Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

1,2-benzisothiazol-3(2*H*)-one; 1,2-benzisothiazolin-3-one

EC Number: 220-120-9
CAS Number: 2634-33-5

CLH-O-0000007051-86-01/F

Adopted

26 November 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1,2-BENZISOTHIAZOL-3(2*H*)-ONE; 1,2-BENZISOTHIAZOLIN-3-ONE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: 1,2-benzisothiazol-3(2*H*)-one; 1,2-benzisothiazolin-3-one
EC number: 220-120-9
CAS number: 2634-33-5
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Germany	Wacker Chemie AG	Company-Manufacturer	1
Comment received				
As a producer of water-based dispersion and binders, including for the construction sector, adhesives, paints, coatings, paper and board manufacture, BIT is one of the few remaining effective in-can preservatives, which we at Wacker Chemie AG have been using safely for our products for decades. Having an efficient preservation is an inevitable part of the formulation process in order to avoid microbial deterioration and ensure quality while maximizing shelf-life of our products. Due to regulatory restrictions, fewer and fewer preservatives remain available, which makes efficient preservation increasingly difficult and threatens the future of water-based formulations. One reason is the impact of the harmonized classification on the approval process of the active substance under the Biocidal Products Regulations. In the case of the isothiazolinones, the SCL for skin sensitization is especially important, as this limit value has resulted in a restriction on the sale for treated articles for the general public in the approval process in the past. Unless the effective and safe use of BIT is safeguarded at the end of this process, then no adequate preservation can be ensured in the future. WACKER therefore supports the suggestion by the Spanish dossier submitter to keep the current specific concentration limit (SCL) for skin sensitization at 500 ppm for BIT. This value is supported by the toxicological data, reflecting the hazard potential of BIT, and is also justified in comparison with the defined SCL of other isothiazolinones. Please consult the attachment for more information.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment SCL for BIT_Consultation_Wacker May 2021_Redacted.pdf
Dossier Submitter's Response
Thank you so much for your support.
RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Germany	Verband der deutschen Lack- und Druckfarbenindustrie e. V.	Industry or trade association	2

Comment received

BIT is used as a preservative for products during storage (in-can preservative, PT 6) in the framework of the biocidal products regulation (BPR) . As microorganisms find ideal growth conditions in water-based paints and coatings, preservatives are indispensable for most solvent-free, water-based paints, coatings and printing inks: they prolong their shelf life and prevent mould formation and bacterial growth. One of the most important properties of a biocide is their broad-spectrum efficacy. Thus, it is not enough if it affects a specific harmful organism in a targeted way as it depends on many factors (production conditions, raw material contamination, etc.) which bacteria are present, and this is generally unknown in advance. Furthermore, the active substance must be compatible with the respective matrix. In this way, the oxygen sensitivity and the stability in the right pH value range play a critical role as well as the odour or potential discolourations. Hence, only few of the in-can preservatives listed in the ECHA BPR article 95 list can be used for paints, coatings and inks. Due to the large number of harmful organisms and potential resistances, it is thus necessary to maintain a range of active substances and the possibility of combining them. Especially in the do-it-yourself sector, it is emerging that this might no longer be safeguarded in the future, due to regulatory restrictions. This threatens the future of water-based paints and coatings. It needs to be stressed that over 70% of the production volume of paints and coatings in Germany is water-based. Looking at the German market for paints and coatings, we estimate that roughly half of the market with a real value of Euro 2.6 billion is affected.
BIT is one of the last remaining rather broadly applicable actives for the preservation of paints, coatings and inks. It shows efficacy against bacteria, fungi and yeasts and is very stable, even at high pH values and is easy to combine. Furthermore, it has a very low volatility , which is important for indoor applications. BIT is typically used in combination with other actives (to cover gaps in the efficacy) at a dosage of 100 to 500 ppm.

The restrictions within the framework of the approval process under the BPR are the main problems for in-can preservatives. In the case of isothiazolinones, the specific concentration limits for skin sensitization are being constantly lowered in the CLH process. As this limit value has resulted in a restriction on the sale for treated articles for the general public in the approval process, this is expected to lead to a crisis for the paint industry as the consumer market will diminish. Many active substances, such as for example MIT, are not efficacious below the proposed limit value. If, at the end of this process, this limit value should be in force for all isothiazolinones, then according to the estimation of our experts, no adequate preservation can be ensured in the future.

The reason for the restriction for consumer uses in concentrations above the SCL– as we understand it – is the assumption that private consumers are not capable of avoiding reversible effects on the skin (e .g. redness, rashes) even though the label on the packaging warns about such effects (hazard phrase and pictogram). This assumption has been used for one active substance approval already (C(M)IT/MIT, Regulation (EU) 2016/131)) and it may be expected to be applied for the other actives as well. In the case of C(M)IT/MIT the SCL may be justified and this biocide is still effective at concentrations below its SCL. However, this is not the case for the other members of the isothiazolinone family. Due to the high importance of this substance as an active for in-can preservation in the paints, coatings and ink industry, but also for many other sectors, we would like to comment on the proposed classification as skin sensitizer. The corresponding specific concentration limit (SCL) may have a high impact on the future use of BIT as a preservative. VdL agrees with the classification proposal and suggest classifying BIT accordingly. However, experience has shown that in the case of the isothiazolinones the ECHA Risk Assessment Committee tends to overlook the different sensitization potential of the individual isothiazolinones and decide to apply the same SCL for all isothiazolinones, despite different SCL proposals from the dossier submitter. We would like to support the dossier submitter's proposal of keeping the current SCL of 500 ppm since it is well supported by the available toxicological data, and it seems highly justified when comparing it with the relative sensitization potential of the other isothiazolinones. It is a more than reasonable approach in terms of consumer protection. More details can be found in the attached document. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2021-05-01_VdL Comment on the planned harmonized classification and labelling of BIT.pdf
Dossier Submitter's Response
Thank you so much for your support.
RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Netherlands		MemberState	3
Comment received				
Agree with the proposal adaptation for C&L. The approach used to derive the algal effect values as discussed in the WG ENV has been taken over.				
Dossier Submitter's Response				
Thank you so much for your comment.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Germany		MemberState	4

Comment received

Please provide reliability scores for all studies as given in the active substance evaluation documents (e.g. DoC II, DoC III) here in the CLH-report as this facilitlates the evaluation and makes it much more transparent.
We also have some formal comments on the dossier.
In section 1.1, table 1 and section 1.2 table 2 of the CLH report the "Degree of purity (%) (if relevant for the entry in Annex VI)" respectively the concentration range of BIT is given. If not relevant for the entry in Annex VI, the given purity should be deleted.
In section 2.1, table 5 the following chemical name is stated as "Dossier submitters proposal":
1,2-benzisothiazol-3(2H)-one;
1,2-benzisothiazolin-3-one
In the row "Resulting Annex VI entry if agreed by RAC and COM" the chemical name remains unchanged as given in the current Annex VI entry:
1,2-benzisothiazolin-3-one (BIT)
We suggest adding the chemical name "1,2-benzisothiazol-3(2H)-one" (as in the given proposal and) as used for the biocidal active substance in the corresponding CAR.
Furthermore, other formal errors could be found in section 2.1, table 5.
- In the row "Current Annex VI entry" and column "Classification/Harzard Class and Category Code(s)", add "*" to the code "Acute Tox. 4". As this is a minimum classification, the correct coding must be "Acute Tox. 4*".
- In the line "Dossier submitters proposal" and column "Classification/Hazard Class and Category Code(s)" the code "Acute Tox. 4" must be listed under "Modify". In the same field, the code "Eye Dam. 1" must be listed under "Retain".
- In the line "Dossier submitters Proposal" and column "Classification/Hazard statement Code(s)" the hazard statement "H318" is missing under "Retain".
- List "GHS05" and "Dgr" under "Retain" in the "Dossier Submittals Proposal" row and "Labelling/Pictogram, Signal Word Code(s)" column.
- In addition, the hazard symbol "GHS07 must be listed under "Remove" instead of under "Modify".
- In the line "Dossier submitters proposal" and column "Labelling/Hazard statement Code(s)" the hazard statement "H318" has to be listed under "Retain". In addition, the hazard statement "H400" must be listed under "Remove.
- In the row "Dossier submitters proposal" and column "Spezific Con. Limits, M-factors and ATEs", the term "(dusts or mists)" should be added to the inhalation information. So that "contention: ATE= 0.25 mg/L (dusts or mists)" would stand. This change must also be made in the row "Resulting Annex VI entry if agreed by RAC and COM" and column "Spezific Conc: Limits, M-factotors and ATEs".

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE_CA comment_BIT BfC.pdf

Dossier Submitter's Response

Thank you so much for your comments.
- Reliability should be added to the first column of each summary table.
- Since purity is not relevant for the entry in Annex VI, it should be deleted from sections 1.1. and 1.2.

- We agree with the inclusion of the other name in the "Resulting Annex VI entry if agreed by RAC and COM" row in section 2.1, Table 5. - We agree with the modifications suggested by DE in section 2.1, Table 5.
RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2021	Germany	I&P Europe - Imaging and Printing Association	Industry or trade association	5
Comment received				
see attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment IP Position Paper BIT reclassification - May 2021.pdf				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2021	Germany	<confidential>	Company-Downstream user	6
Comment received				
Benzisothiazolinone (BIT) is used as in-can preservative in many of our products (water based paints and coatings and similar products). In-can preservation is essential for water-based products. Only special cases, e.g. products with pH-values greater 11, allow for formulation without in can preservatives - but these concepts can´t be generalized for all water based products. Due to its very low volatility BIT is preferred over other isothiazolinones (Methyl-Isothiazolinone (MIT), Chlormethyl-Isothiazolinone (CIT)) especially for products for indoor application. MIT can be detected in indoor air in considerable amounts after application of MIT-preserved paints. Cases of allergic reactions of persons staying in rooms painted with MIT-preserved paints due to MIT emissions are reported. BIT emission to indoor air is negligible and has to the best of our knowledge never caused any problems. BIT is thus of great importance for the production of water-borne paints and coating. As we are afraid that BIT might be - despite of the SCL of 500 ppm as proposed by the CLH dossier submitter - assigned with the same SCL of 15 ppm as other Isothiazolinones, we wish to comment on this hazard class (see below).				
Dossier Submitter's Response				
Thank you so much for your comment.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
06.05.2021	France		MemberState	7

Comment received

FR comment on Physical hazards:
Pages 12-13: Please, detail the results of hazard tests (flammability, explosive, oxidising properties

Dossier Submitter's Response

Flammability	**EBITTF (Lonza Cologne GmbH, LAMIRSA S.A. and Thor GmbH)**	Not highly flammable	CAR; Report No. B 053/2006	The test item began to melt immediately. No propagation of flames or smouldering was observed within the testing period of 2 minutes. Because it was impossible to ignite the test item in the main test was not performed. Therefore, the test item is not considered as highly flammable according to EEC-Guideline A.10.
	Nutrition & Biosciences (Switzerland) GmbH Lanxess Deutschland GmbH	Not highly flammable	CAR; Report No. 1606/0043	The test material has been determined to be not highly flammable as it failed to ignite in the preliminary screening test. Therefore, the test item is not considered as highly flammable according to EEC-Guideline A.10.
	Troy Chemical Company B.V.	Not highly flammable	CAR; Study No. 62630	The test item did not burn with a flame or smolder along 250 mm of the test substance strip within 2 minutes, and therefore was not considered highly flammable. Therefore, in accordance with the ECC-Guideline A.10, no further testing of its flammability is required.
Explosive properties	**EBITTF (Lonza Cologne GmbH, LAMIRSA S.A. and Thor GmbH)**	Thermal Sensitivity: No Reaction Mechanical Sensitivity (shock): No Reaction Mechanical Sensitivity (friction): No Reaction TGAI has no explosive properties.	CAR; Report No. B 003/2007	It can be reported that there is neither explosive property induced by flame, by shock nor by friction according to the EEC-guideline A.14.
	Nutrition & Biosciences (Switzerland) GmbH Lanxess Deutschland GmbH	No explosive properties were observed	CAR; Report No. 1606/0043	It can be reported that there is neither explosive property induced by flame, by shock nor by friction according to the EEC-guideline A.14.
	Troy Chemical Company B.V.	The molecular structure of BIT indicates that the substance has no explosive properties.	CAR	In spite of the presence of chemical groups in the molecule which are associated with explosive properties according to the ECHA Guidance on the Application of the CLP criteria (version 5.0, July 2017), a read across can be established with other isothiazolones (e.g. MIT, CMIT, MBIT) with similar oxygen balance and chemical groups indicators of explosive properties. These isothiazolones have no explosive properties according to their ARs and CLH reports, therefore, it can be anticipated that the BIT will not have explosive properties. Therefore, taking the read across into account and the studies submitted by the rest of applicants, the explosive properties of BIT are not foreseen .

