Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

3-iodo-2-propynyl butylcarbamate; 3-iodoprop-2-yn-1-yl butylcarbamate

EC Number: 259-627-5
CAS Number: 55406-53-6

CLH-O-0000007358-66-01/F

Adopted

14 September 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 3-IODO-2-PROPYNYL BUTYLCARBAMATE; 3-IODOPROP-2-YN-1-YL BUTYLCARBAMATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

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

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Substance name: 3-iodo-2-propynyl butylcarbamate; 3-iodoprop-2-yn-1-yl butylcarbamate
EC number: 259-627-5
CAS number: 55406-53-6
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.02.2023	Germany	European Union IPBC Task Force	Company-Manufacturer	1
Comment received				
- ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments IPBC TF_Statement_CL_ENV_public_23-02-16.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL_IPBC TF_Statement_Studies_CL_ENV_23-02-16.zip				
Dossier Submitter's Response				
The attachments in question, which provided a summary of the IPBC Task Force's position to the DS's proposal to amend the M-factor of IPBC for chroninc aquatic toxicity, has been reviewed and its content considered in the DS's response to Comment 9.				
RAC's response				
Please see answer to comment No. 9.				

Date	Country	Organisation	Type of Organisation	Comment number
15.02.2023	Germany		MemberState	2
Comment received				
Please check Table 13 for the application form (dust or liquid aerosol) in which the mixture consisting of 40.1 % active substance was used, as the table and the summary do not seem to be in agreement. Please note that in Annex I to the CLH report (p. 17 section 4.1) table 6.1.3/02/2 (regarding mortality rates) is referred to, but this table does not exist in the document.				

Dossier Submitter's Response

Where the IPBC content of the liquid aerosol is stated in the CLH report, it is given as 40.1% in all cases. In Table 13, the presentation of infomation in column 3 (i.e. 'Test substance (including purity) …' should have more clearly indicated that the dust comprised Technical active substance IPBC (Troysan Polyphase P-100), Purity 98.2% (information in the first and second pargaraphs), whereas the liquid aerosol comprised Technical active substance IPBC (Troysan Polyphase P-100), purity 98.2%, as a liquid formulation comprising 40.1% IPBC (information in the third and fourth pargaraphs). The term 'Dust' should have been placed at the start of the first paragraph, and the term 'Liquid aerosol' at the start of the third paragraph.

Thank you for the observation regarding the missing table (Table 6.1.3/02/2); the table in question is presented below:

Table A6.1.3/02-2: Summary Acute Inhalation Toxicity

Group number	Dose [mg/L]	Type of exposure	Sex	Number of dead / number of investigated	Time of death [day]
I	1.7	Dust	male female	5/5 5/5	1 – 8 1 – 5
II	0.38	Dust	male female	0/5 0/5	-- --
VI	0.72	Dust	male female	3/5 3/5	2 – 7 4 – 7
III	3.4	Liquid Aerosol	male female	5/5 5/5	1 – 3 1 – 3
IV	1.8	Liquid Aerosol	male female	5/5 5/5	1 – 2 1 – 4
V	0.45	Liquid Aerosol	male female	0/5 0/5	-- --
VII	0.75	Liquid Aerosol	male female	4/5 1/5	1 – 2 2
LD_{50} values		dust: 0.68 mg/L for combined sexes 0.67 mg/L for males 0.67 mg/L for females liquid aerosol: 0.78 mg formultion/L for combined sexes 0.63 mg formultion/L for males 0.99 mg formultion/L for females			

RAC's response

RAC has taken note of your comment.

Date	Country	Organisation	Type of Organisation	Comment number
13.02.2023	Germany	European Union IPBC Task Force	Company-Manufacturer	3

Comment received

None

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-02-13_documents submitted for public consultation.zip
Dossier Submitter's Response
The attachment in question, which provided a public summary of the IPBC Task Force's position to the DS's proposal to amend the classification of IPBC for acute inhalation toxicity, and a MSDS-type document, has been reviewed and its content considered in the DS's response to Comment 7.
RAC's response
RAC has taken note of your comment.

Date	Country	Organisation	Type of Organisation	Comment number
06.01.2023	Netherlands	<confidential>	Company-Downstream user	4
Comment received				
IPBC is also used as PT6 in e.g. pigment pastes for the (artist color) paint industry and in our case we use it as an effective fungicide for modelling material for children				
Dossier Submitter's Response				
Reference to use of IPBC as a fungicide for wood preservation (i.e. use in Product Type (PT) 8) in Section 1.2 'Intended uses and effectiveness' of the CLH report was intended as an example. It was included as the CLH report was generated using the 'combined CAR & CLH report template for assessment/proposal for harmonised classification and labelling for biocidal active substances', with the template in question having been used for compliation of the Renewal Assessment Report (RAR) for IPBC in PT8. It is argueable whether Section 1.2 is relevant for the CLH report. Lack of reference to other PTs for which IPBC is an approved active substance will not influence the outcome of the CLH report evaluation.				
RAC's response				
RAC has taken note of your comment.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
16.02.2023	Germany	European Union IPBC Task Force	Company-Manufacturer	5
Comment received				
- ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments IPBC TF_Statement_CL_ENV_public_23-02-16.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL_IPBC TF_Statement_Studies_CL_ENV_23-02-16.zip				
Dossier Submitter's Response				
The attachment in question, which provided a public summary of the IPBC Task Force's position to the DS's proposal to amend the M-factor of IPBC for chroninc aquatic toxicity, has been reviewed and its content considered in the DS's response to Comment 9. (Based on the contents of the attachments listed above, and listed as relevant for Comments 1, 5 and 9 at the end of this document, it seems that Comment 5 should have				

