BUREAU FOR CHEMICAL SUBSTANCES

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Dimethyl glutarate

EC No 214-277-2

CAS No 1119-40-0

Evaluating Member State(s): Poland

Dated: 15 October 2015

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2014

Member State concluded the evaluation without any further need to ask for 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

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

Dimethyl glutarate (DMG) was originally selected for substance evaluation in order to clarify suspected risks about:

- endocrine disrupting (ED) properties for the human health (ED properties for environment was not assessed),

- wide dispersive use,

- consumer use

- high aggregated tonnage.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

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	X

4. FOLLOW-UP AT EU LEVEL

4.1. 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** (e.g. change in supported uses, applied risk management measures, etc.)	
*This conclusion can be reached e.g. if the outcome of a test on hazardous properties clarified that substance is not hazardous, the exposure data shows no risk. This can be due to the fact that the data was originally available in the registration dossiers or was obtained due to a substance evaluation decision. **This conclusion can be reached if registrants changed their registrations e.g. the supported uses, applied risk management measures, reduction of the aggregated tonnage, cease of manufacture etc.	

During the evaluation process the particular emphasis was placed on the potential ED properties which could be linked with possible reprotoxicity of DMG. The information on toxicity to reproduction as well as on endocrine disruption submitted in the registration dossier was considered as relevant and adequate. The analysis of data demonstrated no adverse alterations thus in taking into account an ED definition, DMG was not recognized as ED.

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

Dimethyl glutarate (DMG) was originally selected for substance evaluation in order to clarify suspected risks about:

- endocrine disrupting properties
- wide dispersive use
- consumer use
- high aggregated tonnage.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Identity of the substance and physical and chemical properties	The analysis of the presented data revealed lack of HPLC or GC chromatogram. Therefore eMSCA recommends the registration dossier to be updated with the results of the HPLC or GC analysis (chromatograms) or another valid constituent separation technique for quantification of the composition.
Classification and labelling	The substance does not require classification regarding physical properties, health effects and environmental effects.
Environmental fate properties	The submitted information is sufficient for evaluation environmental fate properties. DMG is readily biodegradable, has low potential for adsorption and it is volatile. Bioaccumulation of DMG in aquatic and terrestrial organisms is not expected.
Human health hazard assessment	The submitted study results are sufficient for evaluation of toxicokinetics and health effects of DMG. DMG is expected to be rapidly absorbed into the blood stream following oral exposure, has the potential to be absorbed through the skin, and is expected to be rapidly metabolized, including by olfactory epithelial cells, to methanol, monomethyl glutarate, and glutaric acid. Excretion of DMG's metabolites is expected to be primarily in urine. The substance is of low oral, inhalation and dermal toxicity. DMG is not irritant to the skin and eyes. It is not skin or respiratory sensitiser. The main finding observed following repeated inhalation

	exposure is degeneration/atrophy of the olfactory mucosa. This effect is considered as species dependent and not relevant to humans. From the available data, the eMSCA concludes that there is no evidence that the substance would be carcinogenic, mutagenic or reprotoxic. DMG is not considered to be an endocrine disruptor.
Environmental hazard properties	The submitted information is sufficient for evaluation of short and long-term toxicity to fish, aquatic invertebrates and algae and toxicity to terrestrial compartment and microorganisms. The evaluation of available data indicates that the potential hazard of the DMG, to the environment is moderate to low.
PBT and vPvB assessment	DMG does not meet the criteria for persistence, bioaccumulation and toxicity.

7.2. Procedure

The evaluation was performed based on the registration dossier (IUCLID file) and Chemical Safety Report (CSR) as well as on the other, additional information available in scientific databases and publications.

In assessed endpoints there is a reference to registration dossier not to specific reports included in the dossier, except for cases where data come from scientific publically available information.

All the information was assessed regarding reliability for evaluation of the main grounds of concern and other effects of dimethyl glutarate on human health and the environment. The particular emphasis was placed on the possible endocrine disrupting properties of DMG. Other aspects as physical and chemical properties, environmental fate, human health hazard assessment, environmental hazard assessment, PBT and vPvB assessment have been checked and described in general.

The assessment of exposure was not performed as DMG is not classified according to Directive 67/548 or Regulation 1272/2008 nor PBT or vPvB

The results of the evaluation are documented in this report.

