Biocidal Products Committee (BPC)

Opinion on the application for approval of the active substance:

Mecetronium ethyl sulphate (MES)

Product type: 1

ECHA/BPC/356/2022

Adopted

27 September 2022

Opinion of the Biocidal Products Committee

on the application for approval of the active substance Mecetronium ethyl sulphate (MES) for product type 1

In accordance with Article 90(2) 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 non-approval in product type 1 of the following active substance:

Common name:	**Mecetronium ethyl sulphate (MES)**
Chemical name:	**Dimethylethylhexadecylammonium ethylsulfate**
EC No.:	**221-106-5**
CAS No.:	**3006-10-8**

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 BODE Chemie GmbH on 31 July 2007 the evaluating Competent Authority Poland submitted an assessment report and the conclusions of its evaluation to ECHA on 7 January 2022. In order to review the assessment report and the conclusions of the evaluating Competent Authority, the Agency organised consultations via the BPC (BPC-44) and its Working Groups (WG-II-2022). Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

Adoption of the BPC opinion

Rapporteur: Poland

The BPC opinion on the application for approval of the active substance Mecetronium ethyl sulphate (MES) in product type 1 was adopted on 27 September 2022.

The BPC opinion was adopted by majority.

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

The overall conclusion of the BPC is that the Mecetronium ethyl sulphate (MES) in product type 1 may not be approved. The detailed grounds for the overall conclusion are described in the assessment report.

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 MES in product type 1. MES is a quaternary ammonium compound.

The pure active substance is a white powder solid. The active substance is manufactured as technical concentrate (TK) as an aqueous solution. The concentration of MES in the technical concentrate as manufactured is min. 24.8% w/w. Specifications for the reference source (technical concentrate and dry weight calculation) are established. The minimum purity of the active substance evaluated is 85% w/w (dry weight calculation). Five relevant impurities were identified with a maximum content of (all dry weight calculation): i) dodecylethyldimethylammonium ethyl sulphate: 0.2% w/w; ii) tetradecylethyldimethylammonium ethyl sulphate: 1.2% w/w; iii) sodium ethylsulfate: 5% w/w; iv) diethylsulphate: 0.003% w/w; v) ethanol: 8% w/w.

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 are available for the active substance as manufactured and for its impurities. Validated analytical methods are available for the relevant matrices: soil and water (although they are of insufficient sensitivity). No analytical methods for air, animal and human body fluids and tissues nor food and feeding stuff are considered as relevant as exposure is considered unlikely for the intended uses.

A harmonised classification according to Regulation (EC) No 1272/2008 (CLP Regulation) is available for MES.

(Current) Classification according to the CLP Regulation	
Hazard Class and Category Codes	Skin Corr. 1, H314 Eye Dam. 1, H318 Aquatic Acute 1, H400 Aquatic Chronic 1, H410
Labelling	
Pictograms	GHS05, GHS09
Signal Word	Danger
Hazard Statement Codes	H314: Causes severe skin burns and eye damage H410: Very toxic to aquatic life with long lasting effects.
Suppl. Hazard Statement Code	EUH071: Corrosive to the respiratory tract
Specific Concentration limits, M-Factors	Aquatic Acute 1; M=100 Aquatic Chronic 1; M=1000

The proposed classification and labelling for MES according to Regulation (EC) No 1272/2008 (CLP Regulation) is:

(Proposed) Classification according to the CLP Regulation	
Hazard Class and Category Codes	Skin Corr. 1, H314 Eye Dam. 1, H318 Aquatic Acute 1, H400 Aquatic Chronic 1, H410
Labelling	
Pictograms	GHS05, GHS09
Signal Word	Danger
Hazard Statement Codes	H314: Causes severe skin burns and eye damage H410: Very toxic to aquatic life with long lasting effects.
Suppl. Hazard Statement Code	EUH071: Corrosive to the respiratory tract
Specific Concentration limits, M-Factors	Aquatic Acute 1; M=10 Aquatic Chronic 1; M=10
Justification for the proposal	
The EC50 value from the short-term daphnia study is 0.016 mg/L and from the algae study the EC50 value is 0.0231 mg/L, i.e. between 0.01 and 0.1 mg/L. Hence Acute Category 1 with M factor 10 is warranted. The NOEC value from long-term studies (fish, reliability index of 1) is 0.00056mg/L, i.e. between 0.0001 and 0.001 mg/L, but the substance is readily biodegradable. Hence Chronic Category 1 with M factor of 10 is warranted.	

