SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Dimethyl disulphide

EC No 210-871-0

CAS No 624-92-0

Evaluating Member State(s): Germany

Dated: July 2017

Evaluating Member State Competent Authority

BAuA
Federal Institute for Occupational Safety and Health
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Year of evaluation in CoRAP: 2014

Before concluding the substance evaluation a Decision to request further information was issued on: 27 April 2016
Based on the registration updates provided by the registrant and further information supplied during the follow-up phase, the evaluating Member State concluded the evaluation without the need for further information requirements according to Article 46(1).

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

Dimethyl disulphide (DMDS) was originally selected for substance evaluation in order to clarify concerns about:

- Exposure of environment and related risks for the individual environmental compartments

- High (aggregated) tonnage

- Other exposure/risk based concern

During the evaluation also other concerns were identified:

In the registration dossier DMDS has been self-classified for acute oral, inhalation and dermal toxicity, eye, skin and respiratory tract irritation, skin sensitisation and for reproductive toxicity.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Dimethyl disulphide has been subject to dossier evaluation by ECHA and a decision on a testing proposal for this substance was issued on 6 February 2012 requiring the testing of viscosity as required in Annex IX, 7.17 according to OECD guideline 114.

A proposal for harmonised classification and labelling of dimethyl disulphide has been prepared by industry according to CLP art. 37(2). In agreement with CLP art. 37(4), the ECHA Risk Assessment Committee (RAC) "(...) shall adopt an opinion on any proposal submitted pursuant to paragraphs 1 or 2 within 18 months of receipt of the proposal." The date of receipt of the CLH dossier for dimethyl disulphide was 16 May 2017.

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	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	X

No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

The eMSCA has evaluated the available hazard data on DMDS and regards the following classification as appropriate for the substance:

Table 1

CLASSIFICATION AND LABELLING FOR DMDS AS CONSIDERED APPROPRIATE BY THE EVALUATING MEMBER STATE COMPETENT AUTHORITY			
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Pictograms, Signal Word**	**Specific Concentration limits, M-Factors**
Acute Tox. 3	H301: Toxic if swallowed	GHS06: Skull and crossbones; Danger	
Acute Tox. 3	H331: Toxic if inhaled	GHS06: Skull and crossbones; Danger	
Eye Irrit. 2	H319: Causes serious eye irritation	GHS07: Exclamation mark; Warning	
Skin Sens. 1B	H317: May cause an allergic skin reaction	GHS08: Health Hazard; Danger	
STOT SE 3	H335: May cause respiratory irritation	GHS07: Exclamation mark; Warning	
Aquatic Acute 1	H400: very toxic to aquatic life	GHS09: environment; Warning	M = 1
Aquatic Chronic 1	H4110: very toxic to aquatic life with long lasting effects.	GHS09: environment; Warning	M(chronic) = 10

During the course of the evaluation, a proposal for harmonised classification and labelling of DMDS was submitted by ARKEMA France to the Agency according to Art. 37(2) CLP (cf. Table 10).[2] The eMSCA considers an entry in Annex VI of CLP for DMDS as appropriate to warrant the safe use of the substance. However, it should be noted that the CLH proposal for acute oral toxicity deviates from the classification considered appropriate by the eMSCA. The eMSCA considers that the available data warrants classification as Acute Tox. 3, H301.

[2] Link to the CLH report on ECHA website: https://echa.europa.eu/documents/10162/31cfdcb9-cd91-2c73-e864-8977ac989a75

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

Not applicable on the basis of the current information.

4.1.3. Restriction

Not applicable on the basis of the current information.

4.1.4. Other EU-wide regulatory risk management measures

Some companies registered dimethyl disulphide as a transported isolated intermediate according to Art. 18 REACH. During the substance evaluation the eMSCA has evaluated the information provided within these registrations and concludes that some of the uses currently covered by these registrations should not be considered as intermediate uses.

The concerned uses are:

- Use of DMDS in refineries as hydrotreating catalyst activator
- Use of DMDS in petrochemical sites as anti-coking agent
- Use of DMDS for propane dehydrogenation

According to the ECHA "Guidance on intermediates" and in the eyes of the eMSCA these uses of DMDS have to be regarded as non-intermediate and therefore the reduced information requirements according to REACH Art. 18 cannot be claimed for the registration of DMDS for these uses. It should be noted that the status claimed for very similar uses differs between registrations with some registrants claiming DMDS as an intermediate within the scope of these uses while other registrants maintain a full registration with exposure scenarios and further description for the respective uses in their registration.

The eMSCA is of the opinion that the registration status of the corresponding registrations has to be changed to a full registration.

The registrations of DMDS according to Article 18 REACH encompassing these uses therefore deviate from the ECHA "Guidance on intermediates". Thus, in the eyes of the eMSCA they may be not compliant with the REACH Regulation which may potentially lead to an increased risk for human health and/or the environment due to the inherent hazard properties of DMDS detailed in this report.

The eMSCA will inform the National Enforcement Authorities (NEAs) via PD NEA (Portal Dashboard NEA) via the Forum for Exchange of Information on Enforcement (Forum) about this deviation in the registration status.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

The review of information on operational conditions and related environmental exposure during the evaluation period raised doubts regarding the assumed efficiency of the waste water treatment process in the exposure assessment for the use of dimethyl disulphide as intermediate for production of other chemicals. Since no descriptive information about the treatment process was available the eMSCA was not able to conclude whether the assumed efficiency could be regarded as realistic or whether downstream users might be

able to achieve it. The description of operational conditions and related predicted environmental concentrations and risks were regarded as being plausible from the eMSCA's perspective.

Following a request for further information in a substance evaluation decision prepared by the eMSCA, the registrant provided a site specific assessment for the only downstream user undertaking the application as intermediate for production of other chemicals.

The provided information on applied tonnage, site specific operational conditions and monitoring data for concentration of DMDS in the effluent of the site's waste water treatment plant was considered as acceptable by the eMSCA. The eMSCA was able to assess a more reliable environmental exposure assessment in the follow-up. The revised predicted exposure concentrations (PECs) in the different environmental compartments were compared to the predicted no effect concentrations (PNECs) which were derived by the eMSCA. The PEC: PNEC ratio was below the trigger value of 1 in every single compartment – therefore, no unfavourable effects on organisms are expected.

Based on the current knowledge there is no indication regarding unacceptable risks for organisms in the environment from the registered uses of DMDS.

5.2. Other actions

Not applicable.

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

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLH dossier: classification for acute oral and inhalation toxicity, eye and respiratory tract irritation and for skin sensitisation, acute and chronic aquatic hazard according to CLP	23/05/2017-07/07/2017 (Duration of public consultation)	Industry
Information of NEAs through the Forum	11/2017	eMSCA

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

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

- Exposure of environment and related risks for the individual environmental compartments

- High (aggregated) tonnage

- Other exposure/risk based concern

During the evaluation also other concerns were identified. The additional concerns were:

- In the registration dossier dimethyl disulphide has been self-classified for acute oral, inhalation and dermal toxicity, eye, skin and respiratory tract irritation, skin sensitisation and for reproductive toxicity.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Abiotic degradation: hydrolysis	Concern not substantiated after registrant had provided further information. No further action.
Abiotic degradation: photolysis	No additional concern identified. No further action.
Biotic degradation: screening tests	No additional concern identified. No further action.
Biotic degradation: simulation tests (water and sediments)	No additional concern identified. No further action.
Biotic degradation: simulation tests (soils)	No additional concern identified. No further action.
Environmental distribution: Adsorption/desorption	Concern not substantiated after registrant had provided further information. No further action.
Environmental distribution: volatilisation	No concern identified but has an impact on interpretation of studies on substance properties.
Environmental distribution: modelling results	No concern identified. Depending on route of initial release all environmental compartments might be exposed. No further action.
Bioaccumulation	No concern identified due to high volatility and low log Kow. No further action.

Toxicokinetics (absorption, metabolism, distribution and elimination)	No concern identified. No further action.
Acute toxicity: oral, inhalation, dermal	Concern for acute dermal toxicity not substantiated. Concern for acute oral and inhalation toxicity confirmed; harmonised C&L process ongoing.
Irritation: Skin	Concern not substantiated. No further action.
Irritation: Eye	Concern for serious eye irritation confirmed; harmonised C&L process ongoing.
Irritation: Respiratory tract	Concern for respiratory irritation confirmed; harmonised C&L process ongoing.
Skin sensitisation	Concern for skin sensitisation confirmed; harmonised C&L process ongoing.
Reproductive toxicity	Concern not substantiated. No further action.
Environmental hazards	No additional concern identified; harmonised C&L process ongoing.
PBT and vPvB assessment	No additional concern identified due to low potential for bioaccumulation; no further action.
Exposure of environment and related risks for the individual environmental compartments	Concern clarified after submission of additional information by registrant(s). No further action.

The eMSCA has concluded that the existing information on the human health toxicity of dimethyl disulphide indicates that the substance fulfils the criteria for classification and labelling for acute oral and inhalation toxicity, eye and respiratory tract irritation and for skin sensitisation according to CLP (Table 3).

7.2. Procedure

The substance was identified by the German Member State Competent Authority (MSCA) to be of high concern for the environment because of the high aggregated tonnage from the individual registrations and the expected high emissions to the environment. As the substance is regarded to have a very low Predicted No Effect Concentration (PNEC) for environmental species, even low concentrations in the environment might cause undesired effects in the different environmental compartments. Therefore in May 2013 dimethyl disulphide was proposed for substance evaluation in accordance with article 44(1) of the Regulation (EC) No 1907/2006 (REACH Regulation).

On 2014-03-26 ECHA published the CoRAP and initiated a substance evaluation of dimethyl disulphide. During the process of substance evaluation all data available by October 2014 were taken into account.

The evaluation of the environmental fate and pathways and ecotoxicological information has been based on data presented by the registrants IUCLID Dossiers, and Chemical Safety Report (CSR 03/2014). In addition, information from the evaluation as new active substance under the Plant Protection Products Regulation (EC) 1107/2009 (Active Substance evaluation) has been considered.

The evaluation of the human health toxicity has mainly been based on data presented in the registration dossier by the registrant(s). In addition, reviews by a variety of international bodies/regulatory programs (NIOSH; OSHA; U.S. EPA (HPV)) and original publications have been evaluated by July 2014. Where relevant, the original publications were reviewed and evaluated as indicated in the text. In addition, literature was searched in the on-line databases DIMDI, Toned (HSDB, Towline incl. PubMed), ISI Web of Knowledge, and Scopus.

The evaluation of the effects of the substance on environmental organisms (ecotoxicity and bioaccumulation) together with the degradation, exposure and fate & behaviour in the environment has mainly been based on data presented by the registrants (IUCLID dossiers, and Chemical Safety Report (CSR 2014)). In addition literature was searched in the on-line databases (ISI Web of Knowledge and Scopus).

This substance evaluation includes all environmental and human health endpoints. The evaluation as well as the documentation in the evaluation report focusses on certain aspects with relation to the initial concerns. Moreover, the available information in the registration dossiers and the chemical safety report (CSR) were checked for plausibility and indications of additional concerns for dimethyl disulphide.