been listed under the heading 'OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment'.)
RAC's response
RAC agrees with the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
15.02.2023	Germany		MemberState	6
Comment received				
The DE CA does not agree with the DS's proposal for a modified classification of 3-iodo-2-propynyl butylcarbamate as Acute Tox. 2, H330. For acute inhalation toxicity two LC50 tests, both according to OECD TG 403 [Doc. No. 523-002, Doc. IIIA, Section A6.1.3/02, 1990 and Doc. No. 523-003, Doc. IIIA, Section A6.1.3/03, 1994) as well as one acute inhalation toxicity limit test according to OECD TG 403 [Doc. No. 523-001, Doc. IIIA, Section A6.1.3/01, 1985] are available. It is argued that, contrary to the former RAC opinion it can be assumed that the unknown components of the mixture used in the acute inhalation toxicity key study (after liquid aerosol exposure) would have no toxicologically relevant effects. Thus, the active substance (40.1 % of which is present in the mixture) would be the only reason for the acute toxic effects. In the DS's opinion this would justify a pro-rata correction and thus, the study would show effects supporting a classification as Acute Tox. 2. Basically, there would be the possibility that the effects are due to the active substance alone. However, in our opinion it cannot be excluded that the unknown ingredients of this mixture have also an acute toxic effect. This is also supported by the acute inhalation toxicity study (Doc. No. 523-003, Doc. IIIA, Section A6.1.3/03), where the LC50 values after exposure to the single substance suggest the existing harmonised classification as Acute Tox. 3. Considering the fact that all three studies listed in the dossier were already available to the RAC at the time of the harmonised classification, the DE CA would not be able to support the modified classification as Acute Tox. 2 (H330) on the basis of these mentioned data and argumentation at the moment.				
Dossier Submitter's Response				
Refer to the DS's response to Comment 7, which notes that the approach taken by the DS in its proposal to modify the classification of IPBC for acute inhalation toxicity may not be justifiable based on information on the composition of the liquid aerosol that was submitted by the IPBC Task Force during the Public Consultation on the CLH report. Regarding the RAC's evaluation (RAC Opinion, November 2012) of the studies of the acute inhalation toxicity of IPBC, the DS believes that the RAC was unaware (due to the manner the data were presented in the DS's CLH report of June 2011) that the LC_{50} values for the liquid aerosol were acutally for the liquid aerosol (containing 40.1% IBPC) rather than being values for IPBC presented as a liquid aerosol (i.e. not corrected for the concentration of IPBC in the aerosol test item). Likewise, the DS believes that potential toxic and or (ant)agonistic effects of other components of the liquid test item were not considered by the RAC. Based on the DS's re-evaluation of the study (including the study's stated intentions and lack of information to suggest that the liquid aerosol was not a simple solvent formulation), the DS proposed pro-rata correction of the LC_{50} values obtained for the liquid formulation.				

Regarding the availability of three studies of the acute inhalation toxicity of IPBC, the DS considers the key study of [redacted] (1990) (Doc. No. 523-002), in which the liquid aerosol (and a dust of IPBC) were tested to be the most reliable. In the study of [redacted] (1994) (Doc. No. 523-003), the LC_{50} value for a composite of two acute inhalation exposure experiments was 0.67 mg/L: in one experiment, the respirable fraction was high (~ 75 – 80%), but the range of tested concentrations too low to allow derivation of a LC_{50}, while in the other experiment the respirable fraction was low (~ 19 – 27%) though the tested concentrations sufficiently high to yield a LC_{50} (0.88 mg/L). As latter value is ~ 0.20 mg/L above the 'composite' LC_{50} value (of 0.67 mg/L), the toxicity observed in the first experiment can be predicted to be equate to a LC_{50} value of ~ 0.50 mg/L. In the study of [redacted] (1985) (Doc. No. 523-001) no particle size distribution was available, and RAC discounted this study.