Oxidising properties	**EBITTF (Lonza Cologne GmbH, LAMIRSA S.A. and Thor GmbH)**	No oxidizing properties were observed	CAR; Report No. B 001/2007	The single results from all tests are summarized in the following table: mixture / Maximum burning rate (mm/s) Oxidiser / Cellulose / 1.24 Test item / Cellulose / 0.92 The maximum burning rate of the test item/cellulose mixture was significantly smaller than that of the reference mixture. Therefore the active substance was not classified as an oxidizing test item according the ECC.Guideline A.17.
	Nutrition & Biosciences (Switzerland) GmbH Lanxess Deutschland GmbH	No oxidizing properties were observed	CAR; Report No. 1606/0043	The test material has been determined not to have oxidising properties as the test material/cellulose mixtures failed to propagate combustion at a rate greater than or equal to that of barium nitrate/cellulose mixtures according to EEC-Guideline A.17.
	Troy Chemical Company B.V.	The molecular structure of BIT indicates that the substance has no oxidising properties. Therefore, a study is not required	CAR	According to the ECHA Guidance on the Application of the CLP criteria (version 5.0, July 2017), the classification procedure for oxidizing properties does not need to be applied since the substance contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen

RAC's response

RAC thanks the Dossier Submitter for the response provided above. However, since the physical hazards were not open for comments during the consultation, this information was not assessed in the RAC Opinion.

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2021	Germany	Remmers GmbH	Company-Downstream user	8

Comment received

Benzisothiazolinone (BIT) is one of the last remaining in-can-preservative active substances which can be used in water based coatings. There are many other PT6 substances, but most of them are not suitable for use in coatings due to technical reasons (discolouring, stability of a. s. and formulation, adhesion). All other technical suitable alternatives like Pyrithiones and Formaldehyde-releasers have already been "classified" mostly as CMR substances (or will get classified in the next years), so that their usage especially in consumer products is very limited. Without technically feasible in can preservatives, water based coatings will underly a severe risk of microbial decay, producing high volumes of waste, leading to wastage of resources and promoting a higher share of solvent based coatings specifically in the consumer products area.

Dossier Submitter's Response

Thank you so much for your comment.

RAC's response

RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United States of America	American Coatings Association	Industry or trade association	9

Comment received

The American Coatings Association (ACA) appreciates the opportunity to comment on the classification of BIT. ACA supports the comments submitted by the European Council of Paint, Printing Ink and Artists' Colours Industry (CEPE). We both support the harmonized classification proposed by the authorities in Spain for BIT, which is based on the strict application of the Classification, Labelling and Packaging (CLP) criteria to the latest BIT data.

Effective preservatives are essential for in-can preservation of coatings prior to use. BIT is one of the few remaining effective in-can preservatives and has historically been used in Europe to protect waterborne coatings. BIT is used at concertation's below the specific concentration limit (SCL) of 0.05% (500 ppm), with no evidence of induction of skin sensitisation from its presence in coatings. Setting a lower limit could have severe consequences (increased spoilage for example) under the Biocidal Products Regulation for consumer use of treated articles (including paints), by misrepresenting hazards associated with paint and coatings products and confusing consumers.

We support CEPE's call for careful examination of data leading to induction of skin sensitization from which a sound SCL can be set. In summary, ACA supports the harmonized classification proposed by the authorities in Spain for BIT.

Please let me know if you have any questions regarding our comments.

Sincerely,

/s/
<confidential>
Vice President, Health, Safety and Environmental Affairs
American Coatings Association

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACA BIT comments 5142021 _Redacted.pdf

Dossier Submitter's Response

Thank you so much for your support.

RAC's response

RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Task Force	Company-Manufacturer	10

Comment received

CLH Report pages 8 and 9

ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT CLH-report commenting table_BIT Task Force_Redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BIT CLH-report commenting table_BIT Task Force.pdf
Dossier Submitter's Response
Thank you so much for your comments. We only disagree with the removal of the information gathered from the RAC opinion on MBIT since we have only evaluated the information about BIT, not MBIT.
RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	Belgium	CEPE	Industry or trade association	11
Comment received				
CEPE as downstream user of BIT would like to stress the importance of this in-can preservative biocide active substance and hereby submits information on the skin sensitization property in order to support the valude for induction as proposed by the dossier submitter. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CEPE position on BIT public consultation final 20210514_Redacted.pdf				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	British Coatings Federation	Industry or trade association	12
Comment received				
The British Coatings Federation is the sole UK trade association for manufacturers of decorative coatings, printing inks, industrial coatings and wallcoverings, representing a £4 billion value industry and the interests of over 200 member companies. We welcome the opportunity to provide comments on the proposed harmonised classification and labelling of 1,2-benzisothiazolin-3-one (BIT), and in particular with regards to the proposed Specific Concentration Limit (SCL). ECHA note – An attachment was submitted with the comment above. Refer to public attachment BCF Submission to the Public Consultation on 1,2-benzisothiazolin-3-one.pdf				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	Netherlands	Sherwin Williams	Company-Downstream user	13
Comment received				
BIT is a highly effective preservative for low VOC water-based product formulations. It functions across a wide spectrum of pH and demonstrates excellent efficacy against a wide range of microorganisms. Due to limited availability of suitable alternatives1, BIT is an increasingly important biocide in our and our customer's applications. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT CP_final.pdf				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Switzerland	Dow Europe GmbH	Company-Downstream user	14
Comment received				
Dow welcomes the opportunity to comment on the proposed harmonized classification of BIT. We use preservatives in our products to prevent microbial growth, enabling a longer shelf-life and improved product integrity, thus reducing waste and the overall environmental impact of our products. Furthermore, it allows for the substitution of solvents in numerous products, thereby contributing to improved human and environmental health by permitting substitution to safer, aqueous based formulations. BIT is an incredibly effective and increasingly important preservative since it is efficacious against a wide number of micro-organisms, stable across a wide-range of pH and in a diverse range of formulations. As an active substance undergoing review under Regulation (EU) 528/2012, a considerable set of human health and environmental data exists for this substance. Therefore, in reviewing the classification of BIT, we would urge the RAC to consider the toxicological data existing for BIT alone, and that read-across to other isothiazolinones is neither necessary nor warranted on the basis that BIT shows significant differences in reactivity, potency, physcochemical properties and general toxicity. Furthermore, since CLP is concerned with the intrinsic hazard of a substance, the data generated on the substance itself is considered the most relevant and pertinent for classification purposes. This approach would be identical to the recent case of Sodium Pyrithione where, despite sharing a common moiety with Zinc Pyrithione, the use of read-across was not employed in deciding the final classification due to its inherently different behaviour from a physicochemical and toxicological perspective.				
Dossier Submitter's Response				
Thank you so much for your comment.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Belgium	A.I.S.E.	Industry or trade association	15
Comment received				
AISE supports the harmonised classification proposed by Spain for BIT with regards to Skin Sensitization. AISE provides in its comments additional toxicological data to support the proposed classification as Skin Sensitising Category 1B with a concentration limit of 500 ppm (C ≥ 0.05%) for BIT. ECHA note – An attachment was submitted with the comment above. Refer to public attachment AISE CLH BIT Comments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Confidential Reports.7z				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Austria	ADLER Werk Lackfabrik Johann Berghofer GmbH & Co KG	Company-Downstream user	16
Comment received				
"ADLER-Werk Lackfabrik Johann Berghofer GmbH & Co KG" is a producer of solvent-based and water-based paints and coatings. During the last years the ratio of water-based coatings increases. Where it is possible, solvent-based paints and coatings should be replaced by water-based paints and coatings. For our water-based paints and coatings Benzisothiazolinone (BIT) is important especially for the DIY sector. BIT is a broadly used preservative for water-based formulations and is one of the few remaining effective in-can preservatives, which we have safely used in our products for decades. Since microorganisms find ideal growth conditions, microbial deterioration needs to be avoided to ensure that our products can safely be used, sustain their functionality, and have the necessary shelf-life. Due to regulatory restrictions, fewer and fewer preservatives remain available, which it makes efficient preservation increasingly difficult and threatens the future of water-based formulations. One reason is the impact of the harmonized classification on the approval process of the active substance under the Biocidal Products Regulations. In the case of the isothiazolinones the specific concentration limit (SCL) for skin sensitization is especially important and hence we would like to comment on this hazard class specifically. The scientific data clearly demonstrates that BIT is a moderate sensitizer. We fully support the proposal of the dossier submitter Spain to keep the current SCL of 500 ppm for skin sensitization for BIT, which is in line with the available toxicological data. The conclusions on skin sensitization must be based on results of validated studies with a standardized exposure. Human case studies, without a standardized exposure cannot be validated and can only be considered as supporting additional evidence. The potency of BIT is much lower than that of the other isothaizolinones that have already been harmonized classified (e.g. CIT/MIT, MIT, MBIT). We would like to stress that this needs				

to be reflected in the setting of the SCL. To the best of our knowledge, the use of BIT in our products has never led to increasing cases of sensitizations.
Dossier Submitter's Response
Thank you so much for your support.
RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2021	Germany	<confidential>	Company-Downstream user	17
Comment received				
Water-based coatings and printing inks must be protected from microbial growth, as the aqueous environment in combination with, for example, waxes offers good growth conditions for bacteria and molds. Without the addition of effective in-can preservatives the shelf-life of water-based coatings and inks is not sufficient. Benzisothiazolinone (BIT) is a preservative very often found in our water-based raw materials. It has a harmonised classification for skin sensitisation with a SCL 500 ppm. BIT is effectively used at concentrations less than this SCL. This biocidal active ingredient is one of the last still readily available and effective in-can preservatives that we have been using safely in our products for decades. As a producer of water-based coatings and inks for graphical industry (food packaging etc.), an efficient preservation is highly important for our products. As consequence of regulatory restrictions, fewer and fewer preservatives remain available. Therefore, an efficient in-can preservation is more and more difficult and threatens the future of our water-based formulations. Here, the tightening of the harmonized classification plays an important role regarding the approval process of the active substance in accordance with the biocidal product regulations. In the case of isothiazolinones the specific concentration limit (SCL) for skin sensitization is especially important and hence we would like to comment on this hazard class specifically.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2021	Germany	Wöllner GmbH	Company-Downstream user	18
Comment received				
We, Wöllner GmbH, are using Benzisothiazolinone (BIT) since many years as a preservative in some of our aqueous based formulations. Furthermore, some of or our customers are also using this substance for the function of preservation. The choice of available and appropriate preservatives is getting smaller and smaller, due to growing tighter regulatory restrictions. As regards to BIT, the specific concentration limit (SCL) for skin sensitization is under review. Therefore, we would like to share our opinion with you, about this issue.				

The advantages of BIT are in particular visible at systems with higher pH-values, especially for paint manufacturers. Due to the higher pH-values, lower amounts of biocides are necessary, but there is a limitation in appropriate biocides at such high pH. By lowering the SCL of BIT, the choice of applicable biocides will be reduced.
Dossier Submitter's Response
Thank you so much for your comment.
RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2021	Germany	<confidential>	Company-Downstream user	19
Comment received				
We are a formulator of water-based printing inks (for industrial uses) and BIT is one of our most important in-can preservatices. It is one of the few remaining effective biocides in that segment and it is nearly impossible to produce such water-based products without BIT or other isothiazolinones. We are more and more afraid how this substance class has come under fire in the past years.				
Dossier Submitter's Response				
Thank you so much for your comment.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Belgium	EPDLA, Sector Group of the European Chemical Industry Council (CEFIC)	Industry or trade association	20
Comment received				
The European Polymer Dispersion and Latex Association (EPDLA), a Cefic Sector Group, would like to contribute to this public consultation. When doing so, we would like to kindly address our comments in the position/statement attached herewith. ECHA note – An attachment was submitted with the comment above. Refer to public attachment EPDLA comments concerning the proposed harmonized classification and labelling of BIT_FINAL May 2021_Redacted.pdf				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Switzerland	Dow Europe GmbH	Company-Downstream user	21

Comment received

Dow is in agreement with the proposed classification of BIT as acute tox Cat. 4 Harmful if swallowed, however we wonder whether the appropriate LD50 value has been chosen for the ATE. The dossier submitter has selected an acute toxicity study in which the purity of the material is not specified and where only male animals are exposed to 3 dose levels of BIT (female animals being exposed to the lowest dose only). Whilst little information is presented in the dossier, we would advocate that the most appropriate study to choose for the ATE would be study referenced as AIII6.1.1/2 (2003a) since this study appears to be guideline compliant, with both male and female animals exposed to a highly pure test material and where 4 dose groups are employed which would allow for more accurate estimation of the LD50. We therefore consider the ATE for BIT should be 582 mg/kg.
Dow is in agreement with the proposed classification for inhalation toxicity

Dossier Submitter's Response

Thank you so much for your comment. We disagree with Dow's reasons to disregard the study AIII6.1.1/2 (1994a) to stablish the oral ATE: looking at the results of the other studies it is clear that there are no different effects or potency between males and females; effects are clear at the selected doses; purity is not stated (according to the study it was responsibility of the sponsor) so it is impossible to know if it was higher or lower than the other studies. In addition, there are no deviations from the guideline followed that invalidate the study. For this reason, the ATE should be 454 mg/kg, the most restrictive of the five studies.