In July 2015 the draft decision was sent to the registrant(s) which enabled them to provide comments on the information requested as foreseen in article 50(1) of the REACH legislation. In doing so, requests in the initial draft decision on further information regarding the substance's adsorption behaviour and abiotic degradation processes due to hydrolysis was provided. This helped the eMSCA evaluate the information on both endpoints already available in the registration dossier on a more detailed and made the specific requests superfluous.

In preface of the discussion of the information request in ECHA's Member State Committee the first version of the updated draft decision was sent to the Member State Competent Authorities and ECHA for commenting in October 2015. Because of the comments received the eMSCA decided to refine the request for further information on operational conditions for the specific use of dimethyl disulphide as intermediate in chemical synthesis effecting the environmental exposure and risk – in this case especially the assumed efficiency of the waste water treatment technology.

The decision was adopted in the 46th meeting of ECHA's Member State Committee in February 2016. In July 2016 the registrant(s) provided the requested information, which was evaluated in the follow up evaluation by the eMSCA. Following this evaluation the eMSCA concluded that no further information needs to be requested to clarify the concerns.

7.3. Identity of the substance

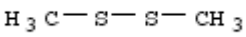
Table 4

SUBSTANCE IDENTITY	
Public name:	Dimethyl disulphide
EC number:	210-871-0
CAS number:	624-92-0
Index number in Annex VI of the CLP Regulation:	N/A
Molecular formula:	$C_2H_6S_2$

Molecular weight range:	94.19 g/mol
Synonyms:	Methyl disulfide (8CI); 2,3-Dithiabutane; (Methyldithio)methane; DMDS; Dimethyl disulfide; Dimethyl disulphide; Dithioether; NSC 9370; Sulfa-Hitech

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

Structural formula:



7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES		
Property	**Value**	**Remarks**
Physical state at 20°C and 101.3 kPa	light yellow liquid with an strong garlic odour	
Melting/freezing point	–84.7°C at 1013.25 hPa	
Vapour pressure	*4.12E-09 hPa at 25 °C*	Study report, according to EPA *OPPTS 830.7950;* dynamic method
Boiling point	109.2°C @ 1013.25 hPa	Study report, according to EPA OPPTS 830.7220, dynamic method
Surface tension	72.1 mN/m at 20°C, 1g/L 33.6 mN/m at 20°C, 100vol% 32.8 mN/m at 25°C, 100vol%	Study report, OECD 115 Measured values cited in Beilstein
Water solubility	2.7 g/L at 20 °C, pH = ca. 6.0	Study report, OECD 105; flask method
Partition coefficient n-octanol/water (Log K_{ow})	log P_{ow}: 1.91 at 20°C, pH ca. 6.7	Study report, OECD 105; flask method
Granulometry		According to column II of Annex VII, this endpoint study record is a waiver for the form of this substance is liquid.
Stability in organic solvents and identity of relevant degradation products		The test does not need to be conducted because the stability of the substance in solvents is not considered as critical.
Dissociation constant	The difference between the conductivity of water and the DMDS solutions (concentration 0.014 mol/l) is not significant. Therefore it can be concluded	Study report, according to OECD 112; conductivity measurement

	that the test item does not dissociate.	
Viscosity	Dynamic viscosity: 0.5944 mm^2/s at 20.14 °C 0.4952 mm^2/s at 40.12 °C Kinematic viscosity: 0.619 mPas at 20 °C 0.585 mPas at 25 °C	Study report, according to OECD 114; capillary method Measured, cited in Beilstein

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t[3]	☐ 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

During the substance evaluation year, the disseminated tonnage band for the substance was 10,000-100,000 tpa which likely included tonnage from uses claimed as intermediate.

Overview of uses

Table 7

USES	Use(s)
Uses as intermediate	in chemical synthesis
Formulation	
Uses at industrial sites	in refineries as hydrotreating catalyst activator in petrochemical sites as anti-coking agent
Uses by professional workers	No use
Consumer Uses	No use
Article service life	No use

[3] The disseminated total tonnage band has been calculated by excluding the uses claimed as intermediate, for details see the Manual for Dissemination and Confidentiality under REACH Regulation (section 2.6.11): https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0

According to ECHA's dissemination website the substance is used in the following products: pH regulators and water treatment products. This substance has an industrial use resulting in manufacture of another substance (use of intermediates).

ECHA has no registered data indicating whether or into which articles the substance might have been processed.

The substance is also used in other applications not being reflected in the registration dossiers:

- Dimethyl disulphide is a natural occurring food additive in onion, garlic, milk and cheese, meats and some mushrooms but also in artificial form as savoury flavours or fruit flavours. It is also used for flavouring wines and beers.
- Dimethyl disulphide is also used in the production of various pesticides. DMDS and chlorine are reacted with borontriflouride phenolate to produce 4-(methylthio)phenol. Thiophene and DMDS are blended with combustible hydrocarbon fuel gas to impart a gassy odor to the fuel gas. DMDS is used as a sulfiding reagent to control catalyst activity.
- In the United states dimethyl disulphide is used as substitute for bromomethane in fumigation applications.

There is no information regarding uses advised against. Further deliberations of the eMSCA on the registered uses are contained in section 5.2 of the report.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No entry for dimethyl disulphide in Annex VI CLP currently exists. However, there is currently a proposal under consideration which has been submitted by ARKEMA France to the Agency according to Art. 37(2) CLP (cf. Table 10).

Table 8

PROPOSAL FOR HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION UNDER CONSIDERATION						
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**	
	dimethyl disulphide	210-871-0	624-92-0	Flam. Liq. 2, Acute Tox. 4, Acute Tox. 3 Eye Irrit. 2 Skin Sens. 1B, STOT SE 3 Aquatic Acute 1 Aquatic Chronic 1	H225 H302 H331 H319 H317 H335 H400 H410	 M-Factor = 1 M-Factor = 10

It should be noted that this CLH proposal deviates from the classification considered appropriate by the eMSCA regarding the hazard classes for acute oral toxicity (eMSCA proposal: Acute Tox. 3, H301).

7.6.2. Self-classification

Compared to the proposal for harmonised classification and labelling which has been brought forth by industry, no additional hazard classes have been notified in the registration(s). The current self-classification corresponds to the proposed harmonised classification.

The following hazard classes are notified among the aggregated self-classifications in the C&L Inventory in addition to the classification proposed by industry:

Skin Irrit. 2	H319
Repr. 2	H361

The following hazard classes are notified among the aggregated self-classifications in the C&L Inventory and deviate from the classification proposed by industry:

Acute Tox. 2 (oral)	H300
Acute Tox. 3 (oral)	H301
Acute Tox. 1 and 2 (inhalation)	H330
Acute Tox. 4 (inhalation)	H332
Acute Tox. 2 (dermal)	H310
Acute Tox. 4 (dermal)	H312
Skin Sens. 1 B	H317

7.7. Environmental fate properties

Degradation

Abiotic degradation

The registrant provided a study on abiotic degradation due to hydrolysis. The executive summary provided with the registration dossier indicates that the substance is not subject to degradation via hydrolysis under environmental conditions.
Based on the information provided in the registration used for evaluation and in an updated dossier provided by the registrant after he had received the initial draft decision for commenting as foreseen in the REACH legislation in article 50(1) the eMSCA can support this conclusion.

In the registration dossier there are two study summaries on abiotic degradation of dimethyl disulphide in the atmosphere under presence of OH radicals and other reactive substances occurring in the atmosphere. The study summaries presented the outcome of a QSAR calculation and a laboratory study using a smog chamber. The results of both studies indicate atmospheric half-lives of 1.7 hours or less, depending on the concentration of OH radicals and the presence of other reactive substances.
Based on the information provided the eMSCA can support this conclusion.

Biotic degradation

Screening tests on biodegradation

As part of the registration dossier the registrant provided two study summaries on readily

biodegradation according to OECD test guideline OECD 301D respectively OECD 310. Both studies show that dimethyl disulphide can be degraded by microorganisms. But in both cases the determined degradation rate did not reach the relevant trigger value of the respective OECD test guideline necessary to judge that the substance fulfils the criteria of being rated as "readily biodegradable". In the overall conclusion the registrant rated the substance as "not readily biodegradable", but moderately or partly biodegradable.
Based on the information provided the eMSCA can support this conclusion.

Simulation tests on biodegradation

The registrant provided two study summaries on biotic degradation in water/sediment systems according to test guideline OECD 308. The simulation test considered degradation under aerobic respectively anaerobic conditions using 14C-radiolabelled test substance. In both studies biodegradation was no relevant path of removal because volatilisation was found to be the dominant process. For example in the aerobic test more than 90 percent dissipation of the parent substance was detected within several hours in the organic volatile traps. No major degradation product was observed during the course of the study in any of the matrices. The registrant calculated a half-life of 2.8 hours and less for the simulation studies in water sediment systems and argued that biotic degradation is not a relevant path for removal.
The eMSCA can agree to the registrant's conclusive summary. Nevertheless the deviations in test procedure to the requirements of Guideline OECD 308 might have impacted the test result. Even when low, an influence of photolytic degradation and temperature on measured biotic degradation cannot be excluded.
With regard to persistence, it is insufficient to consider removal via volatilisation alone to be a proof non-persistence as this is a simple transfer from one environmental compartment to another (see REACH guidance, section R.11.1.3.1). From the eMSCA's point of view it is not possible to conclude about biodegradation behaviour of DMDS in water-/sediment systems. As the design of the test methods known are not applicable to highly volatile substances a final conclusion on persistence in water-/sediment systems cannot be drawn.

The registrant also provided two study summaries on biotic degradation in different soils according to test guideline OECD 307 using 14C radio labelled test substance. The simulation test considered degradation under aerobic respectively anaerobic conditions. Degradation products detected in relevant concentrations (> 10 percent amount of applied substance) were methansulfonic acid and methanethiol. Again volatilisation was identified as main pathway for removal of dimethyl disulphide and it is not possible to conclude about the persistency of dimethyl disulphide as the information on half-lives have to be regarded as dissipation half-lives.

Overall conclusion on persistency

From the eMSCA's point of view it is not possible to conclude about biodegradation behavior of DMDS in water-sediment systems or soil systems. With regard to persistence, it is insufficient to consider removal via volatilisation alone as this is a simple transfer from one environmental compartment to another (see REACH guidance, section R.11.1.3.1). As the known test designs for both of the environmental compartments are not applicable to highly volatile substances and no modified or non-standard test method is known which might be used for clarification a final conclusion on persistence in soil systems cannot be drawn.

Environmental distribution

Adsorption/desorption

The low n-octanol/water partitioning coefficient (log K_{ow} = 1.91) indicates that the substance has a low tendency for absorption.
The registration dossiers contain results from an experimental test according to test guideline OECD 106 together with results from QSAR calculations. The test results are in a range of log Koc = 1.61 to 1.64.
The eMSCA has reviewed the available information and performed QSAR calculations which resulted in log K_{OC} values in a similar range.

Volatilisation

Information on volatilisation is not a standard information requirement according to Annexes VII to X of the REACH legislation. As the registrant provided data for this endpoint and used it for conclusions in the assessment of the biodegradation behavior of the substance, this endpoint was also reviewed by the eMSCA during substance evaluation.
The registrant provided data for the substance specific Henry's Law Constant. The constant was determined to be 105 Pa*m³*mol-1. The substance therefore has to be rated as highly volatile.
The eMSCA supports this conclusion because calculation of the Henry's Law Constant during the process of the substance evaluation resulted in the same value.