Below, a brief summary of two additional acute inhalation toxicity studies (i.e. not included in the CLH report of 11.11.2022) and their results is provided. The information presented, and Study Summaries (compiled by the DS) of the two studies, are provided in the document 'Additional data relevant for acute inhalation toxicity classification of IPBC_13.04.2023.pdf' embedded below. The additional studies were performed according to OECD TG 403 'Acute Inhalation Toxicity', version of 7 September 2009 (i.e. the current version) and under GLP. Both studies employed nose-only exposure. Whole-body exposure was used in the studies presented in the CLH report of 11.11.2022. OECD TG 403 notes (Section 12) that nose-only is the preferred mode of exposure. This is re-iterated in Section 5.1.7., Point 83, of the OECD 'Guidance document on inhalation toxicity studies – Series on Testing and Assessment, No. 39', Second Edition of 6 July 2018 (ENV/JM/MONO(2009)28REV1). Both additional studies were compliant with the recommendation of Section 15 of OECD TG 403 for particle size distribution of the test material, i.e. mass median aerodynamic diameters (MMAD) ranging from 1 to 4 µm with a geometric standard deviation (σg) in the range of 1.5 to 3.0.

Additional data relevant for acute in

Brief summary of the studies and their results

Study 1

Performed according to OECD TG 403 and under GLP. Reliability score of 1.

CRL:(WI) Wistar strain rats (5 individuals of both sexes, 3 exposure groups) were exposed (nose-only) to mean achieved atmosphere concentrations of IPBC dust of 0.050, 0.205 and 0.494 mg/L, with acceptable particle size distribution at all exposure concentrations: MMAD (mean & range for the 3 groups) of 2.69 (2.47 – 2.90) µm.

Mortality was observed on Day 1 and 2 post-exposure, with 7 of 10 animals in the highest exposure group, and 6 of 10 animals in the mid exposure group, dying during this period. Refer to the summary of mortality table below.

Study 1: Summary of Mortality

Group number	Dose [mg/L]	Type of exposure	Sex	Number of dead / number of investigated	Time of death [day]
2	0.050	Aerosol (dust) of IPBC	male female	0/5 0/5	– –
3	0.205	Aerosol (dust) of IPBC	male female	4/5 2/5	Day 1 or Day 2 Day 1
1	0.494	Aerosol (dust) of IPBC	male female	4/5 3/5	Day 1 or Day 2 Day 1 or Day 2

All animals that died on-study had collapsed lungs, with the lungs described as "dark discoloration, red, diffuse, all lobes".

Acute inhalation median lethal concentrations (4h LC_{50}) and 95% confidence limits for the IPBC test material were:

Females: 0.33 (not calculated) mg/L
Males: 0.17 (0.05 – 0.42) mg/L
Both sexes: 0.23 (0.13 – 0.45) mg/L

The values for males, females, and the combined sexes fall with the range > 0.05 to ≤ 0.5 mg/L that characterises Category 2 for acute inhalation of dust/mist in the Globally Harmonised Classification System, i.e. Acute Tox. 2, H330 – Fatal if inhaled.

Study 2

Performed according to OECD TG 403 and under GLP. Reliability score of 2.

RccHan™:WIST strain rats (5 individuals of both sexes, 5 exposure groups) were exposed (nose-only) to mean achieved atmosphere concentrations of IPBC as a liquid aerosol (absolute ethanol as solvent) of 0.05, 0.21, 0.52, 0.53 and 5.03 mg/L, with acceptable particle (droplet) size distribution at all exposure concentrations: MMAD (mean & range for the 5 groups) of 1.83 (1.23 – 2.30) µm.

Mortality occurred predominantly during the exposure period and first hour post exposure; all 10 animals in the highest exposure group, and 12 of the 13 animals from the 0.52 and 0.53 mg/L groups that died on-study died during this period. Refer to the summary of mortality table below.

Study 2: Summary of Mortality

Group number	Dose [mg/L]	Type of exposure	Sex	Number of dead / number of investigated	Time of death [day]
5	0.05	Liquid Aerosol (20% w/w IPBC)	male female	0/5 0/5	– –
3	0.21	Liquid Aerosol (20% w/w IPBC)	male female	2/5 2/5	During exposure or Day 1 During exposure or Day 1
4	0.52	Liquid Aerosol (20% w/w IPBC)	male female	3/5 4/5	During exposure During exposure

2	0.53	Liquid Aerosol (40% w/w IPBC)	male female	3/5 3/5	During exposure or 1 hour post-exposure During exposure or Day 1
1	5.03	Liquid Aerosol (40% w/w IPBC)	male female	5/5 5/5	During exposure or 1 hour post-exposure During exposure or 1 hour post-exposure

All animals that died on-study had lungs described as either "pale", "unusually dark", or with "dark patches"; the lungs of some of the animals that survived also showed dark patches. Gaseous distention of the intestine and/or stomach showed a tendency for dose-proportionality, being observed in 5 of the 10 animals (both male and female) the highest exposure group.

Acute inhalation median lethal concentrations (4h LC_{50}) and 95% confidence limits for the IPBC test material were:

Females: 0.303 (non-calculable) mg/L
Males: 0.365 (0.256 – 0.514) mg/L
Both sexes: 0.337 (0.267 – 0.418) mg/L

The values for males, females, and the combined sexes fall with the range > 0.05 to ≤ 0.5 mg/L that characterises Category 2 for acute inhalation of dust/mist in the Globally Harmonised Classification System, i.e. Acute Tox. 2, H330 – Fatal if inhaled.

Key data from the two studies are summarised in the table below.

