Biocidal Products Committee (BPC)

Opinion on the application for approval of the active substance:

Ethylene oxide

Product type: 2

ECHA/BPC/272/2020

Adopted

3 December 2020

Opinion of the Biocidal Products Committee

on the application for approval of the active substance ethylene oxide for product type 2

In accordance with Article 89(1) of Regulation (EU) No 528/2012 of the European Parliament and of the Council 22 May 2012 concerning the making available on the market and use of biocidal products (BPR), the Biocidal Products Committee (BPC) has adopted this opinion on the application for approval in product type 2 of the following active substance:

Common name:	**Ethylene oxide**
Chemical name:	**Oxirane / Ethylene oxide**
EC No.:	**200-849-9**
CAS No.:	**75-21-8**

Existing active substance

This document presents the opinion adopted by the BPC, having regard to the conclusions of the evaluating Competent Authority. The assessment report, as a supporting document to the opinion, contains the detailed grounds for the opinion.

Process for the adoption of BPC opinions

Following the submission of an application by the EtO BPD Consortium on 1 December 2009, the evaluating Competent Authority NO submitted an assessment report and the conclusions of its evaluation to ECHA on 5 March 2020. In order to review the assessment report and the conclusions of the evaluating Competent Authority, the Agency organised consultations via its Working Groups (WG-III-2020). Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

Information on the fulfilment of the conditions for considering the active substance as a candidate for substitution was made publicly available at https://echa.europa.eu/potentialcandidates-for-substitution-previous-consultations on 9 April 2020, in accordance with the requirements of Article 10(3) of Regulation (EU) No 528/2012. Interested third parties were invited to submit relevant information by 8 June 2020.

Adoption of the BPC opinion

Rapporteur: Norway

The BPC opinion on the application for approval in of the active substance ethylene oxide in product type 2 was adopted on 3 December 2020.

The BPC opinion takes into account the comments of interested third parties provided in accordance with Article 10(3) of BPR.

The BPC opinion was adopted by consensus. The opinion is published on the ECHA webpage at: http://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/bpc-opinions-on-active-substance-approval.

Detailed BPC opinion and background

1. Overall conclusion

Ethylene oxide fulfils the criteria set in Article 5(1)(a), (b) and (c) of Regulation (EU) No 528/2012. The overall conclusion of the BPC is that ethylene oxide in product type 2 should normally not be approved, unless at least one of the conditions for derogation set in Article 5(2) of Regulation (EU) No 528/2012 is met. The process related to the demonstration of whether one of these conditions are met, is not within the remit of the BPC[1].

2. BPC Opinion

2.1. BPC Conclusions of the evaluation

a) Presentation of the active substance including the classification and labelling of the active substance

This evaluation covers the use of ethylene oxide in product type 2, as a gaseous sterilant. Specifications for the reference sources are established.

The physico-chemical properties of the active substance and biocidal product have been evaluated and are deemed acceptable for the appropriate use, storage and transportation of the active substance and biocidal product.

Validated analytical methods for ethylene oxide as manufactured are not feasible. Various quality control methods are however available to determine the impurities present in the batches, and semi-quantitative analytical methods are used to confirm that ethylene oxide as manufactured has a high purity. Hence, the purity of ethylene oxide as manufactured is determined indirectly.

An Occupational Exposure Limit (OEL) has been established for ethylene oxide [Directive (EU) 2017/2398 amending Directive 2004/37/EC established for the protection of workers from the risks related to exposure to carcinogens or mutagens at work].

A REACH substance evaluation from 2012 is also available.

The following table lists the harmonised classification and labelling for ethylene oxide according to Regulation (EC) No 1272/2008 (CLP Regulation), as amended by Commission Delegated Regulation (EU) 2020/217 of 4 October 2019 (the 14th ATP to CLP):

Classification according to the CLP Regulation	
Hazard Class and Category Codes	Flam. Gas 1 Press. Gas (Note U*) Carc. 1B Muta. 1B Repr. 1B Acute Tox. 3 Acute Tox. 3 STOT SE 3 STOT SE 3 STOT RE 1 Skin Corr. 1 Eye Dam. 1

[1] See document: "Further guidance on the procedures related to the examination of the exclusion criteria and the conditions for derogation under Article 5(2) (CA-Nov14-Doc.4.5-Final).

