COMPILED COMMENTS ON CLH CONSULTATION

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Last data extracted on 05.10.2023

Substance name: bronopol; 2-bromo-2-nitropropane-1,3-diol
CAS number: 52-51-7
EC number: 200-143-0
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	1
Comment received				
General Comments from the European producers of water-based polymer dispersions: The According to the CLH report P. 66 "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." Therefore, Bronopol is a valuable Active Substance for biocidal products in water-based dispersions. Furthermore, Bronopol is readily biodegradable in water, opposite to degradation in the air which is not relevant for water-based products. Based on algae studies, Bronopol shows long-term toxicity to aquatic organisms being the reason for the proposed future classification regardingH410 (M=10) and H400 (M=100). We would like to underline that the future classification H410 (M=10)/H400 (M=100) will have an impact on the downstream legislation, e.g., EU Ecolabel (Regulation EU 312/2014) which is why this Active Substance should be considered for further derogation. These derogations should be granted to ensure a broad spectrum of Active Substances with a different mode of action to avoid development of microbial resistances. A holistic approach would be necessary when considering biocide active ingredients, here: Bronopol. The European authorities are making it via CLP, the biocidal product regulation and few additional country-specific hurdles one by one, product by product, "drop by drop" more difficult, not to say: impossible, to preserve water-based products without the need to classify and label end products. The latest example is the exclusion of DBNPA, i.e. the non-approval for PT6. Labelling obviously has a negative effect on the marketability of such environmentally friendly water-based products. Having so many consumer products labelled with hazard warnings can hardly be the intention of the authorities, as this will lead to "dumbing down" the consumer so that he or she will ignore the really important hazard labels.				

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	2
Comment received				

In the present CLH dossier, some study results are summarized only in very concise form and with partial omission of parameters that are of crucial importance for assessing the effects (quantitative metrics, comparison with historical control data, or statistical evaluation). This makes it difficult to provide a sound assessment of the classification suggestions made, especially since many studies were not available to us. In our understanding, a CLH dossier should be a functional stand-alone document that ideally provides information on all effects that may be relevant for classification without necessarily having to rely on further documents (such as study reports). Apart from that a typing error has been noticed in chapter A.3.4.3 on page 109. It is written "Skin Dam. 1" and should probably be "Eye Dam. 1".

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	3
Comment received				
According to the CLH report P. 15, the "data" for carcinogenicity are "conclusive but not sufficient for classification". Based on all the available data provided and the conclusions drawn on P.156 and seq. of the CLH report for Bronopol, there is no classification and labelling for Carcinogenicity according to CLP. A risk assessment was not required for this hazard.				

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	4
Comment received				
We agree with the dossier submitter's evaluation that the existing dataset provides no convincing evidence to classify Bronopol for carcinogenicity.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	5
Comment received				
According to the CLH report P. 15, the data for mutagenicity are conclusive but not sufficient for classification. Based on all the in vivo available data provided and the conclusions drawn on P. 152 of the CLH report, Bronopol is not genotoxic, and classification and labelling should not be required. A Risk Assessment was not required for this hazard.				

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	6
Comment received				
We agree with the dossier submitter's evaluation that the existing dataset provides no convincing evidence to classify Bronopol for mutagenicity. However, we propose, as in the biocide assessment, to include further data from the studies in the summary table (A-32), such as HCD, mutant frequency and cytotoxicity. This would significantly improve transparency and acceptance.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	7

Comment received

According to the CLH report P. 15, the data for Reproductive toxicity are conclusive but not sufficient for classification.
Based on the available data and conclusion drawn in P. 173 of the LCH report, Bronopol is considered to be non-reprotoxic. Therefore, classification and labelling for reproductive toxicity should not be required. A risk assessment was not required for this hazard.

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	8

Comment received

We propose to consider further data on maternal toxicity in the assessment for the endpoints of sexual function and fertility as wells as developmental toxicity (e.g. comparable to the biocide dossier). From our point of view, the effects on reproductive toxicity have to be discussed critically.
Sexual function and fertility:
Three animal studies are listed in the dossier under the endpoint "sexual function and fertility" (two-generation drinking water reproduction study in CD rats according to OECD TG 416, two-generation study in rats according to IRDC SOP, one-generation study in rats according to FDA guideline). In the designated key study, several effects meeting the definition of reproductive toxicity occurred in the highest dose group:

