Committee for Risk Assessment

RAC

Annex 2
Response to comments document (RCOM) to the Opinion proposing harmonised classification and labelling at EU level of

2-methyl-1,2-benzothiazol-3(2*H*)-one; [MBIT]

EC Number: -
CAS Number: 2527-66-4

CLH-O-0000001412-86-209/F

Adopted

8 June 2018

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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 public 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 public 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.

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Substance name: 2-methyl-1,2-benzothiazol-3(2H)-one; [MBIT]
EC number: -
CAS number: 2527-66-4
Dossier submitter: Poland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Germany		MemberState	1
Comment received				
The German CA is of the opinion that, even though this approach is described in the current guidance document, that labelling only with H400 and not H411 is not appropriate as both hazard statements are neither duplications nor a redundancy. Dropping H411 would remove the communication of the long term aspect of the hazard. Additionally this specific derogation from the labelling provisions is neither included in the introductory paragraph of Annex III of the CLP regulation nor in Section 1.4.10.5.3.3. of the GHS. As classifications for acute toxicity for three routes are proposed the German CA strongly recommends also proposing ATE values for the three hazard classes to facilitate uniform and reproducible classification of mixtures, especially in the context of biocidal product authorisation. ECHA note – An attachment was submitted with the comment above. Refer to public attachment DEMSCA_Attachment 1.pdf				
Dossier Submitter's Response				
In reference to environmental classification and labelling MBIT is proposed to be classified as Aquatic Acute 1; H400 (Very toxic to aquatic life) and Aquatic Chronic 2; H411 (Toxic to aquatic life with long lasting effects) and labelled with H410 (Very toxic to aquatic life with long lasting effects). The hazard statement H411 includes the communication of the long term aspect of the hazard. If we used H400 and H411 on the label together a recipient would obtain incoherent information: "Very toxic to aquatic life…" and "Toxic to aquatic life…".				

The hazard statement H410 includes both information about the acute effect on aquatic life and the communication of the long term aspect of the hazard.
If statements H400 and H411 result from classification from practical point of view it is proposed to assign the hazard statement H410 on the label instead of both H400 and H411 (Table 4.1, p. 552 in Guidance on the Application of the CLP Criteria, Version 5.0, July 2017).
We agree with the approach as described in the Guidance and propose the hazard statement H410 (Very toxic to aquatic life with long lasting effects) on the label.

As classifications for acute toxicity for three routes toxicological result Acute Toxicity Estimates – ATE values have been included in the text of the proposal (pages: 25, 26, 27) proposed.

Refering to the public attachment DEMSCA_Attachment 1.pdf according to skin sensitising effects (Skin Sens. 1A) please see the response to the comment no 9.

RAC's response

Addition of ATEs is noted.
RAC notes that the DS's proposal for labelling is standard practice following Article 27 of CLP and Guidance on the Application of the CLP Criteria (Table 4.1, p. 552), Version 5.0, July 2017.

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2017	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	2

Comment received

MBIT is a new biocide active substance under the BPR (regulation (EU) No 528/2012), which is currently evaluated. The Biocidal Product Committee has recently concluded that MBIT in product type 6 (in-can preservatives) may be approved. We are aware that the public consultation on the proposed classification should only consider toxicological arguments on inherent properties. Nevertheless, we would like to use the opportunity to highlight the importance of new actives for in-can preservatives.

Over 70% of the production of paints and printing inks in Germany is water-based. The increased use of water-based formulations contributed to the reduction of VOC emissions and is beneficial in terms of occupational health, for consumers and the environment. However, most of these products need preservatives to prevent microbial growth. We estimate that alone in the German market for paints and printing inks a business volume of around 2.6 billion € is relying on in-can preservatives. We are currently observing that more and more active substances are no longer available due to the restrictions imposed in the review process. Especially in the Do-It-Yourself (DIY) sector the future of water-based dispersion paints is in danger. With many old actives being no longer available on the market, new actives are needed in order to maintain our water-based formulations.

We remain available to provide further information.