RAC's response

In agreement with the DS, RAC proposes to use the lowest LD_{50} (454 mg/kg bw) for the ATE, derived from the Anonymous, 1994a study. Although the purity of the substance is not specified and it used only male rats, as the sex of the animals does not appear to affect the results, and the study was done according to the OECD TG 401 and under GLP, there is no reason to disregard it.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Task Force	Company-Manufacturer	22

Comment received

CLH Report Page 17

ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT CLH-report commenting table_BIT Task Force_Redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BIT CLH-report commenting table_BIT Task Force.pdf

Dossier Submitter's Response

Thank you so much for your support.

RAC's response
Thank you for your comment. RAC has included the inhalation study (Anonymous, 2012) you refer to in the RAC opinion for BIT.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Common Interest Group (BIT CIG) consists of the 6 participants Nutrition & Biosciences (Switzerland) GmbH, Laboratorios Miret, S.A., Lanxess Deutschland GmbH, Lonza Ltd, Thor GmbH and Troy Chemical Company BV.	Company-Manufacturer	23

Comment received
Section 3, Page 20 ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT Common Interest Group_CLHComments_Final_v2r.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL STUDIES.zip
Dossier Submitter's Response
Thank you so much for your support in the classification and for the additional information. Since both studies follow the same guideline and neither has major deviations, the most restrictive LC_{50} (0.5 vs. 0.25 mg/L) between the two should be chosen as ATE, which in this case is the one proposed by us. We attach the assessment of this study conducted in the BPR Review Programme (DocIIA.pdf) and the corresponding summary submitted by the applicant (DocIIIA.pdf).
RAC's response
Thank you for your comment. RAC has included the inhalation study (Anonymous, 2012) you refer to in the RAC opinion for BIT. Both studies give LD_{50}s which correspond to Category 2 ($0.05 < LC_{50} \leq 0.5$). RAC proposes to use the lowest LD_{50}, calculated for males in the Anonymous (2007) study to derive an ATE.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Switzerland	Dow Europe GmbH	Company-Downstream user	24

Comment received
Dow disagrees with the removal of the classification as Skin Irritation Cat. 2 (H315). Whilst true that several studies in animal models do indicate BIT is not an irritant, several studies listed in the dermal sensitization section of the dossier describe irritation reactions in humans (Plaza M.E. and Rheins L.A. 1991 and Davies R.E. et al 1975). In addition,

false positive, irritant responses are observed in clinical patch testing. According to ECHA guidance on IR & CSA Section R.7.2.4.2 existing human data can be used for classification and labelling decision making. Furthermore, according to the ECHA guidance on the application of the CLP criteria section 3.2.2.6., human data indicating the substance is an irritant may be used to assign Skin Irritation Cat. 2 classification. We therefore consider the current classification as Skin irritation Cat. 2 should be retained.
Dossier Submitter's Response
Thank you so much for your comment. We disagree with Dow's point of view about the human studies in the skin sensitization section. Out of 21 studies only 4 show any skin irritation. Of these 4 studies, 3 of them (Plaza and Rheins, 1991, Davies *et al*., 1975 and Andersen and Hamann, 1984) cannot be used to assess this endpoint because the exposure periods were too long (24 h-48h) using a semi-occlusive approach. The reaction observed in a worker in a manufacturing plant was minor, even though the substance was undiluted, the clothing may have acted as an occlusive and it is not known how long it took to remove the substance from the body. For these reasons it is more appropriate to use the animal data, which show no irritation in five different studies supporting the removal of the classification of Skin Irrit. 2.
RAC's response
RAC agrees that although the OECD TG 404 studies do not support classification of BIT for skin irritation, the human studies demonstrate that irritation of the skin does occur (Damstra *et al.*, 1992; Davies *et al*., 1975; Andersen and Hamann, 1984; Freeman, 1984). The OECD TG 404 studies on rabbits used 4 hours application, while the human studies used longer periods. The doses showing irritating effects in the human studies on the other hand, are 1-3 orders of magnitude lower (500-10000 ppm=0.05-1.0 %), compared to the animal studies. Therefore RAC proposes to retain the Skin Irrit. 2 classification.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Task Force	Company-Manufacturer	25
Comment received				
CLH Report page 22 ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT CLH-report commenting table_BIT Task Force_Redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BIT CLH-report commenting table_BIT Task Force.pdf				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Common Interest Group (BIT CIG) consists of the 6 participants Nutrition & Biosciences (Switzerland) GmbH, Laboratorios Miret, S.A., Lanxess Deutschland GmbH, Lonza Ltd, Thor GmbH and Troy Chemical Company BV.	Company-Manufacturer	26
Comment received				
Section 4, Page 21 ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT Common Interest Group_CLHComments_Final_v2r.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL STUDIES.zip				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Germany		MemberState	27
Comment received				
The CLH proposal lists seven animal studies and one human volunteer study for skin irritation/corrosion. Five of the seven studies (Anonymous, 2007 (IIIA6.1.4.a/01); Anonymous, 2002 (IIIA6.1.4/1); Anonymous, 2003 (IIIA6.1.4.b/02); Anonymous, 1993 (IIIA6.1.4/1); Anonymous, 1993 (REACH Registration dossier)) were conducted according to OECD guideline 404, or comparable standards and were allocated a reliability of 1 by the dossier submitter (Information according to DoC IIA or DoC III of the active substance evaluation documents as prepared by ES, not from the CLP report). These studies show results leading to non-classification of BIT according to CLP concerning skin irritation/corrosion. Additionally, two studies (Anonymous, 1985 (TC C&L document); Anonymous, 1980 (TC C&L document) conducted on guinea pigs with a BIT concentration of 1 % showed non-specified strong irritation. Due to lack of further documentation, these studies have a very limited informative value. The unnamed study conducted on human volunteers from 1992 (Anonymous, 1992 (TC C&L document) mentioned on page 21 of the CLH proposal contains a unit error (% and mg). Please correct. Concentrations of 0.8 and 0.16 % showed skin irritation. Due to limited documentation this study has a limited informative value.				

There are some more human data on the skin irritating effect of BIT from experiments made to determine skin sensitising properties than provided by the DS under the endpoint. They have limited informative value but are mentioned here for completeness.
A study conducted by Plaza and Rheins, 1991 (IIIA6.12.6/01) showed, that three of 111 human volunteers experienced irritation during challenge phase. Documentation of the study is limited.
A case study in 2003 by the "Specialty Electronic Materials Switzerland manufacturing plant" documented skin irritation on worker skin after exposure to pure BIT.
The 1975 study by Davies et al. (TC C&L document) reported skin-irritation in 27 of 45 volunteers during both induction and challenge phases. This is a very high frequency, but it should be noted that propylene glycol was used as a vehicle for BIT. Propylene glycol has been identified as a penetration enhancer by the study authors. This assessment was accepted by ES. In addition, the purity of the active substance was not stated in the report.
Another study with high irritation frequency is that of Andersen and Hamann 1984 (TC C&L document). 121 of 404 dermatitis subjects showed skin irritation at 1 % BIT. The mixture used in this study was generated from Proxel XL and Proxel HL in alcohol. Proxel XL is a mixture of 20 % BIT in propylene glycol. Proxel HL is a 30 % BIT mixture in morpholine di- and triethanolamine. Morpholine is classified as Skin Corr. 1B H314 according to CLP, di-ethanolamine as skin Irrit. 2 H315. Triethanolamine is not classified according to CLP. It is therefore not clear to what extent the co-formulants of the BIT mixtures have contributed to skin irritation.
Significantly less patients (seven of 466) showed skin irritation after exposure to 0.5 % Proxel XL (0.1 % BIT in water).

According to relevant guidance documents, rabbit/animal skin is more susceptible to skin irritation than human skin (CLP Guidance page 271 and Guidance IR&CSA Section R.7.2.4.2).

Due to the higher level of documentation and standardisation and the higher susceptibility of rabbits/animals compared to humans, animal studies are preferred over human studies, and the non-classification of BIT regarding skin irritation is supported.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE_CA comment_BIT BfC.pdf

Dossier Submitter's Response

Thank you so much for your support.

RAC's response

RAC agrees that the OECD TG 404 studies do not support classification of BIT for skin irritation. Nevertheless, the human studies demonstrate that irritation of the skin does occur (Damstra *et al.*, 1992; Davies *et al*., 1975; Andersen and Hamann, 1984; Freeman, 1984). The OECD TG 404 studies on rabbits uses 4 hours application, while the human studies used longer periods. The doses showing irritating effects in the human studies on the other hand, are up to 3 orders of magnitude lower (500-10000 ppm=0.05-1.0 %), compared to the animal studies. Therefore RAC proposes to retain the Skin Irrit. 2 classification.
In the study of Anderson and Hamann (1984), the human study did not use Proxel HL, only Proxel XL and BIT, so the sensitizing effect of morpholine di- and triethanolamine do not have to be taken into account.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Germany	Wacker Chemie AG	Company-Manufacturer	28

Comment received

WACKER supports the suggestion by the Spanish dossier submitter to keep the current SCL for skin sensitization at 500 ppm and considers this supported by toxicological data and a correct reflection of the hazard potential. The 500-ppm value is also justified in comparison with the defined SCL of other isothiazolinones, as it takes into consideration the difference in their relative sensitization potential and the substance-specificity.

Based on the available data, BIT is undoubtedly a sensitizer, as are all members of the isothiazolinone family. Therefore, classification as Skin Sens. 1; H317 (may cause allergic skin reactions) is warranted. However, from the overview of the key results of different isothiazolinones (including BIT) from the RAC opinion in 2018, the obtained EC3 values of BIT differ significantly from the others of the isothiazolinone family. The results of the LLNA studies indicate that BIT, in contrast to the other isothiazolinones, is rather a moderate sensitizer (corresponding to category 1B at EC3 values > 2 %). The results from GPMTs also give a comparable picture (BIT sensitize more than 30% of animals after challenges with intradermal doses higher than 1%).

In this context it is important to understand the sensitization process as a highly specific two-stage immune reaction, which is started by the formation of an antigen(BIT)-protein-complex. Apparently, considering the available data, a higher induction threshold can be assumed in the case of BIT than for other isothiazolinones. This presence of a higher induction threshold is well supported by the obtained EC3 values in the LLNA studies and by the available human data (Alomar A. et al., 1984, or Andersen K.E. and Veien N.K., 1984 and 1985).

In the majority of cases of human patch tests, sensitization is observed at (predominantly) 1000 ppm, but not at < 500 ppm or only with very low incidences or unclear boundary conditions. It could be that the affected persons are already sensitized by BIT and the 10-fold lower threshold for elicitation was triggered. Considering all available data, it can be assumed that a SCL of 500 ppm adequately reflects the hazard potential of BIT. Already sensitized persons are protected by the hazard statement EUH208 (Contains <BIT>. May produce an allergic reaction) with a derived limit of 50 ppm.

Please consult the attachment for more information.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment SCL for BIT_Consultation_Wacker May 2021_Redacted.pdf

Dossier Submitter's Response

Thank you so much for your support.

RAC's response

RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Germany	Verband der deutschen Lack- und Druckfarbenindustrie e. V.	Industry or trade association	29

Comment received

Concerning the sensitization potency of BIT several validated studies, where the exposure is standardized, are available. These studies have also been summarized in previous RAC opinions on other isothiazolinones.

Non-human data

Mouse Local Lymph Node Assay (LLNA, OECD 429)
There are different LLNA tests from 1991, 1999 and 2005, giving EC3 values of 4.8%, 32.4%, 10.4%, 2.3%, respectively.
According to table 3.6. of the Guidance on the Application of the CLP criteria this clearly indicates a moderate sensitizer (EC3 > 2, Skin Sens 1 B).