Distribution modelling

Information on distribution of the substance between different media is no standard information requirement according to Annexes VII to X of the REACH legislation. As the registrant provided data for this endpoint and uses it for conclusions in the assessment of the biodegradation behavior of the substance this endpoint was also reviewed by the eMSCA during substance evaluation and complement information from the eMSCA was added.
The outcome of the different models and the substance properties point to the fact that in a first step the majority of DMDS will be released into the compartment air. This refers to emissions from STP and from water via volatilisation. Nevertheless it is expected that the substance predominantly will end up in the compartments soil and water once it is released to the environment. The reason is the high water solubility of 2700 mg/l which will lead to indirect exposure to soil from rain. Surface waters are expected to be exposed, too. This assessment is supported by the outcome of the eMSCA's calculations on distribution modelling according to the MacKay Level III model which takes into account the distribution processes between the different environmental compartments.

7.7.1. Bioaccumulation

Aquatic bioaccumulation

The bioaccumulation study has been waived by the registrant(s). DMDS is not expected to bioaccumulate in aquatic organisms based on the available information concerning its physico-chemical properties, i. e. high water solubility (2.7 g/L) and low log K_{ow} (1.91).

Terrestrial bioaccumulation

The bioaccumulation study has been waived by the registrant(s). Regarding the low Log Kow (1.91) accumulation of DMDS in organisms is not to be expected. DMDS has a low potential for sorption on soil/sediment particles based on a measured K_{oc} of 42. Moreover

due to its high volatility potential, DMDS is not expected to remain in relevant concentrations in soil as demonstrated in aerobic and anaerobic soil metabolism tests

Summary and discussion of bioaccumulation

Based on intrinsic properties of DMDS (high volatility) and existing data related to log K_{ow} (1,91) and K_{oc} (42), it is considered that DMDS is not a candidate for further work concerning bioaccumulation potential for both aquatic and terrestrial compartments.

Secondary poisoning

Not relevant for the substance evaluation due to the low log K_{OW}.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

A possible or supposed toxic effect of the substance on the species of the different compartments and trophic level is not an object of the initial concern. The check of the end points gave no indications to additional concerns.

However, an overview of the checked endpoints is given to support the statements of the PNEC derivation at this point and the classification and labelling.

Table 9

ECOTOXICOLOGICAL INFORMATION ON DMDS			
Endpoint	**Value**	**Source**	**Remarks**
Aquatic toxicity	***$PNEC_{water}$ (freshwater):*** ***Daphnia freshwater NOEC/10: 0.25 µg/L*** ***$PNEC_{water}$ (saltwater):*** ***Daphnia freshwater NOEC/10: 0.25 µg/L*** ***$PNEC_{water}$ (intermittent release):*** ***Fish freshwater LC50/100: 9.7 µg/L***		
fish short-term freshwater	96h-LC_{50} = 0.97 mg/L	(TL8, 2007c)	Key value
fish long term saltwater	28d-NOEC = 0.47 mg/L	(TL5, 2011c)	Key value
fish long term freshwater	28d-NOEC = 0.96 mg/L	(TL5, 2011b)	Key value
daphnia short-term freshwater	48h-EC_{50} = 1.82 mg/L	(TL8, 2007a)	Key value
daphnia short-term freshwater	48h-EC_{50} = 7 mg/L	(TL12, 1996)	Key value
crustacea short-term saltwater	96h-EC_{50} = 5 mg/L	(TL9, 2007b)	Key value

mollusc short term saltwater	96h-EC_{50} = 14 mg/L	(TL9, 2007a)	Supp. study
daphnia long-term freshwater	21d-NOEC = 0.025 mg/L	(TL5, 2011a)	Key value
crustacea long-term saltwater	28d-NOEC = 0.46 mg/L	(TL5, 2011d)	Key value
algae freshwater	96h-ErC_{50} = 6.7 mg/L 96h-NOEC = 0,17 mg/L	(TL9, 2008b)	Key value
algae saltwater	96h-ErC50 = 3.9 mg/L 96h-NOEC = 0.95 mg/L	(TL9, 2008c)	Key value
aquatic plant	7d-EC50 = 3.1 mg/L 7d-NOEC = 5.5 mg/L	(TL9, 2008a)	Key value
toxicity to microorganisms	***No PNEC can be derived***		
Activated sludge	3h-EC_{50} > 1.000 mg/L	(TL4, 2001)	Key value
sediment toxicity	*waived*		
terrestrial toxicity	***$PNEC_{soil}$:*** ***Collembolan NOEC/10: 1mg/kg***		
earth worm short term	14d-EC_{50} = 31.8 mg/kg	(TL8, 2007b)	Key value
arthropods Acute and Long term	28d-NOEC = 10 mg/kg	(TL10, 2006a)	Key value
arthropods Long term	16d-NOEC = 100.9 mg/kg	(TL10, 2006b)	Key value
arthropods Long term	14d-NOEC > 1.000 mg/kg	(TL10, 2006c)	Key value
arthropods short term	48h-LD_{50} > 100 µg/animal	(TL9, 2008g)	Key value
Plants Long term	21d-LOEC = 600 lb/A	(TL9, 2008d) (TL9, 2008e) (TL9, 2008f)	Key value
toxicity to soil microorganism			
soil	28d-EC_{50} > 14.580 mg/kg 28d NOEC = 180 mg/kg	(TL8, 2007e)	Key value
soil	28d-EC_{50} > 15.000 mg/kg 28d NOEC = 15.000 mg/kg	(TL8, 2007d)	Key value
toxicity to birds	***No PNEC (derivation due to secondary poisoning is not relevant)***		
bird acute inhalative	4h-LC_{50} > 478 mg/kg	(TL11, 2005)	Key value
bird acute oral	4h-LC_{50} > 478 mg/kg 21d-LD_{50} = 342 mg/kg	(TL9, 2006)	Key value

7.8.2. Terrestrial compartment

Not assessed.

7.8.3. Microbiological activity in sewage treatment systems

Not assessed.

7.8.4. PNEC derivation and other hazard conclusions

Cf. section 7.8.

7.8.5. Conclusions for classification and labelling

There is no current harmonized classification of dimethyl disulphide with respect to environmental hazards, but the ECHA Risk Assessment Committee (RAC) will adopt an opinion on CLH also with respect to environmental hazards by 15 November 2018.

In the substance evaluation the environmental hazards were checked. Evaluation performed on the available data led to the conclusion that harmonised classification is warranted. In the following table conclusions for classification or non-classification of dimethyl disulphide based on the examination of the existing ecotoxicity data for the environmental endpoints are given.

Table 10

CONCLUSION FOR CLASSIFICATION AND LABELLING - ENVIRONMENT			
Endpoint	**Species**	**Value/Effect**	**Classification proposal (Criteria)**
Short term aquatic toxicity	fish	96h-LC_{50} = 0.97 mg/L	**Classification proposal:** Aquatic Acute 1, H400: Very toxic to aquatic life M-factor: 1
long term aquatic toxicity ready biodegradability	daphnia	21d-NOEC = 0.025 mg/L Degradation: 53% day 28 Non-rapidly degradable	**Classification proposal:** Aquatic Chronic 1, H410: Very toxic to aquatic life with long lasting effects M-factor: 10

7.9. Human Health hazard assessment

The data submitted for registration on the human health endpoints were suitable and sufficient for evaluation. No further information is required.

Dimethyl disulphide is currently not listed in Annex VI of CLP Regulation, but RAC will adopt an opinion on CLH with respect to flammable liquids, acute toxicity, skin

corrosion/irritation, serious eye damage/eye irritation, skin sensitisation, germ cell mutagenicity, reproductive toxicity, specific target organ toxicity after single and repeated exposure, aspiration hazard and hazardous to the aquatic environment by 15 November 2018. Self classification notifications for dimethyl disulphide by industry are available in the C&L Inventory (http://echa.europa.eu/information-on-chemicals/cl-inventory). The available information on the substance and the evaluation conducted has led the eMSCA to the conclusion that a harmonised classification and labelling of dimethyl disulphide is warranted. The eMSCA considers that the existing information on the human health toxicity of dimethyl disulphide indicates that the substance fulfils the criteria for classification for acute oral and inhalation toxicity, eye and respiratory tract irritation and skin sensitisation.

7.9.1. Toxicokinetics

No concern was identified.

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity

The data for acute toxicity of dimethyl disulphide was obtained from experimental animal testing. The data submitted for registration on the endpoint acute toxicity were suitable and sufficient for evaluation. No further information required.

Acute toxicity: oral

For the acute oral toxicity, results from 6 experimental studies in rats are submitted by the registrants, whereof one study was considered as key study by the registrants, and one study as supporting study. From the four further studies, two studies using the ATC method according to OECD TG 423 in Wistar rats showed LD_{50} values in the range of greater than 56 mg/kg bw but less than 500 mg/kg bw. The reliability of the remaining two studies was assessed with 4 (not assignable), since the analytical purity of the test substance was unknown. Additionally, acute oral toxicity results from a study in Wistar rats provided from U.S. EPA (2012), and U.S. EPA, Office of chemical safety and pollution prevention (2010) are discussed for this endpoint by the eMSCA. In all studies dimethyl disulphide was used as test material. The results of the most relevant experimental studies on acute toxicity after oral administration are summarised in the table below.

Table 11

EXPERIMENTAL DATA ON ACUTE TOXICITY		
Reference Species; strain; sex; testing method	**LD_{50}**	**Specific methods; results**
TL13 (2010) **Rat**; Sprague-Dawley; female (6/dose); OECD TG 423/ B.1 tris, ATC method	LD_{50}(rat female) ≥ 300 mg/kg bw	DMDS (purity 99.88 %) was administered in corn oil by gavage to 6 fasted female rats. No mortality; clinical signs included hypoactivity, hypersalivation, piloerection and dyspnoea.
TL14 (1986) **Rat**; Sprague-Dawley; male, female (5/sex/dose)	LD_{50}(rat male, female) in the range of 290-500 mg/kg bw	DMDS undiluted (purity: 99.31 %) or as a suspension (10 mL/kg) in polyethylene glycol 300 via gavage and then observed for 14 days following dosing.

B.1		No mortalities at 100 mg/kg bw and 350 mg/kg bw. Mortalities at 290 mg/kg bw (30 %) and 500 mg/kg bw (100 %).
U.S. EPA (2012), U.S. EPA, Office of chemical safety and pollution prevention (2010) **Rat**; Wistar; male, female (5/sex/dose) EPA 870.1100/protocol similar to B.1	LD_{50}(rat male, female) = 190 mg/kg bw (150-240 mg/kg bw)	DMDS (purity: commercial grade) as a suspension in 3 % carboxymethyl cellulose via gavage at 125, 188, 250, 375 or 500 mg/kg bw and then observed for 14 days following dosing. Males: mortalities in all but the low-dose group: 125 mg/kg bw (0/5), 188 mg/kg bw (5/5), 250 mg/kg bw (3/5), 375 mg/kg bw (5/5), and 500 mg/kg bw (5/5); Females: mortalities at all doses: 125 mg/kg bw (1/5), 188 mg/kg bw (1/5), 250 mg/kg bw (4/5), 375 mg/kg bw (5/5), 500 mg/kg bw (5/5)

Acute oral toxicity studies in rats resulted in the following LD_{50} values: > 300 mg/kg bw (female) and in the range of > 290 mg/kg bw and < 500 mg/kg bw/d (male/female). A lower LD_{50} value was reported from a third study (U.S. EPA 2012, U.S. EPA, Office of chemical safety and pollution prevention 2010): 190 mg/kg bw (range of 150-240 mg/kg bw) for male and female rats. It is concluded that dimethyl disulphide is acutely toxic after oral administration.