- gestation survival and postimplantation loss: Gestation survival of the F2 generation decreased to 91.9% (control: 99.4%), while post-implantation loss increased to 18.80% (control: 6.81%). Both values are outside the historical control data and effects are therefore considered substance-related. However, gestation survival and post-implantation loss fall under the endpoint "developmental toxicity" rather than "sexual function and fertility". The number of pubs born dead also increased distinctly in the high-dose group (1.1 vs. control: 0.1). The dossier submitter did not carry out its own evaluation of this metric, however, it is not comprehensible why this 11-fold increase is described in the study report only as a "slight increase" and how there can be no statistical significance here.
- sperm parameter:
The epididymal sperm count (total and conc/g) of the P2 generation of the high-dose group is outside the maxima of the historical control data (HCD) and clearly below the long-term mean of the HCD. Even though the values of the control group are already below the HCD and there is no statistical significance, a substance-related effect cannot be excluded: At least for the total sperm count, there seems to be a dose-response relationship, the fertility index, which is directly dependent on sperm quality, also decreased in the high-dose group, and the supplemental studies mentioned in the dossier that could help to clarify the picture, were not available.
- mating & fertility index: Mating and fertility indices are reduced compared to the control groups and are just below the HCD.
- dystocia: In the high-dose group, two cases of dystocia occurred, which are to be classified as treatment-related, as dystocia very rarely occurs spontaneously (in the last ten studies of the executing laboratory together only once). As a severe effect, dystocia is relevant for classification.

The dossier submitter is of the opinion that the observed effects are not relevant for classification since the animals in the high dose group showed signs of systemic toxicity at a level suitable to discard these effects. Considering the group means, there is only a moderate decrease in body weight gain from GD 0-21 in both P1 and P2 generation while the absolute body weights decrease only < 10% in both F1 and F2 generation in the high dose group. Only the body weight gain from GD 14-21 shows a pronounced decrease in both P1 and P2 generation. The effects on body weight correlate with reduced feed and water consumption, probably due to decreased palatability. Regarding the absolute and relative organ weights, there are minor effects in kidney and thyroid gland, which are mostly within the HCD and should not be interpreted as signs of excessive systemic toxicity due to their small deviation from the control group and the presumed lack of biological relevance. Histopathological examination revealed minor abnormalities in various organs (liver, stomach, thyroid gland and kidney), whose grading, however, failed to exceed the level "slight" and therefore cannot be considered indicative of excessive systemic toxicity.
The dossier submitter describes in the CLH dossier that the majority of the observed reprotoxic effects occurred in six animals of the high dose group, some of which showed signs of severe systemic toxicity. According to the study report, animals #3426, #5433, and #5441 showed severe systemic toxicity in the form of severely reduced body weight gain (GD 14-21). However, for the other three animals that showed strong reprotoxic effects (#3437, #5426, #5428) no evidence of strong systemic toxicity can be found in the study report. Even if the endpoints “gestation survival”, “postimplantation loss” and “number of pubs born dead” are adjusted for the mentioned animals with signs of strong systemic toxicity, values outside the HCD still result. In summary, the systemic toxicity that occurred in the experiment may not be sufficiently significant to allow the relevance of the reprotoxic effects found to be discarded for classification.

Developmental toxicity:
For the endpoint "developmental toxicity", three animal studies are referred to in the CLH dossier, of which only the designated key study was available to us. In this study, both skeletal and visceral variations and malformations were observed in the high-dose group, some of whose incidence was outside the HCD, including (foetuses (litters)/ all foetuses (all litters)):
- ectopic/fused kidneys/ureters (high dose: 3 (1)/ 215 (25) versus ctr: 1 (1) / 224 (25))
- hydroureter (high dose: 3 (1)/ 215 (25) versus ctr: 1 (1) / 224 (25))
- right-sided oesophagus (high dose: 7 (3)/ 215 (25) versus ctr: 0 (0) / 224 (25))
- fused centra (high dose: 3 (2)/ 215 (25) versus ctr: 0 (0) / 224 (25))
- missing caudal vertebrae/centra (high dose: 1 (1)/ 215 (25) versus ctr: 0 (0) / 224 (25))

The study authors claimed that these effects are due to the maternal toxicity. However, this cannot be checked, because the data of the individual dams are not available.
Again, the dossier submitter is of the opinion that these effects are not relevant for classification due to the presence of excessive systemic toxicity. As indicators of systemic toxicity, a decreased faeces quantity and effects on body weight are specified. In this regard, it can be stated that not even the particularly sensitive body weight gain shows statistically significant effects, no significant effects on organ weights occurred and also no treatment-related gross pathologic observations. We are of the opinion that a reduced faeces quantity, which was also only recorded semi-quantitatively, is not sufficient reason alone to assess the effects seen as not relevant for classification.
In conclusion, due to the relatively low incidence of the effects observed (skeletal and visceral malformations, dystocia), classification of Bronopol as category 2 for reproductive toxicity (H361) seems appropriate. To substantiate a non-classification proposal, further data demonstrating relevant maternal toxicity would be needed.