b) Intended use, target species and effectiveness

The intended uses of MES are hygienic and surgical hand disinfection for professional use as well as non-professional use for home-dialysis and non-professional use for visitors of patients in intensive care units. The properties of the active substance were claimed as bactericidal, yeasticidal and virucidal. Products, containing MES as an existing active substance, are employed as broad-spectrum microbiocides for hygienic and surgical hand disinfection.

Studies with biocidal products containing only the active substance show that MES is effective in irreversibly inactivating gram-negative and gram-positive bacteria and yeasts which are representative for the organisms in long contact times (60 min for all bacteria and 15 min for yeast). The contact time for hygienic hand disinfection should be maximal up to 1 min.

The available information for MES does not show bactericidal and yeasticidal activity during the contact time of up to 1 minute provided for the intended use hygienic hand disinfection.

The efficacy studies with the representative biocidal product (containing 0.2% of MES as well as 30% propan-1-ol and 45% propan-2-ol) concern also surgical hand disinfection as well as virucidal activity. However, the submitted efficacy studies with MES as sole active substance do not concern surgical hand disinfection and are not sufficient to prove virucidal activity.

Resistance is not reported, however, adaptive mechanisms against quaternary ammonia detergents based on efflux pumps have been reported for bacteria. In general, quaternary ammonium compounds have been in use for many years, with no indication that their efficacy is diminishing over time. Nevertheless, occasional increase in tolerance to quaternary ammonium compounds has been reported in the literature. Therefore, as the development of resistance is possible for such uses, at the stage of product authorization strategies of resistance management will be reviewed, if needed.

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

Human health

The oral and dermal LD50 was identified with > 600 mg a.s./kg bw. Pathology results indicated that the toxicity of the test substance after oral administration is due to primary local effects in the gastro-intestinal tract.

MES is corrosive to skin and causes eye damage. The acute dermal irritation/corrosion study conducted with 4% MES caused severe skin reactions, which were irreversible tissue damage. MES is corrosive to skin at 4%, whereas a GCL in CLP is 5%. Based on RAC opinion of 2018, a preparation containing only 4% MES caused such skin responses and therefore much more severe irreversible effects would be expected for active substance MES.

Tests in animals and humans indicate that a concentration of 0.2% is not irritant to skin. No sensitizing effects of MES were observed. A sub-chronic gavage study in rats resulted in a NOAEL for local effects of 45 mg/kg bw/day, corresponding to NOAEC of 0.9 % MES. MES did not show mutagenicity *in vitro* and *in vivo*. No long-term/carcinogenicity studies were performed with MES, because long time experience in humans using biocidal products containing 0.2% MES does not indicate a tumorigenic potential of the substance.

MES was tested in a teratogenicity study in rabbits. Based on the local effects, decreased food intake, decreased body weight gain and mortality were observed. The NOAEL for local maternal effects was set at 12 mg/kg bw/day, corresponding to NOAEC of 0.6% MES. Effects on male and female reproductive performance was investigated in a one-generation reproduction toxicity study in rats. A NOAEL for local maternal effects of 10 mg/kg bw/day was determined, corresponding to a concentration of 0.1% MES.

The relevant impurity diethylsulphate (DES) has a harmonised classification of Carc. 1B, Muta. 1B (CLP) and is included in the Candidate List of Substances of Very High Concern (REACH) and the List of Substances Prohibited in Cosmetic Products (Annex II of the Regulation (EC) No 1223/2009 of the European Parliament and of the Council). Considering the identified hazard properties of DES, its presence may lead to concern in relation to the human health risk assessment, although at the maximum content in the reference specification there is no impact on the classification of the active substance. Taking into account that a semi-quantitative approach based on local effects was used in the risk assessment of MES, the concern is if the performed risk assessment also covers DES.

