Biocidal Products Committee (BPC)

Opinion on the application for approval of the active substance:

2-bromo-2-nitro-1,3-propanediol (bronopol)

Product type: 11

ECHA/BPC/408/2023

Adopted

12 December 2023

Opinion of the Biocidal Products Committee

on the application for approval of the active substance 2-bromo-2-nitro-1,3-propanediol (bronopol) for product type 11

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 approval in product type 11 of the following active substance:

Common name:	**bronopol**
Chemical name:	**2-bromo-2-nitro-1,3-propanediol**
EC No.:	**200-143-0**
CAS No.:	**52-51-7**

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 the BPC opinion

Following the submission of application by Lanxess Deutschland GmbH, Microbial Control (Switzerland) GmbH and BASF SE in July 2007, the evaluating Competent Authority Spain submitted an assessment report and the conclusions of its evaluation to ECHA in March 2023. In order to review the assessment report and the conclusions of the evaluating Competent Authority (eCA), the Agency organised consultations via the BPC (BPC-49) and its Working Groups (WG-III-2023). Revisions agreed upon were presented and the assessment report and the conclusions were amended accordingly.

Adoption of the BPC opinion

Rapporteur: Spain

The BPC opinion on the application for approval of the active substance 2-bromo-2-nitro-1,3-propanediol (bronopol) in product type 11 was adopted on 12 December 2023.

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

The overall conclusion of the BPC is that 2-bromo-2-nitro-1,3-propanediol (bronopol) in product type 11 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 bronopol in product type 11 for the preservatives for liquid-cooling and processing systems.

Specifications for the reference source 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 products.

Validated analytical methods are available for the active substance as manufactured and for the relevant and significant impurities. Validated analytical methods are available for soil, air, water and sediment.

Harmonised classification for bronopol is available. A proposal has been submitted to ECHA to change this classification, as indicated below.

The current entry for bronopol in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) is:

Harmonized classification according to the CLP Regulation	
Hazard Class and Category Codes	Acute Tox. 4 H302 Acute Tox.4 H312 Skin Irrit. 2 H315 Eye Dam. 1 H318 STOT SE 3 H335 Aquatic Acute 1 H400
Labelling	
Pictogram codes	GHS09 GHS05 GHS07
Signal Word	Danger
Hazard Statement Codes	H302 Harmful if swallowed H312 Harmful if contact with skin H315 Causes skin irritation H318 Causes serious eye damage H335 May cause respiratory irritation H400 Very toxic to aquatic life
Specific Concentration limits, M-Factors	Aquatic Acute M=10

The proposed classification and labelling for bronopol according to CLP Regulation is:

Proposed classification according to the CLP Regulation	
Hazard Class and Category Codes	Acute Tox. 3 H301 Aute Tox. 4 H312 Acute Tox. 3 H331 Skin Irrit. 2 H315 Eye Dam. 1 H318 STOT SE 3 H335 Aquatic Acute 1 H400 Aquatic Chronic 1 H410
Labelling	
Pictogram codes	GHS09 GHS05 GHS06
Signal Word	Danger
Hazard Statement Codes	H301 Harmful if swallowed H331 Toxic if inhaled H315 Causes skin irritation H318 Causes serious eye damage H335 May cause respiratory irritation H410 Very toxic to aquatic life with long lasting effects
Specific Concentration limits, M-Factors	Oral: ATE = 193 mg/kg bw Dermal: ATE = 1600 mg/kg bw Inhalation: ATE = 0.588 mg/L Aquatic acute M= 100 Aquatic chronic M= 10
Justification for the proposal	
Although this biocidal active substance has a current entry in Annex VI of CLP regulation, it is necessary to update the current human health and environmental hazards due to differences in acute toxicity, aquatic acute and aquatic chronic hazards, as well as, its ATEs and M-Factors with the current harmonised classification.	

b) Intended use, target species and effectiveness

Bronopol is intended to be used as a cooling water preservative (e.g. in open and closed recirculating cooling systems). Preventive treatment with continuous dosing as well as curative treatment with shock dosing is intended.

Typical target organisms are bacteria, algae and fungi. The main target organism from a public health standpoint is *Legionella pneumophila*.

Against bacteria a high efficacy of the active substance and the product was demonstrated within the assessment: preventive efficacy is demonstrated at the concentration of 2 mg/L Bronopol and curative efficacy could be accepted at 5 mg/L after a contact time of 24 hours.

Against fungi, only an innate efficacy of the active substance was demonstrated, but not of the product. Likewise, only the innate efficacy of the active substance against two species of algae was tested.

Within the assessment, the supported safe rate of the active ingredient for PT11 uses against bacteria is 2 – 20 mg/L of water matrix to be preserved.

