SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

2,2’-oxydiethanol

EC No 203-872-2

CAS No 111-46-6

Evaluating Member State: Hungary

Dated: 07 September 2016

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2015

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

Further information on registered substances here:

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

DISCLAIMER

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

Foreword

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

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

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

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

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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

2,2'-oxydiethanol was originally selected for substance evaluation in order to clarify concerns about:

- suspected carcinogenic property
- suspected mutagenic property
- specific target organ (kidney) toxicity
- high aggregated tonnage
- wide dispersive use
- consumer use.

During the evaluation also another concern was identified. The additional concern was:

- skin irritation.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

2,2'-oxydiethanol is included in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).

Prior to the substance evaluation, compliance check was conducted on the substance. The evaluating Member State had no information of other completed/ongoing processes relevant for this substance.

3. CONCLUSION OF SUBSTANCE EVALUATION

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

Table 1

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

4. FOLLOW-UP AT EU LEVEL

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

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	X
Actions by the registrants to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.)	

The initial and additional concerns were removed based on the data in the updated registration dossier and in the publicly available literature.

During the substance evaluation the evaluating Member State found the data on exposure insufficient and this finding was communicated to the Registrant, who updated his registration and significantly amended the data on exposure. Furthermore, an additional concern (skin irritation) was raised during the evaluation, which has been communicated to the Registrant in the course of informal consultation. In response to the concern indicated by the evaluating Member State, the Registrant updated the dossier with an in vitro skin irritation test.

Taking into account the new information, the evaluating Member State was able to conclude on every concerned endpoint and found no potential, inadequately controlled risks, hence there is no need for follow-up action at EU level.

5.2. Other actions

Not applicable.

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

Not applicable, see section 5.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

2,2'-oxydiethanol was originally selected for substance evaluation in order to clarify concerns about:

- suspected carcinogenic property
- suspected mutagenic property
- specific target organ (kidney) toxicity

- high aggregated tonnage
- wide dispersive use
- consumer use.

During the evaluation also other concern was identified. The additional concern was:

- skin irritation.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Carcinogenicity	In the key carcinogenicity study in rat performed under GLP with oral administration of 2,2'-oxydiethanol following an N-ethyl-N-hydroxyethylnitrosamine pretreatment for tumour initiation there was no increased tumour appearance compared to control. On the basis of the clear findings reported in the key study, the evaluating Member State concludes that 2,2'-oxydiethanol has no carcinogenic potential and the initial concern was removed.
Mutagenicity	2,2'-oxydiethanol proved to be not mutagenic in reliable in vitro bacterial mutagenicity, cytogenicity, sister chromatid exchange and mammalian cell gene mutation tests. The only available reliable in vivo test, the mammalian erythrocyte micronucleus assay also gave negative result. As a consequence, no mutagenic potential of 2,2'-oxydiethanol could be verified. Based on the available information,2,2'-oxydiethanol has no mutagenic potential and the initial concern was removed.
Specific target organ toxicity	2,2'-oxydiethanol causes metabolic acidosis, cortical necrosis (proximal tubule cell death) resulting in permanent renal failure. However, it was established in human proximal tubule cells in vitro that it is the metabolite of 2,2'-oxydiethanol rather than the parent compound itself, which is responsible for the adverse effects on the kidney. Moreover, the NOAEL from the oral rat study is above the guidance value (10 < C ≤ 100 mg/kg body weight/day) for classification for that category. Thus, the evaluating Member State supports the above conclusion and the initial concern is removed.
Toxicity to reproduction	In the main fertility study toxic effects of 2,2'-oxydiethanol were found on fertility and malformations were observed, but only at the highest dose tested (6125 mg/kg bw/day). It is likely that these observed effects were secondary symptoms to general maternal toxicity caused by continuous exposure.

	Further to this another study did not reveal any fertility effects or signs of developmental toxicity. The available developmental toxicity studies did not show any specific effects on offspring development. Considering all of the available results, the evaluating Member State concluded that there is no specific concern related to reproductive and developmental toxicity of 2,2'-oxydiethanol that requires further investigation in this substance evaluation.
Human exposure	There is no concern for risks posed by 2,2'-oxydiethanol if appropriate good practice is followed. If a use scenario cannot realise the containment (insufficient technical control measures) of 2,2'-oxydiethanol, appropriate personal protective equipment needs to be applied to avoid skin contact (gloves, protective clothing) and inhalation (respiratory protection) especially in cases when aerosol formation is substantial and temperature is high. Consumers' risk is possible only during misuse and accidental poisoning. This conclusion of the evaluating Member State is reinforced by the fact that, despite the high tonnage production, ill-health due to 2,2'-oxydiethanol was reported only in misuse cases. Therefore the concern related to consumer exposure is removed.
Irritation	In a Draize skin irritation test performed on rabbits, no 2,2'-oxydiethanol-related skin reactions were found (Guillot et al. 1982). These results were supported by an in vitro skin irritation test (OECD TG 439). Based on these results the Evaluating Member State concluded that 2,2'-oxydiethanol was clearly not irritant and the concern was removed. Based on the study results, no concern was identified by the evaluating Member State regarding the eye irritating properties of 2,2'-oxydiethanol.
Environmental fate properties, hazard assessment	The study results showed that the substance is biodegradable, therefore the bioaccumulation of 2,2'-oxydiethanol is considered unlikely. Based on the available data the substance is not persistent in the environment and the 2,2'-oxydiethanol does not have the potential to cause long-term adverse effects in the environment. Based on the assessed data 2,2'-oxydiethanol is not harmful to aquatic organisms and therefore there is no need for classification and labelling in this regard. Based on the available data, the evaluating Member State concludes that there is no concern for the environment.

7.2. Procedure

The substance evaluation started in March of 2015. The evaluating Member State's intention was to conduct a full substance evaluation, focusing on the initial concerns, however, evaluating other endpoints as well, in order to exclude any further potential concerns.

The evaluating Member State conducted a literature search to gather all relevant new information on the concerned endpoints, complementing the results of the previous search conducted in the screening process. The publicly available studies are listed in the report and a complete list can be found in the References part of the report. The information for which the evaluating Member State does not report if a reference comes from the registration dossier.

During the evaluation process extensive communication took place with the Registrant, who represented the members of the joint registration and he provided the evaluating Member State all the relevant studies which were used in the registration dossier.

The experts of the evaluating Member State analysed all available information regarding the examined endpoints to conclude on the properties of the substance and the potential EU-level Risk Management Measures warranted by risks controlled inadequately, and to identify any arising needs to ask for further information.

The original focus of the evaluation was on the initial concerns and the toxicity to reproduction was also included.

The evaluating Member State found the available data in the registration dossier insufficient to draw conclusions on human exposure. However, after extensive communication between the evaluating Member State and the Registrant, an update of the registration dossier was submitted with workplace measurement data, and the Registrant also provided reliable explanation on the model used, and thus satisfied the data needs.

During the evaluation process a further potential concern was raised. Regarding skin irritation, the available information was deemed insufficient to conclude on the irritative potential of the substance. Therefore, the evaluating Member State highlighted to the Registrant the need of further information and suggested an OECD guideline study to be conducted. The Registrant offered to perform the suggested study still during the evaluation process and provided unequivocal results in the above mentioned dossier update.

The evaluating Member State did not confirm any of the initial concerns. Furthermore, based on the negative results of the other endpoints of concern, the evaluating Member State did not identify any concern related to potential ED properties of the substance. Thus, no detailed evaluation of this endpoint was performed.