Key data from the two studies

Study, test animal, form of test item, and mode of exposure	**MMAD** µm (mean & range for exposure groups)	**4h LC_{50} mg/L (median & 95% confidence limits)**		
		females	**males**	**Combined sexes**
Study 1 (2014) CRL:(WI) Wistar rats Dust Nose only	2.69 (2.47 – 2.90)	0.33 (-)	0.17 (0.05 – 0.42)	0.23 (0.13 – 0.45)
Study 2 (2014) RccHan™:WIST rats Liquid aerosol Nose only	1.83 (1.23 – 2.30)	0.303 (-)	0.365 (0.256 – 0.514)	0.337 (0.267 – 0.418)

Conclusion

The two studies are considered to support amendment of the Harmonised Classification of IPBC for the end-point acute inhalation toxicity from 'Acute Tox. 3, H331 – Toxic if inhaled' to 'Acute Tox. 2, H330 – Fatal if inhaled'.

The most appropriate ATE is the value of 0.17 mg/L (dusts and mists) obtained for male CRL:(WI) Wistar strain rats in Study 1.

RAC's response

RAC has taken note of the comment, the two additional studies presented and the conclusion of the DS.

Date	Country	Organisation	Type of Organisation	Comment number
13.02.2023	Germany	European Union IPBC Task Force	Company-Manufacturer	7

Comment received

This comment refers to A.3.2.3. Acute inhalation toxicity:
The CLH report for IPBC (CLH 2022) proposes a change in the Acute Toxicity Estimate (ATE) for inhalation toxicity to 0.31 mg/L and to classify IPBC as Acute Tox. Cat. 2, H330, fatal if inhaled. This value is in the view of the IPBC Task Force an overestimation of the actual ATE of the substance and does not represent the intrinsic inhalation hazard of IPBC. As explained in this document, this value (ATE 0.31 mg/L) should not be considered as it was generated in the presence of co-formulants that adversely influence the intrinsic toxicity of the pure substance.

In the acute inhalation toxicity study with 3-iodo-2-propynyl butylcarbamate (IPBC) performed by Anonymised (1990), Doc No. 532-002, Doc. IIIA, Section A6.1.3/02, two different forms of IPBC were tested: (i) pure IPBC dust and (ii) the liquid formulation Anonymised containing 40% IPBC and 10-15% DMSO as solvent. Further details on the composition can be found in the attached documents.

The LC50 of the dust was reported as 0.68 mg/L whereas the LC50 of the liquid formulation / aerosol was reported as 0.78 mg/L. Although the dust had over twice the active ingredient content of the liquid formulation, the powders´ LC50 was only slightly lower than the LC50 of the liquid formulation. The reason for this difference was unclear and the authors of the inhalation study speculated that the difference could be attributed to particle/lung deposition differences, better absorption properties of the liquid formulation or the toxicity of other ingredients in the liquid formulation.

The particle size distribution of the dust and the liquid aerosol, as well as the toxicological profile of the liquid components could not explain the study results. However, up to 15% (range: 10-15%) of the liquid formulation consists of DMSO which has permeation enhancer properties. The influence of formulations on percutaneous absorption as well as on acute inhalation toxicity studies is well known in scientific literature and in OECD guidelines. In the OECD Guidance Document on Acute Inhalation Toxicity Testing No 39, it is written on page 28, cf 65: "[T]he kind and concentration of vehicle should not interfere with the outcome of the study with regard to the airborne test article's analytical stability or toxicity. Ideally, the vehicle selected should be non-toxic with water being given first preference".

It is considered that up to 15% DMSO in a liquid formulation of IPBC can increase IPBC penetration rates enhancing its transport capacity through membranes. Because the acute toxicity inhalation study was performed as a whole-body inhalation study, DMSO may have enhanced the permeation of IPBC through the skin, orally from fur cleaning, and via the lung. Since DMSO in the formulation can enhance the absorption of IPBC through membranes, study results of a formulation containing DMSO do not represent the true hazard properties of the pure substance. Therefore, the LC50 of the dust reported as 0.68 mg/L is relevant for the acute inhalation toxicity classification of pure IPBC and the LC50 of the liquid formulation containing up to 15% DMSO reported as 0.78 mg test item/L (equivalent to 0.31 mg IPBC/L) represents an overestimate.

In conclusion, the LC50 of IPBC is 0.68 mg/L and IPBC classification with regard to acute inhalation toxicity should remain i.e. H331 (toxic if inhaled), Acute Tox. 3.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-02-13_documents submitted for public consultation.zip

Dossier Submitter's Response

Based on information on the composition of the liquid aerosol formulation submitted by the IPBC Task Force during the Public Consultation on the CLH report, the approach taken by the DS for adjusting the LC_{50} value determined for the liquid aerosol may not be justifiable. Consequently, the adjusted LC_{50} value identified by the DS may not be suitable for amending the acute inhalation classification of IPBC, or for setting an ATE value (dusts and mists) for IPBC. (Accordingly, the acute inhalation toxicity data obtained for the liquid aerosol formulation may not be suitable for supporting the findings of other studies used to set the current classification of IPBC for acute inhalation toxicity.)