Labelling	
Pictogram codes	GHS02 GHS08 GHS06 GHS05
Signal Word	Danger
Hazard Statement Codes	H220 H350 H340 H360Fd H331 H301 H335 H336 H372 (nervous system) H314 H318
Specific Concentration limits, M-Factors	inhalation: ATE = 700ppm (gases) oral: ATE = 100 mg/kg bw
Justification for the proposal	

* Note U (of CLP as amended by Commission Delegated Regulation (EU) 2016/918 of 19 May 2016): When put on the market gases have to be classified as 'Gases under pressure', in one of the groups compressed gas, liquefied gas, refrigerated liquefied gas or dissolved gas. The group depends on the physical state in which the gas is packaged and therefore has to be assigned case by case. The following codes are assigned: Press. Gas (Comp.), Press. Gas (Liq.), Press. Gas (Ref. Liq.), Press. Gas (Diss.). Aerosols shall not be classified as gases under pressure (See Annex I, Part 2, Section 2.3.2.1, Note 2).

b) Intended use, target species and effectiveness

The intended, evaluated use of the active substance ethylene oxide is the industrial sterilisation of single use medical devices, which cannot be sterilised by other means, before these are made available on the market. This is a highly specialised industrial use. The ethylene oxide sterilisation of medical devices must comply with ISO 11135:2014 (Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices).

The sterilisation occurs in large industrial units. Ethylene oxide is introduced into a sealed, stainless steel chamber which contains the medical devices to be sterilised. On completion, ethylene oxide from the sterilisation chamber is exhausted to the atmosphere via a catalytic converter which converts ethylene oxide to carbon dioxide and water, typically with an efficiency of 99.9 %. In some cases, acid scrubbers convert the ethylene oxide to ethylene glycol with an efficiency in the range of 99.5 to 99.9 %. The sterilised medical devices are transferred to an aeration cell in order to remove any residual ethylene oxide from the medical devices and packaging.

Other possible uses, which have not been supported by sufficient data to carry out an evaluation, include in-house sterilisation of medical equipment in hospitals, and sterilisation of books, musical instruments, and museum artifacts.

Ethylene oxide is a highly reactive alkylating agent and reacts with proteins, amino acids and nucleic acids.

For the active substance, the innate biocidal activity towards bacterial spores of *Bacillus atrophaeus* is demonstrated through ISO 11135:2014 validation studies documenting the efficacy of an ethylene oxide sterilisation process. *B. atrophaeus* is a recommended standard organism for the validation of ethylene oxide sterilisation, according to ISO 11138-2:2017,

Sterilization of health care products-Biological indicators, Part 2: Biological indicators for ethylene oxide sterilization. At an ethylene oxide concentration of 300 mg/L in the sterilisation chamber, a biocidal effect with a sterility assurance level (SAL) of 10^{-6} was obtained (i.e. a probability of 10^{-6} for a viable microorganism occurring on the sterilised devices). Other factors than the ethylene oxide concentration, such as temperature, pressure, humidity and pH, will affect the sterilisation process. These parameters must also be precisely defined and validated for each specific ethylene oxide sterilisation process (including the specific medical devices which are to be sterilised). For a given ethylene oxide sterilisation process, other ethylene oxide concentrations than 300 mg/L can be used, provided that the process as a whole is validated in accordance with ISO 11135:2014.

The representative biocidal product is composed of 100 % ethylene oxide. No separate efficacy assessment of the representative biocidal product has been carried out.

The efficacy was considered sufficiently demonstrated for the active substance approval, but at the product authorisation stage, additional information should be submitted, to ensure that efficacy against all target organisms and compositions of the biocidal products is sufficiently documented.

Many factors will affect the efficacy of ethylene oxide, resulting in micro-organisms being more resistant under certain conditions, e.g. low humidity. However, true ethylene oxide resistance is not expected, as the development of resistance towards a substance with such a basic mode of action towards several vital molecules within the cell is unlikely.

c) Overall conclusion of the evaluation including need for risk management measures

Human health

Ethylene oxide is a highly reactive gas and classified with numerous hazardous human health properties. Ethylene oxide is toxic if swallowed and toxic if inhaled. In addition, ethylene oxide may cause drowsiness or dizziness. Ethylene oxide is corrosive to skin, and implicitly considered to cause serious eye damage. Ethylene oxide is also an active substance that causes respiratory irritation. In addition, ethylene oxide causes adverse effects on fertility and there are also indications of developmental effects of ethylene oxide. Based on this, it was concluded that ethylene oxide may damage fertility and that it is suspected of damaging the unborn child. Ethylene oxide also causes damage to the nervous system after repeated exposure.

Ethylene oxide has been shown to be genotoxic and the evaluated studies provide conclusive evidence that ethylene oxide is carcinogenic in two species (rat and mice). Based on this, the critical endpoint of ethylene oxide is genotoxic carcinogenicity with a non-threshold mode of action, and a conservative semi-quantitative risk assessment has been performed for the active substance. The BPR methodology for the risk assessment of non threshold carcinogens was followed as described in the BPR guidance when deriving the DMELs (Derived Minimal Effect Level) for professionals and the general public living in the surrounding area.