In order to get a full overview, the evaluation was supplemented with environmental fate properties and hazard assessment. The data evaluated in this context also did not reveal any concerns regarding persistency and biodegradability.

Taking into account the new information gathered during the substance evaluation, the evaluating Member State was able to conclude on every concerned endpoints and found no potential risk, which would not be adequately controlled. Therefore, no further RMM is deemed needed at the EU-level.

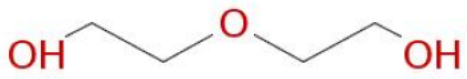
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	2,2'-oxydiethanol
EC number:	203-872-2
CAS number:	111-46-6
Index number in Annex VI of the CLP Regulation:	603-140-00-6
Molecular formula:	$C_4H_{10}O_3$
Molecular weight range:	106.1204 g/mol
Synonyms:	2,2'-oxybisethanol Ethanol, 2,2'-oxybis- Diethylene glycol

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

Structural formula:



7.4. Physico-chemical properties

The Registrant gathered enough available experimental data (literature data) to support the submitted physical and chemical properties of 2,2'-oxydiethanol.

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	0.008 hPa at 25°C
Water solubility	1000 g/L at 20°C
Partition coefficient n-octanol/water (Log P_{ow})	-1.98 LogP_{ow}
Flammability	-
Explosive properties	-
Oxidising properties	-
Granulometry	-
Stability in organic solvents and identity of relevant degradation products	-

Dissociation constant	-

7.5. Manufacture and uses

7.5.1. Quantities

According to the information on the dissemination site of ECHA, the aggregated tonnage per year is 100 000-1 000 000 tonnes.[2]

7.5.2. Overview of uses

Table 6

USES	Use(s)
Uses as intermediate	Intermediate in chemical synthesis
Formulation	Formulation & (re)packing of substances and mixtures; Use in water-treatment chemicals (industrial); Production of Polymers, filled polymers, foams, coatings, adhesives, sealants; Solvent
Uses at industrial sites	Use as Intermediate; Use as Process chemical; Production of polymers; Use in Paints/ Coatings; Use in Cleaning agents; Use in lubricants; Use in metal-working fluids; Use in water-treatment chemicals; Use in laboratories
Uses by professional workers	Use in Paints/ Coatings /Adhesives/ Sealants/ Foams/ Polymers / filled Polymers; Use in Cleaning agents; Use in metal-working fluids; Use in/as de-icing/anti-icing applications/agents; Use in laboratories; Use in water-treatment chemicals; Use as a fuel; Use in agrochemicals
Consumer Uses	Use in Paints/ Coatings / Surface treatment products; Use in Cleaning agents; Use in heat transfer and hydraulic fluids; Use in/as de-icing/anti-icing applications/agents; Production of rigid foam; Use in Biocidal products; Use as a fuel; Use in adhesives and sealants; Use of inks/ink components
Article service life	Solvent

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 7

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)				
Index No	**EC No**	**CAS No**	**Classification**	**Notes**

[2] 08/02/2016

	International Chemical Identification			Hazard Class and Category Code(s)	Hazard statement code(s)	Spec. Conc. Limits, M-factors	
603-140-00-6	2,2' – oxybisethanol diethylene glycol	203-872-2	111-46-6	Acute Tox. 4 *	H302	-	-

7.6.2. Self-classification

- In the registration(s)*:*

In addition to the harmonised classification, the Registrants have given the following self-classification:
STOT RE 2, H373: May cause damage to organs through prolonged or repeated exposure. Affected organs: kidney Route of exposure: Oral

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

Eye Irrit. 2, H319: Causes serious eye irritation.
Skin Irrit. 2, H315: Causes skin irritation.
STOT SE 3, H336: May cause drowsiness or dizziness

7.7. Environmental fate properties

7.7.1. Degradation

Guideline/Test Method	Test type	Parameter	Inoculum	Inoculum adaptation	Initial conc.	Degradation	Reference
OECD 301A	ready	BOD	activated sludge, domestic	not specified	45 mg/L	>90% after 28 day	study report
OECD 301B	ready	CO_2 evolution	activated sludge, domestic	non-adapted	44 mg/L	71% after 28 day	study report

Several screening tests are available, but the data do not fulfil the ready biodegradability criteria clearly. According to the available study reports, the substance fulfils the criteria in a 28-day period, but not in the 10-day window. Further to this, in case of the OECD 301A test, it is not known if the inoculum is adapted. In addition, in case of the OECD 301B test, the reference material was 2,2'-oxydiethanol as well.

However, based on the above data, it can be concluded that 2,2'-oxydiethanol is biodegradable.

Also the tests above clearly support that the substance is not persistent in the environment and that 2,2'-oxydiethanol does not have the potential to cause long-term adverse effects in the environment.

As regards the abiotic degradation of 2,2'-oxydiethanol in the troposphere due to indirect photodegradation was calculated by AOPWIN v1.92. The half-life is 17.24 hours with a degradation rate of 22.34 x 10^{-12} cm^3.$molec^{-1}$.sec^{-1}. therefore the substance rapidly degrades in the air compartment.

7.7.2. Environmental distribution

The adsorption behaviour of 2,2'-oxydiethanol was investigated with KOCWIN v2.00. The estimated K_{OC} from log K_{OW} (-1.98) is 0.08 L/kg. The absorption potential of the substance is low.

2,2'-oxydiethanol is a water miscible compound. Therefore, the estimation of the Henry's Law constant from the ratio of the vapour pressure to the water solubility cannot be calculated. The estimated value was 2.06 x 10-4 Pa.m^3.mol^{-1} at 25 °C by HenryWin v3.20 (bond contribution methodology).

7.7.3. Bioaccumulation

The substance is biodegradable and the value of log K_{OW} is -1.98. Therefore, the bioaccumulation of 2,2'-oxydiethanol is considered unlikely. The measured BCF for fish is 100 (Freitag at al. 1985) which supports the conclusion of low bioaccumulation potential.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

The algae data 100 mg/L were used by the Registrant for PNEC derivation, however this was only a limit test conducted with pentaethylene glycol. Other available data show, the NOEC for 2,2'-oxydiethanol can be expected to be higher.

The evaluating Member State's conclusion, that 2,2'-oxydiethanol is not harmful to aquatic organisms, is in agreement to that of the Registrant,.

However, the evaluating Member State took only the 2,2'-oxydiethanol tests into account for the assessment. The read-across data and the QSAR were only used as supporting information.

Many tests are available, but, in many cases, there was no effect reported, even with the highest concentrations used. Therefore, these tests were not taken into account in the assessment. In the chapters below, only the 2,2'-oxydiethanol tests and the data used for the PNEC are discussed.

7.8.1.1. Fish

Fish species	Method	Duration	Results
Pimephales promelas	special, flow-through	96 h	LC_{50}: 75200 mg/L

Oncorhynchus mykiss	EPS 1/RM/9 (EC 1990/1996)	96 h	LC_{50}: 66000 mg/L
Dicentrarchus labrax	OECD 1992	96 h	EC_{50}: 40300 mg/L
Dicentrarchus labrax	similar to OECD 215	28 day	growth rate NOEC: 5660 mg/L

Numerous scientific studies have been published concerning the acute toxicity of 2,2'-oxydiethanol to fish. In the study performed with a salt-water species, *Dicentrarchus labrax* according to the OECD 203 (1992) guideline, the EC_{50} after 96 hour exposure was found to be 40300 mg/L, which is the lowest value for this endpoint in the available literature.

