Biocidal Products Committee (BPC)

Opinion on a request according to Article 38 of Regulation (EU) No 528/2012 on

Questions on unresolved objections during the mutual recognition procedure of a PT 5 biocidal product family intended for disinfection of drinking water for animals

ECHA/BPC/385/2023

Adopted

7 June 2023

Opinion of the Biocidal Products Committee

On unresolved objections during the mutual recognition procedure of a PT 5 biocidal product family intended for disinfection of drinking water for animals

In accordance with Article 38 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, the Biocidal Products Committee (BPC) has adopted this opinion on questions concerning unresolved objections during the mutual recognition procedure of a PT 5 biocidal product family intended for disinfection of drinking water for animals.

This document presents the opinion adopted by the BPC.

Process for the adoption of the opinion

ECHA received a request from the Commission on 15 February 2023. ECHA acts as the rapporteur in this type of procedures as agreed at BPC-3. The Efficacy Working Group (EFF WG) and the Environment Working Group (ENV WG) were consulted at the meetings of 21 March 2023 (WG-I-2023). The rapporteur presented the draft opinion to the BPC-47 meeting of 5 - 8 June 2023. Following the adoption of the opinion at BPC-47, the opinion was amended according to the outcome of the discussion.

Adoption of the opinion

Rapporteur: European Chemicals Agency (ECHA)

The BPC opinion was reached on 7 June 2023.

The BPC opinion was adopted by consensus of the members having the right to vote.

The opinion is published on the ECHA website at: https://echa.europa.eu/bpc-opinions-on-article-38.

Further details of the opinion and background

1. Request for the opinion

Article 38 of Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (the BPR) establishes that, if so, requested by the Commission, pursuant to Article 36(2) or Article 37(2), the Agency shall issue an opinion within 120 days from the date on which the question was referred to it.

On 15 February 2023, ECHA received a request for a BPC opinion from the Commission to address the questions relative to unresolved objections during the mutual recognition of the biocidal product family (BPF) "INTEROX Biocidal Product Family 2" containing hydrogen peroxide, intended for disinfection of drinking water for animals in reservoirs.

The Commission has requested ECHA to formulate an opinion via the BPC on the following questions in order to decide on the authorisation of the BPF:

1. Can it be considered that the tests provided in the application show efficacy of the BPF for 'the intended use':
    - Are the deviations from the pass criteria of EN 1276:09 acceptable and properly justified?
    - Can the modified test EN 1276:09 designated by the applicant as simulated-use test be considered as simulating the practical conditions of intended use appropriately?
2. Taking into account the additional test results provided by the applicant following the closure of the referral, can it be considered that efficacy for the intended use has been demonstrated, meaning that the products of the BPF meet the condition in Article 19(1)(b)(i) of the BPR?
3. What is the correct classification for environmental hazards of the products of the BPF according to the CLP Regulation?

The Commission further indicated that, when addressing the above-mentioned questions, any available information shall be taken into account by the BPC, and in particular:

- The Product Assessment Report (PAR) of "INTEROX Biocidal Product Family 2";
- The report of the additional simulated-use test provided by the applicant on 10 May 2021.

2. Background

The application for authorisation of the biocidal product family "INTEROX Biocidal Product Family 2" was submitted to the reference Member State (rMS) Finland on 26 January 2017.

The biocidal products of the BPF "INTEROX Biocidal Product Family 2" are disinfectants (PT 5) containing hydrogen peroxide at the concentration of 35.5 – 49.9 % (w/w) and are intended to disinfect animal drinking water in reservoirs. Animals include poultry, pigs, cows, goats and sheep. The BPF consists of two biocidal products, i.e. "INTEROX DW 35" and "INTEROX DW 50" belonging to two different meta-SPCs. Target organisms are bacteria. The products can be used indoor and outdoor by professional users.

