Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one; [OIT]

EC Number: 247-761-7
CAS Number: 26530-20-1

CLH-O-0000001412-86-255/F

Adopted

30 November 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON OCTHILINONE (ISO); 2-OCTYL-2*H*-ISOTHIAZOL-3-ONE; [OIT]

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: octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one; [OIT]
EC number: 247-761-7
CAS number: 26530-20-1
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Germany		MemberState	1
Comment received				
The German CA generally agrees with the dossier submitter's proposals for classification of OIT. Specific comments are provided for the hazard classes Acute toxicity and Skin sensitization.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Your support has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Germany	Thor GmbH	Company-Manufacturer	2
Comment received				
On the whole we welcome the conclusions of the Dossier Submitter with respect to classification of OIT for acute dermal toxicity, skin and eye corrosivity and skin sensitisation category 1A. However we provide comments for consideration regarding: 1) The proposed classification for Acute Oral Toxicity. 2) The applicability of inhalation classification to liquid substances of low volatility. 3) The proposed Specific Concentration Limit for Dermal Sensitisation.				
Dossier Submitter's Response				
Thank you for your support. See also response to comments 9 (acute toxicity) and 15 (skin sensitisation).				
RAC's response				
See responses relating to acute toxicity and skin sensitisation.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON OCTHILINONE (ISO); 2-OCTYL-2*H*-ISOTHIAZOL-3-ONE; [OIT]

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Switzerland	Dow Europe GmbH and Thor GmbH	Company-Manufacturer	3
Comment received				
On the whole we welcome the conclusions of the Dossier Submitter with respect to classification for acute dermal toxicity, skin and eye corrosivity and skin sensitization category 1A. However we provide in attachment further evidence and comments for consideration regarding; 1) the study selected as key for acute oral toxicity classification 2) the applicability of inhalation classification to substances of low volatility and study selection for acute inhalation classification 3) the proposed Specific Concentration Limit for Dermal Sensitisation In support of arguments made concerning point 3 above, additional confidential information has been provided to assist the Rapporteur and RAC in their deliberations. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Manufacturers Comments on the Human Health Hazards of OIT.docx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Koralone confidential composition.xlsx				
Dossier Submitter's Response				
Thank you for your support. See also response to comments 11 (acute toxicity) and 14 (skin sensitisation).				
RAC's response				
See responses relating to acute toxicity and skin sensitisation.				

Date	Country	Organisation	Type of Organisation	Comment number
17.04.2018	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	4
Comment received				
OIT is a biocidal active substance under the BPR (regulation (EU) No 528/2012), which is currently evaluated for several product types. OIT is a potent fungicide and is mainly used in paints and coatings as film-preservative (PT 7), but also as in-can (PT 6) and wood preservative (PT 8). CLP classification is hazard-based and hence the actual risk is not considered. However, the classification (e.g. setting specific concentration limits for skin sensitization) has direct consequences for the approval of active substances under the BPR, which we would like to point out. The use of OIT as biocidal active substance in PT 6, PT 7 and PT 8 is considered as safe. However, we fear that the proposed specific concentration limit of 50 ppm would lead to a de facto ban of OIT in many Do-It-Yourself (DIY) applications, since typically higher concentrations are needed (see also specific comments). Dry-film preservation is most important for organic resin-based coatings and prevents the growth of microorganisms like algae and fungi on coated surfaces, such as the facades of buildings. Currently there are only very few substances left, which can be used as film preservatives and act as fungicides and those are also under pressure due to the CLH and BPR processes, such as Zinc pyrithion. Thus, if the number of actives available on the market is further decreasing, the film-preservation as a whole is at risk. To be effective				

usually a dosage of at least 250 ppm of OIT is needed, which is significantly above the proposed specific concentration limit of 50 ppm. Therefore, we fear that the proposed classification will have the consequence that façade paints with a functioning film-preservation might in future no longer be available for DIY applications. Hence, they can only be applied by professional painters, thus burdening homeowners with higher costs.

Functioning dry film preservation of façade paints and plasters is essential in view of sustainability of buildings thanks to enlarging renovation cycles and thermal insulation. Preventing algae and fungi growth on façades leads to retaining of water repellence, thus, maintaining long lasting effective thermal insulation of houses.

Concerning the in-can preservatives, we are currently also observing that more and more active substances are no longer available due to the restrictions imposed in the review process under the BPR. Especially in the DIY sector the future of water-based dispersion paints is in danger. 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. With more and more active substances being no longer available, the remaining actives become increasingly important, since the alternatives for substituting actives become scarce. OIT is a strong fungicide and hence can be used in conjunction with bactericides. Although it is not suitable for all applications, it is essential to have this option available. However, a concentration of 50 ppm OIT is at the threshold of efficacy and hence higher concentrations are often needed. Furthermore, operating at the threshold increases the risk that a resistance is developed. Hence, the proposed threshold also endangers the availability of OIT as in-can preservative in DIY applications, thus further intensifying the shortage of usable actives.

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 this additional information about the importance of this substance to industry. Our dossier provides an assessment of how the substance should be classified, based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation.

According to the regulatory process, it was not for this dossier to assess the impact of the classification, or the way in which the substance may in future be viewed under the Biocide Product Regulation.