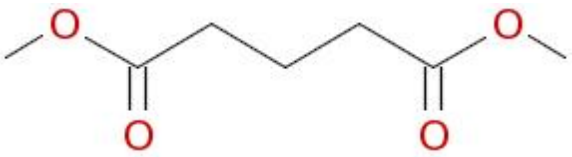
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	dimethyl glutarate
EC number:	214-277-2
CAS number:	1119-40-0
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C7H12O4
Molecular weight range:	160.1678
Synonyms:	Glutaric acid, dimethyl ester, pentanedioic acid

Type of substance **x** 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
Vapour pressure	8.3 Pa at 20 °C
Water solubility	63.1 g/L at 20 °C
Partition coefficient n-octanol/water (Log Kow)	Log Kow (Pow): 0.49 at 20 °C
Flammability	Non flammable
Explosive properties	Non explosive
Oxidising properties	No oxidising properties
Granulometry	Substance is marketed or used in a non solid or granular form
Stability in organic solvents and identity of relevant degradation products	The substance is a solvent and as such it is not used in other solvents
Dissociation constant	Due to its structure it is not justified to estimate the dissociation constant
Viscosity	2.53 mm^2/s at 20°C
Granulometry	Not applicable. Substance is marketed or used in a non solid or granular form.

7.5. Manufacture and uses

7.5.1. Quantities

Table 6: Aggregated tonnage (per year)

☐ 1 – 10 t	☐ 10 – 100 t	**x** 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

Table 7

USES published on ECHA website	Use(s)
Uses as intermediate	Dimethyl glutarate is used as solvent and intermediate.
Formulation	
Uses at industrial sites	Manufacture of dimethyl glutarate Use as an intermediate Formulation & (re)packing of substances and mixtures Uses in Coating Use in Cleaning Agents Use in Oil and Gas field drilling and production operations Lubricants Metal working fluids / rolling oils Blowing agents Use as binders and release agents Use as a fuel Functional Fluids Use in laboratories Polymer Production Rubber production and processing Polymer processing Water treatment chemicals Mining chemicals
Uses by professional workers	Uses in Coating Use in Cleaning Agents Use in Oil and Gas field drilling and production operations Lubricants Metal working fluids / rolling oils Use as binders and release agents Use as a fuel Functional Fluids De-icing and anti-icing applications Road and construction applications Use in laboratories Explosives manufacture & use Polymer processing Water treatment chemicals Use in Agrochemicals
Consumer Uses	Uses in Coating Use in Cleaning Agents Lubricants Use in Agrochemicals Use as a fuel Functional fluids De-icing and anti-icing applications Other Consumer Uses Water treatment chemicals
Article service life	

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

DMG is not classified according to CLP Regulation (Regulation (EC) 1272/2008) criteria.

7.6.2. Self-classification

Self classification notifications for dimethyl glutarate (EC Number: 1119-40-0) are available in the C&L Inventory (http://echa.europa.eu/pl/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/128251). In the following table an overview (dating of January 2015) of notifications for dimethyl glutarate is given.

Classification		labelling		Number of Notifiers
Hazard Class and Category Codes	**Hazard Statement Codes**	**Hazard Statement Codes**	**Pictograms, Signal Word Code**	
Not Classified				587 (joint entry)
Acute Tox. 4	H302	H302	GHS07 Wng	47
Skin Irrit. 2 Eye Irrit. 2 Acute Tox. 3	H315 H319 H331	H315 H319 H331	GHS06 Dgr	18
STOT RE 2	H373 (Respiratory system)	H373	GHS07 GHS08 Wng	16
Acute Tox. 4 Acute Tox. 4 Acute Tox. 4	H302 H312 H332	H302 H312 H332	GHS07 Wng	4
Skin Irrit. 2 Eye Irrit. 2 STOT SE 3	H315 H319 H335 (respiratory organs)	H315 H319 H335	GHS07 Wng	1
Skin Irrit. 2 Eye Irrit. 2 STOT SE 3	H315 H319 H335 (not known)	H315 H319 H335	GHS07 Wng	1
Eye Irrit. 2	H319	H319	GHS07 Wng	1

7.7. Environmental fate properties

DMG is readily biodegradable. The substance has low potential of adsorption onto soil and sediment and it indicates that soil and sediment are not expected to be the main target compartments for exposure assessment. Bioaccumulation of dimethyl glutarate in aquatic and terrestrial organisms is not expected.