In the one available long-term fish test, performed according to OECD guideline 215, modified for the same test organism, the salt-water species *Dicentrarchus labrax*, the differences were in the exposure conditions (T= 20 ºC, photoperiod = 14 h lx: 10 h dark, light intensity= 500-800 lx), in the increasing daily food, in the test chamber volume and in the density of organisms (< 1 g/L). As endpoint, the NOEC of 5660 mg/L was reported.

7.8.1.2. Aquatic invertebrates

Invertebrates	Method	Duration	Results
Daphnia magna	EPS 1/RM/11 (EC 1990/1996)	48 h	LC_{50}: 62630 mg/L
Hyalella azteca	EPS 1/RM/33 (EC 1997)	96 h	LC_{50}: 65980 mg/L
Tigropus fulvus	modified ISO 14669	96 h	EC_{50}: 5900 mg/L
Artemia franciscana	semi-static	14 day	NOEC: 25000 mg/L mortality
Tapes philippinarum	modified ASTM E2455-06	28 day	NOEC: 10000 mg/L (mortality) NOEC: 365 mg/L (growth rate)

The available invertebrate toxicological data indicate that *Tigropus fulvus* is the species most sensitive to 2,2'-oxydiethanol. *T. fulvus* showed higher sensitivity (EC_{50}: 5900 mg/L) than the other crustaceans available in the literature.
In the study performed with crustacean *Artemia franciscana*, the NOEC after a 14-day exposure was found to be 25000 mg/L, but it cannot be taken into account as a chronic test because its only endpoint is mortality.

In the same publication, the mollusc *Tapes philippinarum* endpoint population growth NOECs were 10000 mg/L (based on mortality) and 365 mg/L (based on growth rate).

7.8.1.3. Algae and aquatic plants

Algae and aquatic plants	Method	Duration	Results	Reference / Cited by

Scenedesmus quadricauda	cell growth inhibition, static	8 day	TTC: 2700 mg/L	Bringmann G, Kühn R (1978) Bringmann G, Kühn R (1977)
Pseudokirchneriella subcapitata	OECD 201	72 h	NOEC: >100 mg/L growth rate CAS: 4792-15-8	OECD SIDS (2004)
Echinodorus cordifollus (aquatic plant)	special	7 day	LD_{50}: 6238 mg/L	W. Sriprapat, P. Thiravetyan (2011)
Microcystis aeruginosa	cell growth inhibition, static	8 day	TTC: 1700 mg/L	Bringmann G, Kühn R (1978)
Phaeodactylum tricornutum	ISO 10253	72 h	NOEC: 5000 mg/L	-

The 100 mg/L algae data, which was used by the Registrant for PNEC derivation, was only a limit test and it was prepared with pentaethylene glycol (OECD SIDS 2004a). There is one special, alternative test in the study list, where the endpoint was the phytoremediation of 2,2'-oxydiethanol from water. Sriprapat and Thiravetyan (2011) reported the effect of 2,2'-oxydiethanol on an aquatic plant*, Echinodorus cordifolius*. The measured LD_{50} (7days) was 6238 mg/L.

From the available literature, the short term range shows very low toxicity for marine and freshwater algae based on EC_{50} data, similarly to the other two trophic levels. For two test organisms, (*Scenedesmus quadricauda* and *Microcystis aeruginosa*) 8-day, long term cell growth inhibition tests were conducted and the endpoint was the toxic threshold concentration (NOEC), published by Bringmann et al. (1978). In the case of the green algae, the NOEC was 2700 mg/L, but the lowest NOEC value was 1700mg/L in a study performed with cyanophyta. There is one more long term test available: a marine test, performed with the *Phaeodactylum tricornutum* species, resulting a NOEC value of 5000 mg/L.

7.8.1.4. Sediment organisms

The adsorption potential of 2,2'-oxydiethanol is low, therefore the accumulation of the substance is not to be expected in the sediment and was not investigated by the evaluating Member State.

7.8.1.5. Other aquatic organisms

Not evaluated.

7.8.2. Terrestrial compartment

species	Method	Endpoints	Duration	Results	Reference / Cited by
Medicago sativa	EC 2005a	early seedling emergence (EC_{50}), growth (IC_{50}; IC_{25})	21 day	EC_{50}: 18102 mg/kg IC_{50}: 3041 mg/kg IC_{25}: 1297 mg/kg	Stantec Consulting Ltd. (2006)
Hordeum vulgare var. Chapais	EC 2005a	early seedling emergence (EC_{50}), growth (IC_{50}; IC_{25})	14 day	EC_{50}: - IC_{50}: 1779 mg/kg IC_{25}: 419 mg/kg	Stantec Consulting Ltd. (2006)

Elymus lanceolatus	EC 2005a	early seedling emergence (EC_{50}), growth (IC_{50}; IC_{25})	21 day	EC_{50}: 20077 mg/kg IC_{50}: 1471 mg/kg IC_{25}: 818 mg/kg	Stantec Consulting Ltd. (2006)
Eisenia andrei	EC 2004	survival (35-d adult; LC_{50}), growth, reproduction (IC_{50}; IC_{25})	63 day	LC_{50}: 10974 mg/kg IC_{50}: 8868 mg/kg IC_{25}: 4842 mg/kg	Stantec Consulting Ltd. (2006)
Folsomia candida	EC 2005b	survival (LC_{50}), reproduction (IC_{50}; IC_{25})	28 day	LC_{50}: 15689 mg/kg IC_{50}: 7508 mg/kg IC_{25}: 5341 mg/kg	Stantec Consulting Ltd. (2006)

Toxicity tests with three plant and two invertebrate species were provided. The endpoints for the plant tests are shoot and root lengths, shoot and root dry phytomasses and seedling emergence on northern wheatgrass (*Elymus lanceolatus*), barley (*Hordeum vulgare* var. Chapais), and alfalfa (*Medicago sativa*). The invertebrate tests are chronic survival, growth and reproduction tests with one earthworm (*Eisenia andrei)* and one collembola (*Folsomia candida*) species. All tests were conducted following the Environment Canada methods (EC 2005a for plants, EC 2004 for earthworms and EC 2005b for collembola).

The shoot or root dry mass was the most sensitive endpoint for plants. The IC_{50} values based on shoot dry mass and shoot length endpoints ranged from 1471 to 17685 mg/kg. The lowest IC_{50} is 1471 mg/kg for shoot dry mass of northern wheatgrass.

The endpoints for the *Eisenia andrei* test were adult survival after 35 days, number and individual wet and dry masses of offspring at the end of the 63-day test. Increased reproduction was observed at doses ≤ 1600 mg/kg compared to the control. The LC_{50} for adult survival was 10974 mg/kg after 35 days. The NOEC values were not calculated for reproduction and growth rate, only IC_{50} and IC_{25} values are available.

The endpoints for the *Folsomia candida* test were adult survival and juvenile production at the end of the 28-day test. The LC_{50} for adult survival was 15689 mg/kg. The NOEC was not calculated, only the IC values are available.

Further to the data above showing low toxicity to the soil organisms the substance is biodegradable, direct exposure to soil is unlikely and aerial deposition is negligible.

7.8.3. Microbiological activity in sewage treatment systems

An activated sludge respiration inhibition test of 2,2'-oxydiethanol was performed according to the available study report.