Guinea Pig Maximisation Test (OECD 406)
Following challenge, 9 out of 20 animals in the test group reacted positively to 10% w/v test article in ethanol at 24 or 48-hour examinations, giving a response incidence of 45%.
According to table 3.7. of the Guidance on the Application of the CLP criteria this indicates a moderate sensitizer (Concentration for intradermal induction (%w/v) > 1.0, Incidence sensitized guinea pigs (%) ≥ 30, Skin Sens 1 B).

Buehler Method
No reaction was seen at any test or naive control site following challenge. The positive control data confirmed the validity of this test system.
The Buehler Method indicates no sensitization potential.

Summary Non-human data
The non-human data demonstrates that BIT is a moderate sensitizer according to the criteria set out in the CLP guidance. Thus, a generic concentration limit of 1% (10.000 ppm) would apply according to table 3.9.

Human data

In the HRIPT no reactions to BIT occurred at 360 ppm, while 9% of volunteers reacted at 725 ppm. According to the Guidance on the Application of the CLP criteria HRIPT is not a clinical study and is only of historical relevance. Nevertheless, the HRIPT results indicate that the SCL can be set above 360 ppm and below 725 ppm. There is also a possibility of false positives as irritation effects have been observed above 500 ppm.

The diagnostic patch tests show results on patients with dermatitis and could indicate the elicitation threshold for BIT. The results cannot be used for finding the induction threshold relevant for assigning an SCL. It may be worth noting that the BIT concentrations used in the diagnostic patch testing where relatively high considering the concentrations used in the HRIPT study above.

Additional Studies

There is a report indicating that BIT caused skin allergies from PVC gloves containing 20-30 ppm of BIT. The study investigated contact allergy to plastic gloves, which is found as a rare phenomenon. The authors suspect delayed-type contact allergy to benzisothiazolinone from polyvinyl chloride (PVC) gloves. To find relevant cases, they looked through their medical records from 1991 to 2005. The study identified a total of 8 patients who are allergic to benzisothiazolinone and who had experienced exacerbations of their hand dermatitis while using PVC gloves. Patch testing showed that 3 of them had weak allergic or doubtful reactions to the material of the glove. Six of them had used products, which in chemical analysis were shown to contain 9 to 32 ppm of benzisothiazolinone. All patients had displayed hand dermatitis for years and as BIT is an irritant the authors state that the possibility of false-positive reactions to BIT cannot be excluded in the present series of patients. The authors conclude that to their knowledge, there have been no previous reports of contact allergy to antimicrobial agents in plastic gloves. They also conclude that small amounts of benzisothiazolinone in the gloves may sensitize those who already have hand dermatitis. However, these findings in those who already have hand dermatitis only are likely to be due to elicitation or irritant effects. Furthermore, from January 1991 to September 2005, BIT was tested on a total of 2264 patients, and 17 (0.75%) of them had an allergic reaction to it. This means a rather low incidence and would support Skin Sens 1B.
The sensitization threshold (i. e. the elicitation threshold for provoking an effect on the skin) for patients with an existing hand dermatitis is not relevant for the setting of the SCL under CLP (SCL is set for induction of sensitization). Furthermore, as detailed out in the attached document, such human case studies cannot be validated, lack details, do not show dose-response and can hence only be considered "as supporting additional evidence".

Summary of the toxicological data for setting the SCL
The Guidance on the Application of the CLP criteria (version 5.0, chapter 3.4.2.5) states: "SCLs shall be set when there is adequate and reliable scientific information available showing that the specific hazard is evident below the GCL for classification. As such the recommended SCL should normally be as given in Table 3.9 (chapter 3.4.2.5 page 348). However, supported by reliable data the SCL could have some other value below the GCL. Reliable data could be human data from e. g. workplace studies where the exposure is defined."

Following the guidance, the toxicological data clearly demonstrates that BIT is a moderate sensitizer. According to table 3.9 an SCL for a moderate sensitizer should be between 1000 and 10,000 ppm. The currently available robust and guidance-based data clearly supports the dossier submitter's proposal. The available data would even allow for setting a higher SCL, i.e. the CLH submitter's proposal of 500 ppm is sufficiently conservative.

More information and a comparison with other members of the isothiazolinone family can be found in the attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2021-05-01_VdL Comment on the planned harmonized classification and labelling of BIT.pdf

Dossier Submitter's Response
Thank you so much for your support.
RAC's response
RAC agrees that the animal studies indicate that BIT is a moderate sensitizer. RAC also agrees that an SCL for BIT cannot be derived from the studies of dermal patients who developed BIT allergy after a long history of dermatitis, defective skin barrier, combined with exposure to other irritants and constant use of occlusive gloves.

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Germany	IVDK, Institute at the University Medical Center Göttingen	Academic institution	30
Comment received				
From our data, we can conclude that painters and metalworkers handling metalworking fluids have a significantly increased risk of BIT sensitization. Other exposures or occupations were not associated with an increased risk of sensitization to BIT. There is no immunological cross-reactivity between BIT and other isothiazolinones. Occasionally observed concomitant sensitizations to BIT and Methylisothiazolinone may be due to co-exposure. ECHA note – An attachment was submitted with the comment above. Refer to public attachment IVDK Comment on sensitization to BIT.zip				
Dossier Submitter's Response				
Thank you so much for your large and comprehensive analysis. It seems that it can be concluded that there is no cross-reactivity between BIT and the other isothiazolinones and that the sensitized people are mainly workers handling high concentrations of the substance (which would support the classification as Skin Sens. 1B).				
RAC's response				
Thank you for the surveillance data and evaluation, it has been taken into account in the RAC opinion for BIT.				

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Germany		MemberState	31
Comment received				
In summary, skin sensitization Cat. 1A is considered more appropriate than Cat. 1 (current) or Cat. 1B (DS proposal). Clinical data as recently published by Madsen and Andersen (2016) indicate frequencies of occurrence ≥ 2 % in patients from dermatology offices/department of dermatology a result of high frequency (Tab.3.2 CLP Guidance). Human data on incidences in HRIPT and patch tests provided in the CLH-Report in Tab.12 support classification with Skin Sens. 1A (for further details see below). Classification of BIT for the endpoint skin sensitisation should be based on the large amount of human data as described in the Guidance on Application of CLP criteria. Animal experiments should only be regarded as first choice when reliable human data is not available. For isothiazolinones, numerous clinical studies on patch-test results are				

available from the public literature.
Additionally, the Scientific Committee on Consumer Safety SCCS Opinion on Benzisothiazolinone COLIPA n° P96 (European Commission, 2012, Conclusion p. 28) states: "Benzisothiazolinone is known to be a sensitiser in man and has induced sensitisation at circa 20 ppm in gloves. There is no information on what may be safe levels of exposure to benzisothiazolinone in cosmetic products from the point of view of sensitisation. Until safe levels of exposure have been established, the use of benzisothiazolinone in cosmetic products as a preservative or for other functions cannot be considered safe in relation to sensitisation. "

In the following passage we provide a more detailed reasoning for our proposal:

Animal data
For the endpoint skin sensitization, a total of 11 different animal studies are available (6x LLNA, 5x GPMT) of which two LLNAs are listed as key studies according to DoC IIA of the active substance evaluation documents as prepared by ES with assigned reliabilities of 1 or 2. In principle, the animal data confirm the already well-known sensitizing effect for the substance class of isothiazolinones also for BIT. In more detail, 9 (according toES: 8) of the 11 studies show that BIT causes skin sensitization.

Please see Table 1 in the attached document.
LLNA
Five of the LLNAs (Anonymous, 2007; Gerberick et al., 2005; Basketter et al., 1999; Anonymous, 1991; Botham et al., 1991) indicate a classification as Skin Sens. 1B, while one (Anonymous, 2007) indicates a classification as Skin Sens. 1A. The two GLP-compliant LLNAs, rated with a reliability of 1 and 2, respectively, indicate classification as Skin Sens. 1A (EC3 = 1.54%) (Anonymous, 2007) or Skin Sens. 1B (EC3 = 25.8%) (Anonymous, 2007) once each. The study by Anonymous (2007, IIIA6.1.5/01), which determined an EC3 of 1.54%, is GLP-compliant, but was not conducted in complete accordance with the guideline (no use of a positive control, four times induced instead of three times as stated in OECD 429). Moreover, no dose-effect-relation of the EC3 was observed. Thus, we would leave it out of the further assessment.

GPMT
Of the three GPMTs performed according to OECD 406 (Reliability: 1-2, as stated in the Doc. II-A file), two (Anonymous, 2002; Anonymous, 1994) indicate a classification as Skin Sens. 1B, while one (Anonymous, 2003) indicates no classification for skin sensitization. In addition, another GPMT (Anonymous, 1990) performed according to US EPA Guideline 81-6 indicates a classification as Skin Sens. 1A. However, in this study an unusually high challenge concentration that was higher than the induction concentrations was used. Another non-guideline compliant GPMT (Anonymous, 1984) indicates no classification for skin sensitization. In summary, the majority of animal studies performed support a classification of BIT as Skin Sens. 1B (H317).

Human data

Regarding possible sensitizing effects of BIT, 19 different studies with human data are available. Evaluation of these studies according to the criteria of the CLP Guidance (Table 3.2) reveals a skin sensitizing effect with "relatively high frequency" in 16 studies and a "relatively low/moderate frequency" in 3 studies.

Please see Table 2 in the attached document.

The three studies that indicate a "relatively low/moderate frequency" of the effect are studies with unselected dermatitis patients (i.e. studies that are often particularly well standardized according to CLP Guidance chapter 3.4.2.2.3.1) and have large cohort sizes (404-2264 patients), so that a high relevance may be assumed.
However, other studies with a large number of subjects (Aalto-Korte et al., Damstra et al., Ledieu et al.) indicate a "relatively high frequency" of the sensitizing effect of BIT.
Also, a study of Geier et al. (2015), that is not mentioned in the CLP report so far, with a cohort size of 8728 dermatitis patients and a positive rate of 1.8% indicates a "relatively high frequency". Another indication for a "high frequency" is the number of 191 published cases, which considerably exceeds the criterion for a "high frequency" according to table 3.2 of the CLP Guidance (> 100). Summing up, the overall picture of the available human data on BIT points to a skin sensitizing effect with "high frequency".

Isothiazolinones are usually used in very low concentrations and likewise sensitization by BIT has already been described for very low concentrations (Aalto-Korte et al., 2007: ≤ 0.002 % BIT; Alomar et al., 1984: 0.03 – 0.1 % BIT; Roberts et al., 1981: 0.16 % BIT; Freeman et al., 1984: probably 0.19 % BIT), so that the criterion of "relative low exposure" for the parameter "concentration/dose" of table 3.3 of the CLP Guidance is fulfilled. This conclusion is independent of whether one assumes low or high exposure for the parameters "Repeated exposure" and "number of exposures".
According to table 3.4 of the CLP guidance, the combination of "high frequency" and "low exposure" leads to classification in subcategory 1A.
Even if we would assume a "relatively high exposure" due to the ubiquitous use of isothiazolinones and the postulated cross-reactivity to other isothiazolinones (for cross-reactivity refer to the paragraph "SCL" below), no classification for subcategory 1B can be made based on human data due to the "relatively high frequency" determined. In that case the CLP Guidance specifies that classification in category 1 should be applied instead of category 1B if category 1A cannot be excluded (CLP Guidance 3.4.2.2.2 and table 3.4).

Even though the data from animal studies clearly suggest a classification of BIT in subcategory 1 B, we request Spain to discuss the human data on skin sensitization by BIT in more detail as the CLP regulation states that "in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to decide on the classification on a case-by-case basis" (see subsection 3.4.2.2.3.7.).
In that context, we do not share the view of ES that the human data indicate a "relatively high frequency" and "relatively low incidence", as explained and discussed above.

SCL

The available animal studies indicate a "moderate" skin sensitizing potency for BIT, which may result in the assignment of a GCL of 1 % (cf. CLP, tables 3.6-3.9).
However, if there is reliable information that the specific hazard is evident below the GCL, a lower SCL can be assigned.
Such information for BIT is, on the one hand, the reports on sensitizing effects even at very low concentrations (e.g. Aalto-Korte et al., 2007) that could lead to a classification with Skin Sens. 1A, and, on the other hand, the assumption of cross-reactivity to other isothiazolinones (Schwensen et al. 2016, Geier et al. 2015).
The concern of cross-reactivity has already been used in the past by RAC to justify SCLs

for other isothiazolinones (RAC opinions on MIT, 2016, MBIT and OIT, 2018). Therefore, we agree on a SCL but before defining the relevant value the concern of cross-reactivity should be evaluated by the DS ES here in the CLH report.