7.7.1. Degradation

The read-across method was applied to assess biodegradability of DMG on the basis of study conducted on dibasic esters (DBEs). The dibasic esters are discrete short, straight-chain dicarboxylic acid dimethyl esters that differ by one carbon atom (from four to six carbons) in chain length. The basis for considering dimethyl ester (dimethyl succinate, or DMS), pentanedioic acid, dimethyl ester (dimethyl glutarate or DMG), hexanedioic acid, dimethyl ester (dimethyl adipate or DMA) and the dibasic ester mixture (containing DMS, DMG, and DMA) as a category ("dibasic esters category") is similarities in structure, physicochemical properties, and toxicity (U.S. Environmental Protection Agency Supporting Documents for Risk-Based Prioritization, 2008).
The results indicate that DBE is readily biodegradable. Since DMG is the predominant substance in DBEs it can be concluded that DMG is also readily biodegradable.

7.7.2. Environmental distribution

The log Koc of dimethyl glutarate was calculated using USEPA KOCWIN v. 2.0 and is equal from -0.7176 to 1.0649 (corresponding Koc between 10 to 11.61). These results indicate that dimethyl

glutarate is likely to remain in water and not to adsorb to the organic portion of soils and sediments. Dimethyl glutarate is expected to be highly mobile in soil but this movement will be mitigated by rapid biodegradation.

7.7.3. Bioaccumulation

The calculated log Kow of DMG is =0.49 in 20 °C thus the bioaccumulation in aquatic and terrestrial organisms is not expected.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

The evaluation of available aquatic toxicity data for fish, aquatic invertebrates, and aquatic plants indicates that the potential hazard of the DMG, to aquatic organisms is low.

7.8.1.1. Fish

The data submitted in the registration dossier is suitable for evaluation of acute toxicity studies on fish. The 96-h LC50 value was determined to be 30.9 ppm (DMG) and level >18 - <24 ppm (mixture of DMG and DMS). Based on available results it is concluded that DMG shows moderate acute toxicity, however, this is not sufficient to classify the substance in category of acute (short-term) aquatic hazard for fish. The eMSCA supports this conclusion.
The information used for derivation of PNEC is the LC50 (96h) = 30.9 ppm.
As the substance is not classified as dangerous for the environment, is readily biodegradable and has low potential for bioaccumulation and adsorption onto sediment, the MSCA considers that there is no concern for long term toxicity and does not see the need to request further information.

7.8.1.2. Aquatic invertebrates

The evaluation of that endpoint is based on read-across to a reaction mass of DMA, DMG and DMS. Based on available results it is concluded that even if DMG shows slight acute toxicity to Daphnia magna the result is not sufficient to classify the substance in category of acute (short-term) aquatic hazard for aquatic invertebrates. The MSCA supports this conclusion.

EC50 (48h) > 112 - < 150 ppm (v/v)
NOEC 84 ppm (v/v)
LOEC at 112 ppm (v/v).

As the substance is not classified as dangerous for the environment, is readily biodegradable and has low potential for bioaccumulation and adsorption onto sediment, the eMSCA considers that there is no concern for long term toxicity and does not see the need to request further information.

7.8.1.3. Algae and aquatic plants

No studies with only DMG were available. Thus, the evaluation of that endpoint is based on read-across to a reaction mass of DMA, DMG and DMS. The eMSCA considers that there is no concern for long term toxicity and does not see the need to request further information.

72h EC50 > 85 mg/l,
NOEC equal to 36 mg/L
LOEC equal to 85 mg/L.

7.8.1.4. Sediment organisms

The substance is not classified as dangerous for the environment, is readily biodegradable and has low potential for bioaccumulation and adsorption onto sediment. The eMSCA considers that there is no concern for this endpoint and does not see the need to request further information.

7.8.1.5. Other aquatic organisms

No data.

7.8.2. Terrestrial compartment

The substance is not classified as dangerous for the environment, is readily biodegradable and has low potential for bioaccumulation and adsorption onto sediment. The eMSCA considers that there is no concern for the terrestrial compartment and does not see the need to request further information.

7.8.3. Microbiological activity in sewage treatment systems

The study does not need to be conducted if the substance is readily biodegradable and applied test concentrations are in the range of concentrations that can be expected in the influent of a sewage plant, which is the case. The substance is readily biodegradable and the concentrations used in the biodegradation testing are comparable or higher than the concentrations expected in the inflow of a sewage water treatment plan.
The eMSCA considers that there is no concern and does not see the need to request further information.