The applied test protocol was equivalent to ISO 8192 (Test for inhibition of oxygen consumption by activated sludge). The tested inoculum was domestic sludge and after the incubation time (30 minutes) no inhibition was observed at the test concentrations (15, 150, 750, 1995 mg/L), moreover slight promotion was detected of the respiration (+ 17 %) at 750 and 1995 mg/L.

Test data reinforce that the 2,2'-oxydiethanol does not cause inhibition of the degradation activity of activated sludge below 1995 mg/L.

7.8.4. PNEC derivation and other hazard conclusions

In contrary to the Registrant, the evaluating Member State only used the tests conducted with 2,2'-oxydiethanol to determine the PNECs and did not use the read-across and QSAR data.

The evaluating Member State also took the tests conducted on marine species into consideration when determining the freshwater PNEC. Although these are not conventional test species, their test results are similar to the results of the tests conducted on available freshwater species and the test circumstances were available for us to review.

Thus for determining the aquatic PNEC the acute and chronic toxicology data of several taxonomic groups were taken into account for all three trophic levels. Although the most sensitive test organism was not a crustacean, but a mollusc (*Tapes philippinarum,* NOEC: 365 mg/L), and the toxic effect appeared at a much smaller concentration than in the chronic fish and cyanophyta test results, the PNEC derived from that was still greater than the one suggested by the Registrant and was almost the same, as if the PNEC value was given a 50 assessment factor without the chronic mollusc data.

In case of the marine PNEC the dataset was the same and since an additional marine taxonomic group (molluscs) was tested besides the algae and fish NOEC, the assessment factor is 50.

For the STP microorganisms, the 1995 mg/L was considered as NOEC and an assessment factor of 10 was applied.

NOEC values are not determined for chronic terrestrial invertebrate tests. The PNEC was calculated from the lowest IC_{50} of 1471 mg/kg (based on shoot dry mass of northern wheatgrass) with an assessment factor of 1000. This value is lower than the calculated PNEC using the equilibrium partitioning method.

Table 8

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC: 36 mg/L	Assessment factor: 10 Extrapolation method: calculation using assessment factors.
Marine water	PNEC: 7 mg/L	Assessment factor: 50 Extrapolation method: calculation using assessment factors.
Intermittent releases to water	PNEC: 59 mg/L	Assessment factor: 100 Extrapolation method: calculation using assessment factors.
Sediments (freshwater)	PNEC: 28 mg/kg	Assessment factor: - Extrapolation method: EPM
Sediments (marine water)	PNEC: 5.7 mg/kg	Assessment factor: - Extrapolation method: EPM
Sewage treatment plant	PNEC: 200 mg/L	Assessment factor: 10 Extrapolation method: calculation using assessment factors.
Soil	PNEC: 1.5 mg/kg	Assessment factor: 1000 Extrapolation method: calculation using assessment factors.
Air	-	Not relevant. No data are available on biotic effects.

Secondary poisoning	-	Not relevant. The substance has little potential for bioaccumulation.

7.8.5. Conclusions for classification and labelling

The substance is not persistent in the environment and the 2,2'-oxydiethanol does not have the potential to cause long-term adverse effects in the environment.

Based on the assessed data 2,2'-oxydiethanol is not harmful to aquatic organisms and therefore there is no need for classification and labelling in this regard.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

2,2'-oxydiethanol is rapidly absorbed and distributed to organs and tissues in the order kidneys > brain > spleen > liver > muscle > fat. The kidney is the target organ. The half-life of 2,2'-oxydiethanol is dose dependent and doses of 6 mL/kg and 12 mL/kg in rats yielded a half-life of 8 and 12 h, respectively. At higher doses (>17.5 mL/kg), 2,2'-oxydiethanol appears to follow first order kinetics and has a half-life of 3.6 h.

2,2'-oxydiethanol is metabolized by alcohol dehydrogenase to toxic metabolites predominantly, to 2-hydroxyethoxyacetic acid (HEAA) and diglycolic acid (DGA). 2,2'-oxydiethanol cause metabolic acidosis, cortical necrosis (proximal tubule cell death) resulting in permanent renal failure. However, as it was established in human proximal tubule cells in vitro (Landry et al., 2011) that the metabolite of 2,2'-oxydiethanol rather than the parent compound itself is responsible for the adverse effects on the kidney. The evaluating Member State came to the same conclusion.

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity:

Inadvertent exposures to low concentration 2,2'-oxydiethanol products are relatively common but generally do not result in significant toxicity. Large, acute ingestions of misused products containing 2,2'-oxydiethanol may cause life-threatening toxicity. 2,2'-oxydiethanol has been found to be the cause of at least 12 medication-associated mass poisonings in the United States (The Massengill Incident, 1937), South Africa (1969), Spain (1985), India (1986), Nigeria (1990), Bangladesh (1990–1992), Argentina (1992), Haiti (1995–1996), China (2006), Panama (2006), the Worldwide toothpaste incident (2007), and Nigeria (2008).

Initial symptoms of acute toxicity may include nausea, vomiting and headache; with continued use, severe abdominal pain, polyuria followed by oliguria, and acute anuric renal failure with metabolic acidosis. Several cases of neurologic impairment (encephalopathy, demyelinating neuropathy, optic neuritis, unilateral facial paralysis, cerebral oedema and haemorrhages) have also been reported. A median lethal oral dose of 1.49 g/kg bw 2,2'-oxydiethanol (range 0.25-4.9 g/kg bw) was estimated from large-scale intoxication of Haitian children with a paracetamol syrup contaminated with 2,2'-oxydiethanol. However, large overlaps in ranges of lethal and non-lethal doses have been observed for adults and children.

Based on the available literature data it is clear that all cases are due to misuse of the substance and no incident happened under the normal use conditions. As regards cases of misuse it has to be mentioned that, due to its physical properties, 2,2'-oxydiethanol can be used as a counterfeit for pharmaceutical-grade glycerine. Therefore it is recommended

to alert pharmaceutical manufacturers and downstream users to the potential public health hazard of glycerin contaminated with 2,2'-oxydiethanol.

Skin irritation:

In a Draize skin irritation test performed on rabbits, the animals received occlusive skin applications of undiluted 2,2'-oxydiethanol for 23 hours. No skin reactions were found (Guillot et al. 1982).

In a human occluded patch test, 2,2'-oxydiethanol was a mild irritant and the slight skin findings were fully reversible within less than 24 hours.

Since the Registrant took into account the human results about the slight skin irritating effect of 2,2'-oxydiethanol and the evaluating Member State also found some skin irritation data about the substance in a toxicological handbook (Lewis 2004), the evaluating Member State considered that a reliable, internationally accepted *in vitro* skin irritation test according to OECD TG 439 would completely clarify the substance's skin irritating potential of the substance.

Therefore an *in vitro* EpiDerm™ Skin Irritation Test (OECD 439) was performed by the Registrant. In the test human reconstructed epidermis tissues were topically exposed to 2,2'-oxydiethanol for 1 h. The mean relative viability of the exposed tissues was higher than 50% of negative controls, thus 2,2'-oxydiethanol was clearly not irritant according to the GHS classification. Hence this concern was removed.

Eye irritation:

Carpenter and Smyth in their study (1946) applied 0.5 mL of undiluted 2,2'-oxydiethanol into the eyes of rabbits and they did not find any signs of ocular irritation related to the treatment.