Extensive data are available on MES for evaluation of human health effects. The main critical effects associated with MES are due to its corrosive properties. According to the available toxicity studies, no systemic effects in the absence of local effects were observed. Therefore, only a local risk assessment was considered necessary for the use of MES.

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**
Application phase - professionals working in health care areas	Primary exposure. Use of the ready-to-use (RTU) formulation hand disinfectant.	Professionals	Acceptable
Intensive health care patient's visitors	Primary exposure. Visitors of patients in intensive care units disinfect their hands before entry.	Non-Professionals	Acceptable
Home dialysis	Primary exposure. Patients performing home dialysis disinfect their hands before the process.	Non-Professionals	Acceptable

Taking into account the semi-quantitative risk assessment in line with the BPR guidance the health risks are acceptable for the professional and non-professional use.
ED properties:

For the endocrine disruptor assessment for human health a weight of evidence approach, including read across to data from other quaternary ammonium compounds was proposed. However, no sufficient read-across justification was available. Therefore, with regard to human health, EATS-mediated adversity and EATS-related endocrine activity could not be sufficiently investigated following the ECHA/EFSA ED Guidance[1]. It was not possible to conclude on the ED properties of MES in human health.

Environment

In terms of abiotic degradation, the mecetronium cation is not expected to undergo abiotic degradation by hydrolysis and MES is not expected to degrade by photolysis in water. The interaction of MES with atmospheric processes is expected to be negligible. Based on the studies provided and a weight of evidence, it is concluded that MES is readily biodegradable.

MES was found to sorb strongly onto the five test soils, and was poorly desorbed from the soils. The results of the adsorption studies indicate that the ionic linkage to the clay mineral fraction is a more important sorption mechanism than binding to the soil organic matter.

The immobilisation test on *Daphnia magna* and the algae growth inhibition test provide acute endpoint values below the trigger of 0.1 mg/L for T criteria in the PBT assessment. The zebrafish ELS test, the *Daphnia magna* reproduction test and the algae test provide the chronic endpoint values below the trigger value of 0.01 mg/L for T criteria. Based on the available aquatic ecotoxicity data, MES therefore fulfils the T criterion of PBT assessment. MES is classified as very toxic to aquatic life and can cause long lasting effects. (H400, H410).

Regarding toxicity to terrestrial organisms, studies were available on earthworm, soil microflora and non-target plants. The non-target plants were found as the most sensitive group of organisms based on the NOEC values. However, the PNECsoil was derived based on

[1] https://www.efsa.europa.eu/en/efsajournal/pub/5311.

the NOEC from the earthworms study, which had a higher reliably compared to the plant study.

A weight of evidence approach was applied for the bioaccumulation assessment based on the estimated BCF value for fish (47.8 L/kg) and the log Kow of 2.80 (which is based on octanol solubility and the CMC value for ionisable surface active substance), including supportive arguments from the literature. It was concluded that MES does not meet the B criteria of the PBT assessment when considering information available for other quaternary ammonium compounds.

Regarding environmental exposure assessment, a tonnage-based approach and a consumption based approach were followed in the emission estimation.. In the tonnage based approach only one tonnage was applied covering both the claimed professional use and the claimed non-professional uses. As the tonnage based approach represents the worst-case situation over the consumption based approach, and is therefore used for the decision making.

The table below summarises the exposure scenarios assessed.

Summary table: environment scenarios		
Scenario	**Description of scenario including environmental compartments**	**Conclusion**
ESD PT1 professional and non-professional use, tonnage based approach, Tier 2 (refinement based on STP simulation study)	Hygienic hand disinfection by professionals with a non-rinse off product. Environmental compartments: STP, aquatic (surface water, sediment), terrestrial (soil) via STP sludge, groundwater.	Acceptable

Based on the risk assessment in line with the BPR guidance, the risks for STP micro-organisms, surface water, sediment, soil and groundwater are acceptable.