The products are reported in the PAR to work by the following mode of action: *"The antimicrobial action of hydrogen peroxide stems from its ability to form powerful oxidants such as the hydroxyl radical and singlet oxygen. These reactive oxygen species can initiate oxidation of biomolecules and cause irreversible damage to a host of cell components such as enzymes, membrane constituents, and DNA."*

The referral of the disagreement on the evaluation of the BPF "INTEROX Biocidal Product Family 2" was submitted on 17 December 2019 by the initiating concerned Member State (icMS) France to the Coordination Group (CG), in accordance with Article 35(2) of the BPR. The referral was discussed during a teleconference on 23 January 2020 and the CG-39 meeting on 3 February 2020. During the discussions both points of disagreement remained unresolved. One of the unresolved disagreement points is related to the efficacy of the BPF's products against bacteria. Another unresolved point of disagreement is related to the classification of the products of the BPF as Aquatic Chronic 3 (H412). As the CG did not reach a consensus agreement for the above-mentioned two disagreement points, the rMS referred the unresolved objections to the Commission in accordance with Article 36(1) of the BPR.

It has to be noted that at the time of submission of this application to the rMS, there was no applicable efficacy guidance available to develop a testing strategy. The earliest efficacy guidance addressing the disinfection of water for animals in a very limited way, i.e. "Transitional Guidance on Efficacy Assessment for PT1-5" was published in May 2016 and became applicable to applications submitted not earlier than June 2018.

The following issues were identified:

- the applicant provided a data package consisting of phase 2, step 1 test and a modified phase 2, step 1 test designated as simulated-use test;
- the icMS questioned whether the efficacy of these products is demonstrated for the intended use;
- following the closure of the referral, the applicant submitted an additional modified phase 2 step 1 test designated as simulated-use test on 10 May 2021.

3. Answers to the questions from the Commission

The opinion of the BPC has considered the background information provided by the Commission in the opinion's request, the Product Assessment Report (PAR) of the BPF in question and the opinions expressed during the meetings of the Efficacy Working Group (EFF WG) and the Environment Working Group (ENV WG) that took place on 21 March 2023.

Question 1: Can it be considered that the tests provided in the application show efficacy of the BPF for "the intended use"?

- Are the deviations from the pass criteria of EN 1276:09 acceptable and properly justified?

  The EN 1276 standard specifies a test method and the minimum requirements for establishing the bactericidal activity of chemical surface disinfectants. The described test is a laboratory quantitative suspension (phase 2, step 1) test. The goal of a phase 2, step 1 test is to determine at what concentration(s) the disinfectant is effective enough to move on to more rigorous testing, such as a simulated-use test, or field trial. So far, due to the lack of a standardised phase 2, step 1 test for determining the efficacy of drinking water disinfectants the EN 1276 standard is recommended to be used.

  In the EN 1276 standard *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Enterococcus hirae* and *Enterococcus faecium* (for products used in temperatures ≥ 40°C) are listed as obligatory test organisms. The products shall demonstrate at least a 5 decimal logarithm (lg) reduction for all obligatory test organisms when tested under defined test conditions, i.e. using appropriate test temperature, contact time and soiling.

  The test report provided by the applicant shows > 5 lg reduction at the concentration of the product of 200 g/l for *E. coli, P. aeruginosa* and *S. aureus*. For *E. hirae* only 4.2 lg reduction is achieved at the concentration of the product of 400 g/l. The lower lg reduction achieved by *E. hirae* is considered as a deviation from the pass criteria of the EN standard.

  In general, the deviations from the test conditions required by the EN standard, or applicable efficacy guidance, such as contact time, temperature, or soiling could be acceptable if properly justified. The respective lg reduction criterion is of high importance and is the core requirement when setting up an effective disinfection strategy. Bacteria are diverse microorganisms and can vary in their susceptibility to disinfectants. Testing multiple bacterial strains is necessary to ensure that the disinfectant is effective against a broad range of microorganisms that could be present in the water. Therefore, the product at a certain concentration must achieve in accordance with the EN 1276 standard the required lg reduction of 5 (99.999% of bacteria are inactivated) against all bacterial strains tested, which is the starting point for further, more advanced testing. A deviation from the pass criteria usually cannot be accepted, especially when the efficacy data are generated to support the disinfection of drinking water as it is necessary to ensure that the water is safe for human or animal consumption.

