



lebensministerium.at

**SUBSTANCE EVALUATION  
CONCLUSION DOCUMENT**  
**as required by REACH Article 48**  
**for**

**Ethylene oxide**  
**EC No 200-849-9**  
**CAS No 75-21-8**

**Evaluating Member State: Austria**

**Evaluator: Umweltbundesamt GmbH on behalf of the  
Austrian Federal Ministry of Agriculture,  
Forestry, Environment and Water Management**

Dated: November 2013

## Evaluating Member State Competent Authority

Substance Evaluation of ethylene oxide (EC No 200-849-9, CAS No 75-21-8) was performed by the Umweltbundesamt GmbH (Spittelauer Lände 5, 1090 Vienna) on behalf of the Austrian Competent Authority, the Austrian Federal Ministry of Agriculture, Forestry, Environment and Water Management (Stubenring 1, 1010 Vienna, Austria).

### Contact:

Max Kinzl, Dr.

Department: Chemicals & Biocides

T: +43-(0)1-313 04/5655

F: +43-(0)1-313 04/5660

[Stoffbewertung@umweltbundesamt.at](mailto:Stoffbewertung@umweltbundesamt.at)

Umweltbundesamt GmbH

Spittelauer Lände 5

1090 Wien

Österreich/Austria

### Year of evaluation in CoRAP: 2012

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

**Please find (search for) further information on registered substances here:**

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

## 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.

In order to ensure a harmonised approach, ECHA in cooperation with the Member States developed risk-based criteria for prioritising substances for substance evaluation. The list of substances subject to evaluation, the Community rolling action plan (CoRAP), is updated and published annually on the ECHA web site<sup>1</sup>.

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 the Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. In this conclusion document, the evaluating Member State shall consider how the information on the substance can be used for the purposes of identification of substances of very high concern (SVHC), restriction and/or classification and labelling. With this Conclusion document the substance evaluation process is finished and the Commission, the registrants of the substance and the competent authorities of the other Member States are informed of the considerations of the evaluating Member State. Thus this conclusion document is not reflecting an official position of ECHA. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes.

---

<sup>1</sup> <http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan>

## CONTENTS

<b>Foreword</b> .....	<b>3</b>
<b>CONTENTS</b> .....	<b>4</b>
<b>1. CONCERNS SUBJECT TO EVALUATION</b> .....	<b>5</b>
<b>2. CONCLUSION OF SUBSTANCE EVALUATION</b> .....	<b>7</b>
<b>3. JUSTIFICATION FOR THE CONCLUSION ON THE NEED OF REGULATORY RISK MANAGEMENT</b> .....	<b>10</b>
3.1. NEED FOR FOLLOW UP REGULATORY ACTION AT EU LEVEL .....	10
<b>3.1.1. Need for harmonised classification and labelling</b> .....	10
<b>3.1.2. Need for Identification as a substance of very high concern, SVHC (first step towards authorisation)</b> .....	10
<b>3.1.3. Need for restrictions</b> .....	10
<b>3.1.4. Proposal for other Community-wide regulatory risk management measures</b> .....	10
3.2. NO FOLLOW-UP ACTION NEEDED .....	10
<b>4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS</b> .....	<b>10</b>
References	

## 1. CONCERNS SUBJECT TO EVALUATION

Ethylene oxide was originally selected for substance evaluation in order to clarify suspected risks about:

- Human health: CMR
- Human exposure: High aggregated tonnage

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

- Classification and labelling
- Environmental hazard and exposure assessment

Ethylene oxide was proposed for substance evaluation based on Article 45(5) of the REACH regulation. The evaluation was covering all sections of the chemical safety assessment given in the IUCLID dossiers and chemical safety reports of the registrants. Following main concerns were identified before and during Substance Evaluation by the evaluating Member State.