Mode of action: Bronopol reacts with thiol-groups of amino acids and enzymes (e.g. cysteine). It catalytically oxidises thiol-groups to disulphide bonds with rapid consumption of oxygen. Bronopol is not destroyed during the oxidation of thiol-groups. If the thiol-groups are too far apart or lie in close proximity to electronegative polar groups, oxidation will not occur or be hindered. In the absence of air (oxygen), Bronopol seems to act as an oxidizing

agent. Reduction of growth rate following the induced bacteriostasis probably reflects irreversible damage to the cell, possibly through the generation of oxygen radicals. The results suggest a dual action of Bronopol, with catalytic oxidation of accessible thiols being responsible for the growth inhibition and generation of free radicals causing cell death.

The mode of action of Bronopol is complex and multi point, therefore the development of resistance is less likely than for those biocides that have a simple single target site of action. A relevant resistance mechanism based on inactivation of electrophilic biocides such as bronopol by overproduction and/or excretion of sulfhydryl-containing compounds (i.e. cysteine or glutathione) is theoretically plausible but not yet found in real life.

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

Human health

Bronopol is a substance toxic if swallowed or if inhaled and harmful in contact with skin. Bronopol causes skin and respiratory tract irritation and serious damage to the eye.

The critical endpoints for bronopol are driven by its local toxicity: skin irritation for the dermal route, respiratory tract irritation for the inhalation route and stomach irritation for the oral route. A local risk assessment is therefore required for these effects.

Unspecific systemic effects observed as increase in liver and spleen weights and vomiting in a 90-day oral toxicity study are also seen with bronopol but at higher dose levels. Since mild adverse systemic effects cannot be excluded, systemic AEL has been derived and a systemic risk assessment performed to supplement the local risk assessments.

The information on mutagenicity provided by the applicant were two *in vitro* gene mutation in mammalian cells assays (OECD TG 476) and two UDS assays (OECD TG 486) as the corresponding *in vivo* follow-up. However, the BPC working group concluded that the *in vitro* studies were not sufficiently reliable, and the *in vivo* studies were not accepted based on relevance and lack of sensitivity. Therefore, the information was not sufficient to draw conclusions on mutagenicity. It would not have been possible to perform additional studies needed to draw conclusions on mutagenicity within 10 working days following the WG discussion and therefore these were not requested by the WG.

Bronopol has been studied, with a database containing information for all levels described in the OECD CF 2012 and in the ECHA/EFSA Guidance on the identification of endocrine disruptors.

EATS-modalities have been considered as sufficiently investigated. The available mammalian toxicity studies demonstrate that the principal target organ of bronopol is the kidney, wherein adversity is not considered to be mediated by an endocrine mode of action. No pattern of bronopol-related adverse effects in endocrine-sensitive organs or endpoints was identified in available OECD CF levels 4 and 5 *in vivo* toxicity studies. No causal or mechanistic link could be established between bronopol and indicative EATS effects, and the available OECD CF levels 1 and 2 *in silico* and *in vitro* data did not provide evidence of an endocrine MoA.

Conclusively, as the available animal studies do not provide consistent evidence for any EATS-related adversity which may be linked to an endocrine activity, the substance does not meet the Endocrine Disrupting (ED) criteria with regard to humans (Scenario 1a).

After evaluating the exposure and characterizing the risk to human health of the biocidal products and treated articles according to the pattern of use requested by the applicant, the conclusions for each scenario are:

Summary table: human health scenarios			
Scenario[+]	**Primary or secondary exposure and description of scenario**	**Exposed group**	**Conclusion**
Post-application	**Primary exposure** Exposure towards residues during cleaning of the dispensing pumps.	Professionals	Not possible to conclude due to insufficient information related to mutagenicity.*
Post-application	**Primary exposure** Exposure towards residues during system inspection and monitoring	Professionals	Not possible to conclude due to insufficient information related to mutagenicity.*
Post-application	**Primary exposure** Exposure towards residues during cleaning of the fouled systems	Professionals	Not possible to conclude due to insufficient information related to mutagenicity.*
Post-application	**Primary exposure** Exposure during disposal of waste	Professionals	Not possible to conclude due to insufficient information related to mutagenicity.*
Post-Application	**Secondary exposure** Exposure to aerosols	General Public	Not possible to conclude due to insufficient information related to mutagenicity.*

* Since the reference values do not cover possible genotoxicity, due to data gap on mutagenicity, it is not possible to conclude on the acceptability of the risk.
[+] The application is covered by the post-application.

For the human exposure two population groups are potentially exposed: professional users and the general public via indirect exposure. Primary and secondary exposure was considered where relevant.

Concerning the systemic effects, acceptable risks were identified for professionals for primary exposure.

With regard to secondary exposure, acceptable risks were identified for the corresponding scenario.