Refer to the DS's response to Comment 6, which includes a summary of data from two additional acute inhalation toxicity studies (i.e. not included in the CLH report of 11.11.2022) which are considered to support classification of IPBC as 'Acute Tox. Cat. 2, H330 – Fatal if inhaled), with an ATE of 0.17 mg/L (dusts and mists).

RAC's response

RAC has taken note of your comment.

Date	Country	Organisation	Type of Organisation	Comment number
17.02.2023	France		MemberState	8

Comment received

We agree with the demonstration and work proposed by DK eCA in the CLH report supporting a change of the classification of the substance IPBC from Acute Tox cat 3 H331 to Acute Tox cat 2 H330 (Fatal if inhaled). However, regarding the choice of ATE for IPBC, DK eCA used the ATE derived from both male and female data. FR CA noted that the ATE that would be derived specifically from male data, while keeping the same classification (Acute Tox cat 2 (H330, Fatal if inhaled), is more conservative. Therefore, we suggest to use the most conservative ATE of 0.25 mg/L (derived from males only) instead of the proposed ATE of 0.31 mg/L (derived from combined sexes).

Dossier Submitter's Response

The DS agrees with proposal (and rationale) to use an ATE of 0.25 mg/L (dusts and mists), derived from males only – if the approach to adjusting the toxicity data for the liquid aerosol proposed by the DS is valid. However, as noted in the DS's responses to Comments 6 and 7, the approach it proposes may not be justifiable based on data for the composition of the liquid aerosol submitted by the IPBC Task Force during the Public Consultation on the CLH report.

Please see the DS's response to Comment 6, which includes a summary of data from two additional acute inhalation toxicity studies (i.e. not included in the CLH report of 11.11.2022) which are considered to support classification of IPBC as 'Acute Tox. Cat. 2, H330 – Fatal if inhaled', with an ATE of 0.17 mg/L (dusts and mists).

RAC's response

RAC has taken note of your comment.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
16.02.2023	Germany	European Union IPBC Task Force	Company-Manufacturer	9

Comment received

The IPBC TF holds the opinion that the change of the M-factor from 1 to 10 related to Aquatic Chronic toxicity is not justified.

New studies performed under the BPR for the renewal of the active substance IPBC in PT8 confirm the results of the studies which were evaluated in the context of the harmonized classification of IPBC in 2012. The criteria of the CLP related to the assessment of the M-factor as well as the definition of a substance to be regarded as rapidly degradable have not been changed since.

IPBC has to be considered as rapidly biodegradable. The conclusions drawn in the RAC opinion on IPBC adopted 28 November 2012 which are reflected in the current Annex VI entry are considered to remain valid for the reasons included in the statement. [….]

In the RAC opinion from 2012 it is concluded that the degradation products do not have an impact on the environmental hazard classification of IPBC.
New data are available for PBC (aquatic acute toxicity – algae study) and 2-PBC (aquatic acute toxicity -algae and invertebrates) which supports the conclusion from 2012.
The data were not considered in the published CLH report (IPBC – eCA DK; 11 November 2022). [….]

Based on the degradation data it is concluded that IPBC is rapidly degradable. The DT50 values in water and soil at 12 °C are 1.42 days and 0.266 days, respectively.

The toxicity of the degradation products PBC and 2-PBC regarding aquatic organisms is quite lower than the toxicity of the parent IPBC. Iodide and iodate are both natural substances which are ubiquitously distributed in the environmental compartments and should therefore not be regarded as hazardous to the aquatic environment.

Therefore, it can be concluded that the M-Factor for IPBC for Aquatic Chronic 1 should not be changed from 1 to 10.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments IPBC TF_Statement_CL_ENV_public_23-02-16.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CONFIDENTIAL_IPBC TF_Statement_Studies_CL_ENV_23-02-16.zip

Dossier Submitter's Response

The DS consider that IPBC is not rapidly degradable, please also refer to our response to comment 12. Your statement does not take into account the toxicity of iodine in the environment which is essential for the conclusion on the classification of IPBC. Iodide and iodate being naturally occurring substances is not relevant to the conclusion regarding the classification of IPBC. Please also note that for iodine a harmonised classification as aquatic acute cat. 1 already is in place.

RAC's response

RAC acknowledges that based on a ready biodegradability test according to OECD TG 301F, IPCB is considered as not readily biodegradable. The inherent biodegradability test

according to OECD TG 302 indicate primary degradation, however it cannot be concluded on inherent biodegradability. Test is not suitable for the assessment of rapid degradation due to the lack of DOC data and the optimised conditions in the test that stimulate adaptation of microorganisms increasing the biodegradation potential.

IPBC is hydrolytically stable in aqueous solution at relevant pH with DT50 of 267, 248 and 229 – 539 at pH 5, 7 and 9 respectively at 25 0C. As well IPBC is stable to direct and indirect photolysis in the aquatic environment.