RAC's response

RAC notes that this comment does not relate to the hazardous properties of OIT, and agrees with the DS's response.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON OCTHILINONE (ISO); 2-OCTYL-2*H*-ISOTHIAZOL-3-ONE; [OIT]

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2018	Belgium	CEPE	Industry or trade association	5
Comment received				
The revised proposed threshold for skin sensitization ten times lower than the existing level is of concern to us due to the negative consequence it will trigger under the Biocide Product Regulation. OIT is a valuable preservative to protect our products. We attach a document to explain our views. ECHA note – An attachment was submitted with the comment above. Refer to public attachment CEPE input public consultation OIT 201803.pdf				
Dossier Submitter's Response				
Thank you for this additional information about the importance of this substance to industry. Our dossier provides an assessment of how the substance should be classified, based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation. According to the regulatory process, it was not for this dossier to assess the impact of the classification, or the way in which the substance may in future be viewed under the Biocide Product Regulation.				
RAC's response				
RAC notes that this comment does not relate to the hazardous properties of OIT, and agrees with the DS's response.				

Date	Country	Organisation	Type of Organisation	Comment number
04.05.2018	Norway	Jotun A/S	Company-Downstream user	6
Comment received				
Very low specific concentration limits (SCLs) for skin sensitizers have been proposed for in-can (PT6) and film preservatives (PT7). Use of these preservatives are essential for interior and exterior paints, as alternatives do not exist. In practice, however, these low SCLs mean the substances cannot be used in consumer paints as these will be classified as skin sensitizing. The reason for this – as we understand it – is that the consumer cannot be trusted to use skin protection. In lieu of the fact that; - the hazard label on the tin warns about the skin sensitizing property incl name of the sensitizer, (informed labeling) - although substances are extreme sensitizers per se their relatively low concentrations in the consumer paint makes the paint a weak/ moderate sensitizer - the effects of an allergic response are reversible upon cessation of exposure - consumer paints represent a low risk as they are; o used infrequently o not intentionally used on the skin o spills are expected to be quickly removed we sincerely ask for an opportunity to continue putting consumer paints classified as skin sensitizing on the market under the conditions that we supply gloves with the products.				

Dossier Submitter's Response
Thank you for this additional information about the importance of this substance to industry and the request that consumer paints classified as having skin sensitising potential be allowed to remain on the market. Our dossier provides an assessment of how the substance should be classified, based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation. It was not for this dossier to assess the impact of the classification, or the way in which products containing OIT (or other senstisers) may in future be viewed under the Biocide Product Regulation.
RAC's response
Thank you for your comment. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	France		MemberState	7
Comment received				
According to the CAR, the IUPAC name is 2-Octyl-isothiazol-3(2H)-one and the CA name is 2-(n-Octyl)-2H-isothiazol-3-one				
Dossier Submitter's Response				
Thank you for your comment regarding the identifiers used in the CAR (Jan 2017). The primary identifier used in the CLH report was advised by ECHA during the dossier submission process: 2-octyl-2H-isothiazol-3-one; [OIT].				
RAC's response				
RAC agrees with the DS's response.				

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Netherlands		MemberState	8
Comment received				
The Dutch CA does not support the proposal to adapt the classification as Aquatic Acute 1 (M=100) and Aquatic Chronic 1 (M=10). Effect concentrations expressed as mean measured test concentrations are preferred to effect concentrations expressed as initial measured test concentrations. Consequently, this could affect the M factor for chronic aquatic classification.				
Dossier Submitter's Response				
OIT is an isothiazolinone with a specific mode of action in algae which means mean measured concentrations would not represent the environmental hazard for algae. More specifically, OIT is taken up by algal cells and transformed so it no longer exists. This process occurs rapidly and induces algal toxicity. This means that test item losses vary between treatments – at high doses, losses are in fact lower because algal uptake declines as the cells die (i.e. fewer viable algal cells remain). Mean measured endpoints would be unrealistically conservative as they would not reflect the dose required to induce the observed level of toxicity. This conservativeness increases with lower exposure concentrations and with time. Therefore, it is unclear how representative a dose-response curve based on mean measured endpoints would be. This would not provide an accurate model to predict the				

test item concentration required to induce the observed level of toxic response, i.e. an E_rC_{50}.
On this basis, taking a non-standard approach (i.e. endpoints based on initial measured concentrations when >20% losses) is considered appropriate to describe the level of test substance required to produce a specific toxic response regardless of exposure time.

This approach was recently discussed for another isothiazolinone (MBIT, CAS:2527-66-4) at RAC-45 and agreed as appropriate with algal hazard classification endpoints based on initial measured concentrations.

Overall, we consider the OIT hazard classification should reflect algal endpoints based on initial measured concentrations.

RAC's response

RAC agrees with the Dossier Submitter's view.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Switzerland	Dow Europe GmbH and Thor GmbH	Company-Manufacturer	9

Comment received

See attachment

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Manufacturers Comments on the Human Health Hazards of OIT.docx
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Koralone confidential composition.xlsx

Dossier Submitter's Response

Acute Oral Toxicity
We note the different values obtained with 96.4% active and the substance formulated with propylene glycol. From the information available to us, it is our understanding that the 1987, 1977 and 1991 studies were conducted on a solution consisting of OIT (46.7 or 45%) and propylene glycol only. Therefore, we remain of the opinion that these studies cannot be discounted and support classification in Category 3.

Acute Inhalation Toxicity
Again, we note the discrepancies in the data between the nose only and whole body exposure studies. However, whilst the possibility of additional exposure cannot be ruled out in the whole body study, it is not clear whether this accounts entirely for the discrepancy in the LC50 values identified in the two studies. In the whole body study, necropsy revealed gas-filled stomachs in the decedents; the study summary notes that this finding is often seen in rats that die as a result of respiratory distress and is due to swallowing air during attempts to breath. As such, it is proposed that the results of the whole-body study cannot be discounted and support classification in Category 2.