ED properties:

With regard to non-target organisms (NTO) a weight of evidence approach was applied in the ED assessment.. The adverse effects observed in the ecotoxicological studies available for MES were associated with general toxicity. The available information provides no indication for potential endocrine disruption with regard to adverse effects which might be relevant at the population level for non-target organisms. However, the EATS-mediated adversity and EATS-related endocrine activity were not sufficiently investigated according to the ECHA/EFSA ED Guidance.

It was agreed that based on the information provided it is not possible to conclude on the ED properties for NTOs. In addition, it was concluded that extending the weight of evidence approach would not be sufficient to conclude on the ED properties of MES for non-target organisms. Instead, further testing data would be required to complete the assessment.

Overall conclusion

In the performed risk assessment no unacceptable risks were found for human health and the environment. However, no conclusion on the ED properties for humans as well as for non-target organisms can be drawn based on the available data. Subsequently, it is proposed to not approve this active substance for use in PT 1.

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)	no classification	MES does not fulfil criterion (a) of Article 5(1)
	Mutagenicity (M)	no classification	
	Toxic for reproduction (R)	no classification	
PBT and vPvB properties	Persistent (P) or very Persistent (vP)	not P or vP	MES 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 or vB	
	Toxic (T)	T	
Endocrine disrupting properties	Section A of Regulation (EU) 2017/2100: ED properties with respect to humans	No conclusion can be drawn based on the available data	No conclusion can be drawn whether MES 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	No conclusion can be drawn based on the available data	
	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. MES does not fulfil criteria (b) of Article 10(1).		
Concerns linked to critical effects other than those related to endocrine disrupting properties	MES does not fulfil criterion (e) of Article 10(1).		
Proportion of non-active isomers or impurities	The active substance does not fulfil criterion (f) of Article 10(1).		

Consequently, the following is concluded:

MES does not meet the exclusion criteria laid down in Article 5(1)(a), (b), (c), (e) of Regulation (EU) No 528/2012. MES does not meet the conditions laid down in Article 10(1)(b), (d), (f) of Regulation (EU) No 528/2012, and is therefore not considered as a candidate for substitution. No conclusion can be drawn whether MES fulfils criterion (d) of Article 5(1) and/or criterion (e) of Article 10(1).

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).

2.2.2. POP criteria

MES meets T criterion but not B and not P and not vPvB criteria of PBT criteria. Therefore, the active substance does not meet the criteria for POP.

2.3. BPC opinion on the application for approval of the active substance mecetroniumethyl sulphate (MES) in product type 1

In view of the conclusions of the evaluation it is proposed that MES shall not be approved and included in the Union list of approved active substances in product type 1.

Following the establishment of the ED scientific criteria in the Commission Delegated Regulation (EU) No 2017/2100 it has to be determined if an active substance is considered to have ED properties or not. The implementation of these scientific criteria is described in the note "Implementation of scientific criteria to determine the endocrine –disrupting properties of active substances currently under assessment"[4]. For MES it is concluded that insufficient data is available to conclude on section A (ED properties with respect to humans) as well on section B (ED properties with respect to non-target organisms) of Commission Delegated Regulation (EU) No 2017/2100. Therefore, in line with paragraph 11 of the note referred to above it is concluded that MES shall not be approved considering that the conditions set out under Article 4(1) of the BPR are not met, in particular because the data submitted (data elements 8.13.3 and 9.10 of Annex II) in the dossier were insufficient.

MES does not fulfil the criteria according to Article 28(2)(a) of the BPR to enable inclusion in Annex I of Regulation (EU) 528/2012 as MES gives rise to the following concerns: it is classified as corrosive (Skin Corr. 1, Eye Dam. 1) and toxic to aquatic life (Aquatic Acute 1, Aquatic Chronic 1).

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[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 (available from https://circabc.europa.eu/sd/a/48320db7-fc33-4a91-beec-3d93044190cc/CA-March18-Doc.7.3a-final-%20EDs-%20active%20substances%20under%20assessment.docx).