According to the CLP guidance, simulation test data for surface waters are preferred over the aquatic sediment or soil simulation test data in relation to the evaluation of rapid degradability in the aquatic environment. Thus, the aerobic soil degradation study provided in the previous RAC opinion was not taken into account as a new reliable and valid study in two different aquatic systems under aerobic conditions has been provided. The new study following OECD TG 308 in two different aquatic systems under aerobic conditions (river and pond) indicates a mean DT50 of 1.42 days at 12°C. However, ultimate degradation (as mineralisation) was at a level of 49.3% for the river system and 70.6% AR for pond system after 28 days. Mean CO2 formation would be at the level of 59.95% AR after 28 days and do not achieve degradation of > 70 % within 28 days.

In addition, in the river and pond systems two metabolites (PBC and 2-PBC) have been further investigated, although, the iodine-moiety metabolites have not. PBC is the initial metabolite of IPBC and all identified metabolites do not contain the iodine-moiety, so release of iodine from IPBC is inferred. Overall, iodine is a metabolite of IPBC formed during metabolism of IPBC. For the metabolites PBC and 2-PBC, it can be sufficiently demonstrated that they do not fulfil the criteria for classification as hazardous to the aquatic environment. However, it cannot be demonstrated that degradation products from iodine-moiety (iodide, iodate and iodine) do not fulfil the criteria for classification as hazardous to the aquatic environment. Available information shows that iodine has a harmonized classification as Aquatic Acute 1. In addition, the REACH registration specifies that iodine has a NOEC (72 hours) of 0.025 mg/L for aquatic algae. Available information shows that iodide could also be classified as hazardous to the aquatic environment with an LC50 of 0.83 mg/L for *Daphnia magna*.

The CLP guidance indicates that substances are considered rapidly degradable if "*…b) The substance is demonstrated to be ultimately degraded in a surface water simulation test with a half-life of < 16 days (corresponding to a degradation of >70 % within 28 days); c) …if the substance is demonstrated to be primarily degraded biotically or abiotically e.g. via hydrolysis, in the aquatic environment with a half-life <16 days (corresponding to a degradation of >70 % within 28 days), and it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment …*".
Consequently, RAC considers that IPBC is not readily biodegradable and although available data indicates it undergoes primary degradation it cannot be concluded as inherently biodegradable. Is hydrolytically stable and is stable to direct and indirect photolysis in the aquatic environment. IPBC degraded in a surface water simulation test with a half-life < 16 days. However, there are no scientific evidence to demonstrate that ultimate biodegradation (i.e. full mineralisation) has been achieved at level > 70 % within a 28-day period. It cannot be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

Date	Country	Organisation	Type of Organisation	Comment number
15.02.2023	Germany		MemberState	10

Comment received

We fully agree to the proposal to change the chronic M-factor to 10.

Section A4.1.1.2.1: On page 51 it is stated that: "In additional tests it was shown that IPBC is rapidly transformed in the environment to PBC, constituting the major degradation product of IPBC. PBC has a substantially lower toxicity to the environment than IPBC. Refer to section A4.1.1.3.1 Biological sewage treatment." However, there are no additional information given in section A4.1.1.3.1 Biological sewage treatment. If in fact no further data is available, this paragraph should be removed. Otherwise, the information would have to be supplemented accordingly.

Section A4.1.1.3.2: New data from Water/sediment studies were reported but there the geometric means are derived from two points, but the geometric mean value is to be determined from 4 or more data points from a water-sediment system (or soil). Therefore, the corresponding worst case DT50 should be used here instead. In the case of IPBC, however, it would be marginal higher.

Section A4.1.1.3.6 and A4.1.1.3.6.1: It is not quite clear why the information to the soil degradation studies are not relevant for the CLH report. According to the CAR of IPBC, they also show rapid metabolization of IPBC. Otherwise, the corresponding line in the summary table in section A4.1.1.3.7 regarding the soil could also be removed.

Dossier Submitter's Response

Thank you for your support.

The DS agree that the cited sentence from section A4.1.1.2.1 on page 51 should have been deleted.
The DS agree that the DT50 should be based on the worst case DT50 and not the geomean.
As a surface water/sediment simulation test (according to OECD TG 308) is included in the dossier, the DS consider that degradation in soil is not necessary. Please refer to the conditions to determine when a substance is considered not to be rapidly degradable (p. 498-499 of the Guidance on the application of the CLP criteria). Please also refer to DS response to comment 12.