Based on the available oral LD_{50} values from acute oral toxicity studies with rats, DMDS fulfils the criteria for classification for acute oral toxicity according to the CLP Regulation. Therefore, based on the acute toxic value of 190 mg/kg bw (range of 150-240 mg/kg bw) for male and female rats dimethyl disulphide shall be classified as Acute Tox. 3, H301 (Toxic if swallowed.) according to CLP (Annex I, Part 3, Table 3.1 Acute toxicity category 3: 50 < ATE ≤ 300 mg/kg bw).

Acute toxicity: inhalation

For the acute inhalation toxicity, results from three experimental studies in rats are submitted and were declared as key studies by the registrants. In these studies DMDS was used as test material. The reliability of a further study was assessed with 4 (not assignable), since the analytical purity of the test substance was unknown. Results of the relevant study on acute inhalation toxicity are given in the following table.

Table 12

EXPERIMENTAL DATA ON ACUTE INHALATION TOXICITY		
Reference Species; strain; sex; testing method	**LD_{50}**	**Specific methods; results**
TL15 (2005); U.S. EPA (2012); U.S. EPA, Office of chemical safety and pollution prevention (2010) **Rat;** Sprague-Dawley; male, female (5/sex/dose); 4h as a vapour via whole body inhalation EPA OPPTS 870.1300/protocol similar to OECD TG 403	LC_{50}(rat male, female) = 1310 ppm equivalent to 5.05 mg/L/4h (with 95 % confidence limits of 4.49-5.66 mg/L/4h)	DMDS (purity 99.72 %), 4h exposure and then observed for 14 days following exposure mortalities: 0/10 at 847 ppm (~3.3 mg/L), 4/10 at 1188 ppm (~4.62 mg/L), 4/10 at 1308 ppm (~5.09 mg/L), 9/10 at 1650 ppm (~6.42 mg/L); all death occurred during exposure or immediately following exposure

In a single study in male and female rats exposed to dimethyl disulphide vapours the LC_{50} value was 1310 ppm equivalent to 5.05 mg/L/4h (with 95 % confidence limits of 4.49-5.66 mg/L/4h). Based on the available data it is concluded that dimethyl disulphide is acutely toxic by inhalation.

Based on the available data, dimethyl disulphide fulfils the criteria for classification for acute inhalation toxicity according to the CLP Regulation. The LC_{50} value of dimethyl disulphide was 1310 ppm equivalent to 5.05 mg/L/4h (with 95 % confidence limits of 4.49-5.66 mg/L/4h). On the basis of this study and in accordance with CLP (Annex I, Part 3, Table 3.1 Acute toxicity category 3 (vapour): 2.0 < ATE ≤ 10.0 mg/L/4h) dimethyl disulphide shall be classified as Acute Tox. 3, H331: Toxic if inhaled.

Acute toxicity: dermal

For the acute dermal toxicity, results from four experimental studies in rabbits and one in rats are submitted by the registrants. In these studies dimethyl disulphide was used as test material, however, information on the analytical purity of the tested samples in the rabbit studies is missing. The results of experimental studies on acute dermal toxicity are summarised in the following table.

Table 13

EXPERIMENTAL DATA ON ACUTE DERMAL TOXICITY		
Reference Species; strain; sex; testing method	**LD_{50}**	**Specific methods; results**
TL19 (2007) **Rat**; Wistar; male, female (5/sex) EPA OPPTS 870.1200/protocol similar to OECD TG 402	LC_{50}(rat male, female) > 5000 mg/kg bw	DMDS (purity: 99.2 %) with 5 % emulsifier and 1 % isobornyl acetate via the dermal route at 5000 mg/kg bw coverage: semi-occlusive, for 24h and observed for 14 days following dosing no mortality; post exposure, clinical signs: instances of wetness and soiling of the anogenital area, chromorhinorrhea, sagging eyelids, emaciated appearance, few faeces, lethargy, ataxia, wet red substance on anogenital area and nose/mouth area
TL6 (1986) **Rabbit**; New Zealand White; male, female (5/sex) EPA OPPTS 870.1200/protocol similar to OECD TG 402	LC_{50}(rabbit male, female) > 2000 mg/kg bw	DMDS (purity: not given) via the dermal route at 2000 mg/kg bw, coverage: occlusive, for 24 h and observed for 14 days following dosing; no mortality; post exposure, clinical signs: heavy breathing, loss of righting reflex, spontaneous spasms, papillary dilation and constriction, unwillingness to stand, lethargy, excessive salivation, flared nostrils
TL6 (1985a) **Rabbit**; New Zealand White; male, female (5/sex) EPA 40 CFR 163.81-2/protocol similar to OECD TG 402	LC_{50}(rabbit male, female) > 2000 mg/kg bw	DMDS (purity: not given) via the dermal route at 2000 mg/kg bw, coverage: occlusive, for 24 h and observed for 14 days following dosing; no mortality; post exposure, clinical signs: none

TL6 (1985) **Rabbit**; New Zealand White; male, female (5/sex) OECD TG 402/EU B.3	LC_{50}(rabbit male, female) > 2000 mg/kg bw	DMDS (purity: not given) via the dermal route at 2000 mg/kg bw, coverage: occlusive, for 24 h and observed for 14 days following dosing; no mortality; post exposure, clinical signs: apathy and prostration
TL16 (1988) **Rabbit**; New Zealand White; male, female (5/sex) EPA OPP 81-2/ protocol similar to OECD TG 402	LC_{50}(rabbit male, female) > 2000 mg/kg bw	DMDS (purity: not given) via the dermal route at 2000 mg/kg bw, coverage: occlusive, for 24 h and observed for 14 days following dosing; no mortality

The dermal LD_{50} for rabbits was > 2000 mg/kg bw (4 studies). In rats the dermal LD_{50} was > 5000 mg/kg bw. Based on the available data it is concluded that dimethyl disulphide is not acutely toxic after dermal administration.

The dermal LD_{50} value of dimethyl disulphide observed in male and female rabbits and rats was greater than 2000 mg/kg bw. Based on these LD_{50} values and in accordance to the CLP Regulation no classification is warranted with respect to acute dermal toxicity.

Conclusion for acute toxicity: The concern for acute oral and inhalation toxicity is confirmed, meeting the criteria for classification and labelling according to CLP criteria.

Corrosion/Irritation

The evidence for skin, eye and respiratory tract irritation of dimethyl disulphide was obtained from animal testing. Sufficient information is available for the evaluation of skin, eye and respiratory tract irritation. No further information is required.

Irritation: Skin

To evaluate the skin irritation potential of dimethyl disulphide, results from two experimental studies in rabbits are available, whereof one study was considered as key study and the other as supporting study by the registrants. In both studies dimethyl disulphide was used as test material. The results of relevant studies on skin irritation are summarised in the following table.

Table 14

EXPERIMENTAL DATA ON SKIN IRRITATION		
Reference Species; strain; sex; testing method	**Results**	**Remarks**
TL18 (1985a)	slightly irritating to skin	DMDS (purity: 98.98 %) was applied undiluted to the skin of 6 rabbits, coverage: semi-occlusive, for 4 hours

Rabbit; New Zealand White; 6 (sex not specified) OECD TG 404		Erythema score: 1.78 of max. 4 (mean) (time point: 24+48+72h); not fully reversible within: 72h) Oedema score: 1.22 of max. 4 (mean) (time point: 24+48+72h); not fully reversible within: 72h)
TL6 (1985b) **Rabbit**; New Zealand White; 6 (sex not specified) EPA 40 CFR 163.81-5/ protocol similar to OECD TG 404	slightly irritating to skin	DMDS (purity: unknown) was applied undiluted to the shaved skin of 6 rabbits, coverage: occlusive, for 24 hours Erythema score: 1.03 of max. 4 (mean) (time point: 24+48+72h); fully reversible within: 10 days Oedema score: 0.11 of max. 4 (mean) (time point: 24+48+72h); fully reversible within: 48h)

Dimethyl disulphide has been shown to be slightly irritating to the skin of rabbits. The overall mean scores (after 24h, 48h, and 72h) for erythema and eschar formation and oedema were 1.78 and 1.22, respectively, in the key study. The slight skin irritation observed in the second study was reversible within 10 days.

In the registration dossier dimethyl disulphide has been self-classified for skin irritation. However, based on the available data, dimethyl disulphide does not fulfil the criteria for classification for skin irritation according to the CLP Regulation.

Irritation: Eye

The potential of dimethyl disulphide to induce ocular irritation was evaluated in two studies with rabbits. One study was considered as key study by the registrants, and one further study as supporting study. In both studies dimethyl disulphide was used as test material. The results of experimental studies on eye irritation are summarised in the following table.

Table 15

EXPERIMENTAL DATA ON EYE IRRITATION		
Reference Species; strain; sex; method	**Results**	**Remarks**
TL18 (1985b) **Rabbit;** New Zealand White; 6 (sex not specified) OECD TG 404	irritating to eyes	single dose of 0.1 mL of DMDS (purity: 98.98 %) undiluted was instilled into the conjunctival sac of the eye for 24h; eyes were not rinsed following the test substance instillation Cornea score: 0.83 of max. 4 (mean) (time point: 24+48+72h); not fully reversible within: 72h) Iris score: 1 of max. 2 (mean) (time point: 24+48+72h); not fully reversible within: 72h) Conjunctivae score: 1.33 of max. 3 (mean) (time point: 24+48+72h); not fully reversible within: 72h) Chemosis score: 1.89 of max. 4 (mean) (time point: 24+48+72h); not fully reversible within: 72h)

TL6 (1985c) **Rabbit;** New Zealand White; 9 (4 males and 5 females) EPA 40 CFR 163.81-4/ protocol similar to OECD TG 404	slightly irritating to eyes	single dose of 0.1 mL of DMDS (purity: unknown) undiluted was instilled into the conjunctival sac; eyes of 3 rabbits were rinsed after 20-30 sec., and of 6 rabbits were not rinsed after administration 2 rabbits (unwashed eyes): corneal opacity, transient , disappeared by 7 days 9 rabbits (washed and unwashed eyes): transient hyperaemia and chemosis, disappeared 24h and 96h Cornea score: 0.33 of max. 4 (mean) (time point: 24+48+72h); not fully reversible within: 7 days) 0 of max. 4 (mean) (time point: 24+48+72h) Iris score: 0 of max. 2 (mean) (time point: 24+48+72h) 0 of max. 2 (mean) (time point: 24+48+72h) Conjunctivae score: 1.32 of max. 3 (mean) (time point: 24+48+72h); fully reversible within: 7 days 0.66 of max. 3 (mean) (time point: 24+48+72h); fully reversible within: 72h Chemosis score: 1 of max. 4 (mean) (time point: 24+48+72h); fully reversible within: 7 days 0.44 of max. 4 (mean) (time point: 24+48+72h); fully reversible within: 72h

Dimethyl disulphide is irritating to eyes of rabbits. The mean score for iris over 24, 48 and 72 hours obtained in a key study was equal to the threshold value (iris ≥ 1) for classification as irritating to the eyes.