  Nevertheless, it has to be noted that the EN 1276 standard is designed to test disinfectants intended for surface disinfection in food, industrial, domestic, and institutional areas. Several members of the EFF WG evaluating PT 5 active chlorine-based disinfectants noted that these products cannot pass the 5 lg reduction criterion in EN 1276 tests at typical in-use concentrations that have long been established. In addition, it was acknowledged that the active chlorine concentration in drinking water cannot be increased to a level that allows these products to pass this criterion. Consequently, the adapted EN 1276 standard mentioned in the Volume II, Efficacy – Assessment and Evaluation, Parts B+C (Vol. II,

Parts B+C) guidance is considered as not obligatory for PT 5 active chlorine-based disinfectants. Efficacy of such products should be demonstrated with a simulated-use test and/or a field trial. The results presented in the submitted test report based on EN 1276 for this dossier and other reports available in comparable dossiers for products based on hydrogen peroxide indicate that these products are facing difficulties in achieving the required 5 lg reduction at the intended in-use concentration. Based on the available evidence, it would be advisable to carefully consider and potentially implement a similar strategy for drinking water disinfectants containing hydrogen peroxide as already established for PT 5 products containing active chlorine.

- Can the modified test EN 1276:09 designated by the applicant as simulated-use test be considered as simulating the practical conditions of intended use appropriately?

  The simulated-use test is conducted in the laboratory under rigorous conditions, which mimic real-life conditions with the aim to evaluate the performance of a disinfectant. It should have the ability to accurately estimate the efficacy of a disinfectant for the claimed use.

  The performed test based on the modified EN 1276 standard is designated by the applicant as the simulated-use test. In this test all four test organisms, i.e., *E. coli, P. aeruginosa, S. aureus* and *E. hirae* required by the EN 1276 standard were tested under the modified conditions, like temperature of 15^{o}C, soiling reflecting dirty conditions in drinking water (>15 mg/l dissolved organic carbon (DOC)) and longer contact time. Two of them only, i.e., *E. coli* and *E. hirae* achieved the required 5 lg reduction at the concentration of the product of 14 g/l and contact time of 24 hours.

  Generally, modifications made to efficacy standards are focused on altering the testing conditions and do not involve changes or replacements of the tested organisms. The product did not achieve the required 5 lg reduction against all tested organisms, however, *E. coli* and *E. hirae* could be accepted as representative test organisms for the intended use. They represent gram-negative and gram-positive bacteria respectively.

  Regarding the modified test conditions, such as temperature, soiling and contact time they reflect appropriately the practical conditions of the intended use. However, the tested volume of 10 ml leads to serious concerns as this is very small compared to the volume of water in reservoirs for animals. This situation does not reflect real-life conditions, therefore could not simulate the effect of mixing the product with a large volume of water. To support rapid mixing of these products with water the applicant provided the test report "Hydrogen Peroxide - Mixing Study". In this study, in the beaker to a small volume of hydrogen peroxide (10 ml) water was added in 5 steps of 2 litres each. After each addition, the solution was either left standing or mixed for 5 minutes using a stirrer bar and then measured concentrations of hydrogen peroxide were compared. The results show that the same concentrations are obtained at each step with and without mechanical mixing, suggesting that hydrogen peroxide is readily miscible in water. It has to be pointed out that this study cannot be considered representative and reliable for cases where a small amount of hydrogen peroxide is added to a much bigger volume of water. In order to accurately test the product for its intended use, it would be necessary to conduct the test in reverse. This would involve adding a small amount of hydrogen peroxide to a larger volume of water and mixing. Therefore, this study cannot support the proper mixing of these products with water and the small volume tested cannot be considered representative for the volume of water intended to be disinfected.