The German paint and printing ink association (VdL) represents over 180 – mostly mid-sized – manufacturers of paints, coatings and printing inks. The VdL stands for nearly 90 percent of this industry in Germany. In 2016 the German manufacturers of paints, coatings and printing inks realized sales of ca. 8 billion euros and employed

ca. 25,000 staff.
Dossier Submitter's Response
Thank you for your comments. The CLH proposal is based on the physico-chemical, toxicological and ecotoxicological reflection of intristic properties of MBIT only. Unfortunately the socio-economical impact is not considered in the harmonization process. The socio-economical analysis is taken into consideration in authorization and restriction processes of chemical substances.
RAC's response
RAC notes that this comment does not relate to the hazardous properties of MBIT. As the DS also stated, socio-economical impacts are not under consideration here. Assessment of an authorisation or a restriction proposal would be a separate process.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2017	Switzerland	Dow Europe GmbH	Company-Manufacturer	3
Comment received				
As the manufacturer of 2-methyl-1,2-benzothiazol-3(2H)-one (mBIT), Dow welcomes the opportunity to provide comments and input to the proposed harmonized classification and labelling of mBIT and thank the Rapporteur Member State for their thorough assessment and appropriate interpretation of the data in accordance with current guidance. Overall, Dow is in agreement with the proposed classification of mBIT for the following hazard endpoints; Acute Tox. 3, H301 Acute Tox. 3, H311 Skin Corr. 1B, H314 Eye Dam. 1, H318 Skin Sens. 1A, H317 Aquatic Acute 1, H400 Aquatic Chronic 2, H411 However we would like to provide additional information for consideration concerning the proposed acute inhalation classification of mBIT as Acute Tox. 3, H331.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
RAC notes the manufacturer's agreement with the proposed classification.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Germany		MemberState	4
Comment received				
Page 29 Inhalation: Acute Tox. 3 is proposed by the DS, based on a study using a formulation of 24% MBIT resulting in a rat Inhalation LC50 > 0.53 mg a.s. (MBIT)/L and the CLP concentration limits for Category 3 of 0.5 < LC50 ≤ 1.0 mg/L (mist). It should be noted that: The LC50 of > 0.53 mg/L is very close to the concentration limits for Category 2.				

The study was performed with a formulation of MBIT rather than the active substance, resulting in some uncertainties
MIT, which is chemically related to MBIT, is classified as Category 2 for acute inhalation toxicity.
Accordingly, classification of MBIT in Category 2 rather than Category 3 should be discussed.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DEMSCA_Attachment 1.pdf

Dossier Submitter's Response

The acute inhalation study could not be conducted on MBIT but on commercial product (a formulation of 24% MBIT). After 4 hour aerosol inhalation, rat LC50 > 0.53 mg a.i. (MBIT)/L. The value 0.5 mg is simultaneously the converted acute toxicity point estimate for category 3 dust/mist (according to Table 3.1.2 of Annex I).
Thus we suggest classification in category 3 (Acute Tox. 3; H331) because in our opinion there are no arguments for category 2 (in particular, there were no fatalities during the study).

Refering to the public attachment DEMSCA_Attachment 1.pdf according to skin sensitising effects (Skin Sens. 1A) please see the response to the comment no 9.

RAC's response

In the acute inhalation study, the LC_{50} was determined to be higher than the only tested dose of 0.53 mg/L (not equal to it). The dose level tested is at the low end of the criteria for Cat. 3, and conducting testing on a formulation instead of the active substance does indeed result in some uncertainties. However, there was no mortality or clear signs of toxicity observed at the tested dose level. Therefore, RAC agrees with the DS that Cat. 2 would not be justifiable. Furthermore, RAC is of the opinion that there are no justifications for classification of MBIT as Cat. 3 either, as there are no data indicating that the LC_{50} would be within the range of the criteria. RAC concluded that EUH071 ("corrosive to the respiratory tract") shall be added.

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Finland		MemberState	5

Comment received

Hazard class Acute Tox. 3; H301 – Toxic if swallowed:
Acute oral toxicity test conducted with MBIT resulted in LD50 value of 175 mg/kg. The result meets the criteria for Acute Tox. 3; H301.
FI CA supports the proposed classification of Acute Tox. 3; H301 for MBIT.

Hazard class Acute Tox. 3; H311 – Toxic in contact with skin:
FI CA considers that the estimated LD50 value would be closer to 2000 mg/kg than below 1000 mg/kg, because three out of five animals died at dose of 2000 mg/kg. Therefore, Acute Tox. category 4; H312 ($1000 < LD50 \leq 2000$) would be more appropriate than the proposed Acute Tox. category 3; H311 ($200 < LD50 \leq 1000$).