Guillot et al. in their study (1982) treated the eyes of 6 male albino rabbits with 0.1 mL of 2,2'-oxydiethanol at test concentrations ranging from 10 to 100 %. Reading of the treated eyes was done after 1 h, 24 h, 2 days, 3 days, 4 days and 7 days following the application. The results were evaluated using the evaluation scale of 0 to 110 by Kay and Calandra (1962) (J. Soc. Cosme. Chem. 13: 281–289, 1962, modified). 2,2'-oxydiethanol resulted in a mean ocular index of 11.67 which was below 15, and there was no indication for corneal opacity. Thus, 2,2'-oxydiethanol was not irritating to the eye of rabbit under the test conditions applied.

Based on the results of the above studies, no concern was identified by the evaluating Member State regarding the eye irritating properties of 2,2'-oxydiethanol.

7.9.3. Sensitisation

OECD SIDS initial assessment profile and other reliable studies (among them a GLP and guideline study with reliability factor 1) showed that 2,2'-oxydiethanol has no sensitising effects, hence there is no concern regarding the sensitising property of 2,2'-oxydiethanol.

7.9.4. Repeated dose toxicity

Oral short-term exposure of rodents results in tremor, lethargy, piloerection, decreased renal function, retinopathy, increased serum aspartate aminotransferase activity, microscopical and ultrastructural myocard changes. At high doses, renal failure may develop and lead to death. 2,2'-oxydiethanol exposure produce the clinical signs of toxicity resemble those reported in humans.

Chronic toxicity from prolonged and repeated exposure to 2,2'-oxydiethanol are associated with kidney, and to a lesser degree, liver effects.

The damaging effects of 2,2'-oxydiethanol on the kidneys after prolonged oral exposure are considered as the critical effects. In the key study (oral exposure study in rats) oxalate crystaluria, increased urine volumes after concentration tests were found in the first (98 days) and second (225 days) experiment. Vacuolization of the tubular epithelium (hydropic degeneration) and tubular necrosis were the histopathological findings. For the crystaluria and increased urine volumes after concentration tests, the results in the male and the female rats were inconsistent, and no clear dose-response relationships was observed for these effects. Therefore, the evaluation is based on the histopathological findings. Hydropic degeneration of the kidneys started to occur at oral dose levels of 1550 mg/kg bw/day for 14 weeks and was not seen at 300 mg/kg bw/day. The conclusion is that the NOAEL for hydropic degeneration is 300 mg/kg bw/day (0.4% 2,2'-oxydiethanol in food) in the male rats.

Exposure by inhalation of vapours is negligible due to 2,2'-oxydiethanol's low vapour pressure at room temperature. Inhalation exposure may become significant when aerosols are formed or when 2,2'-oxydiethanol is heated during processing.

To determine whether an atmosphere containing aerosolized ethylene glycol in a concentration that could be tolerated by human volunteers for most of each 24 hour period would have any deleterious action on man, in a prison hospital twenty volunteers were exposed during 20 to 22 h per day to aerosolized ethylene glycol in mean daily concentrations between 3 and 67 mg/m^3 (Wills, 1974). The irritative phenomena became common when the concentration of ethylene glycol in the ambient air was raised to about 140 mg/m^3. The irritative effect practically excludes the possibility of 2,2'-oxydiethanol absorption from the respiratory tract of a healthy individual.

Based on the NOAEL established in the key study and on the supporting studies no concern is indicated in this regard. Hence the initial concern was removed.

7.9.5. Mutagenicity

In vitro data:

An Ames test was performed with 2,2'-oxydiethanol on *Salmonella typhimurium* at 1, 3, 10, 30 and 111.8 milligram per plate with strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 with and without metabolic activation. No mutagenic activity was observed in this test.

A later reverse mutation assay was performed under GLP on *Salmonella typhimurium* TA 1535, TA 100, TA 1537, TA 98 and *Escherichia coli* WP2 uvrA. The dose range was 33 µg-5000 µg/plate (standard plate test) and 33 µg-5000 µg/plate (preincubation test) both with and without metabolic activation. Similarly to the above test, no mutagenic activity was observed.

Another Ames test was performed with 2,2'-oxydiethanol on *Salmonella typhimurium* strains TA 98, TA 100, TA 102 and TA 104, and *Saccharomyces cerevisiae* strain D 7 and D 61 with and without metabolic activation. In case of *S. typhimurium* doses are not known. A weak mutagenic activation was observed in strain TA 104 with S9 activation (maximum: 2.2 fold increase over the spontaneous frequency at 315 µmol 2,2'-oxydiethanol/plate). In case of *S. cerevisiae* no mutagenic activation was observed. (Klimisch reliability factor 3) (Krug et al, 1986).

In addition, a cytogenetic assay was performed on Chinese hamster ovary (CHO) cells with 2,2'-oxydiethanol. The doses ranged from 10mg/mL to 50 mg/mL with and without metabolic activation. 2,2'-oxydiethanol proved to be negative in the test. No cytotoxic activity was observed.

Genotoxicity assay was also performed on Chinese hamster ovary (CHO) cells in CHO/HGPRT mutation test. The doses ranged from 30 mg/mL to 50 mg/mL with and without metabolic activation. Remarkable cytotoxic or genotoxic activity was not observed.

Sister chromatid exchange (SCE) assay was performed with 2,2'-oxydiethanol on Chinese hamster ovary (CHO) cells by doses up to 50mg/mL both with and without metabolic activation. 2,2'-oxydiethanol was neither genotoxic nor cytotoxic in this assay.

In vivo data:

Micronucleus assay was performed under GLP on bone marrow cells of male NMRI mice by a single intraperitoneal administration of 2,2'-oxydiethanol. Doses were 500 mg/kg, 1000 mg/kg and 2000 mg/kg body weight. The animals were sacrificed 24 and 48 hours after administration in the highest dose group and in the vehicle controls and 24 hours after administration in other groups. A slight inhibition of erythropoesis was detected at 2000 mg/kg bw at 48 hour sacrifice. 2,2'-oxydiethanol was negative in this assay. The effect of different glycols was investigated on male rats with dominant lethal tests. Glycols gave positive result. No data on doses, number of animals are available (Barilyak et al. 1987).

The effect of 2,2'-oxydiethanol on the frequency of chromosome aberrations was examined. Doses were 7500, 5000, 2500, 1250, 625, 312.5, and 0 mg/kg both intraperitoneal and per os. The results appeared to be negative. (Yoshida et al. 1986).

Micronucleus test was performed by single intraperitoneal or single per os administration. The dose of 60% of LD_{50} was applied in both tests. An increase in the number of micronuclei was observed after i.p. but not after p.o. administration. No data on species, tissue, number of animals and cells. (Klimisch reliability factor 4) (Krug et al. 1986, abstract only).

2,2'-oxydiethanol proved to be not mutagenic in reliable in vitro bacterial mutagenicity, cytogenetic, sister chromatid exchange and gene mutation in mammalian cells tests. The only available reliable in vivo test, the mammalian erythrocyte micronucleus assay gave negative result.

Based on the available information,2,2'-oxydiethanol has no mutagenic potential and the initial concern was removed. Classification and further studies are not necessary.

7.9.6. Carcinogenicity

The initial concern of the evaluating Member State regarding the potential carcinogenicity of 2,2'-oxydiethanol was based on the finding that weanling rats fed with 2 and 4% 2,2'-oxydiethanol for two years developed more frequently bladder stones what may irritate epithelial tissue and cause enhanced cell division and epithelial hyperplasia. In the contrary, no enhanced bladder stone formation was reported in another study (Hiasa et al. 1990). Bladder stone formation might be initiated by the impurities in the 2,2'-oxydiethanol used for the experiments as ethylene glycol, which is metabolized in part to oxalic acid what enhances the precipitation of calcium oxalate in the kidneys and in the bladder.