- The substance has harmonised classification as Carc. 1B and Muta. 1B. Based on the available data it can be assumed that ethylene oxide acts via a non-threshold mode of action. Therefore, a DMEL<sup>2</sup> should be derived for this substance. The registrants have derived a DMEL chronic inhalation worker of 2mg/m<sup>3</sup> which corresponds to an additional cancer risk of 4:1000. This DMEL-value is different from the value derived for worker exposure by the German AGS (Ausschuss für Gefahrstoffe) which is 23.6µg/m<sup>3</sup>, based on an additional cancer risk of 4.10<sup>-5</sup>. The DMEL derivations were reassessed by the evaluating Member State, confirming that differences in DMEL values are solely due to the different assumptions for cancer risks.
- High volumes of the substance are manufactured/applied in the EU. The provided exposure assessments of the registration dossiers were based on ECETOC-TRA, a Tier 1-exposure estimation software tool, which is considered to be conservative in principle. This means that derived exposure levels would tend to overestimate exposure rather than to underestimate it. The exposure scenarios were described only by use descriptors and the parameters needed for using ECETOC-TRA. However, as the substance is manufactured/applied by many sites and the ES are not described/discussed in detail, it was uncertain, if the real situations at work place were covered by the ESs given in the registration dossiers. An assessment by the evaluating Member State revealed that initial assumptions (input parameters used for ECETOC-TRA) did not match the real situations. Therefore, as a result of interaction with the registrants the evaluating Member State received more detailed background information and descriptions of the human exposure scenarios during the first year of evaluation. The registrants submitted measured data and a new approach for the human exposure assessment. The registrants have included these data and the new approach in an update of the registration dossiers. Based on these data, the concern was clarified.
- The environmental exposure assessment was not performed initially by the registrants based on their justification that there is no need for classification referring to environmental hazards. No data on long-term toxicity to fish and aquatic invertebrates were provided. These tests were waived based on section 3 paragraph 3.2(b) of Annex XI of the REACH regulation 1907/2006 amended by Commission regulation (EC) No 134/2009. The evaluating Member State considered waiving of a quantitative or qualitative environmental exposure assessment as not acceptable, also because the waived tests might have led to a classification related to environmental hazards. In informal interactions the evaluating Member State invited the registrants to provide

---

<sup>2</sup> DMEL Derived Minimal Effect Level

further information on environmental exposure. The registrants provided an environmental exposure assessment referring to the release and corresponding risk management measures applied. The evaluating Member State concluded that the concern had been clarified and that no further information on environmental hazard and exposure assessment was needed.

## 2. CONCLUSION OF SUBSTANCE EVALUATION

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

Conclusions	Tick box
Need for follow up regulatory action at EU level <i>[if a specific regulatory action is already identified then, please, select one or more of the specific follow up actions mentioned below]</i>	
<i>Need for Harmonised classification and labelling</i>	X
<i>Need for Identification as SVHC (authorisation)</i>	
<i>Need for Restrictions</i>	
<i>Need for other Community-wide measures</i>	X
No need for regulatory follow-up action	

As available data were considered to be sufficient for chemical safety assessment and covering relevant topics of concern, no new data/tests were considered to be required by the evaluating Member State. Therefore, substance evaluation was finalised after the first year of evaluation and the submission of revised registration dossiers in December 2012 by the registrants.

Following points taken should be highlighted:

### **Sensitisation:**

Ethylene oxide is covered by index number 603-023-00-X in Annex VI, part 3, Table 3.1 (list of harmonized classification and labelling of hazardous substances) of Reg. (EC) No 1272/2008 (CLP regulation). Referring to this list, the substance is not classified as skin sensitizer.

Table: Harmonized classification and labelling of ethylene oxide according to CLP

Index No	Classification		Labelling	
	Hazard Class and Category Code(s)	Hazard statement codes	Pictogram, Signal Word Codes	Hazard statement codes
603-023-00-X	Flam. Gas 1	H220		H220
	Press. Gas	H350	GHS02	H350
	Carc. 1B	H340	GHS04	H340
	Muta. 1B	H331	GHS06	H331
	Acute Tox. 3 *	H319	GHS08	H319
	Eye Irrit. 2	H335	Dgr	H335
	STOT SE 3	H315		H315
	Skin Irrit. 2			

Nevertheless, there is sufficient evidence to conclude a need for classification as skin sensitiser Category 1:

In mice and rats treated by parenteral application of ethylene oxide protein conjugates, the formation of specific IgE antibodies was demonstrated. By means of transfer tests, the specificity of the IgE antibodies could be demonstrated in vivo (Chapman, 1986, reviewed in SCOEL 2012).

Skin sensitization studies in guinea pigs by Woodard (1971), however, were negative (reviewed in ATSDR, 1990).

Dermal application studies using human volunteers by Sexton (1950) and Shupack (1981) have provided some evidence that ethylene oxide is a skin sensitizer. Thiess (1963) did not observe skin sensitization in ethylene oxide plant workers (average exposure: 10.4 years) which were challenged with a single dermal application of 1% ethylene oxide (reviewed in ATSDR, 1990). Anaphylactic reactions in dialysis patients with attacks of sneezing, retrosternal burning pains, larynx oedema, bronchial obstruction and hypersecretion, flushing and pruritus and sometimes even anaphylactic shock have been described by several authors (Bommer, 1985, Röckel, 1989, Rumpf, 1985). There exist different potential causes for the observed effects, however, various authors came independently to the conclusion that by far the main factor in the provocation of such reactions is allergy of immediate type to ethylene oxide. In these cases the presence of conjugates of ethylene oxide with human serum albumin (HSA) have been demonstrated by RAST (radiosorbent test) (Bommer, 1985, Grammer, 1984, Röckel, 1989, Rumpf, 1985). Ethylene oxide HSA specific IgEs occurred more frequently in dialysis patients compared to the control group and patients with increased IgE levels had allergic complications more frequently than patients without antibodies. IgE levels decreased when other sterilisation methods were applied instead of ethylene oxide and clinical symptoms had suddenly improved. Re-exposure to ethylene oxide sterilised materials resulted in reappearance of the clinical symptoms (Bommer et al., 1985) (reviewed in SCOEL 2012).