Moreover, the reliability of this test based on the modified EN 1276 standard is doubtful due to the lack of replicates. Replicates are important to enhance the reliability of the test results especially when the test conditions are modified. Replicates are recommended in the EN 1276 standard as well as Volume II, Part B+C efficacy guidance.

To summarise, the modified EN 1276 test is considered of low reliability due to too many deficiencies and therefore cannot be considered as a simulated-use test mimicking appropriately the practical conditions of the intended use.

In conclusion, the phase 2, step 1 test and the modified EN 1276 test cannot be considered as a sufficient data package to support the efficacy of these products for the intended use.

Question 2: Taking into account the additional test results provided by the applicant following the closure of the referral, can it be considered that efficacy for the intended use has been demonstrated, meaning that the products of the BPF meet the condition in Article 19(1)(b)(i) of the BPR?

In the additional test report based on the modified EN 1276 standard *E. coli A3* and *E. faecium* Teltow 11 were used as test organisms. The product passed the required 5 lg reduction against both tested bacteria under dirty conditions for the veterinary area (more demanding than specified in the standard, i.e., 10 g/l bovine albumin+10 g/l yeast extract) at 20°C and a concentration of 14 g/l for 12 and 24 hours contact times.

Regarding the modified test conditions, such as soiling and contact time they reflect appropriately the practical conditions of the intended use. With reference to the temperature, preferably 15°C should be used to appropriately mimic the intended use.

And as in the previous modified test, also here there is a lack of replicates which is advised by the EN 1276 standard and Volume II, Part B+C efficacy guidance.

In conclusion, taking into account the whole available data package, i.e. phase 2, step 1 test in accordance with EN 1276, modified test designated by the applicant as simulated-use test based on EN 1276 and the additional test provided by the applicant following the closure of the referral it is considered that efficacy for the intended use has not been demonstrated, meaning that the products of the BPF do not meet the condition in Article 19(1)(b)(i) of the BPR.

For efficacy testing of disinfectants, a tiered approach to support the intended use is recommended by the EN 14885 standard and Vol. II, Parts B+C efficacy guidance. Usually, phase 2, step 1 and phase 2, step 2 tests are generally needed in combination to support the efficacy of the disinfectant. The phase 2, step 1 test is a starting point to establish the concentration-contact time relation which needs to be confirmed using a more challenging phase 2, step 2 test. Nevertheless, in this case the results from phase 2, step 1 test show that even a high concentration of hydrogen peroxide in the tested product is not necessarily sufficient and the product cannot pass the required 5 lg reduction against all tested organisms. Such a high concentration of hydrogen peroxide anyway cannot be used to disinfect drinking water, otherwise the residual hydrogen peroxide concentration would exceed 5 mg/l at the point of consumption[1]. Therefore, even if the product would pass the required 5 lg reduction against all four test organisms, it would be reasonable to disregard these results as not being

[1] Assessment Report - Hydrogen peroxide - Product-types 1-6

close to the practical application of the product and to derive the in-use concentration from the simulated-use test.

However, to base the evaluation and to determine the efficacy of the product on one test only, the test has to be of good quality, simulate the real-life conditions and provide good reproducibility. Conducting at least three repetitions permits basic statistical analysis of the results and thus enhances the reliability of the test results, particularly for non-standardised tests. The modified EN 1276 tests due to several deficiencies cannot be regarded as simulated-use test but rather as an adapted phase 2, step 1 test. Therefore, in the light of Article 19(1)(b)(i) of the BPR the biocidal products of the BPF "INTEROX Biocidal Product Family 2" are not sufficiently effective.

Question 3: What is the correct classification for environmental hazards of the products of the BPF according to the CLP Regulation?

Hydrogen peroxide is included in Annex VI (Index number 008-003-00-9) of Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation). The classification, as presented in Annex VI of the CLP Regulation, is the translation of the harmonised classification under Directive 67/548/EEC[2] and does not include classification for environmental hazards. Hydrogen peroxide is listed in the "Registry of classification and labelling (CLH) intentions until outcome"[3] with the expected date of CLH proposal submission of 31 March 2023 by FI. The proposed classification includes Aquatic Chronic 3, H412.