RAC's response

Noted. According to the CLP guidance, simulation test data for surface waters are preferred over the aquatic sediment or soil simulation test data in relation to the evaluation of rapid degradability in the aquatic environment. Thus, the aerobic soil degradation study provided in the previous RAC opinion was not taken into account as a new reliable and valid study in two different aquatic systems under aerobic conditions has been provided.
RAC considers that IPBC is not readily biodegradable and although available data indicates it undergoes primary degradation it cannot be concluded as inherently biodegradable. Is hydrolytically stable and is stable to direct and indirect photolysis in the aquatic environment. IPBC degraded in a surface water simulation test with a half-life < 16 days. However, there are no scientific evidence to demonstrate that ultimate biodegradation (i.e. full mineralisation) has been achieved at level > 70 % within a 28-

day period. It cannot be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

Date	Country	Organisation	Type of Organisation	Comment number
17.02.2023	France		MemberState	11
Comment received				
FR supports the proposal to classify the substance 3-iodo-2-propynyl butylcarbamate (IPBC, CAS number: 55406-53-6) Aquatic Acute 1, H400, M-factor=10, Aquatic Chronic 1, H410, M-factor=10. Nevertheless, we think that acute aquatic toxicity data are relevant for the CLH report and should be added to support the conclusion. We believe that the CLH report should cover all the PTs of the active substance. For now, the CLH report only mentions the PT8, could you please add that it concerns PT6 and 13 as well? Could you please note the following non-critical elements: - P50 in the table: the degree of degradation of the OECD 301F test is 0%, not 24-26%. Indeed, in the study, the degradation of the test item is lower than in the control (i.e -24 to -26% compared to the control). - P50 in the table: the reliability of the 302B study is 2 and not 1. - P59 in the table: please replace "iodidate" with "iodate". - P64 in the table: The test on invertebrates is not an Acute immobilisation but a test on Mortality, reproduction and growth effects of 21 days.				
Dossier Submitter's Response				
Thank you for your support. The DS agree to your comment that acute aquatic toxicity data may be relevant as supporting information. However, no new data on acute aquatic toxicity was provided for the renewal of IPBC in PT8 and you may therefore refer to the previous CLH-report (June 2011) in which all available data can be found. The DS still consider the data submitted for the initial approval of IPBC under the Biocidal Products Directive (98/8/EC) as valid. Reference to use of IPBC as a fungicide for wood preservation (i.e. use in Product Type (PT) 8) in Section 1.2 'Intended uses and effectiveness' of the CLH report was intended as an example. It was included as the CLH report was generated using the 'combined CAR & CLH report template for assessment/proposal for harmonised classification and labelling for biocidal active substances', with the template in question having been used for compilation of the Renewal Assessment Report (RAR) for IPBC in PT8. It is argueable whether Section 1.2 is relevant for the CLH report. Lack of reference to other PTs for which IPBC is an approved active substance will not influence the outcome of the CLH report evaluation. Response regarding non-critical elements: The DS agree to the comment regarding degradation in the OECD 301F test provided on p.50. The DS agree, the reliability of the 302B study is 2 and not 1 (please refer to the study summary in annex 1 to the CLH report). "Iodidate" should have been "iodate" in the table on p. 59.				

The DS agree that the test is not an acute immobilisation test (OECD TG 202). The test was performed as a invertebrate life-cycle test according to the US EPA-FIFRA 72-4 (1982).
RAC's response
Noted. RAC assumes that based on available data and the outcome of the literature search, DS did not propose to change or revise the current harmonized classification on Aquatic Acute. However, for completeness RAC reviews the available data on aquatic acute toxicity. RAC concludes that while the new acute toxicity study for zebra fish (Danio rerio) embryos with 96-h LC50 of 0.349 mg/L is relevant and reliable, it indicates lower toxicity than the available LC50 of 0.067 mg/L for Rainbow trout (Oncorhynchus mykiss) and ErC50 of 0.0530 mg/L for algae Scenedesmus subspicatus. Overall, RAC consider retain the current IPBC classification of Aquatic Acute 1 (H400), with M-factor of 10, based on the valid and reliable aquatic acute endpoints LC50 of 0.067 mg/L for Rainbow trout (Oncorhynchus mykiss) and ErC50 of 0.053 mg/l for Selenastrum capricornutum.

Date	Country	Organisation	Type of Organisation	Comment number
17.02.2023	United Kingdom	Health and Safety Executive	National Authority	12
Comment received				
IPBC (CAS: 55406-53-6) ECHA, 2017 states that where preferred degradation data types (aquatic fate studies listed on preceding page 498) are not available, rapid degradation may be assessed using wider data including soil simulation test data. Previously RAC considered soil simulation data as there were uncertainties regarding available aquatic fate data. However, a new (Anon, 2018) OECD TG 308 study is now available which is considered reliability 1 and should take precedence to soil data. The CLH report includes half-lives from the study demonstrating rapid primary degradation and loss of the iodine species… 'The main degradation pathway of IPBC proceeded in both test systems through the formation of the major metabolites propynyl-butylcarbamate (PBC) and 2-propenyl-butylcarbamate (2-PBC), and finally by the formation of bound residues and CO2'. However, information on ultimate degradation (as mineralisation) is unclear as are levels of iodine species. Is this information available to confirm if IPBC meets the rapid degradation criteria? We note hazard information on iodine species may need to be considered. Some information is already present in Table 20 of the CLH report. However, this does not include a long-term endpoint from the algal study although a NOErC of 0.025 mg/L is included in the online REACH registration for iodine. In terms of chronic toxicity data for IPBC, we note that an ErC10 endpoint is available for the algal study (Anon, 2001) which should be used in preference to the NOEC endpoint. This then results in the long-term NOEC for P. promelas fish (0.0084 mg/L) becoming the most sensitive endpoint for IPBC. In addition, as P. promelas were not the most acutely sensitive fish species, if IPBC is considered not rapidly degradable, the surrogate approach with the acute O. mykiss endpoint should be considered for completeness.				