Hazard class Acute Tox. 3; H331 – Toxic if inhaled:
FI CA is of the opinion that classification for acute inhalation toxicity in category 3 (H331) would not be justified. No mortality or severe toxicity occurred in the study.

Dossier Submitter's Response
Thank you for your supporting the proposed classification of Acute Tox. 3; H301 for MBIT. The dermal LD50 of MBIT technical is judged in the range of 200 – 2000 mg/kg of body weight in rats (the ATE value is estimated as 300 mg/kg) therefore on the base of the precautionary principle the category 3 is assessed in dermal route (Acute Tox. 3; H311). Taking into account the precautionary principle due to lack of additional data we suggested that classification in category 3 (Acute Tox. 3; H331) is the most reliable solution.
RAC's response
Noted, and RAC agrees with the comment from the FI CA (see RAC opinion).

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2017	Switzerland	Dow Europe GmbH	Company-Manufacturer	6
Comment received				
Regarding the proposed classification for Acute inhalation toxicity Dow questions the relevance of assigning an acute inhalation classification to the active substance mBIT based on the physicochemical properties of the technical material. As reported in the Annex XV dossier, mBIT is a crystalline yellow solid of very low vapour pressure with a melting point >50◦C. Due to these properties it is documented in the report that acute inhalation testing was carried out on a formulation containing mBIT and not the active substance itself as this was considered not technically feasible. In order to conduct the study, atmospheres containing aerosols of formulated mBIT were generated which would not be created under foreseeable use conditions. In addition, in acute inhalation studies conducted with other isothiazolinones where mortality was observed, the toxicities and pathological effects reported are directly attributable to the corrosive/irritant effects caused at the site of test material impact. As it is considered impossible to create a high enough air concentration under any use conditions to achieve an acutely toxic effect we would propose, given the mode of action, that labelling EUH 071 would perhaps be more appropriate for formulations containing corrosive concentrations of mBIT and would propose this labelling as more appropriate than H331.				
Dossier Submitter's Response				
Substance MBIT has just been classified as skin corrosive cat. 1B. The study did not show any corrosive effect on respiratory truck and in our opinion EUH 071 would not be necessary. Taking into account the precautionary principle and due to lack of additional data we suggested that classification in category 3 (Acute Tox. 3; H331) is the most reliable solution.				
RAC's response				
Consideration of whether it is possible to create high enough air concentrations under any use conditions to achieve an acutely toxic effect or not is not revelant regarding classification of the substance, as only the intrinsic hazard properties of MBIT are evaluated here (not risk). However, based on the available data, also RAC is of the opinion that labelling as EUH071 is more applicable than classifiying for acute inhalation toxicity.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Finland		MemberState	7
Comment received				
FI CA agrees that MBIT has corrosive properties. However, FI CA considers that the criteria for classification into sub-category 1B may not be met. Corrosive responses (i.e. necrosis) occurred only after 4-hour exposure, which would justify the classification into sub-category 1C. After 1-hour exposure, only severe irritation (grade 4 erythema) occurred.				
Dossier Submitter's Response				
The classification as corrosive category 1B for MBIT was assigned due to lesions after 1-hour exposure: by Day 7 and 14 erythema progressed to severe was observed for two out of three animals. Edema was very slight on Day 7 and absent on Day 14. However, after a profound analysis it should be assummed there is no evidence for corrosive reaction after 1-hour exposure. Only after 4-hour exposure the corrosive reaction was observed (necrosis). Therefore we agree with this comment that corrosive category 1C (Skin Corr. 1C) could be more appropriate to be assigned for MBIT.				
RAC's response				
Noted and RAC agrees with the comment.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Finland		MemberState	8
Comment received				
Due to corrosive properties observed in skin corrosion study, serious damage to eye can be expected also after eye exposure. FI CA supports the proposed classification of Eye Dam. 1; H318 for MBIT.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Germany		MemberState	9
Comment received				
Page 7, 43-45: For the assessment of skin sensitisation two local lymph node assays (LLNA) in mice, a Buehler test in guinea pigs and supporting data in humans (Human repeated insult patch test (HRIPT)) were available in the CLH dossier. In both LLNAs by McMillan (2008) and by Kirk (2009) the Stimulation Index was above 3 at MBIT concentrations of 1 % and 0.7 %, fulfilling the criteria for a "strong" sensitizer, which is further supported by results from the Buehler assay. The supporting data from the HRIPT also show a sensitising potential of MBIT and contribute to the appropriateness of a classification as Skin Sens. 1A. However, although usually a generic concentration level (GCL) of 0.1 % is applied to a				