Lactation:
We agree that the available studies do not indicate that the test substance impairs lactation.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	9

Comment received

The experimental test data presented in the CLH report are reliable and suitable for classification purposes under Regulation (EC) No 1272/2008 (CLP Regulation).
Bronopol has an existing harmonised classification for acute oral toxicity (Acute Tox Cat. 4*; H302 (*minimum classification)) under Regulation (EC) No 1272/2008 (ATP 1 to CLP Regulation). Based on the available data, and as concluded on p. 92 of the CLH report, classification of Bronopol with Acute Tox. Cat. 3, H301 is justified.
Based on the results of the available experimental test data on acute inhalation toxicity, and as concluded on p. 100 of the CLH report, classification of Bronopol with Acute Tox. 3, H331, for acute inhalation toxicity after dust aerosol inhalation is justified according to the criteria of Regulation (EC) No 1272/2008 (CLP Regulation).
Furthermore, Bronopol has an existing harmonised classification with Acute Tox Cat. 4*; H312 (*minimum classification) under Regulation (EC) No 1272/2008 (ATP 1 to CLP Regulation). The available experimental test data support the classification of Bronopol for acute dermal toxicity with Acute Tox. Cat. 4 (H312), as concluded on p. 98 of the CLH report.

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	10

Comment received

Acute oral toxicity
We agree with the dossier submitter’s evaluation that the existing harmonised classification as Acute Tox. 4 should be changed into Acute Tox. 3 based on the lowest LD50. Acute dermal toxicity
The DE CA agrees with the conclusion that one of the four studies can only be used to a limited extent to evaluate acute toxicity due to the small number of animals. Of the remaining three studies, two studies show that the ATE is above the concentration range of a classification according to the CLP-Regulation (EC) No 1272/2008. The third study was used as a key study and requires further discussion. Please provide a more detailed evaluation of whether this study is reliable or not. For this purpose, the following points should be considered more closely: The LD50 value is based on a lethality of 30 % (3/10 animals died in the highest concentration used). Furthermore, in the opinion of the DE CA, it cannot be ruled out that this effect is only due to acute dermal toxicity. The macroscopic examination of the “orange-coloured lungs” suggests an inhalation effect. Here, the information on the application (semi-occlusive or occlusive) is missing in order to make a clear statement. Especially with regard to the formaldehyde releasing possibility of Bronopol, this information is extremely important.
Acute inhalation toxicity
We support the dossier submitter’s proposal of classifying Bronopol with Acute Tox. 3.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	11
Comment received				
Based on all the available data provided, classification as Skin Irrit.2 is already present in the classification for Bronopol and the harmonised classification is not becoming more severe. It should however be noted, that real-world scenarios, when using Bronopol as biocidal active substance, involve much lower concentrations and contact duration.				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Austria	<confidential>		12
Comment received				
A.3.3 Skin corrosion and irritation The dossier submitter proposes to maintain the existing harmonised classification as Skin Irrit. 2. The generic concentration limit for Skin Irrit. 2 to classify mixtures is 10 % (based on Table 3.2.3 CLP Reg). Based on the information derived from human volunteer studies and described in the dossier the NOAEC in humans might be lower and it should be discussed if a SCL can be established for Bronopol. Since setting a SCL has an important impact for classification of mixtures, a derivation of a SCL value needs to be considered and discussed during the process of harmonized classification.				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	France		MemberState	13
Comment received				
Based on the information provided in the dossier, we agree with the proposed classification Skin Irrit.2 – H315 for Bronopol. However, considering the effects observed in other available dermal studies, the setting of a specific concentration limit (SCL) should be foreseen. When applied at a concentration of 0.5% in rabbits (short-term dermal toxicity study, A6.3.2_01), severe skin irritation was observed including erythema and edema with intensive scabbing at the application site. In the long-term dermal toxicity study in mouse (A6.07_02_a to e), slight loss in hair around the treated skin area was observed during the first 3 weeks of treatment with 0.5% Bronopol (highest tested dose). Moreover, an increase incidence of skin papilloma was reported at this dose and related to the irritant potential of the substance. The irritant potential of Bronopol at 0.5%n is also supported by the results of reliable human patch test data presented in Table A-26 of the document. Irritative reactions are reported in humans at concentrations from 0.5%. Regarding the available animal and human data, the setting of a SCL for the irritant potential of Bronopol should be taken into consideration				

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	14
Comment received				
We agree with the dossier submitter’s evaluation that the existing harmonised classification				

as Skin Irrit. 2 should be retained.