References:
Madsen, J., Andersen, K Contact allergy to 1,2-benzisothiazolin-3-one. Contact Dermatitis. 2016; 75(5): 324-6.
Geier J, Lessmann H, Schnuch A, Uter W. Concomitant reactivity to methylisothiazolinone, benzisothiazolinone, and octylisothiazolinone. International Network of Departments of Dermatology data, 2009-2013. Contact Dermatitis. 2015; 72(5):337-9.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DE_CA comment_BIT BfC.pdf

Dossier Submitter's Response

Thank you so much for your comment. We do not agree that there is reliable information in humans. The most current information only allows us to quantify the number of people sensitized to BIT, but not the conditions under which this sensitization took place. This, in addition to affecting the proposed SCL, also affects the proposed subcategorization as Skin Sens. 1B, since the table you have prepared shows frequency but not exposure, which is impossible to elucidate with human data but essential for classification according to the Guidance on the application of the CLP critera (Tables 3.2 to .4 - Relatively high frequency of occurrence of skin sensitisation with relatively high exposure lead to Category 1 or case by case evaluation). To summarize, the most current information does not clearly elucidate that BIT is as potent as the other isothiazolinones, giving greater relevance to animal studies, and there is also no compelling evidence to support an SCL below 500 ppm.

Regarding the animal data, in summary, there are: one GPMT that does not classify BIT as a skin sensitizer, one LLNA that classify it as Skin Sens. 1A and five LLNAs and four GPMTs that classify it as Skin Sens. 1B. However, the LLNA resulting in Skin Sens. 1A has the following drawback: the study was conducted in 1991 prior to the adoption of OECD TG 429, it is a non GLP study consisting of data collected for the purpose of method development.
In one HRIPT (Basketter *et al*., 1999) no reactions to BIT occurred at 360 ppm, while 9 % of volunteers reacted at 725 ppm. According to the Guidance on the Application of the CLP criteria HRIPT is not a clinical study and is only of historical relevance. Nevertheless, the HRIPT results indicate that the SCL can be set above 360 ppm and below 725 ppm. There is also a possibility of false positives as irritation effects have been observed above 500 ppm.
The diagnostic patch tests (Andersen and Hamann, 1984; Andersen and Veien, 1985; Ledieu, 1991; Damstra, 1992; Aalto-Korte, 2006 & 2007) show results on patients with dermatitis and could indicate the elicitation threshold for BIT. The results cannot be used for finding the induction threshold relevant for assigning an SCL. It may be worth noting that the BIT concentrations used in the diagnostic patch testing where relatively high considering the concentrations used in the HRIPT by Basketter *et al*., 1999.
The study investigated contact allergy to plastic gloves (Aalto-Korte *et al*., 2006), which is found as a rare phenomenon. The authors suspect delayed-type contact allergy to BIT from PVC gloves. To find relevant cases, they looked through their medical records from 1991 to 2005. The study identified a total of 8 patients who are allergic to BIT and who had

experienced exacerbations of their hand dermatitis while using PVC gloves. Patch testing showed that 3 of them had weak allergic or doubtful reactions to the material of the glove. Six of them had used products, which in chemical analysis were shown to contain 9 to 31 ppm of BIT. All patients had displayed hand dermatitis for years and as BIT is an irritant the authors state that the possibility of false-positive reactions to BIT cannot be excluded in the present series of patients. The authors conclude that to their knowledge, there have been no previous reports of contact allergy to antimicrobial agents in plastic gloves. They also conclude that small amounts of BIT in the gloves may sensitize those who already have hand dermatitis. However, these findings in those "who already have hand dermatitis" only are likely to be due to elicitation or irritant effects. Furthermore, from January 1991 to September 2005, BIT was tested on a total of 2264 patients, and 17 (0.75%) of them had an allergic reaction to it. This means a low frequency and incidence and would support the classification as Skin Sens. 1B.

In another study by Aalto-Korte *et al*. (2007), BIT was patch tested at 0.05% in petrolatum in 5450 patients and glove material was tested 'as is' with acetone at HUCH. The concentrations of BIT in disposable PVC gloves were analyzed. The study also reported data on 3 previously unpublished BIT allergic patients from the FIOH. 16 patients (0.003%) were positive to BIT. BIT containing gloves were labelled from low-BIT (2–5 ppm) to high-BIT (≥ 20 ppm). The patch test results to the glove material: 3 positive; 4 doubtful; 4 negative patient reactions (out of 11 patients with BIT allergy and PVC glove use). As reported in the study, BIT positive patients were either dental or health care workers who use protective gloves most of their working day and might be exposed to other factors that irritate the skin such as frequent hand washing and the use of disinfectants.

Both diagnostic patch studies indicate low incidence of positivity to BIT (0.88% and 0.29% in Aalto-Korte *et al*., 2006 and 2007 respectively). If both studies are taken together, the overall incidence is 0.47%, which also is considered low. Further, in the 2006 study, a negative reaction index for the test preparation, 0.05% (petrolatum), was reported which characterizes doubtful and/or questionable patch reactions. Patch testing with glove material indicated low positive incidence (2 of 8 and 3 of 11 patients who were positive to BIT and had used PVC gloves in Aalto-Korte *et al*., 2006 and 2007 respectively). Most of the patients have had a relatively long history of hand dermatitis/defective skin barrier because of irritation or pre-existing eczema and the occlusive effect of the gloves probably enhanced percutaneous penetration of BIT so they had become sensitized despite the low allergen concentration. Hence, considering the above factors (constant use of occlusive gloves, exposure to other irritants, long history of dermatitis and a defective skin barrier), the authors did not consider sensitization to BIT in gloves as the primary event. Based on low positive findings to the glove material limited to dental and healthcare workers with previous skin conditions, the study is not considered scientifically robust to be used for establishing a BIT elicitation threshold.

It should be noted that clinical monitoring data and case reports are not suitable for setting substance specific SCLs since it is not possible to accurately quantify the exposure of any individual which subsequently lead to the acquisition of allergic contact dermatitis.

For these reasons, we consider that the human data should be interpreted with caution giving greater relevance to the animal data and that both cases support the classification as Skin Sens. 1B with a SCL of 500 ppm.

RAC's response

RAC agrees that although the animal data indicate classification as Skin Sens. 1B, the human studies indicate Skin Sens. 1A. On the basis of the HRIPT studies, BIT warrants

classification as Skin Sens. 1A (positive responses at ≤ 500 µg/cm^2 (HRIPT – induction threshold)). RAC agrees with the MSCA that the combination of "high frequency" and "low exposure" can be expected for BIT from the data, which leads to classification in subcategory 1A.
There are however several points on which RAC doesn't agree with how the MSCA arrived at allocating "high frequency":

- "Table 3.2 Relatively high or low frequency of occurrence of skin sensitisation" refers to Human diagnostic patch test data, and it is not appropriate to use HRIPT studies in this context as "general population" studies.
- In the HRIPT study of Anonymous (1991), 0/111 subjects were sensitized instead of 2/111.
- In the Ledieu *et al*. (1991) study, 1/977 patients (0.1 %) cross-reacted to 0.05 % BIT, 35 patients (3.6 %) were positive to Kathon CG (CMIT/MIT).
- Frequency of sensitization has to be distinguished between unselected, consecutive patients, and selected dermatitis patients; the frequency leading to high or low/moderate frequency is different for these two populations.

The RAC reasoning is the following:

The frequency of sensitization in diagnostic patch tests on unselected, consecutive patients is 0.3 % (Aalto-Korte *et al.,* 2007), 0.9 % (Andersen and Veien, 1985), 0.25 % and 0.22 % (Andersen and Hamann, 1984), all pointing to low/moderate frequency of skin sensitization (frequency < 1 %).
The frequency of sensitization in selected dermatitis patients is 1.8 % (Damstra *et al.*, 1992), 0.88 % (Aalto-Korte *et al*., 2006), 0.1 % (Ledieu *et al*., 1991) and 1.6 % (Geier *et al.*, 2015). These four studies point to low/moderate frequency of skin sensitization (frequency < 2 %). However, there are two additional studies with higher percentages of frequency of sensitization: the retrospective study by IVDK spanning 20 years in which 2.5 % of the dermatitis patients were found to be sensitized to BIT, and the Madsen study, in which the sensitization rate was 4.7 %. These studies point to relatively high frequency of occurrence of skin sensitisation (≥ 2.0 %). The largest study, with nearly 30000 patients in 3 countries (Germany, Switzerland, and Austria), shows that in recent years sensitization in selected patients has risen to 4.4 %. Therefore, RAC considers that a relatively high frequency of sensitization can be expected for BIT.

There is little information on concentrations inducing sensitization in the workplace/case studies, but 3 of them have concrete values. In the Alomar (1981) publication, 0.03-0.1 % (300-1000 ppm) is used in cutting oils. In the Freeman (1984) publication, a lithoprinter, working without gloves, was sensitized by handling gum arabic containing 0.13 % (1300 ppm) BIT. In the Roberts *et al.* (1981) publication, a mouldmaker was exposed to an oil based emulsion containing 0.16 % (1600 ppm) BIT. This information indicates relatively low exposure to BIT (concentrations < 1.0 %).

RAC therefore concludes that BIT warrants classification as **Skin Sens 1A, H317**: May cause an allergic skin reaction.

SCL setting: none of the studies on concomitant reactions suggest cross-sensitization between BIT and other isothiazolinones; concomitant exposure remains the probable explanation for simultaneous reactions, therefore cross-reactivity to other isothiazolinones does not have to be taken into consideration when setting an SCL for BIT.

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2021	Germany	<confidential>	Company-Downstream user	32
Comment received				
We fully agree with the dossier submitter´s proposal to keep the SCL of 500 ppm for skin sensitization. Based on the available toxicological data BIT has significant lower skin sensitization potential than other isothiazolinones. This must be taken into account when fixing the SCL for BIT. However, we are afraid that a SCL of 15 ppm could be assigned to BIT as it has been the case for Methylisothiazolinone (MIT) and Octylisothiazolinone (OIT), and others. Thus we ask for fixing the SCL for skin sensitization of BIT based on the results of validated studies with standardized exposure. Human case studies (e.g. diagnostic patch tests on patients with dermatitis) may give an indication for the elicitation threshold of BIT, but do not allow for determination of the threshold concentration for the induction of skin sensitization. We fully support the dossier submitter´s conclusion on that issue and to keep the SCL at 500 ppm. As typical concentrations of BIT in water based products are 100-300 ppm, a SCL of 15 ppm would lead to a classification of BIT-preserved paints and coatings as skin sensitizers/H317. This would affect the marketability of these products especially in the consumer sector. A SCL of 15 ppm may even end up in a "active substance approval" for BIT where use in concentration above this SCL is prohibited for consumer products. Furthermore, skin sensitizers may qualify as "substances of concern" under the "Chemicals Strategy for Sustainability". Assignment of the SCL 15 ppm for skin sensitization for BIT would thus not only disregard scientific evidence, but also create unjustified severe impacts on the market of water based paints and coatings.				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
06.05.2021	France		MemberState	33
Comment received				
Page 32: in the section "short summary and overall relevance of the provided information on skin sensitisation", BIT is proposed to be classified Skin sens. 1B with a SCL maintained to 0.05% (= 500 ppm) based on the results of animal and human data. If the proposal of category 1B can be accepted, the SCL has to be revised since the potential of cross-reactivity of BIT with other isothiazolinone has not been addressed in the document. As the chemical structure of BIT is closely related to other isothiazolinone, especially MBIT, the cross reactivity has to be considered in the SCL setting.				
Dossier Submitter's Response				
Several publications point out that the cross-reactivity between BIT and the other isothiazolinones is not so clear. In the studies that seem to demonstrate its existence, it seems to depend on the sensitization dose. Of course, there are also studies that reject cross-reactivity between BIT and the others. The IVDK assessed concomitant reactions to BIT, MIT, and OIT. Less than 10 % of MIT-sensitised patients also reacted to BIT. This could be attributed to co-exposure rather than immunological cross-reactivity (Geier *et al*., 2015). In another patch test series performed				