strong sensitiser, a closer look towards setting of a specific concentration level (SCL) is necessary.
As in recent years a steep increase in frequency of contact allergy through isothiazolinone compounds was seen. Data from structurally related compounds with a similar mode of action need to be considered.
MBIT is structurally closely related to 1,2-Benzothiazol-3-one (BIT) and from the chemical structure also to methylisothiazolinone (MIT) and methylchloroisothiazolinone (CMIT). Therefore it is reasonable to assume that if MBIT would show cross-reactivity to the other isothiazolinones, it would significantly contribute to the broad outcome of isothiazolinone allergy.
Having this in mind, and knowing that SCLs below the GCL were set not only for BIT but also for MIT and CMIT, a lower SCL for MBIT is proposed.
To support this, a comparison regarding the sensitising impact of MBIT and BIT and other isothiazolinones is done. Attachment 1 shows that MBIT can be considered to be a more potent sensitiser (Skin Sens. 1A, potency: strong) than BIT (Skin Sens. 1B, potency: moderate), its closest relative. Therefore it is questionable why a SCL is applied to BIT but no SCL is propopsed for MBIT.

Furthermore, the sensitising capacity of MBIT is comparable to MIT, which – based on potency data from the LLNA - was also considered a “strong” sensitizer. Thus, here for MBIT, and originally for MIT a GCL of 0.1 % was proposed.
However, in March 2016 RAC decided to set a lower SCL of 15 ppm (0.0015 %) for MIT. The decision was based on SCCS Opinions 1-3 on MIT, where human Patch Test data on MIT and CMIT/MIT 1:3 was analysed. Prevalence data show that MIT shows the highest sensitization rates ever reported for a preservative though MIT is only a “strong” not an “extreme” sensitizer in LLNA. But as MIT shows cross-reactivity to the “extreme” sensitizer CMIT and the latter is the more potent allergen and is the principal moiety in CMIT/MIT (SCL 15 ppm), the SCCS suggested that MIT should be safe in rinse-off cosmetic products at 15 ppm (0.0015 %) as well. SCCS stated that “…it cannot be excluded that patients previously sensitised to CMIT/MIT will react to products containing 100 ppm MIT. As a consequence, a SCL of 15 ppm is now set for “rinse-off”, a total ban for the use of MIT in “leave-on” cosmetic products was implemented by legislation from 12.02.2017.
A new publication by Schwensen, J. F. demonstrates impressively the existence of this cross-reactivity between MIT and BIT by LLNA data. BIT and MIT show similar potency in the LLNA. In conclusion, due to the structural similarity (see above) we propose a SCL of 15 ppm for MBIT.
Schwensen JF, et al. (2017). Cross-reactivity between methylisothiazolinone, octylisothiazolinone and benzisothiazolinone using a modified local lymph node assay. Br J Dermatol.176:176-183.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DEMSCA_Attachment 1.pdf

Dossier Submitter’s Response

MBIT is proposed to be classified as skin sensitiser cat. 1A. The concentration limit was estimated on the base of the test results of MBIT substance using the method described by Basketter et al. (2005). According to this method potency of MBIT based on the test both LLNA sensitisation and Buehler method test results MBIT is described as a strong sensitiser (not an extreme sensitiser). Therefore the concentration limit (CL) was estimated as equal to general concentration limit (GCL) 0.1 %.
Having test data about MBIT it does not need to take into account sensitising potency of similar substances (MIT and BIT), but lower GCL of MBIT could be discussed.

Thank you for sending of the DEMSCA_Attachment 1.pdf document. Referring to this document EC3 values of two substances BIT and MBIT confirm our position that MBIT is a stronger sensitiser (category 1A) than BIT which is asumpted as a moderate sensitiser (category 1B).

RAC's response

Noted and RAC agrees with the comment.