Evaluation of the observed dimethyl disulphide effects on the eyes of rabbits was based on the nature, intensity and reversibility of responses. The available eye irritation studies showed that dimethyl disulphide induced reversible effects on the eyes of rabbits. When applied to the eye of rabbits, dimethyl disulphide has produced a positive response of iritis. The mean score for effects on the iris obtained in a key study over 24, 48 and 72 hours was equal to the threshold value (iritis ≥ 1) for classification for eye irritation. Based on these results, dimethyl disulphide meets the criteria for classification and labelling according to CLP as 'Irritating to eyes, category 2, H319: Causes serious eye irritation.'

Irritation: Respiratory tract

Dimethyl disulphide caused respiratory irritation in acute and short-term inhalation toxicity studies in rats. The results of these studies are summarised in the following table.

Table 16

EXPERIMENTAL DATA ON RESPIRATORY TRACT IRRITATION	
Reference Species; strain; sex; method	**Results**
TL15 (2008); TL17 (2008) **Rat**; Sprague-Dawley; male, female (10/sex/dose).	**Respiratory tract irritation** BMD10 % for nasal irritation calculated at 9.3 ppm (0.0358 mg/L) DMDS (purity 99.9 %), target concentrations of 0, 50, 150, 300, and 600 ppm Day 1: $NOAEC_{local}$ not established (< 50 ppm)

Other, special inhalation toxicity study to examine effects on tissues on the upper respiratory tract, exposure: 6h as a vapour via whole body inhalation, for 1 day or 5 consecutive days, in each case termination 24h after exposure Non-guideline study	**$LOAEC_{local\ rat\ male,\ female}$ = 50 ppm (0.195 mg/L)** based on changes in the nasal tissues in both sexes: acute inflammation and degeneration of the transitional and olfactory epithelium, acute inflammation of the respiratory epithelium **$LOAEC_{local\ rat\ male,\ female}$ = 150 ppm (0.583 mg/L)** based on degeneration of the respiratory epithelium Day 5: Port-of Entry (local changes in the nasal tissues) $NOAEC_{local}$ not established (< 50 ppm) ≥ 50 ppm (≥ 0.195 mg/L): hyperplasia of the transitional and respiratory epithelium, regeneration of the olfactory epithelium, hyperplasia of the squamous epithelium (f), acute inflammation of the squamous (m), transitional (f), and olfactory epithelium (m) ≥ 150 ppm (≥0.583 mg/L): acute inflammation of the respiratory epithelium (f) ≥ 300 ppm (≥ 1.168 mg/L): hyperplasia of the squamous epithelium (f) ≥ 50 ppm (≥ 0.195 mg/L): acute inflammation of the squamous epithelium (f) **$LOAEC_{local\ rat\ male,\ female}$ = 50 ppm (0.195 mg/L)** based on changes in the nasal tissues in both sexes (acute inflammation, degeneration, and hyperplasia) Regeneration of the olfactory epithelium occurred in nasal levels II through VI Systemic: $NOAEC_{systemic}$ not established ≥ 300 ppm (≥ 1.168 mg/L): ↑ abs/rel lung weight **$LOAEC_{systemic,\ rat,\ male,\ female}$ = 50 ppm (0.19 mg/L)**, based on ↓ bw and bw gains
TL6 (1985c) **Rabbit;** New Zealand White; 9 (4 males and 5 females) EPA 40 CFR 163.81-4/ protocol similar to OECD TG 404	**Respiratory tract irritation** Acute 24h inhalation exposure study with microscopic examination of the upper respiratory tract DMDS (purity 99.5 %), target concentrations of 0, 5, 9, 12.5, 18 ppm Local effects: Microscopic examination of the nasal turbinates revealed an exposure-related incidence in olfactory epithelial cell degeneration both in terms of the numbers of animals affected and in the severity of the response (particularly levels III, IV and V). An increased incidence of inflammation was noted in the olfactory and respiratory epithelium of the 18 ppm (69 mg/m^3) group as well. **$LOAEC_{local\ rat\ male}$ = 12.5 ppm (48 mg/m^3)** **$NOAEC_{local\ rat\ male}$ = 9 ppm (19 mg/m^3)** Systemic effects: **$NOAEC_{systemic\ rat\ male}$ = 18 ppm (69 mg/m^3, highest concentration tested)**

The available information on dimethyl disulphide indicates that it causes respiratory tract irritation in experimental animals. In a 24h continuous inhalation exposure study, respiratory tract irritant effects were observed in rats exposed to dimethyl disulphide vapours of 12.5 and 18 ppm (equivalent to 0.048 and 0.069 mg/L). The port-of-entry effects were characterized by an increase in the incidence of microscopic lesions: degeneration of the nasal tissues as well as acute inflammation of the respiratory and olfactory epithelia. The NOAEC for local effects was determined at 9 ppm (equivalent to 0.019 mg/L). A further inhalation toxicity study was performed to evaluate the effects of dimethyl disulphide on tissues in the upper respiratory tract when administered as vapour for 6h/day via whole body inhalation exposure to rats once (single exposure) or once a day for a period of 5 consecutive days. Dimethyl disulphide caused port-of-entry

toxicity (nasal irritation and lesions) which appeared to increase in severity with increasing concentration. There were acute inflammation, degeneration and hyperplasia in the nasal tissues after one day and 5 days, respectively, in rats exposed to ≥ 50 ppm (equivalent to 0.195 mg/L), the lowest concentration tested. Accordingly, a NOAEC for respiratory tract irritation could not be established in these studies. Reversibility of the effects on the olfactory epithelium, despite continuous exposure, indicated possible recovery after cessation of exposure. No information was available on the respiratory irritation after dimethyl disulphide exposure in humans.

Dimethyl disulphide induces local cytotoxic irritant effects. Respiratory tract irritation was observed in rats after a 24h continuous inhalation exposure at ≥ 12.5 ppm (0.048 mg/L). Respiratory irritant effects were characterised by a concentration-related increase in the incidence of microscopic lesions. DMDS furthermore caused acute inflammation, degeneration and hyperplasia in the nasal tissues after one day and 5 days, respectively, in a 1- and 5-day inhalation toxicity study (6h/d exposure) in rats at 50 ppm (equivalent to 0.19 mg/L). Reversibility of effects indicated possible recovery after cessation of exposure. On the basis of the respiratory irritant effects observed for a short duration after exposure in rats and which may be reversible as presented in these studies, dimethyl disulphide meets the criteria for classification and labelling as a transient specific target organ toxicant (single exposure) of category 3 for respiratory tract irritation (STOT SE 3, H335: May cause respiratory irritation) according to CLP (Annex I, Part 3.8.2.2.1).

Conclusion for irritation/corrosion: The concern for eye and respiratory tract irritation is confirmed, meeting the criteria for classification and labelling according to CLP criteria.

7.9.3. Sensitisation

Skin Sensitisation

The skin sensitising potential of dimethyl disulphide was investigated in mice and guinea pigs. Results of a mouse LLNA according to OECD TG 429/B.42 and a Buehler assay according to OECD TG 406/B.6 using guinea pigs are available. Additionally, results from three *in vitro* sensitisation studies addressing key steps of the adverse outcome pathway for skin sensitisation as defined by OECD were reported: Direct peptide binding assay (DPRA), Dendritic cell line activation assay (MUSST) and Keratonocyte activation assay (LuSens), which were assessed as further information. In the DPRA a high chemical reactivity of dimethyl disulphide was noted, but an induction of dendritic cell activity or a keratocyte activating potential of dimethyl disulphide was not observed in the MUSST and LuSens, respectively. No human data on the sensitising potential of dimethyl disulphide are available. In the available studies dimethyl disulphide was used as test material. The results of the both animal studies on skin sensitisation are summarised in the following table.

Table 17

EXPERIMENTAL DATA ON SKIN SENSITISATION	
Reference Species; strain; sex; testing method	**Results**
TL3 (2012) **Mouse**; female; CBA LLNA according to OECD TG 429 / B.42	**Skin sensitizer, moderate skin sensitization potency in mice** DMDS (purity 99.8 %) Vehicle: acetone/olive oil (4:1v/v); 2.5, 5.0, 10, 25 and 50 % the irritant potential of the test item was assessed in parallel by measurement of ear thickness on days 1, 2, 3 and 6; result: absence of local irritation due to the absence of a dose-response relationship a second counting was performed to check the disintegration count results; the values obtained at the first count were confirmed; Stimulation index (SI): 2.5 %: 2.99/3.38; 5.0 %: 2.40/2.40; 10 %: 1.90/1.85; 25 %: 3.30/3.58; 50 %: 4.75/4.77 Significant lymph proliferation (SI > 3) was noted at concentrations of 2.5, 25 and 50 %; EC_3-value is approx. 2.5 % Reliability check: hexyl cinnamic aldehyde (CAS 101-86-0), 25 %: 20.98/19.98
TL6 (1985d) **Guinea pig**; male; Hartley; Buehler assay according to OECD TG 406/ B.6	**No skin sensitisation in guinea pigs** DMDS(purity unknown) Induction: undiluted e.d., 10 applications every 2 days (excluding the weekend) for 6h/d; Challenge: undiluted e.d., 10 days after the last induction No irritation was noted following the induction or challenge phases. TG 1./2. chall.: 24/48h: 0/10 Negative control: 24/48h: 0/10 Reliability check: 0.3 % DNCB: 1. chall.: 0/10; 2. chall.: 8/10 severe sensitization

The data for skin sensitisation of dimethyl disulphide was obtained from animal testing according to the existing testing guidelines. The data submitted for registration to the endpoint skin sensitisation are suitable for evaluation. Sufficient information is available for the evaluation of the skin sensitising potential of DMDS. The results of a guideline compliant mouse LLNA indicate that dimethyl disulphide may be considered to be a moderate skin sensitiser. In a second study performed according to the Buehler assay, dimethyl disulphide did not induce skin sensitisation in guinea pigs.

No information was available, whether dimethyl disulphide has led to sensitisation by skin contact in humans.

Data for skin sensitisation of dimethyl disulphide was obtained from animal testing according to the existing testing guidelines. Dimethyl disulphide has shown a clear evidence of skin sensitisation in a guideline compliant mouse LLNA. Dimethyl disulphide induced skin sensitisation in mice with moderate skin sensitisation potency, EC_3-value of 2.5 %. The available results from animal testing are sufficient for a refined evaluation allowing the sub-categorisation of dimethyl disulphide.

Comparing with criteria for hazard category and sub-categories for skin sensitisers according to the CLP Regulation a substance shall be classified for:

Sub-category 1A for skin sensitisation based on animal test results:

LLNA of EC_3-value ≤ 2 %

Based on the available data, sub-category 1A is not appropriate, because the criteria are not fulfilled.

Sub-category 1B for skin sensitisation based on animal test results:

LLNA of EC_3-value > 2 %

Dimethyl disulphide induces skin sensitisation in mice with moderate skin sensitisation potency (EC_3-value of 2.5 %). In comparison to the given criteria for the hazard category and sub-categories for skin sensitisation according to the CLP Regulation dimethyl disulphide fulfils the criteria for classification in the hazard class as skin sensitiser sub-category 1B, H317, because a moderate skin sensitisation potency (EC_3-value of > 2 %) was observed in the mouse LLNA. Based on the available data, dimethyl disulphide meets the criteria for classification in the hazard class as skin sensitiser sub-category 1B, H317: May cause an allergic skin reaction.