at the IVDK only 2 patients reacted simultaneously to C(M)IT/MIT and BIT and 1 patient reacted to BIT and OIT, but not to C(M)IT/MIT (Geier *et al*., 1996). In general, the report submitted by the IVDK for this public consultation states that according to their data: "there is no relevant immunological cross-reactivity between BIT and other isothiazolinones" and co-reactivity to BIT and other isothiazolinones would be probably due to co-exposure.
Craig *et al*., 2017 conducted a patch test series with C(M)IT/MIT, MIT, OIT, and BIT. Only 1 patient each reacted simultaneously to C(M)IT/MIT and BIT; C(M)IT/MIT, MIT and BIT; MIT, OIT and BIT or OIT and BIT, showing that positive reactions to BIT tended to occur in isolation.
In the FIOH, of 647 patients who were patch tested during the period 2012–2017, only two had reactions to both OIT and MIT. The authors concluded, "Allergic reactions to OIT were strongly associated with extreme reactions to MIT, which suggests cross-sensitization. In contrast, BIT reactions were mostly independent" (Aalto-Korte & Suuronen, 2017). The FIOH had earlier reported that of 2264 patients tested during the period 1991–2005 with BIT 20 (0.88%) gave a positive reaction. 4 of these 20 patients reacted to C(M)IT/MIT and 2 to OIT. BIT was not considered to cross react with C(M)IT/MIT or OIT and as per study authors, concomitant reactions to these isothiazolinones supported separate sensitization (Aalto-Korte *et al*., 2006). In another study (Aalto-Korte *et al*., 2007), BIT was patch tested in 5450 patients at the HUCH. None of the BIT allergic patients had patch test reactions to C(M)IT/MIT or to OIT.
A non-systematic patch testing of C(M)IT/MIT-positive Belgian patients during 2010–2012 revealed that 4 reacted to BIT and 8 reacted to both BIT and OIT. Direct exposure to BIT could be determined for only 7 of the 12 BIT-positive patients (Aerts *et al*., 2014).
Ashby *et al*., 1995 evaluated different chemicals in the LLNA. They identified that the heterocyclic sulphur in BIT might form disulphide bonds with thiol sulphurs in proteins. C(M)IT, however, was identified as an electrophilic aromatic alkylating agent. The chemical reactivity of C(M)IT would not apply to BIT.
Furthermore, products with a concentration of BIT greater than 0.005% may be labeled with EUH208. With this element the uncertain possibility that cross-reactivity is real is covered in view of the ambiguous results.

RAC's response

SCL setting: none of the studies on concomitant reactions suggest cross-sensitization between BIT and other isothiazolinones; concomitant exposure remains the probable explanation for simultaneous reactions, therefore cross-reactivity to other isothiazolinones does not have to be taken into consideration when setting an SCL for BIT.

Date	Country	Organisation	Type of Organisation	Comment number
04.05.2021	Germany	Mocopinus GmbH & Co.KG	Company-Downstream user	34

Comment received

1

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Einspruch EU zu BIT öffentlich.docx
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Einspruch EU zu BIT.docx

Dossier Submitter's Response

Thank you so much for your comment.

RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2021	Belgium	<confidential>	Company-Downstream user	35
Comment received				
Given the lower potency of BIT as skin sensitizer compared to CMIT/MIT, it's reasonable to maintain the SCL of 500ppm. Cf. also data provided by EuPIA (Didier Leroy and Johnny Kvernstulen). Allergic reactions are reversible.				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
03.05.2021	Germany	Remmers GmbH	Company-Downstream user	36
Comment received				
To our impression, the available data for BIT do clearly show that this substance is a rather moderate sensitizer especially when compared to other isothiazolinones that have already been harmonized classified (e. g. CIT/MIT, MIT, MBIT). We firmly believe that different sensitization potential of different substances should also be dealt with differently. We regard the proposal of the dossier submitter to be fully sufficient in order to protect future users of coatings protected by BIT as in-can-preservative from being sensitized. We request ECHA's experts to substantiate their assessment on the results of validated studies only and not on non-standardized human case studies or politically driven motives. We have used BIT now for more than 20 years in our products and have never acquired knowledge of any cases where users of our products showed allergic reactions due to the presence of BIT in one of our products used. From this perspective, attmidetly anecdotic, we cannot recognize any concrete need for a SCL for BIT on the same low level as for example CMIT/MIT.				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Task Force	Company-Manufacturer	37
Comment received				
CLH Report page 32				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT CLH-report commenting table_BIT Task Force_Redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BIT CLH-report commenting table_BIT Task Force.pdf
Dossier Submitter's Response
Thank you so much for your support.
RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	Belgium	CEPE	Industry or trade association	38
Comment received				
Please find attached our input. We call for a careful examination of data leading to induction of skin sensitization from which a sound SCL can be set. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CEPE position on BIT public consultation final 20210514_Redacted.pdf				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC agrees that the animal studies indicate that BIT is a moderate sensitizer. RAC also agrees that an SCL for BIT cannot be derived from the studies of dermal patients who developed BIT allergy after a long history of dermatitis, defective skin barrier, combined with exposure to other irritants and constant use of occlusive gloves.				

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Common Interest Group (BIT CIG) consists of the 6 participants Nutrition & Biosciences (Switzerland) GmbH, Laboratorios Miret, S.A., Lanxess Deutschland GmbH, Lonza Ltd, Thor GmbH and Troy Chemical Company BV.	Company-Manufacturer	39
Comment received				
Section 1, Pages 2-18 ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT Common Interest Group_CLHComments_Final_v2r.pdf				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL STUDIES.zip
Dossier Submitter's Response
Thank you so much for your support.
RAC's response
RAC has taken note of your comments. RAC agrees that the animal studies indicate that BIT is a moderate sensitizer. RAC also agrees that an SCL for BIT cannot be derived from the studies of dermal patients who developed BIT allergy after a long history of dermatitis, defective skin barrier, combined with exposure to other irritants and constant use of occlusive gloves. Thank you for the thorough analysis of the cross-reactivity publications.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	Netherlands	Sherwin Williams	Company-Downstream user	40
Comment received				
Sherwin Williams is in agreeement with the proposed classification of Skin Sensitisation 1B with a specific concentration limit of 500 ppm ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT CP_final.pdf				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments. RAC agrees that the animal studies indicate that BIT is a moderate sensitizer. RAC also agrees that an SCL for BIT cannot be derived from the studies of dermal patients who developed BIT allergy after a long history of dermatitis, defective skin barrier, combined with exposure to other irritants and constant use of occlusive gloves.				

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Switzerland	Dow Europe GmbH	Company-Downstream user	41
Comment received				
Dow agrees with the dossier submitters proposal to classify BIT as a Skin Sensitizer Cat. 1B and to maintain the Specific Concentration limit at 0.05% (which triggers the resulting elicitation labelling EUH208 phrase at 0.005% and above). Choice of appropriate sub-category Across animal models and in human volunteer testing, BIT shows a significantly reduced dermal sensitization potency compared to other isothazolinones. In the dossier the results of the animal models, both LLNA and GPMT, indicate that subcategorization as category 1B is most appropriate when comparing these results to the cut off values given in Tables 3.4.3 and 3.4.4 of the guidance to the CLP criteria. The agreement of these two very different models of dermal sensitization gives further confidence in the result. In addition to the animal data, the human data presented supports that BIT is of low potency when evaluating the dermal sensitization hazard compared to other isothiazolinones. Despite the widespread use of BIT in many industrial and consumer				

products, the relative frequency of acquisition of allergic contact dermatitis remains low.
According to Annex I 3.4.2.2.2.2 human evidence for sub-category 1B can include:
(a) positive responses at > 500 µg/cm2 (HRIPT, HMT – induction threshold);
(b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;
(c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.
The information provided by the dossier submitter, combined with the relatively few reports of allergic contact dermatitis in the open literature, would indicate that points b and c in the above criteria would apply in the case of BIT.
Setting of specific concentration limits (SCL) for BIT
Whilst diagnostic patch testing data may be suitable for assigning an appropriate subcategory for classification and labelling it should not be used for assigning specific concentration limits to a substance. This is because almost exclusively, persons presenting at dermatology clinics would have been exposed to formulations containing the allergen of interest, rather than to the pure substance itself. In addition, the concentration and frequency of exposure leading to induction of the individual will affect the elicitation threshold and potentially the subsequent strength of response (+, ++, +++), during diagnostic patch testing.
However, since BIT has a mandatory SCL of 0.05%, the clinical data can indicate the protectiveness of that already existing limit. Given the limited reports of dermal sensitization in the open literature and lack of significant prevalence in the clinical/general population, the clinical evidence is therefore supportive that the current SCL is protective for the vast majority of the population who are exposed to BIT. Allied to this, the elicitation labelling limit of 0.005% allows workers and consumers to be warned if a product contains BIT and thus avoid use of such products.
Protection of persons already sensitized to isothiazolinones
With chemically similar structures there is concern that individuals sensitized to one member of the group may cross-react upon subsequent exposure to BIT. In 2016, Schwenson et al published a paper investigating cross-reactivity of MIT, OIT and BIT in a modified LLNA. The paper has significant deficiencies such as the use of a non-standard protocol and application of irritating concentrations of test items which is known to generate false positives in the LLNA.
Despite this, a number of publications exist in the open literature indicating that in clinical populations there is no significant evidence for cross-reactivity between persons sensitized to other isothiazolinones and subsequently reacting on exposure to BIT or vice versa. This indicates that setting a more restrictive labelling limit is not necessary to protect individuals already diagnosed as allergic to other isothiazolinones.

References
Schwensen et. al. (2016) Cross-reactivity between methylisothiazolinone, octylisothiazolinone and benzisothiazolinone using a modified local lymph node assay. British Journal of Dermatology, 176 (1), pp.176-183
Geier et. al (2015) Concomitant reactivity to methylisothiazolinone, benzisothiazolinone, and octylisothiazolinone. International Network of Departments of Dermatology data, 2009–2013. Contact Dermatitis 72, (5), pp.337-339
Russo J.P, & Aerts O. (2020) In vivo demonstration of immunologic cross-reactivity to octylisothiazolinone in patients primarily and strongly sensitized to methylisothiazolinone Contact Dermatitis Nov;83(5) pp.391-397
Aalto-Korte K. & Suuronen K. (2017) Patterns of concomitant allergic reactions in patients suggest cross-sensitization between octylisothiazolinone and methylisothiazolinone.

Contact Dermatitis. 2017 Dec;77(6) pp. 385-389
Reeder M. & Reck Atwater A (2019) Methylisothiazolinone and isothiazolinone allergy. Cutis Aug;104(2) pp. 94-96

Dossier Submitter's Response

Thank you so much for your support.

RAC's response

RAC has taken note of your comments. The RAC evaluation of the human data lead to a proposal of sub-category 1A, because 2 points are fulfilled:

(a) In HRIPT tests, sensitization occurred at induction doses below 500 µg/cm^2, namely at 64.45 µg/cm^2 (Davies *et al*., 1975) and 90.6 µg/cm^2 (Basketter *et al*., 1999).

(b) Diagnostic patch test data indicated that there is a relatively high and substantial incidence of reactions (4.4 % in selected dermatitis patients), in relation to relatively low exposure (concentrations < 1.0 %).

SCL setting: RAC agrees that none of the studies on concomitant reactions suggest cross-sensitization between BIT and other isothiazolinones; therefore cross-reactivity to other isothiazolinones does not have to be taken into consideration when setting an SCL for BIT.

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Belgium	A.I.S.E.	Industry or trade association	42

Comment received

AISE provides comments through three detailed datasets.
The first dataset, presented in Annex I, covers human skin sensitization data on BIT. AISE summarized the available human data from the CLH report in combination with newly located data (not yet public) from AISE member companies. The latter are historical HRIPTs (Human Repeat Insult Patch Tests), covering nearly 1000 panellists, performed using AISE member consumer products containing BIT, to confirm the absence of skin sensitization effects. All studies support the low risk of using BIT under consumer relevant conditions and further substantiate the current and proposed SCL of 500 ppm for BIT.
The second dataset, presented in Annex II, analyses human and animal data to evaluate the potential risk of BIT cross reactivity (e.g., elicitation in MIT-sensitized individual following exposure to BIT). Human patch testing data of MIT- and BIT-sensitised patients were reviewed and indicate that the fraction of patients that reacts to both isothiazolinones is very small and driven mostly by individuals pre-sensitized to both substances, and not from cross-reactivity. In addition, AISE reviewed a published study in mice conducted to determine whether BIT can elicit an allergenic response following sensitisation with MIT (Schwensen et al, 2016). We identified numerous methodological and reporting deficiencies that obfuscate the intended goal and call into question the author's conclusion of cross-reactivity between these two substances. Overall, it is appropriate to consider that reactions to BIT are independent to those of other isothiazolinones.
The third dataset, presented in Annex III, is a review of two publications (incl. one referenced in the CLH report) from the same research group on the presence of BIT in disposable gloves in the context of skin sensitization. AISE's perspective is that the statement, that some patients may have been sensitized by wearing gloves with BIT, is not scientifically supported. Additionally, based on the very low positive findings to the

glove material and the fact that panellists had compromised skin, the study is not considered scientifically robust to establish a BIT elicitation threshold. Overall, we conclude that the results of those publications are not suitable to be used for determination of a CLP SCL (Specific Concentration Limit) for BIT, furthermore so when considering the quality and amount of BIT data from other sources. Please note that 2 attachments have been submitted (1 non-confidential and 1 confidential). ECHA note – An attachment was submitted with the comment above. Refer to public attachment AISE CLH BIT Comments.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Confidential Reports.7z
Dossier Submitter's Response
Thank you so much for your support.
RAC's response
RAC has taken note of your comments.