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Finland		MemberState	10

Comment received

Two local lymph node assays (OECD TG 429) resulted in EC3 values of less than 2% (0,69% & 1,04%) and Buehler test showed positive response in 20% of animals at 0,18% topical induction dose. The criteria for classification as Skin Sens. 1A; H317 is met. Based on these results, MBIT can be considered as a strong sensitiser and GCL of 0,1% would be appropriate.
FI CA supports the proposed classification of Skin Sens. 1A and GCL of 0,1% for MBIT.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted, but RAC is of the opinion that an SCL is necessary. This view is based on the human data that indicates that MBIT is a potent sensitiser, alike several other isothiazolinones.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	France		MemberState	11

Comment received

We agree that Skin Sens. 1A for MBIT is justified based on the available animal data.

With regards to SCL, we agree that animal data does not support the setting of a concentration limit of 0.001% for extreme sensitiser. Nevertheless, in the human HRIPT study performed with CBIT, the very high numbers of volunteers sensitised (9/45) may justify the setting of a specific concentration limit. Although we acknowledge that there are ethical concerns with this type of study, it would be useful to understand why this study was disregarded by the DS for classification purposes. Moreover, could you please give more information on tested concentration and exposure levels used in this study and consider using the human data to support the setting of a specific SCL.

Dossier Submitter's Response

A specific concentration limit was estimated on the base of animal tests results of MBIT. Additionaly data about human study are not available. There is no direct reliable method to transposition human test results into specific concentration limit but lower GCL of MBIT could be discussed.

For more details regardingl skin sentisitising effects of MBIT see the response to the comment no 9.

RAC's response

Noted and RAC agrees with the comment.

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2017	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	12
Comment received				
Concerning the isothiazolinones it is expected that the implementing regulation approving the active under the BPR will contain a statement that treated articles placed on the market for use by the general public shall not contain the active at a concentration triggering classification as skin sensitizer. If the specific concentration limit for skin sensitization is lower than the threshold of efficacy of the active, the substance is de facto banned from the DIY sector. For consumer protection it is of course necessary to communicate the presence of skin sensitizing substances above a certain threshold. Our industry is committed to ensure a high level of consumer protection and a transparent substance declaration. This is reflected by the self-commitment of CEPE members to communicate the presence of MIT above 15 ppm and the provisions set out in the VdL directive 01. However, we want to point out that the ban of actives for in-can preservation in DIY paints poses severe problems for the future of water-based paints, which should be considered.				
Dossier Submitter's Response				
Thank you for your comments. For more details regardingl skin sentisitising effects of MBIT see the response to the comment no 9.				
RAC's response				
The evaluation for proposing harmonised classification is confined to assessing the intrinsic hazard properties of substances. Therefore, RAC is of the opinion that an SCL is necessary for MBIT in order to protect consumers and workers from skin sensitisation.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2017	Germany		MemberState	13
Comment received				
5.1.3 Degradation, p. 95 ff.: Please note, that there is a difference between ready biodegradability and rapid degradability. In the context of classification and labelling it should be concluded whether a substance is rapidly degradable based on both, information on abiotic (i.e. hydrolysis) and biotic degradation behaviour (ready/inherent biodegradability, simulation tests). For substances which are not readily biodegradable and hydrolytically stable, rapid degradability can still be concluded if the half-life in surface water or even in soil is < 16 days, provided that degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment (Guidance on the Application of the CLP Criteria, Version 4.1, June 2015, pp. 494). We suggest to check this and to summarise all available information on metabolites (IUPAC-name, CAS-No. if available, classification if available) for reference. Nevertheless, since we think that for some of the metabolites no information exists regarding their potential to be hazardous for aquatic environment, we support the conclusion that MBIT has to be classified as not rapidly degradable. 5.4 Aquatic toxicity, table 50, p. 109, OECD Guideline 201 Test with Skeletonema costatum (Softcheck 2009): EC50- and NOEC-values deviate from those for the same study in the draft final CAR document for MBIT in PT6. Please check for correctness. Further, as this study is considered non-valid (as discussed on p.115), this fact should				

also be considered.
5.4.3 Algae and aquatic plants, p. 114:
Please clarify which criteria are meant, e.g. “Study with P. subcapitata was considered to be reliable. All OECD 201 validity criteria in this test were met with exception of criterion 2: mean coefficient of variation for section-by-section growth rates exceeded the trigger value for 0 – 96 hr period.”
5.4.4 p.115, first phrase in the paragraph:
An information is missing in this phrase concerning guidance used for this study - “[…] in compliance with[…]” Please clarify which guidance was used.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DEMSCA_Attachment 1.pdf