Conclusion for skin sensitisation: The eMSC considers that dimethyl disulphide induces skin sensitisation in mice with moderate skin sensitisation potency, meeting the criteria for classification and labelling according to CLP criteria.

7.9.4. Repeated dose toxicity

No initial and no additional concern was identified.

7.9.5. Mutagenicity

No initial and no additional concern was identified.

7.9.6. Carcinogenicity

No initial and no additional concern was identified.

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

The potential of dimethyl disulphide to induce reproductive and/or developmental toxicity was evaluated in various studies with rats and one study in rabbits. In all studies dimethyl disulphide was used as test material. The results of experimental studies on reproductive and developmental toxicity are summarised in the following table.

TABLE 18

EXPERIMENTAL DATA ON REPRODUCTIVE AND DEVELOMENTAL TOXICITY	
Reference Species; strain; sex; testing method	**Results**
TL2 (2006a)	DMDS (purity: 99.8 %)

Key study for reproductive toxicity (fertility) **Rat**; male/female; Sprague-Dawley (30/sex/dose) Two Generation Reproductive Toxicity Study according to OECD TG 416; GLP compliant Inhalation (vapour, whole-body) Exposure duration: 6 h/day, 7 days per week. F0 and F1 males and females were exposed to test atmosphere for a minimum of 70 consecutive days prior to mating. Exposure of F0 and F1 males continued through mating until euthanasia. Exposure of F0 and F1 females throughout mating and gestation until GD 20; no exposure of females from GD 21 until lactation day 4. Re-initiation of exposure on lactation day 5 until euthanasia, but during exposure dams were separated from litters. All F0 and F1 females were allowed to deliver and rear their pups until weaning on lactation day 28.	Vehicle: clean air Exposure concentrations: 5, 20, 80 ppm Results; no mortality; no functional effects on reproduction (estrous cycles, mating and fertility indices, number of days between pairing and coitus, and gestation length, spermatogenetic parameters, ovarian primordial follicles) in any treatment group (F0 and F1); no adverse effects on pups born to exposed dams (F1 and F2); general systemic toxicity at 20 ppm and 80 ppm in F0 and F1 parental males and females with persistent decrements in mean body weights, body weight gains and/or food consumption; potential exposure-related effects on the adrenal glands (increase in incidences of vacuolisation of the adrenal cortex or increased adrenal gland weights relative to final body weight or brain weight) in F0 and F1 parental animals at 80 ppm but not at 5 ppm. **NOAEC$_{\text{(parental systemic toxicity; F0 and F1)}}$:** **5 ppm (male/female)** Based on persistent decrements in mean body weights, body weight gains and/or food consumption, increase in the incidence of vacuolisation of the adrenal cortex or increased adrenal gland weights at 20 ppm. **NOAEC$_{\text{(reproductive toxicity-fertility; F0 and F1)}}$:** **80 ppm (highest tested concentration) (male/female)** No effects on (functional) reproductive parameters. **NOAEC$_{\text{(developmental toxicity; F0 and F1)}}$:** **80 ppm (highest tested concentration)** No effects on (functional) reproductive parameters.
TL2 (2006b) **Rat**; male/female; Sprague-Dawley (12/sex/dose) Reproduction/ Developmental Toxicity Screening Test according to OECD TG 421; GLP compliant Inhalation (vapour, whole-body) Exposure duration: 6 h/day, 7 days per week. F0 and F1 males and females were exposed to test atmosphere for 14 consecutive days prior to mating. Exposure of F0 males continued through mating until euthanasia. Exposure of F0 females throughout mating and gestation until GD 20; no exposure of females from GD 21 until lactation day 4. Re-initiation of exposure on lactation day 5 through GD 27, but during exposure dams were separated from litters.	DMDS (purity: 99.5 %) Vehicle: clean air Exposure concentrations: 5, 50, 150 ppm Results: No mortality; no functional effects on reproduction (estrous cycles, mating and fertility indices, number of days between pairing and coitus, and gestation length, spermatogenetic parameters, ovarian primordial follicles) in any treatment group; evidence of general toxicity more pronounced in F0 males than F0 females; decrements in body weight gain and food consumption at 50 ppm (males only) and 150 ppm (males and females); reduced F1 pup body weights and body weight gains at 50 and 150 ppm; mean F1 male and female body weights and body weight gains reduced further after 1 week of DMDS exposure during the postweaning period (only 1 pup/sex/litter examined). **NOAEC$_{\text{(parental systemic toxicity)}}$: 5 ppm (males)** **50 ppm (females)** Based on decrements in body weight gain and food consumption in the 50 ppm (males only) and 150 ppm (males and females) treatment.

One F1 pup/sex/litter was selected for inhalation exposure beginning following weaning at PND 28 and continuing until PND 34.	**NOAEC$_{(reproductive\ toxicity\ -\ fertility)}$:** **150 ppm (highest tested concentration)** No effects on (functional) reproductive parameters. **NOAEC$_{(neonatal\ toxicity)}$:** **5 ppm (male/female)** Based on reduced body weights and body weight gains at 50 ppm.
TL2 (2006c) Key study for developmental toxicity **Rat**; female; Sprague-Dawley (27/sex/dose) Prenatal Developmental Toxicity Study according to OECD TG 414; GLP compliant Inhalation (vapour, whole-body) Exposure duration: 6 h/day, 7 days/week, GD 6 - 19	DMDS (purity: 99.8 %) Vehicle: clean air Exposure concentrations: 5, 20, 80 ppm Results: lower mean maternal body weight gains and food consumption noted at 80 ppm; lower mean fetal weight and increased mean litter proportions of several skeletal variations (delay in ossification) at 80 ppm. **NOAEC$_{(maternal\ toxicity)}$: 20 ppm** Based on lower mean maternal body weight gains and food consumption at 80 ppm. **NOAEC$_{(developmental\ toxicity)}$: 20 ppm** Based on lower mean foetal weight and increased proportions (mean/litter) of several skeletal variations (delay in ossification) at 80 ppm. **NOAEC$_{(teratogenicity)}$:** **80 ppm (highest tested concentration)** No adverse effect or malformations in pups.
TL1 (1991) **Rat**; female; Sprague-Dawley (30/sex/dose) Prenatal Developmental Toxicity Study according to OECD TG 414; GLP compliant Inhalation (vapour, whole-body) Exposure duration: 6 h/day, 7 days/week; GD 6 - 15 Test duration: until GD 20	DMDS (purity: 99.9 %) Vehicle: clean air Exposure concentrations: 5, 15, 50 ppm Results: no mortality; higher incidences of rough haircoat in dams at 50 ppm; reductions in weight gain of dams at 15 and 50 ppm (16 and 40 % lower than controls, respectively); lower food intake of dams at 50 ppm; litter size smaller than expected in all groups including controls; reduced litter and foetal weights at 50 ppm; slightly higher incidences of retarded ossificationat 50 ppm (considered as delayed maturation due to lower body weight). **NOAEC$_{(maternal\ toxicity)}$: 5 ppm** Based on dose related reductions in maternal weight gain at 15 and 50 ppm **NOAEC$_{(teratogenicity)}$:** **50 ppm (highest tested concentration)** No adverse effects or malformations in pups **NOAEC$_{(embryonic/foetal\ toxicity)}$: 15 ppm** Reduced litter and foetal weights at 50 ppm.
TL2 (2005) Prenatal Developmental Toxicity Study according to OECD TG 414; GLP compliant	DMDS (purity: 99.8 %) Vehicle: clean air Exposure concentrations: 15, 45, 135 ppm Results: transient clinical observations at 45 and 135 ppm on the first day of exposure only; decreased food consumption at 135 ppm throughout the first 2 weeks of

Rabbit; female; New Zealand White (24/sex/dose) Reproduction/ Developmental Toxicity Screening Test according to OECD TG 421; GLP compliant Inhalation (vapour, whole-body) Exposure duration: 6 h/day, 7 days/week, GD 6 - 28	exposure (in absence of effects on maternal body weight gains, findings considered as not adverse); dark red discoloration of or dark red areas on the lungs (generally all lobes) at all exposure levels and in controls; no effects in litters or on litter size; **$NOAEC_{(maternal\ toxicity)}$:** **135 ppm (highest tested concentration)** No adverse effects in dams **$NOAEC_{(developmental\ toxicity)}$:** **135 ppm (highest tested concentration)** No adverse effects in pups **$NOAEC_{(teratogenicity)}$:** **135 ppm (highest tested concentration)** No teratogenic effects

Reproductive toxicity (fertility):

A 2-Generation Reproductive Toxicity Study with rats (key study for reproductive toxicity – fertility) was conducted according to OECD TG 416 to evaluate the potential adverse effects of dimethyl disulphide on male and female reproductive capabilities, including gonadal function, oestrous cyclicity, mating behaviour, conception, gestation, parturition, lactation and weaning of the F0 and F1 generations and F1 and F2 neonatal survival, growth and development. One litter per dam was produced in each generation. There were no functional effects on reproduction (oestrous cycles, mating and fertility indices, number of days between pairing and coitus, and gestation length) at any DMDS-exposure concentration. An exposure level of 80 ppm (highest tested concentration) was considered to be the NOAEC for reproductive toxicity when DMDS was administered via whole-body inhalation to Sprague-Dawley rats, while systemic toxicity was evident in the 20 and 80 ppm group F0 and F1 parental males and females with persistent decrements in mean body weights, body weight gains and/or food consumption. Potential exposure-related effects on the adrenal glands (an increase in the incidence of vacuolization of the adrenal cortex or increased adrenal gland weights [relative to final body weight and brain weight]) were noted in the F0 and F1 parental animals in the 80 ppm exposure group. The NOAEC for parental toxicity was considered to be 5 ppm.

In a Reproduction/Developmental Toxicity Screening Test performed according to OECD TG 421, rats were exposed to dimethyl disulphide at three different concentrations (5, 50 and 150 ppm) prior and during mating, and females were further exposed during gestation and lactation. There were no functional effects on reproduction (mating and fertility indices, number of days between pairing and coitus, and gestation length) at any exposure concentration. Therefore, an exposure level of 150 ppm (highest tested concentration) was considered as NOAEC for parental reproductive toxicity when administered via whole-body inhalation exposure to rats. Evidence of systemic toxicity was more pronounced in the F0 males than in the F0 females and consisted of decrements in body weight gain and food consumption in the 50 ppm (males only) and 150 ppm exposure groups. The NOAEC for parental systemic toxicity was considered to be 5 ppm for males and 50 ppm for females.

Conclusion for reproductive toxicity (fertility):

The eMSCA considers that dimethyl disulphide does not induce reproductive toxicity (fertility) in rats, and thus does not meet the criteria for classification and labelling according to CLP criteria.

Developmental toxicity

In a key inhalation Prenatal Developmental Toxicity Study performed with rats according to OECD TG 414, a maternal LOAEC of 80 ppm and a NOAEC of 20 ppm were determined based on lower maternal body weight gains and decreased food consumption. The LOAEL for foetal/developmental toxicity was considered to be 80 ppm as well, based on lower mean foetal weight and increased mean litter proportions of several skeletal variations (delay in ossification). The NOAEC for foetal/developmental effects was 20 ppm and no teratogenic effects were observed.