Ethylene oxide is exclusively used in dedicated, highly specialised industrial sterilisation plants where workers are specialised and highly trained. Following provisions given in Directive 2004/37/EC, a high level of OCs (operational conditions) and risk mitigation measures (e.g. use of positive pressure self-contained breathing apparatus and protective clothing are used in parts of the process where needed) are applied in order to control and reduce the operator exposure as much as possible. According to Directive 2004/37/EC as amended by Directive (EU) 2017/2398, exposure levels should be below 1 ppm. The DMEL derived for professionals is significantly lower than the OEL given in Directive (EU) 2017/2398: 3 ppb versus 1 ppm.

The process also involves a high degree of automation with continuous monitoring of airborne ethylene oxide concentrations and control of atmospheric emissions. Due to this highly specialised use of ethylene oxide, the exposure to industrial workers involved in ethylene oxide sterilisation is not possible to model in a realistic way using existing exposure models. Monitoring of exposure to personnel at ethylene oxide sterilisation plants is mandatory.

The applicant submitted monitoring data from four ethylene oxide sterilisation plants located in Europe. The data included 49 individual measurements (facility or country not indicated) indicating job categories (e.g. operator, laboratory, engineer, office/admin, warehouse), however the specific tasks performed and PPE (personal protective equipment) and/or RPE (respiratory protective equipment) used were not specified. The monitoring data provided by the applicant were used in the exposure assessment of ethylene oxide.

The table below summarises the exposure scenarios assessed.

Summary table: human health scenarios			
Scenario	**Primary or secondary exposure and description of scenario**	**Exposed group**	**Conclusion**
Industrial user	Actual exposure monitoring data (8 h TWA) from 4 EtO sterilisation plants in Europe compared with the $DMEL_{professional}$. High degree of RMMs expected.	Industrial users	Not tolerable [1)]
Indirect exposure general population living in the surrounding area of sterilisation plants.	No monitoring data from the surroundings of European sterilisation plants are available. Estimated $PEClocal_{air}$ from the ENV evaluation compared with the $DMEL_{general\ public,\ surrounding\ area}$. High degree of RMMs expected.	General population living in the surrounding area of sterilisation plants.	Not tolerable [2)]

[1)] Tolerable lifetime cancer risk level represents an increase of lifetime cancer risk of 1 per 100.000 exposed individuals (10^{-5}) for workers
[2)] Tolerable lifetime cancer risk level represents an increase of lifetime cancer risk of 1 per 1.000.000 exposed individuals (10^{-6}) for the general population

The primary use of ethylene oxide is industrial disinfection of single use medical equipment before these are placed on the market. Professional and non-professional use is not relevant for the evaluated use.

Conclusion of risk characterisation for industrial user:

Actual exposure monitoring data from 4 ethylene oxide sterilisation plants in Europe was compared directly with the $DMEL_{professional}$ value. The monitoring data showed a large variation of the exposure of the industrial workers, all resulting in an exceedance of the DMEL value. The reason behind the large variation of the exposure of the industrial workers was not possible to identify as the specific tasks performed and the specific risk mitigation measures (RMMs) in place for the workers were not indicated in the monitoring data provided. However, even the minimum exposure value resulted in an exceedance of the DMEL of 400% (corresponding to an elevated lifetime cancer risk of 4 per 100 000). The maximum value resulted in a DMEL exceedance of 29000 % (corresponding to an elevated lifetime cancer risk of 3 per 1000). Thus, no acceptable risk for industrial workers involved in ethylene oxide sterilisation could be demonstrated, based on a tolerable elevated lifetime cancer risk of 1×10^{-5}.

Conclusion of risk characterisation for indirect exposure of the general population living in the surrounding areas of European sterilisation plants:

No monitoring data from the surroundings of European sterilisation plants are available. Ethylene oxide from the treatment chamber and the aeration rooms in the sterilisation plant is exhausted to the atmosphere via a catalytic emission control system. A $PEClocal_{air}$ has been calculated to be 1.25×10^{-4} mg/m^3 (equivalent to 0.068 ppb) as an average air concentration 100 m from the source of emission. This distance is considered to represent the average distance between the emission source and the border of the industrial site. Using the $PEClocal_{air}$ resulted in an exceedance of the $DMEL_{\text{general poblic, surrounding area}}$. Hence, no acceptable risk for the general public living in the surrounding area of a sterilisation plant could be demonstrated, based on a tolerable elevated lifetime cancer risk of 1×10^{-6}.

Several monitoring studies of ethylene oxide in air in the surrounding area of sterilisation plants in the U.S. have been published. Some of these values from these monitoring studies exceed the estimated $PEClocal_{air}$ used in the risk assessment. This could indicate an underestimation of the exceedance of the DMEL value. Although significant variation is seen in the monitoring studies, both with regards to the possible atmospheric background levels of ethylene oxide and the air concentrations caused by emissions from the sterilisation plants, these studies clearly indicate a need for EU monitoring data, particularly where the sterilisation plants are located close to residential areas or in urban areas.