We note the comments regarding the low (lack of) potential for exposure to OIT during normal use. However, the CLH dossier provides an assessment of how the substance should be classified based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation.

Specific Concentration Limit
Please see the response to comments 14 and 15.

RAC's response
RAC notes that the comment agreed with the DS with respect to classification for acute dermal toxicity. In the case of acute oral and inhalation toxicity RAC agrees with the DS's response.

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Germany		MemberState	10
Comment received				
The proposal for classification is supported. Due to the numerous data available for acute oral, dermal and inhalative toxicity also the ATE-Values, which are the basis for classification as Acute Tox. 2, H330, Acute Tox. 3, H311 and Acute Tox. 3, H301 should be harmonised and included into column "specific Conc. Limits, M-factors, ATE". Only with harmonised ATE-Values it is possible to correctly classify a mixture containing octhilinone for its acute toxicity.				
Dossier Submitter's Response				
Thank you for the support and the comment about the future application of ATE values.				
RAC's response				
Thank you for the comment. In its opinion, RAC proposes ATE values for all three routes of exposure.				

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Germany	Thor GmbH	Company-Manufacturer	11
Comment received				
Acute oral toxicity As Applicant we disagree with the Acute Tox 3 classification proposed for OIT for the oral route since the study selected as key is a study conducted on a formulated OIT product (Anonymous 1991b) and not on the technical grade active substance. The study selection is not considered appropriate especially since a more recent, guideline and GLP compliant study conducted on technical grade material of purity 96.4 % OIT is available and presented in the dossier (Anonymous 2002a). Considering the LD50 of 500-2000 mg OIT/kg bw (Anonymous 2002a), we suggest that the current harmonised classification of Acute Tox Category 4 should be maintained for OIT. Acute inhalation toxicity As manufacturer supporting the active substance OIT we question the relevance to the end user of labelling OIT for inhalation hazards based on its physicochemical properties, form placed on the market and potential inhalation exposure during normal use. The potential of inhalation exposure to OIT during intended, known or reasonably expected use is not foreseen. Hence, classification for acute inhalation toxicity for the technical material is not warranted. For the same reason supplementary labelling with both EUH 071 (corrosive to the respiratory tract) and STOT SE 3 (transient respiratory tract irritation and narcotic effects) is not justified and should be disregarded. However, should classification for acute toxicity via inhalation be maintained, the key study for classification should be the one performed as nose-only exposure (Anonymous 1986) which would result in Acute Tox Category 3 as the appropriate conclusion. The other acute inhalation toxicity study available used whole-body exposure which we consider inappropriate since considerable exposure both orally (due to grooming), and				

dermally cannot be excluded. These additional exposure routes increase the exposure to the substance significantly and must be considered as irrelevant routes for the classification of the acute inhalation endpoint.

Please note that Thor GmbH fully supports the detailed comments jointly prepared by the manufacturers Dow and Thor GmbH in the document "Manufacturers Comments on the Human Health Hazards of OIT" submitted as public attachment by Dow.

Dossier Submitter's Response

Acute Oral Toxicity

We note the different values obtained with 96.4% active and the substance formulated with propylene glycol. From the information available to us, it is our understanding that the 1987, 1977 and 1991 studies were conducted on a solution consisting of OIT (46.7 or 45%) and propylene glycol only. Therefore, we remain of the opinion that these studies cannot be discounted and support classification in Category 3.

Acute Inhalation Toxicity

Again, we note the discrepancies in the data between the nose only and whole body exposure studies. However, whilst the possibility of additional exposure cannot be ruled out in the whole body study, it is not clear whether this accounts entirely for the discrepancy in the LC50 values identified in the two studies. In the whole body study, necropsy revealed gas-filled stomachs in the decedents; the study summary notes that this finding is often seen in rats that die as a result of respiratory distress and is due to swallowing air during attempts to breath. As such, it is proposed that the results of the whole-body study cannot be discounted and support classification in Category 2.

We note the comments regarding the low (lack of) potential for exposure to OIT during normal use. However, the CLH dossier provides an assessment of how the substance should be classified based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation.

Specific Conentration Limit

Please see the response to comments 14 and 15.

RAC's response

RAC agrees with the Dossier Submitter's view.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Germany		MemberState	12

Comment received

Based on the data presented a classification of octhilinone (OIT) as a skin sensitizer category 1A with a strong to extreme potency is supported. Additionally, the proposal to reduce the current SCL is supported.

However, according to the CAR (UK, 2017) for the approved biocidal active substance OIT in PT 8 (wood preservatives) "a potential for cross-sensitisation between OIT and other isothiazolins has been demonstrated". No reference is given, but recent publications (Schwensen JF, et al. (2017), Aalto-Korte and Suuronen 2017)) support the finding of cross-reactivity between MI (2-methyl-2H-isothiazol-3-one (CAS: 2682-20-4) and OIT. In the CLH report a "cross-potential" observed in two Buehler assays is mentioned, but the data are not presented.

A comparison shows that sensitising capacity of OIT is similar to or even stronger than that of MI. Based on potency data from animal tests MI was considered a "strong" and OIT a "strong to extreme" sensitizer. For a strong sensitizer a GCL of 0.1 % applies, but RAC decided in 2016 to apply a SCL of 0.0015% (15 ppm) for MI due to cross reactivity to CMI (5-chloro-2-methyl-2H-isothiazol-3-one (CAS: 26172-55-4) based on an SCCS Opinion.