In an earlier inhalation Prenatal Developmental Toxicity Study performed with rats according to OECD TG 414, exposure to DMDS at 50 ppm elicited maternal toxicity with associated foetal growth retardation. Although no mortality occurred, maternal toxicity was evidenced as reductions in weight gain were observed in dams exposed to DMDS at 15 and 50 ppm. Furthermore, food intake of dams was decreased in the 50 ppm treatment group. Foetal toxicity was demonstrated by lowered body weights and delayed ossification, while no malformations were noted. In this study, the NOAEC was 5 ppm for maternal toxicity, and 15 ppm for embryonic/foetal effects. No teratogenic effects were observed.

Dimethyl disulphide (DMDS) was also evaluated in an inhalation Prenatal Developmental Toxicity Study in rabbits performed according to OECD TG 414. Although slight transient effects were observed in dams exposed to DMDS at 45 and 135 ppm, the highest tested concentration (135 ppm) was considered to be the NOAEC for maternal toxicity (based on the lack of adverse effects on dams). No effects of DMDS on intrauterine growth and survival were reported and no teratogenic effects were observed. Thus, the highest tested concentration (135 ppm) was considered to be the NOAEC for developmental toxicity (based on lack of adverse effects on litters) when dimethyl disulphide was administered via whole-body inhalation to rabbits.

A Reproduction/Developmental Toxicity Screening Test performed with rats conducted according to OECD TG 421 detected neonatal effects (reduced pup body weights and body weight gains) at 50 ppm and 150 ppm dimethyl disulphide. Mean F1 male and female body weights and body weight gains were reduced further after 1 week of direct test article exposure during the post-weaning period (only 1 pup/sex/litter examined). The NOAEC for neonatal effects was determined to be 5 ppm. The NOAEC for parental systemic toxicity was considered to be 5 ppm for males and 50 ppm for females. In a 2-Generation Reproductive Toxicity follow-up Study with rats conducted according to OECD TG 416, neither functional effects on reproduction nor any adverse effects on pups and pup development were detected at any DMDS-exposure concentration. An exposure level of 80 ppm (highest tested concentration) was considered to be the NOAEC for developmental toxicity when DMDS was administered via whole-body inhalation to rats, whereas the NOAEC for parental toxicity was considered to be 5 ppm (based on decrements in mean body weights, body weight gains and/or food consumption).

Conclusion for developmental toxicity

Based on the findings of the above mentioned 2-Generation Reproductive Toxicity Study in rats and the Prenatal Developmental Toxicity Studies in rats and rabbits, which did not find any teratogenic and developmental effects only at concentrations lower or equal than the concentrations inducing maternal toxicity, the eMSC considers that dimethyl disulphide does not induce developmental toxicity in rats, and thus does not meet the criteria for classification and labelling according to CLP criteria.

7.9.8. Hazard assessment of physico-chemical properties

Not assessed.

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

Since no exposure scenarios for consumers were submitted by the registrants, the eMSCA did not derive DNEL/DMEL values for the general population.

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

There is currently no harmonised classification of dimethyl disulphide with respect to human health hazards, but there is currently a proposal in the CLH process. RAC will evaluate and adopt a CLH opinion by 15 November 2018 on the following hazard classes: flammable liquids, acute toxicity, skin corrosion/irritation, serious eye damage/eye irritation, skin sensitisation, germ cell mutagenicity, reproductive toxicity, specific target organ toxicity after single and repeated exposure, aspiration hazard and hazardous to the aquatic environment.

In the substance evaluation the human health hazards were assessed. Evaluation performed on the available data led to the conclusion that a harmonised classification and labelling is warranted. It should be noted that the CLH proposal for acute toxicity deviates from the classification considered appropriate by the eMSCA.

In the following table the eMSCA's conclusions for classification or non-classification of dimethyl disulphide based on the examination of the existing toxicity data for the human health endpoints are given. However, as soon as a harmonised classification and labelling of dimethyl disulphide is adopted, this harmonised classification and labelling is legally binding at Community level to ensure an adequate risk management throughout the European Community.

Table 18

CONCLUSIONS ON CLASSIFICATION FOR DMDS			
Endpoint	**Route Species**	**Value/Effect**	**Classification proposal (Criteria)**
Acute toxicity	Oral rat	$LD_{50,\ rat,\ male,\ female}$ = 190 mg/kg bw (range of 150-240 mg/kg bw)	**Classification proposal:** Acute Tox. 3, H301: Toxic if swallowed (50 < ATE ≤ 300 mg/kg bw)
Acute toxicity	Inhalation rat	$LC_{50,\ rat,\ male,\ female}$ = 1310 ppm equivalent to 5.05 mg/L/4h 4(with 95 % confidence limits of 4.49-5.66 mg/L/4h)	**Classification proposal:** Acute Tox. 3, H331: Toxic if inhaled (vapour: 2.0 < ATE ≤ 10.0 mg/L/4h)
Acute toxicity	Dermal rabbit rat	$LD_{50,\ rabbit,\ male,\ female}$ > 2000 mg/kg bw	No classification
Irritation	Skin rabbit	slightly irritating to skin	No classification

Irritation	Eye rabbit	Irritating to eyes	**Classification proposal:** Eye Irrit. 2, H319: Causes serious eye irritation (iris ≥ 1)
Irritation	Respiration tract rat	respiratory tract irritation single exposure (6h) or for 6h/d for 5 consecutive days: $LOAEC_{local\ rat\ male,\ female}$ = 50 ppm (0.195 mg/L) 24h exposure: $LOAEC_{local\ rat\ male}$ = 12.5 ppm (0.048 mg/L)	**Classification proposal:** STOT SE 3, H335: May cause respiratory irritation (Annex I, Part 3.8.2.2.1)
Sensitisation	Skin mouse	moderate skin sensitisation potency, EC_3-value of 2.5 %	**Classification proposal:** Skin sensitiser sub-category 1B, H317: May cause an allergic skin reaction (EC_3-value > 2 %)
Repeated dose toxicity	Inhalation whole body, 6h/d, 5d/wk, 4wk recovery, 90-day study Rat (3 studies)	Port of entry: changes in nasal tissues $NOAEC_{local}$ = 5 ppm (0.019 mg/L); $LOAEC_{local}$ = 10 ppm (0.039 mg/L), based on microscopic dose-related changes in the nasal mucosa (minimal to moderate atrophy and micro-cavitation of the olfactory epithelia and respiratory squamous metaplasia in the anterior nasal cavity; degeneration of the nasal olfactory epithelium, nasal level II, in the nasal turbinates), reversible after 4 wk treatment-free recovery period, but squamous cell metaplasia still evident in the 50 ppm and 250 ppm groups $NOAEC_{sys}$ = 10 ppm (0.039 mg/L); $LOAEC_{sys}$ = 20 ppm (0.078 mg/L) based on: ↓ bw and body weight gains in both sexes	No classification (vapour, rat: 0.2 < C ≤ 1.0 mg/L/6h/d)
Repeated dose toxicity	Dermal, 6h/d, occlusive, 28-day study rabbit	Critical effect: dose-dependent skin irritation 1063 mg/kg bw/d: severe erythema 106 mg/kg bw/d: erythema, oedema, and ischemic necrosis, with increased severity and incrustation $LOAEC_{local}$ = 10.6 mg/kg bw/d Systemic effects: 1063 mg/kg bw/d: mortality (5m, 4f), myocarditis and myocardial degeneration (f) 106 mg/kg bw/d: lethargy $NOAEL_{sys}$ = 10.6 mg/kg bw/d	No classification for systemic effects (rat or rabbit: 20 < C ≤ 200 mg/kg bw/d)
Mutagenicity	Other in vitro in vivo	Negative results in: Bacterial reverse mutation assay (Ames test); *In vitro* gene mutation assay, CHO cells; *In vitro* chromosomal aberration in human	No classification Negative in mutagenicity and genotoxicity studies *in vitro* and *in vivo*

		peripheral blood lymphocytes; *In vivo* micronucleus assay, mouse; micronucleus assay rat; *In vitro* unscheduled DNA synthesis, primary rat hepatocytes	
Reproductive toxicity: fertility impairment	Inhalation whole body, 6h/d, 7d/wk rat	Reproductive toxicity: NOAEC = 80 ppm (311.4 mg/m^3), the highest dose tested Parental toxicity: LOAEL = 20 ppm (77.8 mg/m^3), based on ↓ bw, bw gains and food consumption in F0+1 males and females; ↑ incidence of vacuolisation of the adrenal cortex or ↑ adrenal gland weights NOAEC = 5 ppm (19.5 mg/m^3) Offspring/developmental: NOAEC = 80 ppm (311.4 mg/m^3), the highest dose tested, based upon the lack of treatment-related effects on the development of the offspring of both generations	No classification 2-generation toxicity study: no evidence of reproductive organ or mammary gland pathology or of reproductive or postnatal toxicity up to the highest concentration tested; Parental toxicity (F0+F1 males and females adults)
Reproductive toxicity: developmental toxicity	Inhalation whole body, 6h/d, 7d/wk rat rabbit	<u>Rat:</u> Maternal: NOAEC = 20 ppm (77.8 mg/m^3) based on ↓ bw gains, and food consumption Developmental: NOAEC = 20 ppm (77.8 mg/m^3) based on ↓ foetal weight and ↑ mean litter proportions of several skeletal variations) Teratogenicity: NOAEC = 80 ppm (311.4 mg/m^3), the highest dose tested <u>Rabbit:</u> Maternal: NOAEC = 135 ppm (525.5 mg/m^3), the highest dose tested Developmental: NOAEC = 135 ppm (525.5 mg/m^3), the highest dose tested Teratogenicity: NOAEC = 135 ppm (525.5 mg/m^3)	No classification Rat: no developmental toxicity; Rabbit: no developmental toxicity
Neurotoxicity	Inhalation whole body 1) single exposure: 6h rat 2) 6h/d, 7d/wk, 13 wk rat	1) Single exposure (6h): No findings in nervous tissues. 750 ppm (2.92 mg/L), m/f: ↑ increased grooming behaviour and urination, ↓ body temperature, ↓ total motor and locomotor activities 200 ppm (0.778 mg/L): ↓ total motor and locomotor activities (f) $NOAEC_{male}$ = 200 ppm (0.778 mg/L) $NOAEC_{female}$ = 100 ppm (0.389 mg/L) 2) Sub-chronic exposure: No findings in nervous tissues.	No classification No classification regard to STOT RE

		$LOAEC_{male}$ = 80 ppm (0.311 mg/L, highest concentration tested), based on ↓ total motor activity during the 12th week, however, not as apparent for these animals at other time points during the study, no such effects in females $LOAEC_{sys, male}$ = 80 ppm (0.311 mg/L), based on ↓ bw, overall bw gain, and food consumption $NOAEC_{systemic, neurotoxicity, male}$ = 20 ppm (0.0778 mg/L) $NOAEC_{systemic, neurotoxicity, female}$ = 80 ppm (0.311 mg/L)	(vapour, rat: 0.2 < C ≤ 1.0 mg/L/6h/d)

7.10. Assessment of endocrine disrupting (ED) properties

No initial and no additional concern was identified. Not assessed.