Exposure not covered by the evaluation as a biocide:

Once placed on the market, possible release of EtO from the medical devices will not be regulated by the BPR, but by the Medical Device Regulation (MDR, (EU) 2017/745). The accepted residual levels, and thus, secondary exposure of EtO and ethylene chlorohydrin (ECH) under MDR is defined in the ISO-standard ISO 10993-7:2008. Secondary exposure to the general public from medical devices has therefore not been further assessed.

Environment

Ethylene oxide degrades abiotically, through hydrolysis. Due to its high vapour pressure, vaporisation is also a significant dissipation route from the aquatic compartment. Ethylene oxide is readily biodegradable. The atmospheric half-life is long (estimated 38-382 days).

Ethylene oxide hydrolyses to ethylene glycol in freshwater, and to ethylene glycol and ethylene chlorohydrin in saltwater. These degradation products are not considered to be persistent in the environment. The acute aquatic toxicity of ethylene glycol and ethylene chlorohydrin is lower than or within the same order of magnitude as that of ethylene oxide, respectively.

From the intended use of ethylene oxide in PT 2, the only compartment to which there is direct release is the atmosphere. Emissions from the sterilisation chambers are vented through catalytic converters which reduce the amount of ethylene oxide before release through the stack/chimney. Any liquid waste, in the cases where acid scrubbers are used to convert ethylene oxide to ethylene glycol, is handled as toxic waste and is disposed of without emissions to the environment. Hence no release of ethylene oxide to sewage treatment plants (STPs) is foreseen. This has been a prerequisite for the environmental risk assessment and should be a requirement for the sites where ethylene oxide is used as intended. Other possible exposure pathways include indirect exposure of water and soil via deposition from air. However, due to the high vapour pressure of ethylene oxide (149 kPa at 20 °C) and hence rapid volatilisation, partitioning to other compartments is highly unlikely.

Due to the negligible exposure of soil and the aquatic compartment, the environmental risk assessment of ethylene oxide is qualitative except for the calculation of a $PECloca l_{air}$, i.e. an estimated ethylene oxide concentration 100 m from the emission source. This value has been used in the risk characterisation for the general public living in the surrounding areas of European sterilisation plants (see the human health assessment). Any potential risks for terrestrial vertebrates from e.g. inhalation are hence considered addressed by the human health assessment. For soil and water, the risk assessment consists of a qualitative evaluation of the likelihood that harmful effects will occur under the expected conditions of exposure.

The table below summarises the exposure scenarios assessed.

Summary table: environment scenarios		
Scenario	**Description of scenario including environmental compartments**	**Conclusion**
Direct emission to air from industrial sterilisation of single-use medical devices	Calculation of daily emissions ($Eloca l_{air}$) and subsequent $PECloca l_{air}$ in accordance with guidance on the BPR, Vol. IV part B. Based on the following assumptions, representing a realistic worst case (high capacity) sterilisation plant: Amount of ethylene oxide entering the catalytic converter (from the sterilisation chambers + aeration rooms, respectively): 400 kg + 50 kg/d = 450 kg/d Efficiency of catalytic converter, in converting ethylene oxide to carbon dioxide and water: 99.9 %	$Eloca l_{air}$: 0.45 kg/d $PECloca l_{air}$: 1.25×10^{-4} mg/m^3 Qualitative evaluation: There is a toxic potential for terrestrial vertebrates due to the classification of ethylene oxide (e.g. STOT-RE cat. 1 and H372, Muta. 1B, Repr. 1B). Since a risk is identified for the general public[1)], risks to terrestrial vertebrates cannot be excluded.
Indirect emission to water and soil from industrial sterilisation of single-use medical devices	Assessment of the possible partitioning of ethylene oxide from air to water and/or soil, based on enviromental fate and behaviour including physical-chemical properties.	Qualitative evaluation: Due to the fate and properties of ethylene oxide, the expected exposure to water and/or soil is negligible. No harmful effects to aquatic or soil organisms are likely to occur.

1) The risk characterisation for the general public (human health section) is based on a comparison between the $PECloca l_{air}$ and the $DMEL_{general\ public,\ surrounding\ area}$. The PEC exceeds the DMEL. Hence, unacceptable risk is identified for the general public in the surrounding areas of industrial sterilisation plants.