While older (Frank 2000a, b; Frank 2001) repeated insult patch test studies in human volunteers with OIT are the basis for proposing the SCL of 0.005% (0.01% OIT in body lotion; max. 3/207 (1.45%) sensitised subjects), the authors of a recent publication (Aalto-Korte and Suuronen 2017) have found that allergic reactions to OIT have become common during the MI allergy epidemic. Their data show that between 2012 and 2017 2.9% of 647 consecutively tested patients reacted to OIT (0.1% OIT in petroleum) and that patients showing (extreme) reactions to MI also reacted to OIT. Therefore it cannot be excluded that patients previously sensitised to MI will react to products containing OIT.

As the chemical structure of OIT is closely related to other isothiazolinones (especially MI) the cross-reactivity should be considered in SCL-setting to reduce the likelihood that OIT contributes to the rise in isothiazolinone allergy.

References:

Schwensen, J.F. et al. (2016) Cross-reactivity between methylisothiazolinone, octylisothiazolinone and benzisothiazolinone using a modified local lymph node assay Contact Dermatitis 176(1): 176-183.

Aalto-Korte, K., Suuronen, K. (2017) Patterns of concomitant allergic reactions in patients suggest cross-sensitization between octylisothiazolinone and methylisothiazolinone, Contact Dermatitis 77(6): 385-389.

Editorial comments: In table 12 a number of 222 subjects is given for the study by Frank J (2001). On page 32, third paragraph, a number of 207 subjects is given for the same study.

In table 12 no vehicle is given for the study by Emmet 1989. Subsequently different specifications are given: Tween-85 in table 13, petroleum and Tween-85 in the study summary on page 31, propylene glycol on page 32 last paragraph.

Additional comment concerning Respiratory Sensitisation:
Indications from human case studies for chemically similar substance MIT were reported. However, no test results are available for OIT. It should be noted that no validated test systems for this endpoint are available up to now. Based on this, data seem to be lacking for classification.

Dossier Submitter's Response

We recognise the potiential for someone already sensitised to one member of the isothiazolinone class of substances to be sensitive to subsequent exposure to another.

In CLP, provision is made for such sensitivity by application of the labelling phrase EUH208, which usually relates to mixtures containing the skin sensitiser at levels as low as 10% of the concentration limit set for classification. If a specific concentration limit of 50 ppm were agreed for OIT, the "standard" limit for EUH208 would thus be 5 ppm. In

contrast, this labelling phrase is applied at levels as low as 1.5 ppm for mixtures containing C(M)IT/MIT or MIT. Given the potential for cross-sensitivity, RAC may wish to consider if such a limit for EUH 208 could also be applied to OIT to ensure protection of those significant numbers of people already sensitised to this class if substance.
RAC's response
Thank you for your comment and for citing pertinent publications. RAC agrees that cross-reactivity with related isothiazolinones has to be taken into consideration.

Date	Country	Organisation	Type of Organisation	Comment number
17.04.2018	Germany	German Paint and Printing Ink Association (VdL)	Industry or trade association	13
Comment received				
Concerning the isothiazolinones it is expected that the implementing regulation approving the active substance 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 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 in DIY paints has severe socioeconomic consequences, which need to be considered.				
Dossier Submitter's Response				
Thank you for this additional information about the importance of this substance to industry and the request that consumer paints classified as having skin sensitising potential be allowed to remain on the market. Our dossier provides an assessment of how the substance should be classified, based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation. It was not for this dossier to assess the impact of the classification, or the way in which products containing OIT (or other senstisers) may in future be viewed under the Biocide Product Regulation.				
RAC's response				
RAC notes that this comment does not relate to the hazardous properties of OIT, and agrees with the DS's response.				

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Germany	Thor GmbH	Company-Manufacturer	14
Comment received				
We agree with the Dossier Submitter that on the basis of the animal data presented and principally the results of the 3 local lymph node assays (LLNAs) conducted on the technical grade OIT material, the appropriate classification for OIT is as a Dermal Sensitiser Subcategory 1A, with strong potency (in accordance with the Guidance on the application of the CLP Criteria (version 5.0), section 3.4.2.2.5). For dermal sensitisers with the potency 'strong' a GCL of 0.1% (w/v) is applied according to Table 3.9 of the CLP				

guidance. However, we note that under the harmonised classification for OIT the SCL for skin sensitisation is 0.05% (w/v). Following the argumentation line provided in the detailed comments jointly prepared by the manufacturers Dow and Thor GmbH (cf. "Manufacturers Comments on the Human Health Hazards of OIT" submitted as public attachment by Dow) we consider the current SCL for skin sensitisation of 0.05% (500 ppm) as sufficiently protective and thus this limit should be maintained.
Dossier Submitter's Response
Thank you for your careful assessment of the data relating to this endpoint and for the alternative proposal for consideration by RAC. We maintain our view that a SCL of 50 ppm is appropriate and justified for this substance.
RAC's response
RAC notes that the comment agreed with the DS with respect to classification for skin sensitisation and the proposal to maintain the current SCL.