The registrants present additional human data on sensitisation in IUCLID Chapter 7.10.4. Monbaliu (2010) investigated ethylene oxide sensitized patients and Wass (1988) concluded that the changes in titers of IgE and IgG antibodies correlated to the time of ethylene oxide exposure as well as to clinical symptoms of hemodialysis patients. Dolovich (1983) describes acute reactions of a hemodialysis patient becoming sensitized to ethylene oxide.

Ethylene oxide is a direct and potent alkylating agent and reacts with hydroxyl, sulfhydryl, amino and carboxyl groups in human macromolecules. As a hapten it becomes an active allergen after binding to human proteins. For ethylene oxide especially allergies of the immediate type are well documented. In addition, there are case reports describing contact dermatitis caused by ethylene oxide contact (SCOEL, 2012).

### **Conclusion:**

As there is sufficient evidence for ethylene oxide to have skin sensitizing potential a harmonised classification according to Regulation (EC) No. 1272/2008 as skin sensitizer (Category 1), H317 (May cause an allergic skin reaction) is warranted to ensure that workers using ethylene oxide get knowledge about the skin sensitising potential of ethylene oxide.

### **Carcinogenicity:**

So far there is no EU legislation in place setting a Community-wide acceptable risk level for carcinogens. Different risk levels have been set and used in different contexts. REACH Guidance R.8 (ECHA, 2012) gives examples on risk levels used in different countries, organisations and committees. According to the ECHA Guidance, cancer risk levels of  $10^{-5}$  and  $10^{-6}$  could be seen as indicative tolerable risks levels when setting DMELs for workers and the general population, respectively. Kalberlah (2005) discusses the definitions of risk, safety, precaution, acceptable and tolerable risk. This report applies the German traffic light model for exposures to carcinogens

at the workplace and compares the results with already used tolerable risk levels by different institutions/countries. For workers this study reports tolerable risk levels between  $4 \cdot 10^{-3}$  –  $4 \cdot 10^{-5}$  referring to a working lifetime of 40 years and continuous exposure at every working day. This study demonstrates the need to find an EU wide consensus on the size of an acceptable and a tolerable risk level.

The additional working lifetime risk of  $4 \cdot 10^{-3}$  taken by the registrant could be challenged on the basis of the traffic light model mentioned above which would require urgent measures to reduce the risk. The acceptable risk level according to AGS "Ausschuss für Gefahrstoffe" would be  $4 \cdot 10^{-5}$  (with a value of  $4 \cdot 10^{-4}$  proposed as an interim level accepted for the introductory phase until 2018).

Application of working lifetime risk values for workers of  $4 \cdot 10^{-5}$ , as recommended by AGS (2011), would result in the following calculation using same data as the registrants:

$BMD_{10} = 19.4\text{ppm}$  (10% response over background)

$hBMD_{10} = 29.55\text{ppm}$  (corrected for human exposure situation at workplace: 8h/day, 48weeks, 40 years)

Additional working lifetime risk of  $4 \cdot 10^{-5}$  (0.004% over background):

$$\text{DMEL}_{\text{worker, inhalation, long-term}} = 11.8\text{ppb} = 23.6 \mu\text{g}/\text{m}^3$$

The **DMEL = 23.6  $\mu\text{g}/\text{m}^3$**  for workplace exposure to ethylene oxide calculated by the evaluating Member State with an additional risk of  **$4 \cdot 10^{-5}$**  is by factor of 85 lower than the **DMEL = 2mg/ $\text{m}^3$**  calculated by the registrants with an additional risk of  **$4 \cdot 10^{-3}$** . The DMEL = 2mg/ $\text{m}^3$  is used in the current version of the CSRs and in the registration dossiers. The discrepancy results from rounding and the different lifetime risk used.

Notwithstanding the decision on appropriate risk levels and the resulting DMEL it has to be stated that there is a cancer risk remaining at any DMEL level and it is therefore recommended to minimize the exposure as far as possible.

### **Conclusion:**

This substance evaluation underlines the need for a discussion of acceptable risk levels for workers and the general population. Political agreement is needed at Community level. As a consequence no final conclusion on the appropriate DMEL for ethylene oxide can be drawn. Hence, the level of risk cannot be substantiated at this point of time.