The calculation of the $PECloca l_{air}$ is based on realistic worst case assumptions, i.e. a high capacity (worst case) plant, with a catalytic converter efficiency considered realistic for such a facility. As mentioned under section 2.1 b), the catalytic converter efficiency, i.e. the efficiency of converting ethylene oxide to carbon dioxide and water prior to emission to the surrounding air, can in some sterilisation plants be lower than 99.9 %. However, it is considered realistic that a high capacity plant (with a daily use of ethylene oxide of 450 kg/d), which constitutes a worst case, would have a catalytic converter with such an efficiency in place. Furthermore, since ethylene oxide fulfils exclusion criteria laid down in Article 5(1) of Regulation (EU) No 528/2012, emissions should be minimised as far as possible, e.g. by ensuring that catalytic converters/control devices with an efficiency of 99.9 % are in place.

It should be noted that the underlying assumptions for the $PECloca l_{air}$ are are based on rather limited information. Also, ethylene oxide concentrations surrounding a sterilisation plant will depend on both the ethylene oxide use pattern, background concentrations and local atmospheric conditions (especially considering the long atmospheric half-life of ethylene oxide), and are expected to show considerable variation. Ethylene oxide monitoring data from the US in some cases exceed the $PECloca l_{air}$ calculated in this active substance assessment. Similar monitoring data are not available for the EU. Due to the identified unacceptable risk for the general public in the surrounding areas of industrial sterilisation plants (and hence that a risk cannot be excluded for terrestrial vertebrates), a need for monitoring data is identified. Such monitoring data could also be used to reassess the $PECloca l_{air}$.

Based on the evaluation of the data on effects on non-target organisms and the fate and behaviour of both the active substance ethylene oxide and the major hydrolysis degradation products ethylene glycol and ethylene chlorohydrin, any limited indirect exposure of water or soil via the atmosphere is not expected to result in concentrations which are harmful to the environment.

Overall conclusion

Overall, no safe use has been identified for human health when ethylene oxde is used for industrial sterilisation of single use medical devices, which cannot be sterilised by other means, before these are made available on the market. For the environment, a risk to terrestrial vertebrates cannot be excluded due to the inherent properties of the substance and the risk identified for the general public in the human health assessment. No harmful effects to aquatic or soil organisms are likely to occur from the indended use.

2.2. Exclusion, substitution and POP criteria

2.2.1. Exclusion and substitution criteria

The table below summarises the relevant information with respect to the assessment of exclusion and substitution criteria:

Property		Conclusions	
CMR properties	Carcinogenicity (C)	Classification in accordance with Regulation (EC) No 1272/2008: Carc. 1B	Ethylene oxide fulfils criterion (a), (b) and (c) of Article 5(1)
	Mutagenicity (M)	Classification in accordance with Regulation (EC) No 1272/2008: Muta. 1B	
	Toxic for reproduction (R)	Classification in accordance with Regulation (EC) No 1272/2008: Repr. 1B	

PBT and vPvB properties	Persistent (P) or very Persistent (vP)	Not P	Ethylene oxide does not fulfil criterion (e) of Article 5(1) and does not fulfil criterion (d) of Article 10(1)
	Bioaccumulative (B) or very Bioaccumulative (vB)	Not B	
	Toxic (T)	T	
Endocrine disrupting properties	Section A of Regulation (EU) 2017/2100: ED properties with respect to humans	An assessment of the endocrine disrupting properties was conducted; no conclusion could be drawn based on the available data. However, considering the known severe hazard properties of this substance, further data will not be requested in this special case. Consequently, no conclusion can be drawn whether ethylene oxide fulfils criterion (d) of Article 5(1) for human health or criterion (e) of Article 10(1) for the environment.	No conclusion can be drawn on whether ethylene oxide fulfils criterion (d) of Article 5(1) and/or criterion (e) of Article 10(1).
	Section B of Regulation (EU) 2017/2100: ED properties with respect to non-target organisms	An assessment of the endocrine disrupting properties according to Regulation (EU) 2017/2100 was not conducted. Consequently, no conclusion can be drawn whether ethylene oxide fulfils criterion (e) of Article 10(1) for the environment.	
	Article 57(f) and 59(1) of REACH	No	
	Intended mode of action that consists of controlling target organisms via their endocrine system(s).	No	

Respiratory sensitisation properties	No classification required. Ethylene oxide does not fulfil criterion (b) of Article 10(1)
Concerns linked to critical effects other than those related to endocrine disrupting properties	As there is a concern with respect to the increased cancer risk, even when applying restrictive risk mitigation measures, ethylene oxide fulfils criterion (e) of Article 10(1)
Proportion of non-active isomers or impurities	Ethylene oxide does not fulfil criterion (f) of Article 10(1)

Consequently, the following is concluded:

Ethylene oxide does meet the exclusion criteria laid down in Article 5(1)(a), (b) and (c) of Regulation (EU) No 528/2012.

Ethylene oxide does meet the conditions laid down in Article 10(1)(a) and (e) of Regulation (EU) No 528/2012, and is therefore considered as a candidate for substitution.