Fitzhugh and Nelson (1946) in an early chronic oral toxicity study reported increased appearance of renal tumours in male Osborne-Mendel rats following two years oral administration of 2,2'-oxydiethanol over 750 mg/kg bw/day (at 1500 and 3000 mg/kg bw/day doses). The study was conducted without quality control and data records are not fully accessible, no information on the purity of 2,2'-oxydiethanol is known, therefore, it has low reliability.

Another 108 weeks carcinogenicity study was performed in 1990 under GLP (Hiasa et al. 1990) with oral administration of 2,2'-oxydiethanol in 0, 1210 and 2630 mg/kg bw/day for males and 0, 1160 or 2550 mg/kg bw/day for females following an N-ethyl-N-

hydroxyethylnitrosamine pretreatment for tumour initiation. The study found increased water consumption and lung weight in both sexes but no increased tumour appearance compared to control. The study concluded that 2,2'-oxydiethanol does not have carcinogenic or tumour promoter activity, in the study NOAEL was 1210 and 1160 mg/kg bw/day for males and females, respectively.

Based on the available data the evaluating Member State concluded that 2,2'-oxydiethanol has no carcinogenic potential and the concern for carcinogenicity was removed.

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

Fertility

Reproductive toxicity of 2,2'-oxydiethanol was evaluated in a key study on mice using a continuous breeding protocol. In the dose finding part of the study the test material was administered in drinking water for 14 days at doses of 0, 1, 2.5, 5, 7.5 and 10% w/v (corresponding to 0, 750, 1875, 3750, 5625 and 7500 mg/kg bw/day based on actual water consumption). At the doses of 5 (only males), 7.5 and 10% (males and females as well) a decrease in water consumption was observed. Body weight gain was significantly lower in the 5, 7.5 and 10% groups. Piloerection, tremors and lethargy was noted at 7.5 (males) and 10% (males and females). Mortality was observed at the top two dose levels.

In the main, continuous breeding part of the study the animals were exposed during a 7-day premating, 98-day cohabitation and 3-week post-cohabitation period. The test material was administered in drinking water at doses of 0, 0.35, 1.75 and 3.5% w/v (corresponding to 0, 612, 3063 and 6125 mg/kg bw/day). In the high dose group general effects on reproduction were found (F0 generation): statistically significant decreases in the number of litters produced per pair, live pups per litter, proportion of pups born alive and absolute and adjusted live pup weight was noted and the cumulative days to litter increased significantly. At this dose level there was also a significant decrease in the number of pairs producing the third, fourth and fifth litters. Slight maternal toxicity (F0) was observed in the high dose group: the body weight was decreased by 7%. Daily water consumption was significantly increased in the 1.75 and 3.5% groups. No treatment related changes were noted on relative organ weights or histopathology.

The mean body weights of the F1 generation showed a significant decrease compared to controls at the top two dose levels. In the final litters of the 3.5% dose group 12% of the live-born pups and 95% of the pups found dead on postnatal day 0 had craniofacial malformations including exencephaly and cleft palate. 50% of the live malformed pups had died by postnatal day 2. Similar malformations were present in the other litters of the high dose group.

For the evaluation of fertility and reproduction of the F1 generation, pups from mid-dose litters were selected as insufficient live pups were available from the high dose group. Following continuous exposure to 1.75% 2,2'-oxydiethanol the animals were mated and the produced litters were evaluated. No statistically significant effects on mating, fertility or any reproductive parameters were noted in this generation. Body weight was significantly reduced in both F1 males and females (11 and 7%, respectively) and a significant increase in liver weight in males (11%) was also found.

A crossover mating trial of the F0 mice to determine the affected sex was inconclusive, the only effect seen was a small decrease in live pup weight of the 3.5% 2,2'-oxydiethanol females x control males group.

The NOAEL for fertility effects identified from this study was 3063 mg/kg bw/day.

In another supporting two-generation study on rats (Wegener, 1953) 2,2'-oxydiethanol was tested at 2200 mg/kg bw/day. Test material was administered by gavage. No effects on any reproductive parameters were seen, embryotoxicity was not noted. No maternal toxicity was reported. The NOAEL was 2200 mg/kg bw/day.

In one of the available studies toxic effects of 2,2'-oxydiethanol were found on fertility and malformations were noted. However, the adverse effects were present only at the highest dose tested (6125 mg/kg bw/day). The only sign of maternal toxicity recorded in this study was decreased body weight and increased water consumption however the kidney, which is assumed to be the target organ of 2,2'-oxydiethanol, was not examined. The higher levels of water consumption also suggest that some kidney effects may have been present but were not investigated. The NOAEL for kidney effects in repeated dose studies was found to be as low as 128 mg/kg bw/day (225-day study on rats) or 300 mg/kg bw/day (98-day study on rats). The kidney lesions were also present in developmental toxicity studies with mice and rats, with NOAEL values of 559 or 1250 mg/kg bw/day for mice (see below). The shorter dose finding part of the study also indicates that severe toxicity is elicited at higher doses. It is likely that the observed effects on fertility in the main study were secondary symptoms to general maternal toxicity caused by continuous exposure during the production of five consecutive litters. No signs on fertility were noted in the mating of the F1 generation. The supporting study (Wegener, 1953) also did not report any effects on reproductive capacity. Based on the available information the evaluating Member State concluded that 2,2'-oxydiethanol does not have a significant effect on fertility.

Developmental toxicity

Several developmental toxicity studies are available with 2,2'-oxydiethanol. In the key study 2,2'-oxydiethanol was administered by gavage to rabbits in doses of 100, 400 and 1000 mg/kg bw/day. No maternal toxicity or fetotoxicity was observed, the differences are in the range of historical control data and without any biological relevance. No clear dose-response trends could be identified. The NOAEL value for maternal toxicity, embryotoxicity and fetotoxicity was 1000 mg/kg bw/day.

In the supporting studies fetotoxic signs were observed but only at maternally toxic doses. In a study on rats, where 2,2'-oxydiethanol was administered by gavage in doses of 1.0, 4.0 and 8.0 ml/kg bw/day, fetal body weights were significantly reduced at the top dose level. Increased incidence of skeletal variations indicative of delayed ossification was noted in this group, however, there were no malformations or differences in the incidence of external or visceral variations compared to the control group. Maternal toxicity was severe in this study (mortality, kidney lesions, decreased body weight and weight gain, decreased food consumption, increased water consumption, increased kidney and liver weight). The NOEL for maternal toxicity and developmental toxicity was 1 mL/kg bw/day in this study.

Severe maternal toxicity was detected in another study on mice (oral administration by gavage; doses: 1250, 5000 and 10000 mg/kg bw/day). Signs of renal pathology were evident, absolute and relative kidney weight was increased, food consumption was decreased, water intake was significantly elevated. Based on these signs the maternal NOAEL was identified as 1250 mg/kg bw/day. Mean fetal body weight was significantly decreased in the high-dose group, thus the NOAEL for developmental toxicity was set at 5000 mg/kg bw/day. Any morphological abnormalities noted in the study do not show any dose-response trend, no significant effects were revealed.