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	United Kingdom	Health and Safety Executive	National Authority	15
Comment received				
'We note that you have suggested to retain a classification of Skin irritant Cat. 2 and Eye Dam Cat. 1 based on the available data. There are a number of uncertainties with the data and therefore we would welcome a discussion regarding the classification for skin corrosion and irritation based on the following points: • The results in the eye irritation/corrosion study showed grade 4 opacity at 1 hour and destruction of the cornea in 1 animal after application which may indicate potential corrosive properties. • In the two standard acute dermal toxicity studies, severe skin lesions (including eschar formation and necrosis) consistent with contact with a corrosive substance were noted. These lesions persisted for the full duration of the studies. Mortalities were observed (2/5 females) in the 1992 acute dermal study only. It is possible these deaths may be secondary to severe local effects, not systemic toxicity.'				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	16
Comment received				
Based on all the available data provided, classification as Skin Dam. 1 is already present in the classification for Bronopol and the harmonised classification is not becoming more severe. It should however be noted, that real-world scenarios, when using Bronopol as biocidal active substance, involve much lower concentrations and contact duration.				

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	17
Comment received				
We agree with the dossier submitter's evaluation that the existing harmonised classification as Eye Dam. 1 should be retained.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	18
Comment received				
Based on all the available data provided and the conclusions drawn on P.119 of the CLH report for Bronopol, there is no classification and labelling for Skin Sensitisation according to CLP. A risk assessment was not required for this hazard.				

Date	Country	Organisation	Type of Organisation	Comment number

27.09.2023	Germany		MemberState	19
Comment received				
We agree with the dossier submitter’s evaluation that the existing dataset provides no convincing evidence to classify Bronopol for skin sensitisation.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	20
Comment received				
The STOT SE 3 classification is already present in the classification for Bronopol and in the harmonsied classification is not becoming more severe. This is due to there being no studies or test data available as indicated on P.100 of the CLH report.				

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	21
Comment received				
We support the dossier submitter’s proposal of classifying Bronopol with STOT SE 3.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	Belgium	EPDLA, a Cefic Sector group	Industry or trade association	22
Comment received				
The available experimental test data are reliable and suitable for classification purposes in accordance with Regulation (EC) No 1272/2008 (CLP Regulation). As a result, and as concluded on p. 137 of the CLH report, classification and labelling of Bronopol with STOT RE 1 or 2 is not justified according to the criteria of Regulation (EC) No 1272/2008 (CLP Regulation).				

Date	Country	Organisation	Type of Organisation	Comment number
27.09.2023	Germany		MemberState	23
Comment received				
In the sub-chronic oral toxicity studies, the effect "After 6 weeks of treatment, blood pigments and red blood cells were found in the urine" in the 13-week dog study (A6.04.1_02) is suspicious. Apparent nephrotoxic effects are also documented as "renal tubular abnormalities" in the 13-week rat study (A6.04.1_01) and as "nephropathy" in the 90-day rat study (A6_04_1-2). We propose to discuss in more detail whether these effects could be relevant for classification or whether they could be secondary effects in terms of blood cell toxicity?				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number

27.09.2023	United Kingdom	Health and Safety Executive	National Authority	24
Comment received				
Bronopol (EC: 200-143-0; CAS: 52-51-7): The CLH report considers that bronopol is likely to undergo abiotic degradation based on the available experimental information which was predominantly conducted at higher temperatures up to 50oC. Please can the DS consider DT50s at lower temperatures relevant to ecotoxicity testing (e.g. ~20oC) and environmental fate (e.g. 12oC). This information is important to inform on rapid degradability and aid interpretation of the ecotoxicity endpoints. Noting the above question, the key ecotoxicity study for hazard classification is an algal growth inhibition study (Anon., 2006a) with Desmodesmus subspicatus which reports 72-hour endpoints based on geometric mean measured (gmm) bronopol concentrations (given that measured concentrations were not with 20% of nominal concentrations). There is limited information in the CLH report to consider the impact of potential hydrolysis and whether gmm, nominal, initial measured parent or hydrolysis product concentrations are the most relevant. For example, s. 4.1.3.1.1 of ECHA, 2017 notes that 'for substances where the degradation half-life (DT50) is less than 12 hours, environmental effects are likely to be attributed to the hydrolysis products rather than to the parent substance itself'. Therefore, in addition to the above hydrolysis considerations, please can the DS present further information from the D. subspicatus study on treatment preparation, study temperature/pH, and measured concentrations of parent (and hydrolysis products if available) at t=0 hours and t=72h hours. ECHA (2017) Guidance on the Application of the CLP Criteria. Version 5.				

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2023	France		MemberState	25
Comment received				
We agree with the proposal classification Aquatic Acute 1 (H400, M=100) and Aquatic Chronic 1 (H410, M=10). We have only a minor comment, could you please confirm that the algae EC10 used for the chronic classification is a growth rate endpoint? At last, considering the significant degradation of bronopol in aquatic compartment, we support that the reliability of ecotoxicity studies with nominal endpoints should be 3.				