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 aqua : 0.031 mg/L	Assessment factor: 1000 Extrapolation method: assessment factor Fish are the most sensitive (i.e. showing the lowest EC/LC50 value). According to the guidance on information requirements and chemical safety assessment - chapter R10: characterisation of dose [concentration]-response for environment (ECHA 2008), a safety factor of 1000 should be applied to the lowest EC50 value. The 96h LC50 value of the most sensitive species (i.e. Lepomis macrochirus) has been determined to 30.9 ppm. As the relative density of the substance is close to one a value of 30.9 mg/L has been used for the 96hLC50 value.
Marine water	PNEC aqua (marine waters)>: 0.0031 mg/L	Assessment factor: 10000 Extrapolation method: assessment factor No experimental data are available on saltwater species. According to the guidance on information requirements and chemical safety assessment -chapter R10: characterisation of dose [concentration]-response for environment (ECHA 2008), the PNEC are estimated from the results obtained on freshwater species and applying an additional assessment factor of 10.

Intermittent releases to water	PNEC aqua (intermittent releases): 0.31 mg/L	Assessment factor: 100 Extrapolation method: assessment factor According to the guidance on information requirements and chemical safety assessment - chapter R10: characterisation of dose [concentration]-response for environment (ECHA 2008), if intermittent release is identified for a stage of the life cycle, only short-term effects need to be considered for risk characterisation of that stage (only for the aquatic compartment); in this case, the assessment factor can be reduced from 1000 to 100.
Sediments (freshwater)	PNEC sediment (sediment freshwater): 0,15 mg/kg sediment dw	Extrapolation method: partition coefficient No data on sediment organisms is available. According to the guidance on information requirements and chemical safety assessment - chapter R10: characterisation of dose [concentration]-response for environment (ECHA 2008), in the absence of any ecotoxicological data for sediment-dwelling organisms, the PNECsed may be provisionally calculated using the equilibrium partitioning method (EPM). This method was used as outlined in the May 2008 version of Chapter R. 10 of the REACH guidance documents. The derived PNEC-freshwater of 0.031 mg/L was used along with a Koc value of 11.61 L/kg and default values from the guidance.
Sediments (marine water)	PNEC sediment (marine water): 0.015 mg/kg sediment dw	Extrapolation method: partition coefficient No data on sediment organisms is available. According to the guidance on information requirements and chemical safety assessment - chapter R10: characterisation of dose [concentration]-response for environment (ECHA 2008), in the absence of any ecotoxicological data for sediment-dwelling organisms, the PNECsed may be provisionally calculated using the equilibrium partitioning method (EPM). This method was used as outlined in the May 2008 version of Chapter R. 10 of the REACH guidance documents. The derived PNEC-marine water of 0.0031 mg/L was used along with a Koc value of 11.61 L/kg and default values from the guidance.
Sewage treatment plant	PNEC STP>: 10 mg/L	Extrapolation method: assessment factor According to the guidance on information requirements and chemical safety assessment - chapter R10: characterisation of dose [concentration]-response for environment (ECHA 2008), the

		PNECstp is usually derived from results obtained in the most sensitive test system available, regardless of whether this is a test with activated sludge, relevant bacteria or ciliated protozoa. If no standard microbial inhibition test data are available, which is the case here, the PNECstp can also be derived from available ready biodegradability test. An assessment factor of 10 is applied to the test concentration at which no toxicity to the inoculum was observed (i.e. around 100 mg/L).
Soil	PNEC soil: 0.113 mg/kg soil dw	Extrapolation method: partition coefficient No data on soil organisms is available. According to the guidance on information requirements and chemical safety assessment - chapter R10: characterisation of dose [concentration]-response for environment (ECHA 2008), in the absence of any ecotoxicological data for soil organisms, the PNECsoil may be provisionally calculated using the equilibrium partitioning method (EPM). This method was used as outlined in the May 2008 version of Chapter R. 10 of the REACH guidance documents. The derived PNEC-freshwater of 0.31 mg/L was used along with a Koc value of 11.61 L/Kg, a Henry's Law Constant (H) of 0.0745 Pa-m3/mole, and default values from the guidance.
Secondary poisoning	No potential for bioaccumulation	Based on the low potential of bioaccumulation of the substance, no PNECoral has been derived.

7.8.5. Conclusions for classification and labelling

DMG does not require classification for physical-chemical properties and environmental hazard. Self classification of DMG is available in the C&L Inventory (http://echa.europa.eu/pl/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/1282510 (for details see: 7.6.2 Self-classification).

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

The data submitted in the registration dossier is considered to be sufficient for evaluation of toxicokinetics of DMG.
Dimethyl glutarate is expected to be rapidly absorbed into the blood stream following oral exposure, has the potential to be absorbed through the skin, and is expected to be rapidly metabolized, including by olfactory epithelial cells, to methanol, monomethyl glutarate, and glutaric acid. Excretion of DMG's metabolites is expected to be primarily in urine.
Main ADME results:

absorption	Estimated to be rapid.
distribution	Estimated to be blood flow limited to aqueous compartments.
metabolism	Estimated metabolites include: methanol, monomethyl glutarate, and glutaric acid.
excretion	Estimated to be excreted primarily in urine.