Concerning local effects, direct dermal exposure to bronopol is possible.

Risks were assessed for all scenarios listed in the summary table, however as it is not possible to conclude on the mutagenicity of bronopol, no safe uses can be identified for human health.

Environment

Bronopol rapidly degrades in natural waters by abiotic degradation as well as biotically. While the criteria for readily biodegradability were not fulfilled, signs of abiotic degradation (e.g. hydrolysis) were observed indicating that abiotic degradation processes are predominant under the respective test conditions and thus at environmentally relevant pH values:

- Bronopol rapidly hydrolyses at pH 7, and several metabolites are formed from a series of possible reactions. Formaldehyde is one of the metabolites being released from the hydrolyzation of broponol, but due to being readily biodegradable, no risk assessment is needed for this degradation product. The bromide ion can also be considered as a possible formation product. However, the bromide ion does not need to be assessed, as it was not detected in the degradation studies and its presence in the environment is higher than the theoretical concentration derived from bronopol degradation. Some transformation products have been detected in the hydrolysis studies, mainly 2-bromo-2-nitroethanol (2-BNE) as transient product via reversible reactions.

- In the sewage treatment plant (STP) simulation study, in the biotic process, mainly 2-Hydroxymethyl-2-nitro-1,3-propanediol (TNM) is formed. As all emissions take place via the STP, only the degradation product TNM was assessed together with bronopol.

- Toxicity of 2-BNE as an intermediate product is considered covered by bronopol (agreed at WGIV2022) in emissions through STP, where such metabolite is degrading very fast and considering their similar toxicity level. Further, the PNEC for surface water is based on geometric mean value of bronopol, which is rapidly degrading in the algae study and hence the intermediate product 2-BNE could be considered also covered by such PNEC.

No study is currently available on the degradation of bronopol in the soil compartment. Since rapid degradation occurs via both biotic and abiotic pathways, it can be concluded that bronopol will not persist in the environment. In the absence of the study a default half-life in soil of 300 days was used for risk assessment, leading in several cases to an unrealistic risk to groundwater. A study on degradation in soils was consequently initiated. The preliminary results show that bronopol disappears rapidly and a provisionally half-life of around 5 days (20 ºC) for both parent and metabolite was agreed (considering TMN is forming in soil as a worst case) demonstrating that unacceptable emission to groundwater cannot be expected.

A mixture risk assessment for the parent and the metabolite TNM is not needed as the mixture toxicity seems unlikely, because, focusing on the uses and all emissions going through the STP, the risk assessment has considered that all Bronopol is reaching the STP, only abiotic degradation of parent in industrial processes, hence TNM is expected to be formed mainly in the STP, where it is unlikely to coexist with the parent, based on the OECD 314B study which shows that Bronopol transformation rate to TNM is 99.75% for the whole period of parent substance degradation.

For the emission to the sewer, it was shown that bronopol is mainly distributed in the compartment water (>99%). Therefore, the atmosphere is considered to be no relevant compartment for the occurrence of bronopol. Further, bronopol has a very low Henry's Law constant of $1.16*10^{-6}$ $Pa*m^3/mol$ at 25 °C (calculated with EPI suite 4.1.1) and therefore volatilisation is not to be expected.

No bioaccumulation is expected due to the high water solubility and very low LogKow for bronopol and its degradation products.

Bronopol must be considered as not rapidly degradable for classification purposes.

Toxicity of bronopol to aquatic organisms is well documented by acute and long-term studies, being algae the most sensitive species, with a 72 h-EC10 = 0.0048 mg/L (geometric mean measured) for the freshwater algae *Desmodesmus subspicatus*.

The information on endocrine disruption in non-target organisms provided by the applicant was a XETA (OECD TG 248) and FSTRA (OECD TG 229). However, the BPC working group concluded that these studies were not sufficiently reliable and therefore the information was not sufficient to draw conclusions about the ED properties in non-target organisms. It would not have been possible to perform additional studies needed to draw conclusions on ED in non-target organisms within 10 working days following the WG discussion and therefore these were not requested by the WG.

Summary table: environment scenarios		
Scenario	**Description of scenario including environmental compartments**	**Conclusion**
Preservatives for Liquid Cooling Systems - small open recirculating systems with continuous dosing	Emission to municipal sewage treatment plant and indirect emissions via STP to surface water, soil and groundwater. Direct emission to soil via drift.	Not possible to conclude due to insufficient information related to endocrine disrupting properties for non-target organisms.
Preservatives for Liquid Cooling Systems - small open recirculating systems with shock dosing	Emission to municipal sewage treatment plant and indirect emissions via STP to surface water, soil and groundwater. Direct emission to soil via drift.	Not possible to conclude due to insufficient information related to endocrine disrupting properties for non-target organisms.
Preservatives for Liquid Cooling Systems - Closed recirculating cooling systems – Continuous dosing with degradation	Emission to municipal sewage treatment plant and indirect emissions via STP to surface water, soil and groundwater.	Not possible to conclude due to insufficient information related to endocrine disrupting properties for non-target organisms.
Preservatives for Liquid Cooling Systems - Closed recirculating cooling systems – Continuous dosing*	Emission to municipal sewage treatment plant and indirect emissions via STP to surface water, soil and groundwater.	An unacceptable risk was identified for the degradation product TNM with regards to surface water and sediment.