Dossier Submitter’s Response

5.1.3 Main metabolites identified during degradation of MBIT are:

- N-methyl-2-(methylthio)benzamide, CAS No. CAS not available
- 2-(methylcarbamoyl)-benzene sulfonic acid, CAS not available
- 2-carbamoyl-benzene sulfonic acid, CAS No. 41363-39-7

Based on cited in CLH report studies performed with MBIT metabolites, N-methyl-2-(methylthio)benzamide and 2-carbamoyl-benzene sulfonic acid should not be classified, according to CLP Regulation.
Additionally, since the chemical structure and QSAR properties of 2-(methylcarbamoyl)-benzene–sulfonic acid and 2-carbamoyl-benzene–sulfonic acid are very similar (see Table 48 of CLH report), thus it can be assumed that conclusions presented for 2-(methylcarbamoyl)-benzene–sulfonic acid are also relevant for 2-carbamoyl-benzene–sulfonic acid.
In general MBIT metabolites are much less toxic than active substance. Since all of the metabolites endpoints (LC50, EC50 and ErC50) are above 101 mg/L, classification criteria presented in Table 4.1.0 b) (iii) Annex I of CLP, for substances without adequate chronic toxicity data, are not met. Futhermore, logKow of MBIT metabolites provided by QSAR modelling (Table 49. of CLH report) are below 4 indicating no potential to bioaccumulation.

5.4 In the available Assessment Report for MBIT in PT6 from August 2017 there is no endpoint values for *Skeletonema costatum*. Therefore, we cannot check about which deviation you have mentioned. However, as other isothiazolinones, MBIT may be expected to have unique mode of action in algae. Therefore, special assessment in Annex 1 of CLH report (p.123) was performed and may be a reason of deviation in the endpoints interpretation. Please refer to Annex 1 of CLH Report.
Additionally, taking into account that not all validity criteria in the study with *Skeletonema costatum* were met and due to the fact that the lowest available L(E)C50 and NOEC/EC10 values were obtained for the *Pseudokirchneriella subcapitata,* study with *Skeletonema costatum* is not relevant for classification purposes of MBIT.

5.4.3 Regarding OECD 201 validity criteria of algal studies on MBIT please refer to Annex 1 of CLH report (p.123), where all of the validity criteria are described in details and analized.

5.4.4 Acute sediment toxicity test with larvae of *Chironomus dilutus* was conducted in compliance with US EPA OPPTS 850.1735 and ASTM Guideline 1706-05.

RAC's response
Degradation: The Dossier Submitter considers that MBIT is rapidly degradable as the three major degradants are not classifiable for environmental hazard. This is based on acute ecotoxicity data (for fish, invertebrates and algae) for two of the three main degradants (with no relevant acute effects up to 100 mg/L). QSAR estimates are also provided for the two degradants with measured acute ecotoxicity data as well as the third degradant, addressing water solubility, log K_{OW}, degradation and acute ecotoxicity endpoints. The Dossier Submitter has not provided a comparison of predicted and measured data although RAC notes that the QSAR predictions are lower, and would result in classification in all three cases (including the degradant for which there are no measured ecotoxicity data). RAC notes that no further information to support the validity of the QSAR estimates (e.g. QSAR Model Reporting Format and QSAR Prediction Reporting Format) is included in the CLH dossier. Neither measured nor predicted chronic ecotoxicity data are presented (except for chronic endpoints from the algal studies for two of the degradants). Measured and predicted data for structural analogues are not presented. The Dossier Submitter has drawn attention to the similarities of 2-(methylcarbamoyl)-benzene–sulfonic acid and 2-carbamoyl-benzene–sulfonic acid (effectively concluding that they will have the same hazard classification). Although RAC tends to agree, they have not followed the ECHA Read Across Assessment Framework to provide a transparent analysis. RAC agrees that the reported measured acute data suggest that the three main degradants are unlikely to be classifiable for environmental hazard. However, the current CLH report and RCOM do not provide sufficient information to allow independent evaluation of these data and do not confirm the total number of degradants / relative amounts. RAC therefore asked ECHA to perform a QSAR analysis for the degradants, which is summarised as supplemental information in the opinion. On this basis, RAC can not support the Dossier Submitter's proposal that MBIT is rapidly degradable for the purpose of classification. Aquatic toxicity to algae: RAC notes that the Softcheck (2009) study using *Skeletonema costatum* is not considered reliable and so should not be considered further. RAC notes that the OECD Test Guideline 201 (2006 and 2011) validity criterion 2 was not met for the 0-96 hour time period in the Hoberg (2007) study, and the 96 h end point has not been used for the classification proposal. The criterion was met for the 0-72 hours and 0-48 hour time periods. As the 48 and 72 hour endpoints are considered valid, they are suitable for hazard classification. Aquatic toxicity to *Chironomus dilutus*: RAC notes that the study test guideline has been confirmed by the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	France		MemberState	14
Comment received				
We agree with the proposed classification and labelling : Aquatic Acute 1, H400 M-factor=1 Aquatic Acute 2, H411				