The exclusion and substitution criteria were assessed in line with the "Note on the principles for taking decisions on the approval of active substances under the BPR"[2], "Further guidance on the application of the substitution criteria set out under Article 10(1) of the BPR"[3] and "Implementation of scientific criteria to determine the endocrine –disrupting properties of active substances currently under assessment[4]" agreed at the 54th, 58th and 77th meeting respectively, of the representatives of Member States Competent Authorities for the implementation of Regulation 528/2012 concerning the making available on the market and use of biocidal products. This implies that the assessment of the exclusion criteria is based on Article 5(1) and the assessment of substitution criteria is based on Article 10(1)(a, b, d, e and f).

An assessment of the endocrine disrupting properties of ethylene oxide was conducted according to the EFSA/ECHA Guidance for the identification of endocrine disruptors, and the ED assessment of ethylene oxide was discussed at the 13th ED EG metting in November 2018. In general, the experts of the ED EG considered that there was sufficient evidence to conclude on EAS (estrogenic, androgenic and steroidogenic) mediated adversity, but it was not possible to conclude on whether or not this was caused by an endocrine disrupting mode of action due to the lack of mechanistic studies on ethylene oxide. Based on the information available, no final conclusion on the ED properties of ethylene oxide could be made. According to the EFSA/ECHA Guidance for the identification of endocrine disruptors, the way forward in such cases would be to request further data.

However, for this case Annex IV of Regulation (No) 528/2012 applies and in particular the first ("Testing does not appear scientifically necessary") and second heading ((Testing is technically not possible"): further data do not need to be requested. The following argumentation (supported by several experts in the ED EG and confirmed in the Human Health and Environment Working Groups) underpins this:

[2] See document: Note on the principles for taking decisions on the approval of active substances under the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/c41b4ad4-356c-4852-9512-62e72cc919df/CA-March14-Doc.4.1%20-%20Final%20-%20Principles%20for%20substance%20approval.doc)

[3] See document: Further guidance on the application of the substitution criteria set out under article 10(1) of the BPR (available from https://circabc.europa.eu/d/a/workspace/SpacesStore/dbac71e3-cd70-4ed7-bd40-fc1cb92cfe1c/CA-Nov14-Doc.4.4%20-%20Final%20-%20Further%20guidance%20on%20Art10(1).doc)

[4] See document: Implementation of scientific criteria to determine the endocrine –disrupting properties of active substances currently under assessment (https://circabc.europa.eu/sd/a/48320db7-fc33-4a91-beec-3d93044190cc/CA-March18-Doc.7.3a-final-%20EDs-%20active%20substances%20under%20assessment.docx).

1. The already known severe hazard profile of this substance: ethylene oxide fulfils the exclusion criteria of Article 5, paragraph 1a, b and c of BPR given the following classification of the active: Carc. 1B, Muta. 1B and Repr. 1B. As a consequence of these properties, strict RMMs are needed to avoid or minimise occupational exposure as far as technically feasible if EtO is to be used.
2. Furthermore, as a non-threshold mode of action is assumed for tumour formation, a conservative semi-quantitative risk assessment is performed. Consequently, no impact on the risk assessment would be expected if the substance were to be additionally considered as an ED.
3. Handling of ethylene oxide is very challenging. Ethylene oxide is a highly reactive gas - the substance readily reacts with diverse compounds and is explosive at concentrations higher than 3% in air. Based on both the human health hazardous properties and its flammable and explosive properties, special precautions must be taken when handling the substance. Specialised equipment and well-trained personnel are a prerequisite for using ethylene oxide in industrial facilities. Although most routine laboratories do have skilled personnel, it is, according to the applicant, very difficult to find laboratories that have the proper equipment and training for handling of ethylene oxide. It is unwarranted to expose either laboratory personnel or laboratory animals to ethylene oxide, unless it is strictly necessary. Furthermore, even the transport of samples from the factory to the laboratory is difficult. Specialised transport containers must be used, and great care must be taken to avoid accidents.
4. According to the minutes of the 13th ED EG, due to the unspecific alkylating properties of the substance, the available test systems for determining the endocrine activity would be likely to give equivocal results (if tests were performed). If mechanistic studies were nevertheless conducted, it would be difficult to conclude that the mechanism would be solely a (non-) ED MoA.

Hence, a final conclusion on the exclusion criteria related to Article 5(1)(d), and on whether ethylene oxide shall be considered a candidate for substitution related to possible ED effect to Article 10(1)(e) is not possible for ethylene oxide. However, Article 10(1)(e) is in any case considered fulfilled given the nature of the critical effect on human health and the use pattern (even with very restrictive RMMs) of ethylene oxide.