DMG has no bioaccumulation potential.

7.9.2. Acute toxicity and Corrosion/Irritation

The data submitted in the registration dossiert is suitable for evaluation of acute toxicity of DMG. The substance is of low oral, inhalation and dermal toxicity. DMG is not irritant to the skin and eyes. Based on the available information, the eMSCA concludes that classification is not required

Oral: LD_{50} > 5000 mg/kg for rats
Inhalation: LC_{50} > 11.0 mg/l/1 hr for rats
Dermal: LD_{50} > 2000 mg/kg for rats

7.9.3. Sensitisation

The data submitted in the registration dossiert is suitable for evaluation of the skin sensitization. DMG can be concluded as not being sensitizing for the skin.

7.9.4. Repeated dose toxicity

In the submitted subchronic or subacute inhalation toxicity studies the rats were exposed to different concentration of DMG, DMA and DMS as such and in mixture of DBEs. The used concentrations are set in the table below:

Concentration	Reference
Subchronic DMG - 0, 0.01, 0.05, 0.4 mg/L DMA - 0.4 mg/L DMS - 0.4 mg/L	Study report, 2000
Subchronic DBEs mixture (DMG: 66.56%, DMS: 16.9%, DMA: 16.5%) - 0.02, 0.076, 0.39 mg/L - 0.16, 0.40, 1.0 mg/L	 - Study report, 1987a - Study report, 1987b
Subacute DBEs mixture (DMG: 41-60%, DMS: 20-30%, DMA: 20-30%) - 0.1, 0.3, 1.0 mg/L	Study report, 1981

In the key study (study report, 2000) the main findings were degeneration/atrophy of the olfactory mucosa at 0.4 mg/L, decrease in serum testosterone concentrations at 0.05 or 0.4 mg/L DMG, decrease in serum luteinizing hormone (LH) concentrations observed in males exposed to 0.4 mg/L DMG and increase of epididymal sperm counts in males exposed to 0.05 or 0.4 mg/L DMG. The observed hormonal variations, described above, are considered to be of no toxicological significance (See 7.10. Assessment of endocrine disrupting (ED) properties). Olfactory epithelial lesions similar to those seen in the key study were observed at 0.076, 0.39 mg/L in rats males and females, but also in females exposed to 0.02 mg/L (study report, 1987a) and in male and female rats that were exposed to 0.16, 0.40, 1.0 mg/L of DBE (study report, 1987b). The other effects included decreased liver weight in female rats following exposure to mixture of DBEs at 0.16, 0.39, 0.40, 1.0 mg/L and males at 1.0 mg/L and slight increase in relative heart and testes weights in males, slight decrease in absolute spleen weights in males, and a slight decrease in absolute spleen weight in females (study report 1987b).

In the subacute inhalation toxicity study (study report 1981), clinical and pathological observations showed no-compound related changes between exposed groups except the reduction of liver weight in rats at 1 mg/L which recovered after 14 days and were not accompanied by any histopathological changes and thus were not considered to be of biological significance.

Taking into account the available information it can be concluded that the main finding observed following inhalation exposure in all presented studies is degeneration/atrophy of the olfactory mucosa. This effect is considered as species dependent and not relevant to humans (Trela et al,1991, 1992, Morris et al, 1991, Bogdanffy et al, 1991, Keenan, 1990, registration dossier).

The data submitted in the registration dossier is considered suitable for evaluation of toxicity after repeated inhalation exposure.

The following values are taken into account for risk assessment:

- Oral route (14 days, rat): NOAEL = 980 mg/kg bw
- Dermal route (14 days, rat): NOAEL = 1000 mg/kg bw
- Inhalation (90 days, rat): NOAEC (respiratory local toxicity) = 50 mg/m^3

Based on the available information, the eMSCA concluded that classification is not required.

7.9.5. Mutagenicity

DMG was negative in a bacterial reverse mutation assay on Salmonella typhimurium with or without metabolic activation in mammalian chromosome aberration test without metabolic activation (reaction mass of DMA, DMS and DMG) and in mammalian cell gene mutation assay. No genotoxicity was observed in micronucleus assay (studies included in registration dossier).
Based on the available information, the eMSCA concludes that there is no concern for mutagenicity.