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Switzerland	Dow Europe GmbH and Thor GmbH	Company-Manufacturer	15
Comment received				
See attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment Manufacturers Comments on the Human Health Hazards of OIT.docx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Koralone confidential composition.xlsx				
Dossier Submitter's Response				
Thank you for the additional data and your careful assessment of the data relating to this endpoint and for the alternative proposal for consideration by RAC. We maintain our view that a SCL of 50 ppm is appropriate and justified for this substance.				
RAC's response				
Thank you for your analysis, and for providing recent publications relating to cross-reactions of OIT to related isothiazolinones and case studies involving OIT. They have been taken into account in the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2018	Finland	European Environmental and Contact Dermatitis Research Group (EECDRG)	International NGO	16
Comment received				
pages 4, 29-35 The proposed specific concentration limit for skin sensitization is not low enough to protect workers and consumers. We recommend a specific limit of 0.0015%. ECHA note – An attachment was submitted with the comment above. Refer to public attachment EECDRG statement_to_Proposal for Harmonised Classification and Labelling of OIT_08052018.pdf				

Dossier Submitter's Response
Thank you for your careful assessment of the data relating to this endpoint and for the alternative proposal for consideration by RAC. We maintain our view that a SCL of 50 ppm is appropriate and justified for this substance. In CLP, provision is made for such sensitivity by application of the labelling phrase EUH208, which usually relates to mixtures containing the skin sensitiser at levels as low as 10% of the concentration limit set for classification. If a specific concentration limit of 50 ppm were agreed for OIT, the "standard" limit for EUH208 would thus be 5 ppm. In contrast, this labelling phrase is applied at levels as low as 1.5 ppm for mixtures containing C(M)IT/MIT or MIT. Given the potential for cross-sensitivity, RAC may wish to consider if such a limit for EUH 208 could also be applied to OIT to ensure protection of those significant numbers of people already sensitised to this class of substance.
RAC's response
Thank you for your analysis, and for providing recent publications relating to cross-reactions of OIT to related isothiazolinones and case studies involving OIT. They have been taken into account in the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2018	Italy	<confidential>	Company-Downstream user	17
Comment received				
with the proposed limit C ≥ 0,05 % we will have a strong impact on the final classification on our water based products				
Dossier Submitter's Response				
Thank you for this additional information. To clarify, our dossier provides an assessment of how the substance should be classified, based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation. It was not for this dossier to assess the impact of the classification, or the way in which products containing OIT (or other senstisers) may in future be viewed under the Biocide Product Regulation.				
RAC's response				
RAC agrees with the Dossier Submitter's view.				

Date	Country	Organisation	Type of Organisation	Comment number
07.05.2018	Belgium	EPDLA (European Polymer Dispersion and Latex Association), Cefic Sector Group	Industry or trade association	18
Comment received				
General comments for the ECHA public consultation on the proposed harmonised classification and labelling of OIT The following represents a statement of the European Polymer Dispersion and Latex Association - EPDLA – a Cefic Sector Group: The members of EPDLA welcome the opportunity to comment on the proposed harmonised classification and labelling of 2-octyl-2H-isothiazol-3-one (OIT – CAS 26530-20-1). We are aware that the ECHA consultation on the harmonised classification and labelling (CLH) of OIT mainly aims to collect comments on the proposed hazard classes. For this purpose, we fully support the scientific and technical arguments brought forward				

by the OIT manufacturers. We urge that all available data relevant to the substance are reviewed and considered during the future discussions on OIT.
We wish to draw attention to the implications of the proposed classification of OIT in the context of the Biocidal Products Regulation (EU) 528/2012 (BPR), and more specifically the proposal regarding the endpoint of skin sensitisation. OIT is under review for approval as an in-can preservative (product-type 6) under the BPR and may be used for such purpose in polymer dispersions.
The current proposal of the dossier submitter reduces the specific concentration limit (SCL) for the endpoint skin sensitisation from 0.05% to 0.005 %. With the proposed reduced specific concentration limit, the biocidal use of OIT would also be significantly restricted.
This CLH proposal therefore challenges the availability of OIT as a preservative and adds to the increasing complexity which industry is facing to ensure the in-can preservation of waterborne products. The difficulties raised by the one-by-one restrictions of key in-can preservatives have been highlighted to the responsible authorities together with other industry associations .
The technical and regulatory requirements of the BPR and the CLP are reducing the already small number of options for in-can preservation of polymer dispersions. We therefore call for a holistic view on in-can preservatives under the BPR to avoid the negative consequences of losing adequate in-can preservation on consumers' health and the environment.
We therefore ask you to consider our comments in future discussions of the proposed harmonised classification and labelling of OIT.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment EPDLA-Comments on CLH of OIT.pdf

Dossier Submitter's Response

Thank you for this additional information about the importance of this substance to industry and the request for a wider view on in-can preservatives under the Biocide Products Regulation.

Our dossier provides an assessment of how the substance should be classified, based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation. It was not for this dossier to assess the impact of the classification, or the way in which products containing OIT (or other senstisers) may in future be viewed under the Biocide Product Regulation.

RAC's response

Thank you for your comment.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2018	Finland		MemberState	19

Comment received

OIT is currently classified as a skin sensitiser in Category 1, with a specific concentration limit of 0.05%. It is proposed to update this classification to Skin Sens Category 1A with a new specific concentration limit (SCL) of 0.005% based on the available human data.

There are three local lymph node assays (LLNA), Buehler test and a maximisation test in guinea pigs available. In the most reliable LLNA study (Anonymous 2003) the stimulation index was found to be greater than 3 for OIT at doses ≥ 0.5 %. An EC3 of 0.46 % (w/v)

was derived from this study. In all three LLNAs available, the EC3 value was between 0.24 and 0.66 %. The EC value meets the criteria for cat. 1A, according to which EC3 value should be ≤2%. In a guinea pig maximisation Test (GPMT), 100 % of animals showed a response to a 1 % intradermal induction concentration (lowest test concentration). The response rate fulfils the CLP criteria for cat. 1A. In a Buehler test 20 % of animals showed a response at a 0.005 % topical induction dose. The response rate fulfils the CLP criteria for cat. 1A. Based on the results from the LLNA and GMPT studies, the skin sensitisation potency category for OIT can be determined to be "strong" or "extreme".