In an oral gavage study (Ballantyne and Snellings, 2005) mice received 2,2'-oxydiethanol in doses of 0.5, 2.5 or 10.0 mL/kg bw/day (equivalent to 559, 2795 or 11180 mg/kg bw/day) and rats in doses of 1.0, 4.0 or 8.0 mL/kg bw/day (equivalent to 1118, 4472 or 8944 mg/kg bw/day). In the study with mice the NOAEL for maternal effects was 559 mg/kg bw/day, based on mortality, clinical signs and increased water consumption. No teratogenic effects were noted. No increases were seen in the incidence of variations or malformations. At the top dose level fetal body weight was significantly reduced, on the basis of this effect the NOAEL for developmental toxicity was found to be 2795 mg/kg

bw/day. Maternal toxicity in rats was evident at the top and middle dose level. Based on mortality, clinical signs, reduced body weight gain, reduced food consumption, increased water consumption, increased liver weight and renal lesions the NOAEL for maternal toxicity was 1118 mg/kg bw/day. Reduced fetal body weight was seen in the high-dose group, along with an increase in individual skeletal variations. Malformations were not observed. The NOAEL for developmental toxicity was 1118 mg/kg bw/day.

In the available developmental toxicity studies on 2,2'-oxydiethanol developmental effects were seen but only at doses that elicited maternal toxicity. Malformations were not noted in any of these studies. In the continuous breeding study on fertility craniofacial malformations, including exencephaly and cleft palate were found, however these effects were also only present at maternally toxic doses (6125 mg/kg bw/day). Malformations were not reported for the group receiving 3063 mg/kg bw/day. None of the other available reliable developmental studies on mice and rats revealed such effects, even at similar or even higher doses. Based on all of the available results, the evaluating Member State considers that 2,2'-oxydiethanol does not have a significant effect on the development of the offspring.

7.9.8. Hazard assessment of physico-chemical properties

As 2,2'-oxydiethanol is a colorless, nearly odourless and hygroscopic, viscous liquid (GESTIS, 2005) with a sharply sweetish taste (NICNAS, 2009) with bitter aftertaste (Health Council of the Netherlands, 2007), ingestion could be an exposure route, in case of misuse.

It is completely miscible with water and many organic liquids, reacts violently with strong oxidants. The boiling point (Budavari (ed.), 1989) is determined at 245 °C. The vapour pressure (Daubert, 2006) of the registered substance at 25°C is 0.008 hPa. Because of the low vapour pressure and the high boiling point, 2,2'-oxydiethanol has a low volatility.

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

There is no study available that would properly assess the NOAEL of 2,2'-oxydiethanol in humans. However, from the poisoning cases the following conclusion can be drawn. The evaluating Member State concluded that most important possible systemic endpoint for 2,2'-oxydiethanol is renal impairment, which must be ruled out before other endpoints are considered. The evaluating Member State concluded that there is no evidence that systemic doses from inhalation and dermal (and accidental oral) exposure would not sum up. Consequently the evaluating Member State used the hypothesis that there is a combined exposure of different routes.

Hesser (1986) suggested the most cautious per os dose of 0.5 mg/bw kg, which would translate 35 mg for a 70 kg human. The evaluating Member State concluded that this later assessment used unjustifiable uncertainty factors. An even stricter figure appears if the starting point is the minor metabolite diglycolic acid (DAG) and an ultra-conservative approach is taken. DAG is responsible for the renal effect, the LOAEL observed in human cell culture was 50 mmol/liter (Landry et al. 2011). This metabolite concentrates in the proximal tubule and cortical region. The volume of glomeruli in one kidney was found to be 6.6 cm^3 (total range: 1.1-14.8 cm^3) (Hoy et al. 2005). Assuming that DAG is concentrated exclusively in that part of the body, to reach the above concentration a dose of 0.66 (0.11-1.48) mmols is required for a pair of kidneys. If every 2,2'-oxydiethanol molecule would be metabolised into DAG this would be a(n equimolar) dose of 0.0700 (0.0116-0.1570) grams of 2,2'-oxydiethanol. In animal studies 2,2'-oxydiethanol was found to pass unmetabolised around 70-80% (Lenk et al. 1989, Mathews et al. 1991). This would extend the range to 0.0116-0.523 grams. As these calculations do not take into consideration toxicokinetics and toxicodynamics at all (e.g. likely distribution in the body

water area), the evaluating Member State concluded that the calculation and the figures are too conservative.

Furthermore, observations on 2,2'-oxydiethanol poisonings showed that doses that are substantially higher (0.5–1.0 g/kg bw) were associated with acute renal failure (Schier et al. 2011), the dose for a 70 kg human would be 35-70 grams. A steep threshold was observed for kidney toxicity in rats, below which only minor effect was seen. Applying this observation to the above human data, the safe dose can be in the magnitude of some grams (3-7 grams).Taken into consideration the above findings the evaluating Member State concluded that the safe level of 2,2'-oxydiethanol dose in relation to renal damage falls within the above figures (3-7 grams), regardless of the intake route.

Chronic toxicity from prolonged and repeated exposure to 2,2'-oxydiethanol is associated with kidney, and to a lesser degree, liver effects. From key study in Wistar rats, the LOAEL for increased urine volumes is 230 mg/kg bw/day and the NOAEL 100 mg/kg bw/day. The LOAEL for renal hydropic degeneration (vacuolization of the tubular epithelium) is 1.6 g/kg bw/day and the NOAEL 300 mg/kg bw/day.

The study carried out with the similar molecule monoethylene-glycol in healthy volunteers (Wills et al. 1974) demonstrated that airway irritation is an endpoint that has a lower dose descriptor (air concentration). Thus this is appropriate to use for setting the DNEL systemic and local effects – long-term for inhalation.

The evaluating Member State concluded that the above total dose (around 3-7 grams/day for 70 kg human) would be an appropriate starting point to derive a DNEL systemic effects – long-term for the dermal route.

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

Skin and eye irritation:

In a Draize skin irritation test performed on rabbits, no 2,2'-oxydiethanol-related skin reactions were found (Guillot et al. 1982). These results were supported by an in vitro skin irritation test (OECD TG 439), where 2,2'-oxydiethanol was clearly not irritant.

Eye irritation was tested on rabbits. Carpenter and Smyth (1946) did not find any 2,2'-oxydiethanol-related ocular irritation following an undiluted exposure. Guillot et al. (1982) at test concentrations ranging from 10 to 100 % did not find any corneal opacity and the ocular irritation index was less than 15. The evaluating Member State considers that classification of 2,2'-oxydiethanol as irritant is not warranted.

Specific target organ toxicity, repeated dose:

2,2'-oxydiethanol cause metabolic acidosis, cortical necrosis (proximal tubule cell death) resulting in permanent renal failure after prolonged oral exposure. Hydropic degeneration of the kidneys started to occur at oral dose levels of 1550 mg/kg bw/day for 14 weeks and was not seen at 300 mg/kg bw/day. The NOAEL for hydropic degeneration is considered to be 300 mg/kg bw/day in the male rats. The NOAEL from this study is above the guidance value ($10 < C \leq 100$ mg/kg body weight/day for rats after oral exposure), which does not indicate the classification for that category. The evaluating Member State concluded that the metabolite of 2,2'-oxydiethanol rather than the parent compound itself is responsible for the adverse effects on the kidney as it was established in human proximal tubule cells in vitro (Landry et al. 2011).