For environmental hazards, hydrogen peroxide is classified as Aquatic Chronic 3, H412 in the Assessment Report (AR, 2015)[4]) for the active substance approval. The classification is based on the key study with *Daphnia magna* (Meinertz et al. 2008)[5], which was conducted with 35% w/w aqueous solution of hydrogen peroxide. The study is reporting a NOEC of 0.63 mg/l (concentration is expressed as 100% hydrogen peroxide), thus fulfilling the CLP criterion of NOEC ≤ 1 mg/l that leads to Aquatic Chronic 3 classification. Several ENV WG discussions[6] on this issue have led to the conclusion that for hydrogen peroxide containing products the recommended classification in the AR should be followed.

In the PAR for "INTEROX Biocidal Product Family 2" the applicant and the rMS propose that classification as Aquatic Chronic 3 is not warranted, since the key study presented in the AR was performed with a 35% hydrogen peroxide and thus the resulting NOEC would be 1.8 mg/l when expressed as the concentration of the product (i.e. 35% hydrogen peroxide solution). It was argued that based on the bridging principle of the CLP Regulation mixture classification should be applied here, so both products in the BPF should not be classified as Aquatic Chronic 3.

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[2] Dangerous Substance Directive on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

[3] Registry of CLH intentions until outcome – Hydrogen peroxide https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e186a47938

[4] Assessment Report - Hydrogen peroxide - Product-types 1-6

[5] Meinertz JR, Greseth SL, Gaikowski MP, Schmidt LJ. Chronic toxicity of hydrogen peroxide to Daphnia magna in a continuous exposure, flow-through test system. Sci Total Environ. 2008 Mar 25;392(2-3):225-32. DOI: 10.1016/j.scitotenv.2007.12.015. This study was considered acceptable, and the eCA assigned it a reliability index of 2.

[6] ENV WG-II-2019, item 6-1; ENV WG-II-2021, item 7-7

Following the CLP regulation, the approach for the classification of aquatic environmental hazards is tiered (Figure 4.1.2 of Annex I of the CLP Regulation) and is dependent upon the type of information available for the mixture itself and for its components.

Elements of the tiered approach include:

- classification based on tested mixtures,
- classification based on bridging principles,
- the use of 'summation of classified components' and/or an 'additivity formula'.

In this tiered approach, the highest priority has study results with tested mixture. The 35% hydrogen peroxide solution in water is a mixture under the CLP Regulation and so the mixtures approach must be followed. Under the CLP Regulation (section 4.1.3 of Annex I), there is a general obligation to consider data on the whole mixture where this is available and is considered relevant and reliable (section 4.1.3.3 of Annex I).

The following chapters will go through the tiered approach for the products in question, considering the available data.

Classification based on tested mixtures

The key study by Mainertz et al., 2008 for environmental classification is conducted with a 35% mixture of hydrogen peroxide with water. The results (NOEC of 0.63 mg a.i.[7]/l) were based on measured confirmation of the nominal concentrations of the a.i. in the test medium, which is the key aspect when considering the classification of the mixture. Consequently, the endpoint values for the respective concentrations of hydrogen peroxide are as measured in the solution and do not represent the mixture *per se*.

Although testing should ideally be conducted using a technical solution of the a.i., as the water does not contribute to toxicity and does not affect the toxicity of hydrogen peroxide, testing using a dilution of a substance in water does not have an effect on aquatic toxicity where the endpoint values are based on a.i. concentrations (providing that the tested range of the a.i. is sufficient to generate a reliable dose-response curve). Given that the CLP guidance (4.1.4.3) specifies that "*To be valid, it would normally be necessary to show that the tested organism has been exposed to the toxic components of the mixture in proportion to the composition of the mixture, and that this exposure has been maintained for the duration of the test*"[8] the test used to derive the classification for hydrogen peroxide is also suitable for mixture classification as the only part of the mixture relevant for hazard assessment is the a.i.