Dossier Submitter's Response
Thank you for your comment and support. The classification regarding ecotoxicological effect was proposed in the dossier as following: Aquatic Acute 1, H400 M-factor=1 Aquatic Chronic 2, H411
RAC's response
RAC acknowleges the agreement of the French Competent Authority with the proposal.

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2017	United Kingdom		MemberState	15

Comment received

Rapid degradability:

- We note that various metabolites/degradants were identified in the fate studies. Please can you confirm if those presented in the CLH report are exhaustive or were further degradants detected? If additional degradants were detected, please can you detail their peak levels (of initial applied dose or radioactivity) and whether these were chemically identified. This information is required to clarify if all relevant degradants have been identified.
- The CLH presents experimental and predicted acute ecotoxicity endpoints for various degradants. Although the acute endpoints are >100 mg/L, please can you consider their potential chronic toxicity? This should also include the potential for Aquatic Chronic 4 classification.

Chronic toxicity to fish and Daphnia:

- Please can you confirm if the 32-day Fathead minnow NOEC of 0.16 mg a.s./l (Hamitou, 2009b) and 21-day Daphnia magna NOEC of 0.16 mg a.s./l were based on measured or nominal concentrations.

Algal toxicity:

- As mentioned in CLP guidance, we consider it preferable to use ErC10 endpoints to NOErC values (where available) as they are based on a dose-effect relationship rather than an arbitrary treatment concentration.
- Given the mode of action for isothiazolinones, we consider initial measured concentrations are the most relevant for hazard classification as it most accurately reflects the concentration which induces the toxic effect.
- In the key study (Hoberg, 2007), the 48 hour study period is the most sensitive time period. We support this non-standard approach for acute classification. We note that OECD TG 201 refers to shortening the study duration to 48 hours where a 16 fold increase in control cultures is observed. Please can you consider if the study 48 hour endpoints meet this criteria? This is important to consider whether the chronic endpoints are relevant for chronic classification accounting for several generations.
- We also note that in this instance both 48 and 72 hour ErC10 endpoints based on initial measured concentrations are in the range 0.1 to 1 mg/l which is less stringent than the proposed ecotoxicity range of 0.01 to 0.1 mg/l based on the 48 hour NOErC. On this basis, we consider the Aquatic Chronic classification should be based on the ecotoxicity range 0.1-1 mg/l.