### 3. JUSTIFICATION FOR THE CONCLUSION ON THE NEED OF REGULATORY RISK MANAGEMENT

#### 3.1. NEED FOR FOLLOW UP REGULATORY ACTION AT EU LEVEL

##### 3.1.1. Need for harmonised classification and labelling

As there is sufficient evidence for the skin sensitizing potential of ethylene oxide (see chapter 2) an update of the Annex VI ethylene oxide entry of Regulation (EC) No. 1272/2008 to include harmonised classification for skin sensitisation Category 1, H317 (May cause an allergic skin reaction) is warranted to ensure that workers using ethylene oxide get knowledge about the skin sensitising potential of ethylene oxide.

##### 3.1.2. Need for Identification as a substance of very high concern, SVHC (first step towards authorisation)

NA

##### 3.1.3. Need for restrictions

NA

##### 3.1.4. Proposal for other Community-wide regulatory risk management measures

This substance evaluation underlines the need for a discussion of acceptable risk levels for workers and the general population with regard to the carcinogenic potential of substances. Political agreement is needed at Community level. This issue is a matter of principle and does not target ethylene oxide specifically. As there is no agreed acceptable risk level no final conclusion on the appropriate DMEL for ethylene oxide and other "DMEL"-substances can be drawn. Hence, the level of risk of ethylene oxide cannot be substantiated at this point of time.

#### 3.2. NO FOLLOW-UP ACTION NEEDED

NA

### 4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS

Follow-up action	Date for intention	Actor
CLP Annex VI dossier	open	Austria
Harmonisation of acceptable cancer risk on European level	open	European legislators

## References

AGS (Ausschuss für Gefahrstoffe) (2011) ERB-Begründung zu Ethylenoxid. <http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/910/910-ethylenoxid.pdf?blob=publicationFile&v=3>

ATSDR (1990). Toxicological profile for ethylene oxide. <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=734&tid=133>

Bommer J, Barth HP, Wilhelms OH, Schindele H, Ritz E (1985). Anaphylactoid reactions in dialysis patients: role of ethylene-oxide. *Lancet* 28:1382-1384.

Chapman J, Lee W, Youkilis E, Martis L (1986). Animal model for ethylene oxide (EtO) associated hypersensitivity reactions. *Trans Am Soc Artif Intern Organs* 32:482-485.

Dolovich J, Marshall CP, Smith EK, Shimizu A, Pearson FC, Sugona MA, Lee W. (1984). Allergy to ethylene oxide in chronic hemodialysis patients. *Artif Organs*. Aug;8(3):334-7.

ECHA (2012) Guidance on information requirements and chemical safety assessment Chapter r.8: Characterisation of dose [concentration] response for human health. ECHA-2010-G-19\_EN. [http://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r8\\_en.pdf](http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf)

Grammer LC, Roberts M, Nicholls AJ, Platts MM, Patterson R (1984). IgE against ethylene oxide-altered human serum albumin in patients who have had acute dialysis reactions. *J Allergy Clin Immunol* 74:544-546.

Kalberlah F., Bloser M., Wachholz C. (2005) Toleranz- und Akzeptanzschwelle für Gesundheitsrisiken am Arbeitsplatz. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin. Projektnummer F2010.

Monbaliu D, Van Breussegem A, Onsia A, Vandermeersch E, Segers C, Meert W, Kochuyt AM, Pirenne J, Claes K. (2010). Ethylene oxide allergy in patients on hemodialysis waiting for kidney transplantation: logistical nightmare or challenge? A case report. *Transplant Proc.* 42(10):4375-7.

Röckel A, Klinke B, Hertel J, Baur X, Thiel C, Abdelhamid S, Fiegel P, Walb D (1989). Allergy to dialysis materials. *Nephrol Dial Transplant* 4:646-652.

Rumpf KW, Seubert A, Valentin R, Ippen H, Seubert S, Lowitz HD, Rippe H, Scheler F (1985). Association of ethylene-oxide-induced IgE antibodies with symptoms in dialysis patients. *Lancet* 28:1385-1387.

SCOEL (2012) European commission, Employment, Social Affairs & Inclusion. Recommendation from the Scientific Committee on Occupational exposure Limits for ethylene oxide. SCOEL/SUM/160.

Sexton RJ, Henson EV. 1950. Experimental ethylene oxide human skin injuries. *Ind Hyg Occup Med* 32:549-564.

Shupack J.L., Andersen S.R., Romano S.J. (1981). Human skin reactions to ethylene oxide. *J. Lab. Clin. Med.* 98: 723-729.

Thiess AM. 1963. [Observations on the health hazards of ethylene oxide.] *Archiv Toxiko* 20:127-140. (German) (as cited in ATSDR, 1990).

Wass U, Belin L, Delin K. (1988). Longitudinal study of specific IgE and IgG antibodies in a patient sensitized to ethylene oxide through dialysis. *J Allergy Clin Immunol.* 1988 Oct;82(4):679-85.