There are four insult patch test studies investigating the skin sensitisation potential of OIT in humans. In two human repeat insult patch tests, positive responses were observed at a dose of 5 µg/cm2 skin in some volunteers. According to CLP, a positive response observed at ≤ 500 µg/cm2 provides evidence for classification in cat. 1A.

In the study by Emmet et al. (1988) sensitisation reactions were seen in 5/20 volunteers in-duced/challenged with 1000 ppm (0.1%) OIT and in 1/20 volunteers at 500 ppm (0.05 %) OIT. In this study OIT was applied with petroleum and Tween-85 as a vehicle. In the first study by Frank (2000a) no skin sensitisation was observed in 103 subjects induced and challenged with 50 ppm (0.005 %) OIT. In the second study by Frank (2000b) the induction and challenge con-centration of 100 ppm (0.01%) resulted skin sensitization in 1/222 subjects. In these studies, OIT was applied in an aqueous solution. In the third study by Frank (2001) skin sensitisation was observed in 3/222 subjects induced and challenged with 100 ppm OIT in body lotion. In the above mentioned studies, a sensitisation reaction was confirmed by re-challenge.

Based on the available information in the CLH dossier, very low incidences of sensitized indi-viduals have been reported in the studies. The Finnish CA considers that the data represents a borderline case for a lower SCL limit. No sensitised individuals was observed at the exposure level of 50 ppm (0.005 %). However, the Buehler test showed response at a 0.005 % topical induction dose.

Overall, the Finnish CA supports the proposed classification as Skin Sens. 1A, H317 (May cause an allergic skin reaction). The proposal for lowering the SCL to 0.005% needs further discussions.

Dossier Submitter's Response

Thank you for the careful assessment of the data and your agreement on the classification with Skin Sens. 1A, H317.
We welcome a full consideration by RAC of all the information relating to the setting of a specific concentration limit for this classification, which we feel should be 50 ppm. As discussed under Comment 12, RAC may wish to consider the possible provision of a lower limit for the additional labelling phrase EUH208 to address concerns that have been highlighted about the potential for cross-sensitisation.

RAC's response

RAC notes that the comment agreed with the DS with respect to classification for skin sensitisation and noted the proposal for discussion on an SCL for OIT.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON OCTHILINONE (ISO); 2-OCTYL-2*H*-ISOTHIAZOL-3-ONE; [OIT]

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2018	Belgium	CEPE	Industry or trade association	20
Comment received				
The revised proposed threshold for skin sensitization ten times lower than the existing level is of concern to us ECHA note – An attachment was submitted with the comment above. Refer to public attachment CEPE input public consultation OIT 201803.pdf				
Dossier Submitter's Response				
Thank you for this additional information about the importance of this substance to industry. Our dossier provides an assessment of how the substance should be classified, based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation. It was not for this dossier to assess the impact of the classification, or the way in which products containing OIT (or other senstisers) may in future be viewed under the Biocide Product Regulation.				
RAC's response				
RAC agrees with the Dossier Submitter's view.				

Date	Country	Organisation	Type of Organisation	Comment number
04.05.2018	Norway	Jotun A/S	Company-Downstream user	21
Comment received				
See general comments.				
Dossier Submitter's Response				
Thank you for this additional information about the importance of this substance to industry and the request that consumer paints classified as having skin sensitising potential be allowed to remain on the market. Our dossier provides an assessment of how the substance should be classified, based on it's inherent hazards, using the information available to us in accordance with the CLP Regulation. It was not for this dossier to assess the impact of the classification, or the way in which products containing OIT (or other senstisers) may in future be viewed under the Biocide Product Regulation.				
RAC's response				
RAC agrees with the Dossier Submitter's view.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Germany	Thor GmbH	Company-Manufacturer	22
Comment received				
Please refer to above comments made for acute inhalation toxicity.				
Dossier Submitter's Response				
Please see response to comments 9 and 11.				