7.9.6. Carcinogenicity

No information is included in the registration dossier. Environmental Protection Agency (EPA) has evaluated the available toxicity data on dimethyl esters of glutaric acid (2014, data publicly available). Using in silico system DEREK for assessing the potential carcinogenicity it was concluded that DMG did not show any special alerts. Therefore EPA does not expect DMG to be carcinogenic. The eMSCA supports this conclusion.

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

Effects on fertility

The report includes reliable experimental one-generation study results following inhalation exposure of rats (parental generation) to a mixture of DBEs (65.1% of DMG, 17.8% of DMS and 16.8% of DMA) at the concentrations of 0.16, 0.40 and 1.0 mg/L for 14 weeks (study report, 1988). The exposure was continued during the gestation and lactation. Offsprings were not exposed to DBEs.

The exposure to 1.0 mg/l of DBEs resulted in a slight decrease of body weights of male and female parental generation animals and their pups. Other differences related to the slight weight changes of some organs (liver, heart, kidneys or brain) were incidental and not dose-related. They could be a result of a slight body weight differences between test and control groups and were not considered to be of biological significance.

The histopathologic examination of parental animals showed in all exposed groups squamous metaplasia of olfactory epithelium which is the known symptom of exposure to DBEs.

The exposure to DBEs did not affect the following reproduction parameters: male and female fertility index, born-alive index, viability index, lactation index and gestation index.

Certain reproduction parameters as oestrus cycle or sperm measures or histopathology of reproductive organs were not evaluated in the study.

These information may be complemented by the results of a 90-day subchronic inhalation toxicity study following exposure to DMG at the concentrations of 0, 0.01, 0.05, and 0.4 mg/L as well as DMS and DMA (separately) at the concentration of 0.40 mg/L for 90 days (study report, 2000).

In this study the following parameters related to reproduction were evaluated: serum concentrations of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) in males and serum concentrations of estradiol and progesterone in females, sperm parameters as morphology and motility and estrous cycle.

In males exposed to 0.05 and 0.4 mg/L of DMG serum testosterone concentration was significantly decreased in comparison to the control group. Serum LH concentration was decreased following exposure to 0.4 mg/L of DMG. These alterations were accompanied by the increase of epididymal sperm counts observed at 0.05 and 0.4 mg/L of DMG and 0.4 mg/L of DMS. The increase in epididymal sperm counts was also observed for DMA although the effect was not statistically significant. Due to a similar trend, this finding was considered compound-related. The decrease of testosterone concentration at the two highest concentrations of DMG is probably a consequence of the decrease of the LH level. The standard physiological answer to that should be a damage of spermatogenesis and finally a decrease in sperm count. In the discussed study such an effect was not noted. Other sperm parameters were not affected by the exposure. Serum concentration of FSH was not changed. The exposure to DMA and DMS did not result in hormonal alterations. Histopathological examination showed no changes in male reproductive organs. There were no compound-related effects on female estrous cycle.

In the registration dossier two prenatal developmental toxicity studies were submitted. In one of them pregnant female rats were exposed via inhalation to a mixture of DBEs (65.1% of DMG, 17.8% of DMS and 16.8% of DMA) at the concentrations of 0.16, 0.40 and 1.0 mg/L from 7 to 16 days of gestation (study report, 1995). No fetal effects were detected following the exposure hence the NOAEC determined in this study is 1 mg/L.

Another prenatal developmental toxicity study conducted on rabbits via inhalation (at the concentrations of: 0.03, 0.1, 0.3 and 1 mg/L of DMG) indicated no compound-related effects on maternal reproductive functions (study report 2003). The only maternal effect was reduced body weight gain due to reduction of feed consumption. The viability and fetal sex ratio or fetal malformations were not altered by the exposure to DMG. At the concentration of 1 mg/L there was a decrease in the mean number of nidation sites. Considering that in this group a lower mean corpora lutea count was found and that the implantation had occurred before the exposure started, it is concluded that this effect was not exposure-related. Consequently, the decrease in the number of nidation sites resulted in a slightly reduced number of fetuses at 1 mg/L group.

No substance related fetal variations was observed following the exposure. The only effect was an increase in retarded sternebral ossification at 1 mg/L which was considered to be due to an unusually low control group value compared to relevant historical control group data.

The effects of DBEs on reproduction was evaluated based on the results of inhalation exposure to DMG, DMA or DMS separately or in mixture of these three substances. As inhalation is the most relevant route of exposure the studies provided sufficient information on the reprotoxic properties of the substances. All studies presented above were performed according to or equivalent or similar to OECD guidelines and GLP requirements with reliability of 1. They are considered acceptable. The results indicate that the exposure to DBEs does not impair reproductive function in males and females as well as has not impact on the development of fetuses.