2.2.2. POP criteria

Ethylene oxide does not fulfil the criteria for being a persistent organic pollutant (POP).

2.2.3. Identification of potential alternatives substances or technologies, including the results of the public consultation for potential candidates for substitution

A public consultation was carried out to determine if any chemical or non-chemical alternatives are available for the intended use of ethylene oxide, i.e. the industrial sterilisation of single-use medical devices before these are made available on the market. A total of 18 comments were received, from industry (including the applicant) and one non-profit organisation.

Comments received from the industry emphasise that in order to ensure patient safety, it is imperative that medical devices are fully sterilised before use and that all components maintain full functionality over their envisaged lifetime. Information on other available sterilisation methods than ethylene oxide has been provided:

1. Irradiation (gamma, electron beam and X-ray irradiation) is applied commercially for large-scale sterilisation of single-use medical devices. There are, however, known material incompatibilities. Irradiation can induce changes in plastic polymers which can lead to e.g. embrittlement, softening or stiffening of the material. Metals present in the medical devices could act as barriers to radiation and result in incomplete sterilisation.
2. Heat sterilisation (e.g. steam, dry heat sterilisation) uses high temperatures that can damage materials such as plastics and adhesives. Steam sterilisation may also compromise any electronic components or cellulose-based materials in medical devices.
3. Gas sterilisation with formaldehyde, hydrogen peroxide, ozone and nitrogen dioxide: Formaldehyde sterilisation has a lower penetration ability than ethylene oxide and the sterilisation process needs a higher temperature. This makes it unsuitable for several medical devices. Formaldehyde as an active substance is included in the BPR review programme for use in PT 2. Hydrogen peroxide sterilisation is compatible with a wide range of materials, except some packaging materials. It has a lower penetration ability than ethylene oxide. Today, the main use is in hospitals for the resterilisation of medical devices and is not considered an alternative for the intended use. Hydrogen peroxide is approved as a biocidal active substance in PT 2. Ozone also has a good material compatibility. It is used mainly in small-scale applications, it is not known whether ozone could be suitable for industrial applications such as the intended use. Some concerns regarding penetration ability were raised. Ozone generated from oxygen as an active substance is included in the BPR review programme for use in PT 2. Nitrogen dioxide sterilisation was not reported to be widely used. There are material incompatibility issues with some plastics, copper, textile and cellulose-based materials. Nitrogen dioxide as an active substance is not included in the BPR review programme for use in PT 2.
4. Liquid chemical sterilisation e.g. with liquid peracetic acid, is used in smaller settings such as in hospitals for the resterilisation of medical devices. It is argued that today, these methods cannot be scaled for industrial sterilisation of large volumes of single-use medical devices and are hence not seen as suitable alternatives to the intended use.

The industry argues that ethylene oxide can be used in sterilisation processes at low temperatures, it has excellent penetration abilities due to its small molecular size, and it does not have any known material incompatibilities. It is argued that today, ethylene oxide sterilisation is the only suitable method for complex medical devices consisting of different materials, or pre-packaged kits (e.g. surgery kits) containing several medical devices.

Practical and cost-related issues related to the shift from industrial ethylene oxide sterilisation of single-use medical devices to alternative methods are also raised by the industry. It would require extensive efforts and costs related to the redesign of medical devices to avoid material incompatibility issues and hence ensure safe medical devices, and related to the development and establishment of new industrial processes and standards.

According to information from the industry, approximately 50 % of the medical devices on the EU market are sterilised with ethylene oxide. It is stated that today, suitable sterilisation alternatives exist for only 2 % of these devices. The industry further argues that for a medical device, a full conversion to another sterilisation method, if no such alternative already exists, would take several years. One estimation indicates 5 years or more given unlimited capital and resources, one estimation indicates 3-5 years or more, while other estimations indicate 8-12 years or longer. This timeframe includes e.g. the development, testing and optimisation of the technology, adaptation or development of medical devices to ensure material compatibility with the new technology, establishing the necessary infrastructure at the sterilisation facility, and obtaining the necessary regulatory permits.

The responses to the public consultation also include a call for safer alternatives, with particular regard to the health hazards of ethylene oxide. References are made to an innovation challenge initiated by the US Federal Drug Administration (FDA), with the aim of finding alternatives to ethylene oxide sterilisation. The final results from this work is not ready, but the following are listed as selected alternatives which will be investigated further: supercritical CO_2 sterilisation, nitrogen dioxide sterilisation, accelerator-based radiation sterilisation, vaporised hydrogen peroxide sterilisation, and vaporised hydrogen peroxide-ozone sterilisation. The submitter of this comment also refers to a report from the Association for the Advancement of Medical Instrumentation (AAMI), where the above-mentioned practical and cost-related issues is noted as a significant reason for why companies continue using ethylene oxide.