In this case, the existing aquatic toxicity data is representative of both the a.i. and the mixture of the product "INTEROX DW 35", so the classification of the mixture would be the same as for the a.i., i.e. Aquatic Chronic 3 (based on NOEC of 0.63 mg/L for a Rapidly Degradable component/substance).

For completeness, subsequent steps listed in the tiered approach Fig 4.1.2 of Annex I of the CLP Regulation can be considered. The concentration of hydrogen peroxide is above the cut-off value of 1% for Aquatic Chronic 3 (section 4.1.3.1 of Annex I of the CLP Regulation) and therefore must be taken into account in these further approaches.

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[7] a.i. – active ingredient, 100% hydrogen peroxide in this case
[8] Guidance on the Application of the CLP Criteria, version 5.0

Classification based on bridging principles

Where whole mixture data are not available or adequate, the next step is to consider bridging principles, in this case for dilutions. Annex I of the CLP Regulation states "*4.1.3.4.1. Where the mixture itself has not been tested to determine its aquatic environmental hazard, but there are sufficient data on the individual components and similar tested mixtures to adequately characterise the hazards of the mixture, this data shall be used in accordance with the bridging rules set out in section 1.1.3. However, in relation to application of the bridging rule for dilution, sections 4.1.3.4.2 and 4.1.3.4.3 shall be used.*" According to section 4.1.3.4.2 of Annex I of the CLP Regulation, "*Dilution: if a mixture is formed by diluting another tested mixture or a substance classified for its aquatic environmental hazard with a diluent which has an equivalent or lower aquatic hazard classification than the least toxic original component and which is not expected to affect the aquatic hazards of other components, then the resulting mixture may be classified as equivalent to the original tested mixture or substance. Alternatively, the method explained in section 4.1.3.5 may be applied.*" Based on this, the mixture "INTEROX DW 35" would have the same classification as the a.i., resulting in the same outcome as described in the section *Classification based on tested mixtures.* However, Annex I of the CLP Regulation further clarifies the approach for dilutions with water: "*4.1.3.4.3. If a mixture is formed by diluting another tested mixture or substance with water or other totally non-toxic material, the toxicity of the mixture can be calculated from the original mixture or substance*." Consequently, the next step in Fig 4.1.2 and section 4.1.3.5 of Annex I of the CLP Regulation has to be considered to calculate the toxicity of a mixture.

The use of 'summation of classified components' and/or an 'additivity formula'

Following the summation approach calculations outlined in Table 4.1.2 of Annex I of the CLP Regulation for the long-term hazard of the mixture, products in "INTEROX Biocidal Product Family 2" would lead to classification as Aquatic Chronic 3, considering that the content of hydrogen peroxide is 35.5 – 49.9 %.

4. Overall conclusion

Drinking water disinfection is the process of killing harmful microorganisms like bacteria, viruses or parasitic protozoa that may be present in water sources. The purpose of water disinfection is to ensure that the water is safe for human and animal consumption as waterborne diseases can cause a wide range of health problems and can even be life-threatening in some cases. This should be done via an appropriate testing strategy reflecting the intended use under real-life conditions. It is the applicant's responsibility to provide efficacy data from studies designed to mimic the practical use of the products in order to substantiate their efficacy for the claimed use. In principle, the efficacy test reports provided by the applicant are not sufficient to demonstrate the efficacy of the products due to several deficiencies in the tests, such as not fully mimicking real-life conditions and due to lacking repetitions. Therefore, in the absence of appropriate data the efficacy of the products of the "INTEROX Biocidal Product Family 2" is not sufficiently demonstrated.

The products in "INTEROX Biocidal Product Family 2" should be classified as Aquatic Chronic 3, H412. This classification is in line with former ENV WG agreements on the classification of products containing hydrogen peroxide.

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