Taking into account all available information the eMSCA concludes that there is no concern for reproductive toxicity of DMG.

7.9.8. Hazard assessment of physico-chemical properties

DMG is not explosive, not highly flammable in contact with water and has no oxidizing properties.

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

In the absence of acute toxic effect, skin and eye irritation/corrosion, skin sensitisation and effects on fertility or prenatal development leading to Classification & Labelling, no specific DNELs were derived for these endpoints.

No DNEL for repeated dermal exposure was established as the substance is a solvent and repeated exposure might be expected to be irritating to the skin under the occlusive conditions of the study due to the drying and de-fatting of the skin by the solvent. The study protocol used a 6-hour occlusive exposure to the skin for 14 days. Such an exposure condition is designed to ensure the best uptake of the compound through the skin, however it does not represent realistic exposure conditions. The LOEL for irritation from this study is not relevant to a human exposure scenario and therefore cannot be used as a relevant basis for the calculation of a dermal DNEL for local effects.

The starting point for calculation DNEL for repeated inhalation exposure was NOAEC of 50 mg/m^3 established in 90-days study. After applying the relevant assessment factors, a DNEL value of 8.3 mg/m^3 was derived.

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**
Repeated dose toxicity	inhalation	Subchronic, rat	NOAEC: 50 mg/m^3 Target organs: respiratory tract: olfactory mucosa degeneration	DNEL=8.3 mg/m^3	Assessment factors: 3 for intraspecies differences, 2 for time extrapolation

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

According to the classification criteria of Directive 67/548/EEC and Regulation (EC) No. 1272/2008) DMG does not require classification for acute toxicity. DMG is not irritant to the skin and eyes.
DMG proved not to be mutagenic in prokaryotes when tested for gene mutation in bacterial reverse mutation assay and in mammalian cell gene mutation assay. In vivo, a micronucleus assay indicated no genotoxic effect.
DMG proved not to be carcinogenic or reprotoxic.

Acute toxicity oral:	LD50 > 5000 mg/kg
Acute toxicity dermal:	LD50 > 2000 mg/kg
Acute toxicity inhalation:	LC50 > 11.0 mg/l
Irritation /Corrosivity-skin:	not irritating
Irritation /Corrosivity-eye:	not irritating
Sensitisation skin:	not sensitising
Sensitisation respiratory tract:	not sensitising
Repeated dose toxicity: sub-acute	
oral:	NOAEL: 980 mg/kg bw/day (subacute)
dermal:	NOAEL: 1000 mg/kg bw/day (subacute)
inhalation:	NOAEC: 50 mg/m3 (subchronic)
Mutagenicity:	not mutagenic
Carcinogenicity:	not carcinogenic
Reprotoxicity:	not reprotoxic, NOEC: 1000 mg/m3

7.10. Assessment of endocrine disrupting (ED) properties

One of the concerns indicated in the justification for the selection of DMG as a candidate CoRAP substance is potential impact on the endocrine system. The assumption of such properties is based on the results of a rat inhalation study in which a decrease in testosterone and luteinizing hormone was observed.

The starting point for discussion on the possible endocrine disrupting properties of the substance were the results of a subchronic inhalation study (study report, 2000) and reproductive toxicity

studies (study reports, 1988, 1995 and 2003) in context of the ED [2] definition adopted by European Commission.
According to this definition a substance can be considered to be an ED when the link between endocrine properties and an adverse effect is proved. The adverse effect means change in morphology, physiology, growth, life span, development, reproduction which results in impaired functional capacity, to compensate for additional stress or increased susceptibility to other environmental influences (WHO, 2004).

The hypothesis of an endocrine disrupting activity of DMG was based on the results of a study indicating a decrease in serum testosterone and LH concentration in rats. The observed changes could indicate possible reproductive disorders. However, the decrease of testosterone and LH level did not affect sperm parameters as morphology and motility. Furthermore, an increase of epididymal sperm counts was demonstrated in the study. This effect was contrary to the standard physiological answer which should be a damage of spermatogenesis and finally a decrease in sperm count. Therefore reduction of testosterone and LH concentration was considered to be of low toxicological significance.

Another study conducted with a mixture of DBEs (65.1% of DMG, 17.8% of DMS and 16.8% of DMA) at concentrations of 0.16, 0.40 and 1.0 mg/L for 14 weeks (study report, 1988) during gestation and lactation (one-generation study) indicated no effects on the reproduction parameters male and female fertility index, born-alive index, viability index, lactation index and gestation index. The observed results included a slight decrease of body weights of male and female parental animals exposed to 1.0 mg/L of DBEs and their pups and squamous metaplasia of olfactory epithelium in all exposed parental groups.