RAC's response
RAC has noted the comments on inhalation toxicity.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	France		MemberState	23
Comment received				
We agree with the proposed classification for the acute toxicity: H400, M-factor = 100. However, we disagree with the proposed M-factor for the chronic classification. According to the biocidal peer-review of the OIT substance, UK has stated in its draft final CAR that Navicula pelliculosa is the most sensitive species for chronic toxicity. The study was considered valid and a NOEC = 0.071 µg OIT/L has been determined. This value was also used to derive the PNECfreshwater. Therefore, we are of the opinion that this lowest NOEC should be taken into account for chronic classification and the chronic M-factor should be 1000 instead of 10.				
Dossier Submitter's Response				
An algal growth inhibition study with *Navicula pelliculosa* is available (CLH report reference Porch et al, 2011) which is included in the CLH report. The study was provided by industry and reviewed for the purpose of CLH which noted that study controls were only valid for the time period 0 to 48 hours. At the time of initial CLH drafting, it was unclear if shorter duration, non-standard algal endpoints (i.e. 48 hours) were appropriate for hazard classification. The 2016 RAC opinions of MIT (CAS: 2862-20-4) and C(M)IT/MIT (CAS: 55965-84-9)] concluded that shorter duration chronic endpoints are relevant if validity criteria are met. OECD TG 201 (July 2011) validity criteria were met for 0-48 hours including exponential growth over this period. Therefore, a chronic E_rC_{10} from the study is considered valid. Reflecting the OIT mode of action it is appropriate that the endpoint should be based on initial measured (im) concentrations (refer to response to comment 8 regarding use of initial measured endpoints). Based on statistical analysis (CLH report reference Industry analysis, July 2016) and initial measured concentrations, the 48-h E_rC_{10} is 0.000224 mg/l. The Porch et al, 2011 study was simultaneously reviewed in 2016 for Dir. 98/8/EC. This also concluded that only 0-48h endpoints were valid. The review proposed a 48-hour NOEC of 0.000071 mg/l which reflects the lowest treatment as a geometric mean of initial measured concentration and half the Limit of Quantification (LoQ) at 24 and 48 hours. While analytical measurement was not conducted at 24 and 48 hours, the review conservatively considered it was likely the test item would be <LoQ. This NOEC does not appear to be statistically derived as it is noted that due to poor controls the statistical sensitivity of the study is compromised. Instead the review notes that little or no inhibition was observed at the lowest treatment and therefore considers it the NOEC. For the purpose of hazard classification the 48-h E_rC_{10} of 0.000224 mg/l (im) is preferred given its statistical basis compared to the NOEC presented in the CAR.				

It is noted that this value is in the M-factor range 0.0001 to 0.001 mg/l which would result in a revised M-factor of 100 for a non-rapidly degradable substance.
RAC's response
RAC agrees with the Dossier Submitter's view and the opinion has been drafted accordingly.

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Netherlands		MemberState	24
Comment received				
Degradation: Octhilinone is not readily biodegradable (0% mineralization after 28 days, but microbial inhibition cannot be excluded), and hydrolytically stable at pH 4, 7 and 9. Surface water simulation study (OECD TG 309) reported for octhilinone DT50 values (normalized to 12 °C) of 1.1 and 2.3 days, representing rapid primary degradation. Mineralization after 29 days amounted to 36.4-47.9% of applied radioactivity (AR). Three metabolites detected above 10% AR, but not identified. Simulation study using seawater (OECD TG 309) yielded DT50 values normalized to 12 °C of 3 and 4 days, and mineralization of 44.6% AR after 17 days. Various metabolites observed at concentrations less than 10 % AR, but not identified. Can agree with conclusion that octhilinone should not be considered rapidly degradable for classification purposes, as mineralization <70% within 28 days, and while rapid primary degradation observed, it cannot be excluded that one or more metabolites could be classified for environment (in fact, a metabolite identified in photolysis study, NNOMA, meets classification criteria). Bioaccumulation: Surface active substance (35.97 mN/m at 20°C) so HPLC estimated log Kow values (2.5-2.9) not reliable. Log Kow of >3.1 calculated from separate water and octanol solubilities. Acceptable method for surface active substances. However, as experimental BCF is available not very critical. Lipid corrected (but not growth) are 843 and 886 L/kg, exceeding threshold of 500 L/kl. So agreed that octhilinone has potential to bioaccumulate. Ecotoxicity: Data rich CLP dossier. Octhilinone is an isothiazolone biocide, with algae being most sensitive taxon. Agreed to use ErC10 instead of NOE¬rC, also when NOEC lower value. The dossier submitter deviated from standard practice by preferring for acute toxicity ErC50 values determined after 48 hours instead of 72 hours. The 72 hour ErC50 values should be used though. The dossier submitter is requested to justify this deviation. Regarding chronic toxicity agreed that 72 hour ErC10 values should preferably be used instead of 96 hour ErC10 values. For both acute and chronic, effect concentrations expressed as initial measured were chosen instead of mean measured. Mean measured test concentrations should be used though as they reflect the actual concentrations to which the algae have been exposed. For the study by Seyfried (2007) mean measured test concentrations are unfortunately not available for 72 hours, only for 96 hours. The dossier submitter is requested to investigate if 72 hour mean measured concentrations can be extrapolated from the available measurements, or use instead the worst-case 96 hour ErC50 values for classification. This could result in higher M-factor for chronic aquatic toxicity. The study by Hoberg (1996) does report 72 hour mean measured values, but the ErC10 values are less critical compared to 72 hour ErC10 values that are expressed as initial measured. This is unusual, and the Dossier Submitter noted that this				

is due to a better model fit of the data. Nevertheless, mean measured is preferred also for this study.
Dossier Submitter's Response
Thank you for your degradation and bioaccumulation comments. Noting the specific mode of action for isothiazolinones, RAC have previously agreed that shorter duration algal endpoints may be more representative for hazard classification [MBIT (CAS2527-66-4), MIT (CAS: 2862-20-4), C(M)IT/MIT (CAS: 55965-84-9)]. This is because the mode of action induces rapid toxicity and over time cell cultures can recover at lower test concentrations once the test item is depleted. Therefore, RAC previously agreed that more sensitive time-points can form basis of isothiazolinone endpoints. Please refer to response to comment 8 regarding the justification of initial measured endpoints in preference to mean measured endpoints. On this basis, it is not necessary to extrapolate 72 hour mean measured endpoints from 96 hour analytical data. Indeed, it was noted during the RAC MBIT discussion that dose-response curve based on time-weighted endpoints may not be representative and consequently not present an accurate inhibition model due to the difference in losses between treatments.
RAC's response
RAC agrees with the Dossier Submitter's view.