Mutagenicity:

2,2'-oxydiethanol proved to be not mutagenic in reliable in vitro bacterial mutagenicity, cytogenetic, sister chromatid exchange and gene mutation in mammalian cells tests. The only available reliable in vivo test, the mammalian erythrocyte micronucleus assay gave

negative result. Therefore, it can be concluded that 2,2'-oxydiethanol is not mutagenic and classification as mutagenic is not warranted.

Carcinogenicity:

On the basis of the clear findings reported in the available literature data the evaluating Member State does not consider that 2,2'-oxydiethanol has carcinogenic potential and classification as carcinogenic is not warranted.

7.10. Assessment of endocrine disrupting (ED) properties

Based on the negative results of the other endpoints of concern, the evaluating Member State did not identify any concern related to potential ED properties of the substance. Thus, no detailed evaluation of this endpoint was performed.

7.11. PBT and vPvB assessment

The information available to the evaluating Member State does to indicate that 2,2'-oxydiethanol is a PBT substance (see chapter 7.7.1, 7.7.3 and 7.8).

7.12. Exposure assessment

7.12.1. Human health

Based on the available literature data and physico-chemical properties the evaluating Member State concluded that the relevant exposure routes for 2,2'-oxydiethanol are the inhalation and dermal ones. 2,2'-oxydiethanol has low vapour pressure, thus exposure via inhalation can be substantial only when used in high temperatures or when the probability of aerosol formation is high. Intoxication due to dermal exposure was reported only in misuse cases on non-intact skins (Cantarell et al. 1987, Devoti et al. 2015), which are considered to be more permeable. Oral intoxication cases were reported regarding illegal additives to pharmaceuticals and other per os consumer products, outside the EU (Hanif et al. 1995, Junod, 2000, Ferrari and Gianuzzi, 2005, Rentz et al. 2008) or in self-intoxication.

7.12.1.1. Workers

There is little data available on direct and indirect exposure measurements. Findings of 2,2'-oxydiethanol and similar compounds did not show high exposure among professional cleaners (Gerster et al. 2014) or airplane de-icers (Gérin et al. 1997). The analysis of the German MEGA exposure database has revealed 95 percentile workplace air concentrations as low as 1.81 and 2.025 mg/m3 from a wide range of occupational settings (Koch, 2012). The industrial measurement data provided by the Registrant did not raise any concern, either.

Substantial inhalation exposure could occur during aerosol formation or high temperature. However, 2,2'-oxydiethanol has irritant properties to the mucuous membranes. Based on the findings from the similar compound monoethylene-glycol (Wills et al. 1974) the evaluating Member State concludes that irritant effects are so imperative that the workers are driven out of high exposure area and thus prevent substantial inhalation uptake.

There are no proper human studies concerning the dermal uptake, but expert panels raised the issue of skin notation (Health Council of the Netherlands, 2007). Furthermore, the exact formulation of a preparation itself may have a substantial effect on the uptake via the skin. The evaluating Member State concluded that the dermal uptake route may only be significant and would need special preventive attention in scenarios where the skin is in prolonged contact with the substance.

Furthermore, the inhalation and dermal doses may add together to reach a systemic dose concerning a target organ endpoint.

7.12.1.2. Consumers

Exposure is less likely for consumers because 2,2'-oxydiethanol is mainly used in industrial processes (OECD, 2004). Products in everyday use contain only low concentrations of 2,2'-oxydiethanol.

7.12.2. Environment

Based on the negative findings on PBT properties this endpoint was not investigated.

7.12.3. Combined exposure assessment

Not investigated.

7.13. Risk characterisation

Workers:

2,2'-oxydiethanol has local irritant effect on the respiratory tract. Wills et al. (1974) found that over 200 mg/m^3 of monoethylene glycol (a compound structurally similar to 2,2'-oxydiethanol) resulted in irritant effects that are bearable only for minutes. An equimolar concentration for 2,2'-oxydiethanol would result 120 mg/m3. If someone could tolerate such a high concentration and stay for an entire shift (breathing volume: 10 m^3) in an atmosphere of such a concentration, that would result a dose of 2 grams. However, in order to avoid irritant effects, the occupational exposure level must be set to a substantially lower concentration. Based on this calculation, the evaluating Member State concludes that inhalation only is not a concern in relation to kidney damage endpoint. However, it cannot be ruled out that dermal uptake may be a substantial route and together with a high inhalation exposure the RCR may get close to 1. As these risks can be managed by appropriate measures (local exhaust ventilation, protective clothing and gloves) the evaluating Member State concluded that there is no concern for workers' exposure.

In case of the respiratory track irritation endpoint, a substantially lower DEG concentration is indicated by the proposed limit value, under which the substance can be safely used, than for kidney damage.

Consumers:

The evaluating Member State concludes that consumers can be at risk only during misuse and poisoning.

2,2'-oxydiethanol is not released into the environment in great quantities. 2,2'-oxydiethanol readily biodegradable in the environment thus this exposure route i.e. indirect exposure of humans via the environment is negligible.

Human health (combined for all exposure routes):

The evaluating Member State concludes that there is no concern for risks posed by 2,2'-oxydiethanol if appropriate good practice is followed. If a use scenario cannot realise the containment of 2,2'-oxydiethanol, appropriate measures needs to be applied to avoid skin contact (gloves, protective clothing) and inhalation (respiratory protection) especially in cases where aerosol formation is substantial and temperature is high. Consumers' risk is only possible during misuse and poisoning. This conclusion of the evaluating Member State is reinforced by the fact that despite the high tonnage production ill-health due to 2,2'-oxydiethanol was reported only in misuse cases.

Environment (combined for all exposure routes):

There are no concerns regarding environmental hazards and no need for further exposure scenarios.

7.14. References

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7.15. Abbreviations

°C	Degrees of Celsius
µg	micro gram
BCF	Bioconcentration Factor
BoA	Board of Appeal
BOD	Biological Oxygen Demand
bw	bodyweight
CAS	Chemical Abstracts Service
CHO	Chinese Hamster Ovary
cm^3	cubic centimetre
CoRAP	Community Rolling Action Plan
DAG	Diglycolic acid
EC_{50}	Effective Concentration, median
ECHA	European Chemicals Agency
ED	Endocrine Disruptor
EPM	Equilibrium Partitioning Method
et al.	et alii
g	gram

GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GLP	Good Laboratory Practise
h	hour(s)
HGPRT	Hypoxanthine-guanine phosphoribosyltransferase
hPa	hecto Pascal
IC_{50}, IC_{25}	Inhibitory Concentration, median and 25%
i.p.	intra peritoneal
ISO	International Organization for Standardization
kg	kilogram
Koc	Organic Carbon Adsorption Coefficient
Kow	Octanol-Water Partition Coefficient
L	litre
LC_{50}	Lethal Concentration, median
LD_{50}	Lethal Dose, median
LOAEL	Lowest Observed Adverse Effect Concentration
lx	lux
m^3	cubic metre
mg	milligram
mL	milli litre
mmol	milli mol
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative, Toxic
PEC	Predicted Environmental Concentration
PNEC	Predicted No-effect Concentration
p.o.	per os
QSAR	Quantitative Structure-activity Relationship
RCR	Risk Characterisation Ratio
RMM	Risk Management Measures

SCE	Sister Chromatid Exchange
STP	Sewage Treatment Plant
SVHC	Substance of Very High Concern
T	Temperature
t	Tonnes
TTC	Toxic Threshold Concentration
w/v	weight/volume
µmol	micro mol