* the Risk Mitigation Measure "total drainage should be managed as a hazardous waste" as specified in the TAB ENV 126 would be applicable to the closed system scenario.

Risks were assessed for the scenarios in the summary table, however it is not possible to conclude on ED properties for non-target organisms for bronopol.

Overall conclusion

It is not possible to conclude on the risks from the use of bronopol in PT11 due to insufficient information. The information provided is not sufficient to conclude whether bronopol fulfils exclusion criteria regarding mutagenicity. Therefore, it is not possible to conclude on a safe 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)	No classification required	Bronopol does not fulfil criteria (a) and (c) of Article 5(1). Due to a data gap on mutagenicity no conclusion can be drawn with respect to criterion (b).
	Mutagenicity (M)	No conclusion can be drawn	
	Toxic for reproduction (R)	No classification required	
PBT and vPvB properties	Persistent (P) or very Persistent (vP)	not P or vP	Bronopol and its main degradation products do not fulfil criterion e) of Art. 5.1 and do not fulfil criterion d) of Art. 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	Bronopol does not fulfil criterion (d) of Article 5(1) for human health. Due to a data gap, no conclusion can be drawn for non-target organisms and with respect to criterion e) of Art. 10(1).
	Section B of Regulation (EU) 2017/2100: ED properties with respect to non-target organisms	No conclusion can be drawn	
	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. Bronopol does not fulfil criterion b) of Art. 10.1		
Concerns linked to critical effects other than those related to endocrine disrupting properties	No other concerns identified.		
Proportion of non-active isomers or impurities	Bronopol does not fulfil criterion f) of Art. 10.1		

Due to the missing data, the BPC could not conclude on the exclusion criteria (based on the data gap regarding mutagenicity) and on the substitution criteria (based on the data gaps for both mutagenicity and the endocrine disrupting properties for non-target organisms).

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" , with "Further guidance on the application of the substitution criteria set out under Article 10(1) of the BPR" and with "Implementation of scientific criteria to determine the endocrine-disrupting properties of active substances currently under assessment" 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).

Consequently, the following is concluded:

- It is not possible to establish that bronopol does not meet the exclusion criteria, for the following reason:
    - although bronopol does not meet the exclusion criteria as laid down in Article 5(1)(a), (c) and (d) of Regulation (EU) No 528/2012, the provided information is not sufficient to conclude that bronopol does not meet the exclusion criteria as laid down in Article 5(1)(b).
- It cannot be established that bronopol is not a candidate for substitution, for the following reason:
    - according to the Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009, EATS-mediated adversity and endocrine activity have been sufficiently investigated for human health, but not for environment. Consequently, for the endocrine-disrupting properties as defined in Regulation (EU) No 2017/2100, no conclusion can be drawn for environment based on the available data. Hence, it is not possible to establish that bronopol does not meet the conditions laid down in Article 10(1)(e) of Regulation (EU) No 528/2012.

2.2.2. POP criteria

Neither the active substance nor any of the identified degradation products is listed in Annex I of Regulation (EU) 2019/1021.

2.3. BPC opinion on the application for approval of the active substance 2-bromo-2-nitro-1,3-propanediol (bronopol)in product type 11

Information is not sufficient to conclude whether bronopol meets the conditions laid down in Article 4(1) of Regulation (EU) No 528/2012. In particular, the provided information is not sufficient to conclude that bronopol fulfils the exclusion criteria with regard to mutagenicity and a safe use could not be demonstrated for human health.

Consequently, as provided for in Article 9(1)(b), since requisite information and data have not been submitted, it is proposed that bronopol shall not be approved under Regulation (EU) 528/2012 as an active substance in product type 11.

The UDS assay submitted by the applicant to assess the mutagenicity of bronopol was questioned in the Human Health WG based on relevance and lack of sensitivity. Due to time constraints the applicant followed a WoE approach, but this was not accepted by the WG.

Bronopol does not fulfill the criteria according to Article 28(2) to enable inclusion in Annex I of Regulation (EU) No 528/2012, as it is proposed to be classified as H301 (Acute Tox. 3), H331 (Acute Tox. 3) and H335 (STOT SE 3).

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