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Sweden		MemberState	43
Comment received				
The Swedish CA notes that the CLH report does not contain information on the composition of the test materials or test substances in the studies chosen by the DS to support the sub-categorisation. In addition, it is noted that the purity of the test material is low or unknown in several studies. Without information on the compositions of the test materials or the purity, it is not possible to evaluate the relevance of the results for the classification of 1,2-benzisothiazol-3-(2H)-one. Other constituents in the test material could affect the study results regarding potency. Unless the compositions are made available or a justification is provided on how the data is interpreted as relevant for 1,2-benzisothiazol-3-(2H)-one, we propose that 1,2-benzisothiazol-3-(2H)-one retain the harmonised classification as Skin Sens. 1; H317: C ≥ 0,05 %, as Skin Sens. 1A cannot be ruled out in our opinion.				
Dossier Submitter's Response				
The relevance of impurities must be taken into account as long as they can worsen the hazard classification. In this case, since the impurity profile is unknown, it can be assumed that in a worst case they would be increasing the sensitizing potential, so that the BIT would be lower than that observed in the studies. Following this reasoning, classification as Skin Sens. 1B would be the most appropriate.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2021	Austria	ADLER Werk Lackfabrik Johann Berghofer GmbH & Co KG	Company-Downstream user	44
Comment received				
In the case of the isothiazolinones the specific concentration limit (SCL) for skin sensitization is especially important and hence we would like to comment on this hazard class specifically. The scientific data clearly demonstrates that BIT is a moderate sensitizer. We fully support the proposal of the dossier submitter Spain to keep the current SCL of 500 ppm for skin sensitization for BIT, which is in line with the available toxicological data. The conclusions on skin sensitization must be based on results of validated studies with a standardized exposure. Human case studies, without a standardized exposure cannot be validated and can only be considered as supporting additional evidence. The potency of BIT is much lower than that of the other isothaizolinones that have already been harmonized classified (e.g. CIT/MIT, MIT, MBIT). We would like to stress that this needs to be reflected in the setting of the SCL.				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2021	Germany	<confidential>	Company-Downstream user	45
Comment received				
Several LLNAs have shown that BIT is a moderate skin sensitiser (EC3 > 2 %). We fully agree with the proposal of the dossier submitter to keep the current SCL of 500 ppm for skin sensitization for BIT, which is plausible based on the toxicological data available. The conclusions on skin sensitisation must be based on results of validated studies with a standardized exposure. The diagnostic patch testing (on patients), without a standardized exposure cannot be validated and can only be considered as supporting additional evidence. The potency of BIT is much lower than that of the other isothiazolinones with harmonized classification (e.g. CMIT/MIT (3:1), MIT). It is important to us that this must be considered when determining the SCL. Finally, we can assure that the use of BIT in our products has never led to increasing cases of sensitisations.				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

Date		Country	Organisation	Type of Organisation	Comment number
11.05.2021		Germany	Wöllner GmbH	Company-Downstream user	46
Comment received					
Scientific studies show that BIT is a moderate sensitizer. Conclusions on skin sensitization need to be made on validated exposure studies. It is shown, that the sensitizing activity if BIT is much lower than other isothiazolinones. We and our customers never had issues with sensitizing in regards to BIT. We therefore support the proposal of the dossier of the Spanish submitter to keep the existing SCL of 500 ppm.					
Dossier Submitter's Response					
Thank you so much for your support.					
RAC's response					
RAC has taken note of your comments.					

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2021	Germany	<confidential>	Company-Downstream user	47
Comment received				
Unlike other isothiazolinones (such as CMIT/MIT) BIT is a moderate skin sensitizer only. We would like to stress that the much lower potency needs to be reflected in the setting of the SCL. We therefore fully support the proposal of the dossier submitter to keep the current SCL of 500 ppm for skin sensitization for BIT, which is in line with the available toxicological data. We are not aware that BIT has ever caused any induction of skin sensitisation from its presence in our products.				
Dossier Submitter's Response				
Thank you so much for your support.				
RAC's response				
RAC has taken note of your comments.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Task Force	Company-Manufacturer	48
Comment received				
CLH Report pages 53, 54 and 56 ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT CLH-report commenting table_BIT Task Force_Redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BIT CLH-report commenting table_BIT Task Force.pdf				

Dossier Submitter's Response
- Page 53, 11.3: vapor pressure should be expressed as proposed by EBITTF, the value should be amended from 62.76 x 10^{-4} to 6.28 x 10^{-5} Pa at 20ºC. - Page 54, 11.4 (BCF study): it is recomended to include all available studies, even the ones used for additional information. In this case, as this study is additional information, it should be deleted from chapter 11.4 but included in 15.2 Anex II. - Page 56, 11.5 (Terrell study, EC50 value): both values are right, 2.44 mg/L is based on nominal concentrations and 2.24 mg/L is based on measured concentrations. - Page 56, 11.5(algae studies): the values presented in the table 21 are in line with the CAR, table 4.2.1.5-2, in doc IIA, where the recalculated values by eCA are shown. It is clearly explained in section 11.5.3 that these recalculated values were agreed by the ENV WG for biocides, and in table 22 the recalculted values can be compared with the original ones presented by the applicans.
RAC's response
Page 53, 11.3: Noted. The correct value 6.28 × 10^{-5} Pa at 20 ºC. Page 54, 11.4 (BCF study): Noted. Page 56, 11.5 (Terrell study, EC_{50} value): Noted. Page 56, 11.5 (algae studies): Noted. The RAC uses recalculated values.

Date	Country	Organisation	Type of Organisation	Comment number
06.05.2021	France		MemberState	49
Comment received				
FR supports the proposal to classify the substance 1,2-benzisothiazol-3(2H)-one; 1,2-benzisothiazolin-3-one (BIT) (n° CAS: 2634-33-5) Aquatic Acute 1, H400, M-factor=1, Aquatic Chronic 1, H410, M-factor=1. FR has the following comments on the classification proposed for environmental hazards: p. 40 11.1.4.2 Inherent and enhanced ready biodegradability tests (Jenkins 1999 & conclusion): to complete your argumentation, you could stress the importance of the time frame to be considered rapidly degradable (it is unlikely that the substance is demonstrated to be primarily or ultimately degraded biotically or abiotically in the aquatic environment by > 70 % in 28 days). p.40 11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies): "Degradation rates at 12°C …" should be change for "Half-life at 12°C were 22.9 and 29.8 hours, respectively". p.51-52 11.1.4.4 Photochemical degradation: Could you please check and correct the summary for Gilbert (2000). The information we retrieved from ECHA disseminated website states: "A study was conducted to determine the photodegradation of the substance in water as part of a two-phase study, the second phase of which was OECD 301D biodegradation study. In aqueous solution the substance was readily photolysed by the action of natural sunlight. The calculated half-life was 4 h. Therefore it is unlikely that the substance will be persistent in the aquatic environment. A minimum of three metabolites were formed all of which eluted before the substance suggesting that they were more polar (Gilbert, 2000)". From what we understand, there might have been confusion with the study from Adam and Mégel (2009).				

Page 69: In the section "Bioaccumulation potential", it is stated that the log Kow is 0.6. The correct value is 0.64, could you please correct?
Dossier Submitter's Response
Thank you for your support. Regarding the comments: - p. 40 11.1.4.2: Thank you for your comment, the justificaction should be complemented by your proposal. - p.40 11.1.4.3: Thank you for your comment, this should be amended. - p.51-52 11.1.4.4 Photochemical degradation. Thank you for your comment. The text describing Gilbert study should be changed to the one included in ECHA website, and proposed here by FR. - Page 69: In the section "Bioaccumulation potential", the logKow estimated will be amended to 0.64. Thank you for your comment.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Common Interest Group (BIT CIG) consists of the 6 participants Nutrition & Biosciences (Switzerland) GmbH, Laboratorios Miret, S.A., Lanxess Deutschland GmbH, Lonza Ltd, Thor GmbH and Troy Chemical Company BV.	Company-Manufacturer	50
Comment received				
Section 2, Page 19 ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT Common Interest Group_CLHComments_Final_v2r.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL STUDIES.zip				
Dossier Submitter's Response				
Thank you for your comment and support. Regarding the "Additional experimental data on the ecotoxicity of the BIT metabolites mentioned in Annex I of the CLH report (15.1) are not available among the BIT CIG", it has been stated in the Annex that they are not experimental data, but QSAR modelling data.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2021	Netherlands		MemberState	51
Comment received				
Specific comments P.59 Conclusion on acute toxicity to fish The report describes that the geometric mean of 1.5 mg/L is used for the acute fish effect value as five reliable 96-h LC50 values for O. mykiss are available. However, when taking the geometric mean of the individual values (1.9, 2.18, 1.23, 1.49 and 0.74 mg/L), a geometric mean of 1.4 mg/L should be reported. Also, the geometric mean of the D. magna results is slightly different, when recalculated. The CLH reports describes a geometric mean of 3.27 but when recalculating the geometric mean based on the individual values (3.7, 2.9, 4.0 and 2.24 mg/L), the result is 3.13 mg/L. These are only minor comments as these alternative values do not change the proposed classification for acute aquatic toxicity.				
Dossier Submitter's Response				
Thank you for your comment, the value 1.5 mg/L corresponds to an arithmetric mean, but the geomean should read 1.41 mg/L. The same occurs with invertebrates, considering the values 3.7, 2.94, 4.0 and 2.44 mg/L (all based in nominal concentrations), the arithmetric mean is 3.27, and the geomean should read 3.21 mg/L.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	Health and Safety Executive	National Authority	52
Comment received				
We note that 1,2-benisothiazolin-3-one belongs to the isothiazolone class of biocides which have an MoA at the enzyme level that leads to rapid uptake by algae and degradation, in turn causing loss of the substance in algal toxicity test systems. On the basis of the rapid MoA and loss of the test item, we agree that 24-hour algal endpoints based on initial measured or nominal concentrations are suitable for acute hazard classification where these are the most sensitive. To support this approach, it would be useful for the DS clarify whether the OECD TG 201 validity criteria of control specific growth rate ≥0.92 day-1 was met for each of the Pseudokirchneriella subcapitata 24-hour acute endpoints? We are unclear if endpoints using PROXEL formulation are suitable for hazard classification. Please can the DS consider the impact of formulation ingredients and if the endpoints are reliable for hazard classification. If the Smyth et al., (1994) endpoint using PROXEL is considered reliable for hazard classification, we agree with the use of the geomean of the four Pseudokirchneriella subcapitata 24-hour ErC50 values for acute classification. For the aquatic chronic classification, we consider that 24 hours is not a suitable duration to assess long-term effects and we would prefer the use of 72 hour endpoints in line with				

standardised hazard classifications. We think that these 72 hour endpoints should be expressed as initial measured or nominal concentrations given that the test item is taken up by algae so is not available after the initial toxic effect.

We consider that the Pseudokirchneriella subcapitata 72 hour endpoint from the study by Katshuri Raman (2002) is not reliable for aquatic chronic classification because the OECD TG 201 validity criteria for control growth were not met over the 72 hour chronic time period. As there are only three other Pseudokirchneriella subcapitata studies for BIT, it would not be applicable to calculate the geometric mean and instead the lowest 72-hour ErC10 should drive the chronic classification.

The lowest chronic endpoint is the Pseudokirchneriella subcapitata 72-hour ErC10 of 0.057 mg/L based on initial measured concentrations (Smyth et al., 1994). Noting our above comment about the PROXEL test item, if the study is considered reliable for hazard classification, please could the DS clarify if the OECD TG 201 validity criteria for the control growth over the 72 hour test period were met? This endpoint falls in the 0.01-0.1 mg/L range resulting in a classification as Aquatic Chronic 1 with an M-factor of 1 for a not rapidly degradable substance.

The other two Pseudokirchneriella subcapitata 72-hour ErC10 values using BIT are in the 0.1-1 mg/L range which would result in an Aquatic Chronic 2 classification for a not rapidly degradable substance.