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2018	Finland		MemberState	25
Comment received				
FI CA supports the conclusion that octhilinone is not rapidly degradable but it is potentially bioaccumulative. It was stated in the CLH proposal that the mode of action in algae is rapid with uptake and enzyme effects in minutes affecting cell viability and resulting in cell death over hours. FI CA supports the reasoning in the CLH proposal that due to this special mode of action initial substance concentrations can be used to determine aquatic algae toxicity for classification purposes. The acute aquatic toxicity based on the lowest of the reliable toxicity values is between 0.001 and 0.01 mg/L. There are adequate information on long-term toxicity available for all trophic levels. The chronic aquatic toxicity based on the lowest of the reliable toxicity values is between 0.001 and 0.01 mg/L. Based on classification criteria FI CA supports the proposed environmental classification Aquatic Acute 1, H400 with M-factor of 100 and Aquatic Chronic 1, H410 with M-factor of 10 for octhilinone.				
Dossier Submitter's Response				
Thank you for your support. Please note, it is now proposed to update the chronic M-factor based on the Navicula pelliculosa 48-hour E_rC_{10} (refer to comment 23).				
RAC's response				
Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON OCTHILINONE (ISO); 2-OCTYL-2*H*-ISOTHIAZOL-3-ONE; [OIT]

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2018	Germany	Thor GmbH & Dow Europe GmbH	Company-Manufacturer	26

Comment received

Regarding the Annex 1/ 4.1.2.9 "Rapid degradability of organic substances" of the CLP regulation, there is a strong indication that the results of our studies according to OECD 309 demonstrate rapid degradation of OIT.
After 28 days there is less than 30% of the relevant radioactivity associated with parent substance and its metabolites left in the system. Here, none of the metabolites is classified as hazardous to the environment as proven in the attached metabolite identification study (2017).
Consequently, Thor proposes an M-Factor (chronic) of 10.
In support of the argumentation made above, an additional attachment is provided for consideration by the Rapporteur and RAC.

Please note that the provided attachment "Evidence for rapid degradability of OIT_final.pdf" contains detailed comments that were jointly prepared by the applicants Thor GmbH and Dow Europe GmbH.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2018 05 11_E-Fate comments Thor GmbH.7z

Dossier Submitter's Response

OIT undergoes rapid primary degradation in combination with some mineralisation. Review under Directive 98/8/EC included ecotoxicity endpoints for degradants observed in fate testing. This included NNOMA which was observed during an aquatic photolysis study at 12.5% Applied Radioactivity as a mixture with oxamic acid. The ecotoxicity and fate data for NNOMA indicate it would be classified as Aquatic Acute 1, Aquatic Chronic 2.

The OIT metabolite generation and identification report considers data from the two OECD TG 309 simulation studies (CLH references Mamouni 2007a and 2007b) which were conducted in the dark. During these studies the presence of NNOMA was not confirmed indicating it may be formed under light conditions.

The metabolite report identifies numerous degradants which industry notes are not classified as hazardous. However, fate and ecotoxicity data are not presented (experimental or predicted) for these degradants meaning it is unclear if they meet classification criteria.

We note that the fate studies report significant mineralisation and absorbed radioactivity as follows:

% Applied Radioactivity	**Freshwater (Mamouni, 2007a)**	**Seawater (Mamouni, 2007b)**
CO_2 evolution	36.4 – 47.9 (day 29)	34 – 40.4 (day 17)
Absorbed radioactivity	22.7 – 24.4 (day 29)	36.8 – 44.6 (day 17)

While the study authors consider the absorbed radioactivity to be non-extractable residues (NER), there currently isn't a standard agreed method for determining NER (Refer to ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7b: Endpoint specific guidance Version 4.0 June 2017, section R.7.9.4.1).

In addition, unless there is data to the contrary NER are not currently accounted for in the rate of removal. This is discussed further for persistence assessment (Refer to ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment Version 3.0 June 2017) This states that '*residues should be regarded, in the absence of systematic methodology, as non-degraded substance*, unless, on a case-by-case basis, it can reasonably be justified or analytically demonstrated that a certain part of the residues can be considered to be irreversibly bound. Please note that scientific work is on-going to develop the understanding on NER and that the recommendation above is based on current knowledge and experience.* ** Meaning non-degraded parent substance or as relevant metabolite(s) if such is or are formed*.' We welcome RAC discussion and ECHA guidance in this area. On the basis of the above information, OIT cannot be considered to '*degrade biotically or abiotically in the aquatic environment by >70% in 28 days*' or undergo primary degradation degrade to '*degradation products that do not fulfil the criteria for classification as hazardous to the aquatic environment*' [section 4.1.2.9 of CLP Regulation]. Therefore OIT is considered non-rapidly degradable for hazard classification purposes.
RAC's response
RAC agrees with the Dossier Submitter's view.

PUBLIC ATTACHMENTS
1. 2018 05 11_E-Fate comments Thor GmbH.7z [Please refer to comment No. 26]
2. Manufacturers Comments on the Human Health Hazards of OIT.docx [Please refer to comment No. 3, 9, 15]
3. EECDRG statement_to_Proposal for Harmonised Classification and Labelling of OIT_08052018.pdf [Please refer to comment No. 16]
4. EPDLA-Comments on CLH of OIT.pdf [Please refer to comment No. 18]
5. CEPE input public consultation OIT 201803.pdf [Please refer to comment No. 5, 20]

CONFIDENTIAL ATTACHMENTS
1. Koralone confidential composition.xlsx [Please refer to comment No. 3, 9, 15]