The available prenatal developmental toxicity studies revealed no fetal effects in rats exposed to a mixture of DBEs at the concentrations of 0.16, 0.40 and 1.0 mg/L as well as rabbits exposed to 0.03, 0.1, 0.3 and 1 mg/L of DMG. The only observed changes were slightly reduced mean numbers of live fetuses or an increase in retarded sternebral ossification, both at 1 mg/L (rabbits), and were considered not to be associated with the exposure. The effects were attributed to a lower number of corpora lutea and the result of an unusually low control group values compared to relevant historical control group data.

There were also no compound-related effects on male reproductive organs and female estrous cycle as well as on the viability and fetal sex ratio or fetal malformations following a 90-day subchronic inhalation toxicity study on rats. No substance related fetal variations were observed following the exposure. The only effect was an increase in retarded sternebral ossification at 1 mg/L which was considered to be due to an unusually low control group value compared to relevant historical control group data. No evidence of systemic toxicity (except a slight decrease of body weight) that could be considered treatment-related was noted. The lack of systemic toxicity was confirmed in subchronic inhalation toxicity studies (study reports, 1987a and 1987b) and in a subacute inhalation toxicity study (study report, 1981). In these studies the rats were exposed to different concentration of DBEs mixture ranged between 0.02-1.0 mg/L. No effects on clinical chemistry or histopathology were demonstrated in these studies. The study results are described in Point 7.9.4. Repeated dose toxicity.

The data presented above are deemed acceptable by the eMSCA due the high reliability, relevant route of exposure and suitable assessed parameters. The test results reflect the effects of exposure on reproduction parameters, the state of the parental generation and offspring and fetal development. Based on the observations of decreased testosterone and LH levels the above parameters could have been impaired following potential endocrine activity of DMG. This initial hypothesis was considered taking into account the available information and ED definition

The analysis of the data demonstrated that the hormonal changes observed in one study did not lead to further reproductive and developmental disorders. Some alterations observed did not fulfil the "adversity" criterion of the ED definition. In fact the findings were considered to be not adverse as they did not represent functional impairment in the test organism. Based on the above the eMSCA concludes that there is no concern for endocrine disrupting properties of DMG

[2] An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations (WHO/IPCS, 2002).

7.10.1. Endocrine disruption – Environment

Not evaluated because this was not in the area of initial concern.

7.10.2. Endocrine disruption - Human health

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

One initial concern listed in the justification for the selection of DMG as a candidate CoRAP substance was related to the potential effect of DMG on the endocrine system. Due to these potential endocrine disrupting properties DMG should have shown reproductive and/or developmental toxicity in the available studies. This hypothesis was not confirmed by the data – detected changes were of weak biological significance and were not related to the impairment of reproductive functions.

The analysis of the study results led to the conclusion that the observed effects could not be considered as "adverse" in the meaning of the adopted ED definition. Thus as the important criterion of the definition is not fulfilled the eMSCA concludes that there is no concern for endocrine disrupting properties for DMG.

7.11. PBT and VPVB assessment

Conclusion for the persistence (P) criterion

DMG does not meet the criteria for persistence.

Conclusion for the bioaccumulation (B) criterion

DMG does not meet the criteria for bioaccumulation.

Conclusion for the toxicity (T) criterion

DMG does not meet the criteria for toxicity.

7.12. References

Study reports included in registration dossier for Dimethyl Glutarate.

Federal Register/Vol. 79, No. 3 /Monday, January 6, 2014 /Rules and Regulations http://regulations.justia.com/regulations/fedreg/2014/01/06/2013-31582.html

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7.13. Abbreviations

CLP – Classification, Labelling and Packaging
CoRAP – Community Rolling Action Plan
CSR – Chemical Safety Report
DBE – dibasic esters
DMA – dimethyl adipate
DMEL - Derived Minimal Effect Level
DMG – dimethyl glutarate
DMS – dimethyl succinate
DNEL – Derived No Effect Level
ED – Endocrine Disruptor
EPA – Environmental Protection Agency
GC – Gas Chromatography
HPLC – High-Performance Liquid Chromatography
LOEL – Lowest Observed Effect Level
MSCA – Member State Competent Authority
NOAEC - No Observed Adverse Effect Concentration
NOAEL – No Observed Adverse Effect Level
PBT – persistent, bioaccumulative, toxic
SVHC – Substance of Very High Convern
vPvB – very persistent, very bioaccumulative