In relation to the earlier comment about the reliability of endpoints using PROXEL, if the Phaeodactylum tricornutum 72-hour ErC10 of 0.081 mg a.s./L (Smyth and Brown, 1991) endpoint is considered reliable for hazard classification, it would be useful for the DS to confirm whether validity criteria in test guideline [e.g. ISO 10253:2016 Water quality — Marine algal growth inhibition test with Skeletonema sp. and Phaeodactylum tricornutum] were met.

Dossier Submitter's Response

The approach followed for PNEC aquatic derivation from algae studies was discussed in WG-V-2015_ENV and followed by an Adhoc_ENV.
Please see doc IIA in the CAR and RCOM 2021. Please also check the document WGV2015_ENV_6-2_BIT_PT 2_6_9-13_Final minutes_incl AHF.docx and the agreed Adhoc_ENV_BIT document.

The biocidal effect of BIT is described as a two-step process involving rapid inhibition of growth and metabolism leading to a loss in viability of the cells. These effects occur within minutes at the enzymatic level and can result in loss of viability within hours of exposure. The mechanism of action of the isothiazolinones is, however, complex, as these molecules react with several specific enzymes, which are essential within critical metabolic pathways. According to this mechanism of action of BIT uptake through the cell wall and membrane of the algae occurs rapidly, within hours and facilitates the activity of the biocide. Concomitant with uptake and enzymatic inhibition, the isothiazolone ring is cleaved rendering the molecule inactive. This means that the inhibitory effect on algae is directly coupled with degradation of the molecule by the algae. Based on the above we understand that 72h endpoints based on initial measured concentration would not reflect the mode of action of the substance since it would allow for recovery not taking into account the interaction between algal cell density and substance disappereance. Hence, in our opinion

the use of 24h endpoints is justified. Further, in other similar substances, such as MIT, the same approach was followed.

In relation to Proxel, the impurity profile of BIT does not add any additional ecotoxicological hazard and hence Proxel studies are considered valid for classification.

The Symth study 1994 fulfils validity criteria:

- It fulfills exponential growth criteria.
- Mean coefficient of variation section by section = 0.119. It meets the criteria and does not exceed 35%.
- Coef. of variation of average specific growth rates for 72h = 0.031 meets the criteria and does not exceeds 7%
- Initial cell density is 10400 cells/ml.
- Given reliability: 2

Regarding the Kasthuri study and validity criteria we see the following:

- It fulfills exponential growth by more than a factor of 16.
- Mean coefficient of variation section by section is 0.47 and 0.48 for the control and vehicle control respectively. None of them meet the 35% criteria.
- Coefficient of variation of average specific growth rates for 72h = 0.021 meeting the 8% criteria.
- Initial cell density is 12050 cells/ml. Guideline recommends a cell density equal to 10000 cells/ml.
- Reliability of the study: 2.

The reasons why it was evaluated as reliable after the Adhoc follow up in 2015 by all member states, were the following:

- The biological section of the study can be considered good. Between control and vehicle control, each containing 6 replicates, there are not important differences in cell density values. The study is done under GLP.
- The study does not fulfill the second criterion by a 13%. Nevertheless when the study was done, the second criterion did not apply. Besides, there are other cases where a study not fulfilling the second criterion has been accepted. This is the case of MIT.
- Finally, despite there is no analytical verification at the concentrations tested, the study provides data that shows that concentrations of the test substance are maintained within 20% of nominal concentrations making it possible to calculate endpoints based on nominal concentrations. Proper chemical analysis probably would have lead to even lower test concentrations.

We do not have access to the ISO Guidance referred above. The test done with *P. Tricornotum* was given a reliability of 2:

- Initial cell density is 11300 cells/ml.
- It fulfills exponential growth by more than a factor of 16.
- Mean coefficient of variation section by section = 0.42. It does not meet the criterion exceeding 35%.
- Coefficient of variation of average specific growth rates for 72h = 0.019 meets the criteria and does not exceeds 10%.

- Reliability of the study: 2

All in all, and after discussions in the Biocides WG and an assessment of validity criteria for all test available four studies with *P. subcapitata* were considered reliable. The derived endpoints in these studies result in a geomean for the ErC10 of 0.026 mg/L (24h ednpoint), which was selected for risk assessment and classification purposes.

RAC's response

Although, RAC recognises that using 24 hour endpoints was considered by the BPC WG (ENV) and Adhoc ENV expert group, the DS does not clearly indicate that the validity criteria for relevant endpoints were met. However, the DS indicates that each endpoint of the studies was assessed in this regard when the strongest effect occurs and the endpoint was estimated accordingly. Still, as the robust studies were not available to RAC and the DS does not provide the multiplication factor, RAC was not able to confirm that the validity criteria for the control performance on all relevant endpoints were reached. However, RAC acknowledges that 72-h endpoints in the case of BIT based on initial measured concentration would not reflect the mode of action of the substance since it would allow for recovery not taking into account the interaction between algal cell density and substance disappearance.

RAC assumes that the test item PROXEL formulation is suitable for aquatic hazard classification as the impurity profile of BIT does not add any additional ecotoxicological hazard. However, RAC was not able to assess impurities/additivities of PROXEL formulation as this information were not provided.

Regarding validation criteria of the available four studies with *P. subcapitata* RAC would like to stress that all studies with exeption of one (Katshuri Raman, 2002) meet all validity criteria according OECD TG 201. However in the Katshuri Raman, 2002 study OECD TG 201 second criterion "*…the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures must not exceed 35 %...*" was not met. Nevertheless, RAC is aware that after discussions in the BPC WG (ENV) and Adhoc ENV expert group validity criteria for available four studies with *P. subcapitata* were considered reliable. In addition it should be noted that when the study was done, the second criterion did not apply. As well in the past there were cases (MIT) when a study not fulfilling the second criterion was accepted by RAC.

Therefore RAC agrees that provided four OECD TG 201 studies with *P. subcapitata* are reliable and acceptable for classification purpose and that the geometric mean of toxicity values from four studies with *Pseudokirchneriella subcapitata* may be used as the representative toxicity value for this species as indicated in guidance on CLP criteria.

ECHA guidance on Information Requirements and Chemical Safety Assessment Chapter R.7b foresees the possibility to adopt a shorten test period (48-h) with respect to the usual duration of 72-h or 96-h, still the 24-h length for this test is not mentioned in the guidance. The CLP Guidance indicates that acute aquatic toxicity is normally determined using a fish 96-hour LC_{50}, a crustacea species 48-hour EC_{50}, an algal species 72- or 96-hour EC_{50} and/or aquatic plants 7 days EC_{50}. However, CLP Guidance indicates that there can be circumstances, when a weight of evidence approach is appropriate. Chronic toxicity exposure durations can vary widely depending on the test endpoint measured and test species used.

OECD TG 201 allows to use shorter test period if "*… the test which runs over a period of normally 72 hours, in spite of being a relatively brief test duration, effects over several generations can be assessed…..The test period may be shortened to at least 48 hours to maintain unlimited, exponential growth during the test as long as the minimum multiplication factor of 16 is reached.*"

Furthermore, in the past the shorter test period was used by RAC:

- MIT (2-methylisothiazol-3(2*H*)-one CAS number: 2682-20-4): classification based on 24-h E_rC_x values based on initial measured concentration (validity criteria of the control performance were met for the first 24 h).
- MBIT (2-methyl-1,2-benzothiazol-3(2*H*)-one; CAS number: 2527-66-4): classification based on 48-h E_rC_x values based on initial measured concentrations (the validity criteria were met).
- C(M)IT/MIT (Reaction mass 5-chloro-2-methyl-2*H*-isothiazol-3-one and 2-methyl-2*H*-isothiazol-3-one (3:1) CAS number: 55965-84-9): classification based on 48-h E_rC_x values based on mean measured concentration (validity criteria fulfilled at 48h in the algal study).
- DCOIT (4,5-dichloro-2-octyl-2*H*-isothiazol-3-one; CAS number: 64359-81-5): aquatic acute classification based on 24-h E_rC_{50} based on initial measured concentrations (general validity criteria for the test are met including a growth rate higher than 0.92 per day at 24 h). Aquatic chronic classification is based on 48-E_rC_{10} based on initial measured concentrations (instead of 24-hours because 48-h endpoint is more relevant to assess the effect over several generations).
- OIT (octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one; CAS Number: 26530-20-1): classification based on 48-h E_rC_x value based on initial measured concentrations (validity criteria were met for 0-48 hours including exponential growth over this period).

Overall taking into account mode of action of isothiazolinones, confirmations on test criteria validation and indication that each endpoint of the studies was assessed in this regard when the strongest effect occurs, and the endpoint was estimated accordingly as well assuming BPC WG (ENV) and Adhoc ENV expert group opinions, RAC agrees that the use of 24-hours endpoint in case of BIT is appropriate. In addition RAC should pointed out that using 48-hour or 72-hour endpoints in geometric mean (based on initial measured concentrations from two studies (Desjardins and Smyth) and on nominal concentrations from other two studies (Kasthuri and Oldersma)) will give the same outcome regarding classification:

- 24-hour E_rC_{50} of 0.1087 mg/L (geomean)
- 48-hour E_rC_{50} of 0.1696 mg/L (geomean)
- 72-hour E_rC_{50} of 0.1968 mg/L (geomean)
- 24-hour E_rC_{10} of 0.0268 mg/L (geomean)
- 48-hour E_rC_{10} of 0.0529 mg/L (geomean)
- 72-hour E_rC_{10} of 0.0623 mg/L (geomean)

Consequently, RAC is of the opinion that the lowest acute endpoint for aquatic acute classification is the 24-hour E_rC_{50} value for *Pseudokirchneriella subcapitata* of 0.1087 mg/L (geometric mean). The lowest chronic endpoint for aquatic chronic classification is the 24-hour E_rC_{10} value for *Pseudokirchneriella subcapitata* of 0.0268 mg/L (geometric mean).

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
14.05.2021	United Kingdom	BIT Common Interest Group (BIT CIG) consists of the 6 participants Nutrition & Biosciences (Switzerland)	Company-Manufacturer	53

		GmbH, Laboratorios Miret, S.A., Lanxess Deutschland GmbH, Lonza Ltd, Thor GmbH and Troy Chemical Company BV.		

Comment received
Section 5, Page 22 ECHA note – An attachment was submitted with the comment above. Refer to public attachment BIT Common Interest Group_CLHComments_Final_v2r.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL STUDIES.zip
Dossier Submitter's Response
Thank you for your comment. The predictions are included in the CLH report.
RAC's response
Noted.

PUBLIC ATTACHMENTS
1. ACA BIT comments 5142021 _Redacted.pdf [Please refer to comment No. 9]
2. BIT CLH-report commenting table_BIT Task Force_Redacted.pdf [Please refer to comment No. 10, 22, 25, 37, 48]
3. CEPE position on BIT public consultation final 20210514_Redacted.pdf [Please refer to comment No. 11, 38]
4. BIT Common Interest Group_CLHComments_Final_v2r.pdf [Please refer to comment No. 23, 26, 39, 50, 53]
5. BCF Submission to the Public Consultation on 1,2-benzisothiazolin-3-one.pdf [Please refer to comment No. 12]
6. BIT CP_final.pdf [Please refer to comment No. 13, 40]
7. AISE CLH BIT Comments.zip [Please refer to comment No. 15, 42]
8. EPDLA comments concerning the proposed harmonized classification and labelling of BIT_FINAL May 2021_Redacted.pdf [Please refer to comment No. 20]
9. SCL for BIT_Consultation_Wacker May 2021_Redacted.pdf [Please refer to comment No. 1, 28]
10. 2021-05-01_VdL Comment on the planned harmonized classification and labelling of BIT.pdf [Please refer to comment No. 2, 29]
11. IVDK Comment on sensitization to BIT.zip [Please refer to comment No. 30]
12. DE_CA comment_BIT BfC.pdf [Please refer to comment No. 4, 27, 31]
13. IP Position Paper BIT reclassification - May 2021.pdf [Please refer to comment No. 5]
14. Einspruch EU zu BIT öffentlich.docx [Please refer to comment No. 34]

CONFIDENTIAL ATTACHMENTS
1. BIT CLH-report commenting table_BIT Task Force.pdf [Please refer to comment No. 10, 22, 25, 37, 48]
2. CONFIDENTIAL STUDIES.zip [Please refer to comment No. 23, 26, 39, 50, 53]
3. Confidential Reports.7z [Please refer to comment No. 15, 42]
4. Einspruch EU zu BIT.docx [Please refer to comment No. 34]