In conclusion, there does not seem to be suitable alternatives which can sufficiently replace the use of ethylene oxide for the industrial sterilisation of single-use medical devices today. However, there is ongoing research on possible future alternatives to ethylene oxide sterilisation of medical devices. Some of the alternatives mentioned above are relatively new methods used for sterilisation (such as X-ray irradiation), and new developments within these new methods are anticipated during the coming years. Also, even though some of the alternatives are not suitable for the industrial sterilisation of single-use medical devices today, they may have potential for this in the future. Taking into account the hazard profile of the substance and the identified cancer risks, it is important that alternative sterilisation methods are further investigated and established.

2.3. BPC opinion on the application for approval of the active substance ethylene oxide in product type 2

As the exclusion criteria are met, ethylene oxide should normally not be approved unless one of the conditions for derogation set in Article 5(2) of BPR is met.

In view of the evaluation, it is concluded that biocidal products containing ethylene oxide as an active substance used for industrial sterilisation of single use medical devices may not be expected to meet the criteria laid down in points (b)(iii and iv) of Article 19(1) of Regulation (EU) 528/2012.

If ethylene oxide is approved, the approval shall be subject to the following specific conditions:

1. Specification: minimum purity of the active substance evaluated: 99.9 %. No significant, nor relevant impurities are present in the active substance as produced.
2. The authorisations of biocidal products are subject to the following conditions:
    a. The product assessment shall pay particular attention to the exposures, the risks and the efficacy linked to any uses covered by an application for authorisation, but not addressed in the Union level risk assessment of the active substance.
    b. Products shall only be authorised for use in Member States where at least one of the conditions set in Article 5(2) of Regulation (EU) No 528/2012 is met.
    c. In view of the risks identified for the uses assessed, the product assessment shall pay particular attention to:
        i. Workers, industrial use;
        ii. General population living in the surrounding area of sterilisation plants.

d. The amounts of ethylene oxide released to the surrounding air from sterilisation chambers shall be minimised as far as possible, but at least using a catalytic converter or control device providing a 99.9 % ethylene oxide reduction prior to atmospheric emission.

e. Due to the identified unacceptable risk for the general public in the surrounding areas of industrial sterilisation plants (and hence also that a risk cannot be excluded for terrestrial vertebrates), monitoring data in air shall be provided for product authorisation.

f. In addition, monitoring in the vicinity of the plants should be implemented during use to ensure concentrations remain below the DMEL for the general public.

g. According to point (d) of Article 19(4) of Regulation (EU) No 528/2012, products shall not be authorised for making available on the market for use by the general public.

3. The placing on the market of treated articles is subject to the following condition(s):

a. The person responsible for the placing on the market of a treated article treated with or incorporating the active substance ethylene oxide shall ensure that the label of that treated article provides the information listed in the second subparagraph of Article 58(3) of the Regulation (EU) No 528/2012.

The active substance does not fulfil the criteria according to Article 28(2) to enable inclusion in Annex I of Regulation (EU) 528/2012 as it is classified as Carc. 1B, Muta. 1B, Repr. 1B, Skin Corr. 1, Acute Tox. 3, STOT SE 3 (respiratory irritation), STOT SE 3 (drowsiness or dizziness) and STOT RE 1 (nervous system). Furthermore, the active substance fulfils the subtitution criteria set out in Article 10(1) of Regulation (EU) 528/2012.

2.4. Elements to be taken into account when authorising products

1. The active substance ethylene oxide is considered as a candidate for substitution, and consequently the competent authority shall perform a comparative assessment as part of the evaluation of an application for national authorisation.
2. The following recommendations and risk mitigation measures have been identified for the uses assessed. Authorities should consider these risk mitigation measures when authorising products, together with possible other risk mitigation measures, and decide whether these measures are applicable for the concerned product:

a. The use of a biocidal product containing ethylene oxide shall be subject to appropriate risk-mitigation measures to ensure that exposure of humans, animals and the environment is minimised as far as possible.

b. In the case where acid scrubbers are used during the sterilization of medical devices to convert ethylene oxide to ethylene glycol, any liquid waste shall be handled and disposed of as hazardous waste.

c. For any uses resulting in emission to compartments others than air, an environmental risk assessment has to be provided for the concerned compartments at product authorisation.

2.5. Requirement for further information

Sufficient data have been provided to verify the conclusions on the active substance, permitting the proposal for the approval of ethylene oxide.

However, the following studies are required and must be provided as soon as possible but no later than 6 months before the date of approval to the eCA (Norway):

– A fully validated analytical method for detection of ethylene oxide in air, capable of determining ethylene oxide in concentrations below, or equal to, the DMELs (Derived Minimal Effect Levels) established for the biocidal use must be provided.

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