. 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

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

The most likely route of human exposure (workers) to DPGDB is through inhalation or dermal contact. Worker exposure can occur in industrial facilities where the substance is used as chemical intermediate. Since this type of activities is mainly undertaken in closed systems, exposure in general is fairly low.

Manufacture of the substance or use occurs as an intermediate or process chemical or extraction agent. It includes recycling/ recovery, material transfers, storage, maintenance and loading (including marine vessel/barge, road/rail car and bulk container).

DPGDB is not classified for human health end-points therefore an assessment of substance exposure risk to human health was not conducted by eMSCA.

The toxicological properties (no classification) of the substance indicate no severe toxicity with regard to possible exposure of workers.

7.12.1.2. Consumer

DPGDB is not classified for human health end-points therefore an assessment of substance exposure risk to human health was not conducted by eMSCA.

The toxicological properties (no classification) of the substance indicate no severe toxicity with regard to possible exposure of consumers.

7.12.2. Environment

Based on non-classification of the substance and taking into account that DPGDB is readily biodegradable and not bioaccumulative exposure assessment was not assessed by eMSCA comprehensively. Taking into account the data specified by the registrant in the registration dossier eMSCA can agree that there is no overall concern for environment exposure. The PECs are derived by the registrants using the EUSES model.

7.13. Risk characterisation

7.13.1. Human Health risk characterisation

Due to physicochemical properties of the substance (vapour pressure = 0.00016 Pa at 25 °C) there is no risk of inhalation for humans expected. DPGDB it is not classified as a hazardous substance, therefore no risk characterisation assessment is performed by eMSCA.

7.13.2. Environmental risk characterisation

Based on non-classification of the substance and taking into account that DPGDB is readily biodegradable and not bioaccumulative exposure assessment was not assessed by eMSCA. However, taking into account the data specified by the registrant in the registration dossier eMSCA can agree that there is no overall concern for environment exposure. Data shows that RCRs for all local exposure scenarios covering all identified uses including the worst case scenario risk characterisation are <1 indicating that in general the environmental exposures are within the acceptable environmental safety levels. RCRs for regional overall combined exposure scenarios are <1 indicating that the environmental exposures are within acceptable environmental safety levels.

7.14. References

Butz RG, Atallah YH, Yu CC, Calo CJ. 1982. Environmental Safety Assessment of Dipropylene Glycol Dibenzoate. Environ Toxicol Chem. 1(4):337-346

7.15. Abbreviations

AF - Assessment factor

CHO – Chinese hamster Ovary cells

EL50 - effective loading rate required to immobilise 50% of test invertebrates;

eMSCA – evaluating Member State Competent Authority

CMR - Carcinogenic, mutagenic or toxic to reproduction

DNEL - Derived no-effect level

LEV - Local Exhaust Ventilation

LC50 - Lethal concentration

LOAEC - Lowest observed adverse effect concentration

NOAEC - No observed adverse effect concentration

NOAEL - No observed adverse effect level

OECD - Organisation for Economic Co-operation and Development

PPE – personal protective equipment

RCR – Risk Characterisation Ratio

SVHC - Substance of very high concern

WCS – workers contributing scenarios