7.11. PBT and VPVB assessment

No initial and no additional concern was identified. Not assessed.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

Not assessed.

7.12.1.2. Consumer

No consumer uses resulting in consumer exposure to dimethyl disulphide were identified. Therefore, no exposure assessment for consumers was necessary.

According to the CSRs, dimethyl disulphide is used as intermediate in chemical synthesis, in refineries as hydrotreating catalyst activator, in petrochemical sites as anti-coking agent and as laboratory reagent. Furthermore, it is reported that dimethyl disulphide is completely consumed during use, and there are no professional or consumer uses, service life, and waste treatment for dimethyl disulphide. Consequently, no exposure scenarios for consumers were submitted by the registrants.

7.12.2. Environment

Release to the environment of this substance is likely to occur from manufacturing of the substance as such. Also industrial uses might lead to release to the different environmental media. These are: as an intermediate in further manufacturing of another substance (use of intermediates), use in refineries as hydrotreating catalyst activator and use in petrochemical sites as anti-coking agent.

Assessments during substance evaluation not only refer to emissions from the different life cycle steps of one registration dossier but also for all identified life cycle steps of all registrations. A regional background concentration PECregional,compartment for the different environmental compartments (air, water, sediment, soil etc.) was calculated from combined exposure of all registration dossiers and used for assessment of the individual exposure scenarios.

As part of the substance evaluation the outcome of the exposure assessments available were reviewed by calculations of the eMSCA using the operational conditions provided with the exposure scenarios in the Chemical Safety Reports. The only deviation was the use of the aggregated PECregional for the single environmental compartments.

More detailed information on the outcome of the exposure assessment related to individual dossiers is provided in the confidential annex. Here only a short executive summary identified uses of DMDS is provided.

In case of registrations as OnSite Isolated Intermediate (OSII) or Transported Isolated Intermediate (TII) where manufacture and use of DMDS also takes place within the European Union only qualitative descriptions on technical and procedural measures preventing release of DMDS to the different environmental compartments were provided as required for registrations under article 17 and 18 REACH legislation. As there is no obligation to provide Exposure Scenarios for OSII or TII registrations the releases to the environment cannot be calculated based on information on operational conditions in the specific dossier.

The eMSCA conducted a rough estimation of the PECregional in the different environmental compartments assuming low level release. An aggregated regional background concentration PECregional,compartment for the different environmental compartments (air, water, sediment, soil etc.) was calculated from combined exposure of all types of registrations (Art. 14, 17 and 18) and used for assessment of the individual exposure scenarios.

The review of the operational conditions and risk assessments in the exposure scenarios for manufacture of DMDS, use as anti-coking agent and as hydrotreating catalyst activator did not indicate risks for the environment.

The review of the exposure scenarios for the use as intermediate revealed some doubts regarding the assumed effectivity of the mandatory waste water treatment technology. This was because there was no description about the technique itself allowing to rate whether or not the very high effectivity is plausible or not. This might lead to a possible concern for environmental risk characterization ratios (PEC: PNEC) above RCR = 1 in case the waste water treatment turns out to be less effective. Accordingly an information request for further data about the mandatory water treatment technology in place resulted from the substance evaluation process.

As part of the substance evaluation the outcome of the exposure assessments available in the article 14 registration were reviewed by calculations of the eMSCA using the operational conditions provided with the exposure scenarios in the Chemical Safety Reports. The only deviation was the use of the aggregated PECregional for the single environmental compartments. The outcome initially showed indications for exceedance of risk characterization ratio (PEC : PNEC) trigger value 1 for the use of dimethyl disulphide as intermediate for synthesis of other on which indicated adverse effects for organisms in the environmental compartments freshwater and sediment.

The registrant provided the requested data showing that the assessment for this use is based on site specific conditions. The eMSCA recalculated the exposure assessment for the use as intermediate using the provided site specific information on operational conditions and local parameters for the environment. The revised PEC: PNEC ratios are well below the trigger value of 1 and therefore the suspected concern for the environment was refuted.

7.12.3. Combined exposure assessment

Substance evaluation allows the eMSCA to aggregate emissions from the different registrations and calculate a hypothetical aggregated regional concentration. A basic approach was used to calculate the individual regional background concentrations for the separate registrations of DMDS, also as isolated intermediate (OSII and TII).

As no information is available regarding environmental emissions of DMDS resulting from manufacture processes of OSII and TII it was assumed that except of the tonnages manufactured the operational conditions, the release rates from the process and the emission reduction measures in place before release to the different environmental compartments are identical with the parameters in the Exposure Scenario for manufacture of DMDS in the article 10 registration. Even when the results for the manufacturing step might not reflect the real emission situation and will be higher than in reality they were used as inputs for calculation of the aggregated PECregional. Moreover it was assumed that the resulting PECregional cover the regional releases of both – the whole life cycle of the article 10 registration and the OSII/TII registrations.

In a first step the eMSCA used EUSES v2.1.2 for calculation of registrant specific PECregional in the different environmental compartments. For every relevant environmental compartment the PECregional of the individual registrants were aggregated.

The summarised PECregional were used later for calculation of the predicted environmental concentration and risk characterisation in the exposure scenarios of the article 10 registration. The resulting PECregional are presented in the table below:

Table 19

AGGREGATED $PEC_{REGIONAL}$ RESULTING FROM ALL REGISTRATIONS		
	Aggregated value	**unit**
$PEC_{Regional\_(surface\_water)}$	4.11E-06	mg/L
$PEC_{Regional\_(seawater)}$	4.11E-07	mg/L
$PEC_{Regional\_(sediment)}$	7.49E-05	mg/kg (dwt)
$PEC_{Regional\_(air)}$	4.35E-06	mg/m^3
$PEC_{Regional\_(soil\_agric.)}$	2.11E-07	mg/kg (dwt)

$PEC_{Regional\_(soil\_agric.\_porew)}$	8.73E-09	mg/L
$PEC_{Regional\_(soil\_grassland)}$	2.11E-07	mg/kg (dwt)

No overall exposure assessment at local stage was performed for the different uses because wide spread uses of dimethyl disulphide by professional workers or consumers are not supported by the registrants.

7.13. Risk characterisation

The risk characterisation for workers was not assessed (see 7.12.1.1).

No risk characterisation for consumers was performed as no consumer uses resulting in consumer exposure to dimethyl disulphide have been identified (see 7.12.1.2).

The risk characterisation for the environment was performed using the Predicted No Effect Concentrations concluded from the substance evaluation process, which are presented in the table below:

Table 20

RISK CHARACTERISATION FOR THE ENVIRONMENT					
PNEC		**Basis**	**Factor**	**K susp-water**	**RHOsusp**
Freshwater (mg/l)	2.50E-04	Daphnia freshwater 21d NOEC (TL5, 2011a)	10 [1)]		
Seawater (mg/l)	2.50E-04	Daphnia freshwater 21d NOEC (TL5, 2011a)	10 [2)]		
Intermittent release (mg/kg)	9.70E-03	Fish freshwater 96h-LC_{50} (TL8, 2007c)	100 [3)]		
Sediment (mg/kg)	4.37E-04		EPM [4)]	2.009	1150
marine sed. (mg/kg)	4.37E-04		EPM [4)]	2.009	1150
Soil (mg/kg)	1.00E+00	Collembolan soil 28d-NOEC (TL10, 2006a)	10 [5)]		

[1)] Guidance on information requirements and chemical safety assessment Table, R.10-4 Assessment factors to derive a $PNEC_{aquatic}$
[2)] Guidance on information requirements and chemical safety assessment, Table R.10-5 Assessment factors proposed for deriving PNECwater for saltwater for different data sets, note d)
[3)] TGD Guidance on information requirements and chemical safety assessment, R.10.3.3 Calculation of PNEC for water in the case of intermittent releases
[4)] TGD Guidance on information requirements and chemical safety assessment, R.10.5.2.1 Calculation of PNEC for freshwater sediment using equilibrium partitioning

[5)] TGD Guidance on information requirements and chemical safety assessment, R.10.5.3.1 Calculation of PNEC for marine sediment using equilibrium partitioning

The risk characterisation for the regional background concentrations is based on the aggregated values for all registrations of dimethyl disulphide, assessed by the eMSCA during substance evaluation. The aggregated $PEC_{regional}$ refer to all registrations also including the ones being registered as onsite intermediates and transported intermediates, both used under strictly controlled conditions. For the acceptance of conditions for calculation please see section 7.12.3 of this document.

Table 21

RISK CHARACTERISATION FOR REGIONAL BACKGROUND CONCENTRATIONS	$RCR_{regional}$
freshwater	1.64E-02
seawater	1.64E-03
freshwater sediment	1.71E-01
marine sediment	1.71E-02
air	-
soil (grassland)	2.11E-07
soil (agricultural)	8.73E-09
soil	2.11E-07

The values lead to the conclusion that the regional background concentrations normally only contribute to a little extend to the RCRs in the individual exposure scenarios.

No overall risk characterisation at local stage was performed for the different uses because wide spread uses of dimethyl disulphide by professional workers or consumers are not supported by the registrants.

7.14. References

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7.15. Abbreviations

ATE	Acute Toxicity Estimate
BMD10 %	Benchmark Dose representing 10 % response
bw	Body weight
C&L	Classification and Labelling
CAS	Chemical Abstract Service
CLP	Regulation on Classification Labelling and Packaging of Chemicals and Mixtures
CoRAP	Community Rolling Acting Plan
CSR	Chemical Safety Report
d	Day
DMDS	Dimethyl disulphide
DMEL	Derived Minimal Effect Level
DNEL	Derived No-Effect Level
dwt	dry weight
EC	European Community
EC_3	Effective Concentration inducing a stimulation index (SI) of 3 in a standard LLNA
ECHA	European Chemicals Agency, Helsinki
eMSCA	Evaluating Member State Competent Authority
f/F	Female
GHS06	Hazard pictogram, Symbol: skull and crossbones
GHS07	Hazard pictogram, Symbol: exclamation mark
GHS08	Hazard pictogram, Symbol: health hazard
GHS09	Hazard pictogram, Symbol: environment
h	Hour
H	Hazard statement
IUCLID	International Uniform Chemical Information Database
kg	Kilogram
L	Litre
LD/C_{50}	Median Lethal Dose/Concentration (causing 50 % lethality)
LLNA	Local Lymph Node Assay
LOAEL/C	Lowest Observed Adverse Effect Level/Concentration
m/M	Male
m^3	Cubic meter
mg	Milligram
mg/kg bw	Milligrams per kilogram body weight
mg/kg bw/d	Milligrams per kilogram body weight per day
mg/L	Milligrams per litre
mg/m^3	Milligrams per cubic meter
mL	Millilitre
MSCA	Member State Competent Authority
MW	Molecular weight
NOAEL/C	No Observed Adverse Effect Level/Concentration
OECD	Organisation for Economic Co-operation and Development
OECD TG	OECD Test Guideline
PNEC	Predicted No-Effect Concentration
ppm	Parts per million
REACH	Regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals
SEV	Substance Evaluation
SI	Stimulation Index
STOT SE	Specific Target Organ Toxicity – Single Exposure
STOT RE	Specific Target Organ Toxicity – Repeated Exposure
wwt	wet weight