Dossier Submitter's Response
Rapid degradability: • All of the degradants detected during fate studies were presented in the CLH Report. • In general MBIT metabolites are much less toxic than active substance. Since all of the metabolites endpoints are above 100 mg/L, classification criteria presented in Table 4.1.0 b) (iii) Annex I of CLP, for substances without adequate chronic toxicity data, are not met. Futhermore, logKow of MBIT metabolites provided by QSAR modelling (Table 49. of CLH report) are below 4 indicating no potential to bioaccumulation. Chronic toxicity to fish and Daphnia: • Both endpoints, 32-day Fathead minnow NOEC of 0.16 mg a.s./l (Hamitou, 2009a) and 21-day Daphnia magna NOEC of 0.42 mg a.s./l (no 0.16 mg a.s./l, as you have written) (Hamitou, 2009b) are based on mean measured concentration. Algal toxicity: • The lowest endpoint for classification of aquatic chronic hazards is the 48 hours NOE_rC of 0.012 mg a.i./L obtained for freshwater alga species *Pseudokirchneriella subcapitata*. Equivalent E_rC_{10} (48h) is equal 0.09 mg/L (please refer to Annex I of CLH report) which is higher value thus, it was considered less representative endpoint for MBIT. It was agreed at BPC- WG IV/2016 Meeting. • Thank you for your comment, however, at BPC- WG IV/2016 meeting it was agreed that due to fast disappearance of MBIT, final endpoints should be based on mean measured concentration. • According to results of the study on *Pseudokirchneriella subcapitata* presented in Table 1 in Annex I of CLH report, the mentioned criterion of OECD 201 guideline was met. The biomass in the control cultures increased by a factor of 37 within 48-hour period. • As it is written above, it is decided that final endpoints should be based on mean measured concentration. The ecotoxicity range of 0.01 to 0.1 mg/l should be considered.
RAC's response
Degradation: Refer to comment number 13 above. Aquatic toxicity to fish and Daphnia: RAC appreciates the clarification provided by the Dossier Submitter. Aquatic toxicity to algae: RAC agrees that it is appropriate to use 48 hour acute and chronic endpoints from the Hoberg (2007) algal toxicity study as it was performed according to GLP and validity criteria were met for this time period. The Dossier Submitter indicates that the Biocidal Products Committee agreed to use 48 hour endpoints based on mean measured concentrations due to test item losses over the study period, and the NOEC rather than the EC_{10} as it is a lower value. This reflects the use of the data for risk assessment purposes. However, CLP concerns hazard assessment, based on established guidance and taking account of precedents. MBIT is an isothiazolinone with a specific mode of action whereby the substance is taken up by algal cells and transformed. It is this process which induces the toxic response. Given the loss of test item via algal cell uptake over the test period, mean measured concentrations are significantly lower than initial measured concentrations. The use of mean measured concentrations therefore provides an unrealistically conservative estimate of the concentration of test item

required to induce the observed level of toxic response in this case. Instead, RAC considers that initial measured concentrations are appropriate for hazard classification in this context.

In addition, varying losses are observed between low and high dose treatments as at higher doses, high algal inhibition results in lower losses because viable algal cells are not available to take up the test item after the initial toxic response. As test item loss is dependant on algal cell concentrations and differing kinetic losses would be observed across treatments, it is unclear how representative a dose-response curve based on time-weight average concentrations would be for shorter test duration endpoints i.e. 48 hours.

The CLP guidance[1] (section 4.1.3.1.1) states that 'if available, preference is given to EC_{10} values' in place of NOEC values. The E_rC_{10} is a statistically derived term, whereas the NOE_rC depends on the selected treatment concentrations. As the Hoberg (2007) study was performed to OECD Test Guideline 201 and validity criteria were met, the study design is suitable for an E_rC_{10} to be derived. RAC therefore prefers to use the valid E_rC_{10} instead of the NOE_rC for the purposes of hazard classification.

In summary, RAC considers that the following endpoints from the Hoberg (2007) study are appropriate for acute and chronic hazard classification:

- 48h E_rC_{50} of 0.361 – 0.373 mg/L (initial measured concentration) calculated by the evaluating Competent Authority and study author, respectively; and
- 48h E_rC_{10} of 0.129 – 0.157 mg/L (initial measured concentration) calculated by the study authors and evaluating Competent Authority respectively.

This interpretation complements previous RAC opinions (RAC 36, March 2016) for other isothiazolinones (MIT, CAS no.: 2682-20-4; C(M)IT/MIT, CAS no. 55965-84-9), which concluded that algal study results based on initial measured concentrations may be appropriate given the mode of action, and algal endpoints for time periods shorter than 72 hours may be appropriate for classification.

[1]Guidance on the Application of the CLP Criteria Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (2017) Version 5.0 July 2017, referring to OECD (2006) Series on Testing and Assessment Number 54, Current approaches in the statistical analysis of ecotoxicity data: a guidance to application. ENV/JM/MONO(2006)18.

PUBLIC ATTACHMENTS
1. DEMSCA_Attachment 1.pdf [Please refer to comment No. 1, 4, 9, 13]