Finally, given the rapid primary degradation, is further information available regarding the bioaccumulation potential of the degradants?

ECHA (2017) Guidance on the Application of the CLP criteria

Dossier Submitter's Response

Guidance on the Application of the CLP criteria, section 4.1.3.2.3.2, p. 498-499, specifies conditions to be fulfilled in order for a substance to be considered not rapidly degradable (litra a-c).
Litra a is not fulfilled as IPBC was demonstrated not to be readily biodegradable.
Litra b states: The substance is demonstrated to be ultimately degraded in a surface water simulation test with a half-life of < 16 days (corresponding to a degradation of >70 % within 28 days);
In the OECD TG 308 study, two systems was investigated (river and pond). In these systems a mean DT50 of 1.42 days (@ 12°C) was determined, but the $^{14}CO2$ formation was at a level of 49.3% and 70.6% AR (mean = 59.95% AR) at 28 DAT for the river and pond system, respectively. Therefore litra b is considered not fulfilled. In addition, as explained in the CLH report, nor litra c is fulfilled. Therefore the DS consider IPBC to be not rapidly degradable.

The formation of iodine species was not investigated in the OECD TG 308 study. As speciation of iodine is complex and depends mainly on redox potential and pH (Please refer to the CAR for Iodine in PT 1, 3, 4 and 22 (December 2013)), assessment of the fate of iodine in a single study may not bring any usable information.
As a conservative approach, the concentration of iodine species can be predicted by assuming 100% formation of the metabolites (in surface water) and correcting for molecular weight difference. In soil, a 14% formation rate is considered relevant for iodide while a 100% formation rate is considered for iodate (please refer to the CAR for IPBC, PT6 and PT13 and the CAR for iodine in PT1, 3, 4 and 22).

DS response regarding additional information on iodine in the REACH registration dossier available on the ECHA website: Thank you for referring to these additional supportive information.

DS response regarding use of ErC10 instead of NOEC in the algae study: noted. The DS does not consider that this comment changes the conclusion of the CLH report.

The DS is not sure what is meant with the "surrogate approach". The surrogate approach is mentioned for metals in the CLP guidance, but not for organic substances.

DS response regarding bioaccumulation potential of the degradants:
Based on the rapid dissipation of PBC and 2-PBC, bioaccumulation is not considered relevant. In the Danish (Q)SAR database a prediction of Log Kow = 1.64 for PBC was found supporting the conclusion that PBC has a low potential for bioaccumulation (please refer to the embedded document below). The DS consider that 2-BPC similarly will have a low potential for bioaccumulation.

Appendix_comment_12.docx

RAC's response
Noted. Regarding degradation and degradation products please see answer to comment 9. RAC acknowledges that an EC10 is available in the chronic study with algae (Scenedesmus subspicatus). The Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7b / Chapter R.10) and CLP guidance (Part 4) indicate that preference should be given to EC10s over NOECs when available from the same study. Therefore, RAC is of the opinion that the 72-h EC10 of 0.013 mg/L instead of 72-h NOEC of 0.0046 mg/L should be used in classification process according to the CLP criteria. Therefore, RAC concludes that the most sensitive species based on available data becoming to be fish (Pimephales promelas) with a 35-d NOEC of 0.0084 mg/L. Nevertheless, RAC indicates that there are no reliable chronic toxicity data on the most sensitive species under acute toxicity testing. Hence, according to the CLP criteria, classification shall be assessed according to the criteria given in Table 4.1.0(b)(i) and if for the other trophic level adequate acute toxicity data are available according to the criteria given in Table 4.1.0(b)(iii) and should be based on the most stringent outcome: • Based on available chronic toxicity data for fish Pimephales promelas (35 d-NOEC of 0.0084 mg/L), IPCB will warrant classification as Aquatic Chronic 1 with an M-factor of 10 (0.001 < NOEC ≤ 0.01 mg/L), Table 4.1.0(b)(i). • Based on available acute toxicity data for fish Oncorhynchus mykiss (96-h LC50 of 0.067 mg/L), for which no reliable chronic data is available, IPBC warrants classification as Aquatic Chronic 1, with an M-factor of 10 (0,01 < L(E)C50 ≤ 0,1), (Table 4.1.0(b)(iii). Overall, RAC consider that IPCB warrants classification as Aquatic Chronic 1 (H410), with M factor of 10.

PUBLIC ATTACHMENTS
1. Comments IPBC TF_Statement_CL_ENV_public_23-02-16.pdf [Please refer to comment No. 1, 5, 9]
2. 2023-02-13_documents submitted for public consultation.zip [Please refer to comment No. 3, 7]

CONFIDENTIAL ATTACHMENTS
1. CONFIDENTIAL_IPBC TF_Statement_Studies_CL_ENV_23-02-16.zip [Please refer to comment No. 1, 5, 9]