Committee for Risk Assessment

RAC

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

14 September 2023

CLH-O-0000007358-66-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted **on 14 September 2023 by consensus** an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **3-iodo-2-propynyl butylcarbamate;**
3-iodoprop-2-yn-1-yl butyl-carbamate

EC Number: **259-627-5**

CAS Number: **55406-53-6**

Rapporteur, appointed by RAC: **Anna Biró**

Co-Rapporteur, appointed by RAC: **Žilvinas Užomeckas**

Administrative information on the opinion

RAC adopted a first opinion on harmonised classification and labelling of 3-iodo-2-propynyl butylcarbamate (IPBC) on 28 November 2012. IPBC was included in Annex VI to CLP Regulation (EC) No 1272/2008 with ATP06, (see table 1 below).

Denmark has submitted on **11 November 2022** a CLH dossier containing a proposal together with the justification and background information documented in a CLH report.

The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **19 December 2022**.

Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **17 February 2023**.

The only hazard classes open to consultation were acute inhalation toxicity and aquatic toxicity. During the consultation the dossier submitter (DS) itself submitted two new studies concerning acute inhalation toxicity, which were subject to a further targeted consultation (21/04/2023 to 05/05/2023).

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The following table provides a summary of the Current Annex VI entry, Dossier submitter proposal, RAC opinion and potential Annex VI entry if agreed by the Commission.

Table 1 - Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	616-212-00-7	3-iodo-2-propynyl butylcarbamate; 3-iodoprop-2-yn-1-yl butyl-carbamate	259-627-5	55406-53-6	Acute Tox. 3 Acute Tox. 4 STOT RE 1 Eye Dam. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H331 H302 H372 (larynx) H318 H317 H400 H410	GHS06 GHS08 GHS05 GHS09 Dgr	H331 H302 H372 (larynx) H318 H317 H410		M =10 M = 1	
Dossier submitters proposal	616-212-00-7	3-iodo-2-propynyl butylcarbamate; 3-iodoprop-2-yn-1-yl butyl-carbamate	259-627-5	55406-53-6	**Retain** Aquatic Acute 1 **Modify** Acute Tox. 2 Aquatic Chronic 1	**Retain** H400 **Modify** H330 H410		 **Modify** H330 H410		**Retain** M = 10 **Modify** inhalation: ATE = 0.31 mg/L (dusts or mists) M = 10	
RAC opinion	616-212-00-7	3-iodo-2-propynyl butylcarbamate; 3-iodoprop-2-yn-1-yl butyl-carbamate	259-627-5	55406-53-6	Acute Tox. 2 Aquatic Acute 1 Aquatic Chronic 1	H330 H400 H410	GHS06 GHS08 GHS05 GHS09 Dgr	H330 H410		inhalation: ATE = 0.17 mg/L (dusts or mists) M = 10 M = 10	
Resulting Annex VI entry if agreed by COM	616-212-00-7	3-iodo-2-propynyl butylcarbamate; 3-iodoprop-2-yn-1-yl butyl-carbamate	259-627-5	55406-53-6	Acute Tox. 2 Acute Tox. 4 STOT RE 1 Eye Dam. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H330 H302 H372 (larynx) H318 H317 H400 H410	GHS06 GHS08 GHS05 GHS09 Dgr	H330 H302 H372 (larynx) H318 H317 H410		inhalation: ATE = 0.17 mg/L (dusts or mists) M = 10 M = 10	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

IPBC has anti-fungal activity and it has uses that include wood preservative in product type (PT) 8. In PT8, IPBC is active against organisms including wood-rotting fungi (basidiomycetes) and wood-discolouring fungi (blue stain). Biocidal products containing IPBC may be applied to wood via processes such as flow-coating, spraying, vacuum pressure impregnation, automated or manual dipping, and brushing/rolling. The substance has a non-specific mode of action. IPBC has a carbamate structure; the target sites of carbamates in fungi are cell membranes (affecting permeability) and fatty acids.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute inhalation toxicity

Summary of the Dossier Submitter's proposal

The 2022 CLH dossier discussed the same three inhalation studies which were available in the previous CLH dossier (submitted in 2011 and previously considered by RAC). The DS re-interpreted the data in one of the original studies pertaining to exposure to liquid aerosol. All studies lasted for 4 hours, employing whole body exposure, with 5 rats/sex/group.

***Table**: Summary of animal studies originally in the CLH dossier*

Method, Guideline, deviations if any	**Species, Strain, Sex, No/group**	**Test substance**	**Dose levels**	**Value 4h LC_{50}** M: male F: female C: combined sexes	**Reference**
Inhalation, Rat, LC_{50} US-EPA TG 81-3; comparable to OECD TG 403, adopted May 1981 GLP: Yes Reliability: 1	Rat Sprague-Dawley CD® Male, female 5 animals /sex/ group 7 groups	Dust: Technical active substance IPBC (Troysan Polyphase P-100) Purity 98.2% exposure groups' mean MMAD 4.3 µm, range 3.9 – 4.5 µm Liquid aerosol: Technical active substance IPBC (Troysan Polyphase P-100) as a liquid formulation comprising 40.1% IPBC exposure groups' mean MMAD 2.4 µm, range: 1.9 – 2.9 µm	Dust: 0.38, 0.72, 1.7 mg/L 4 hours, whole body Liquid aerosol: 0.45, 0.75, 1.8, 3.4 mg formulation/L 4 hours, whole body	Dust: 0.67 mg/L: M/ F 0.68 mg/L: C Liquid Aerosol: 0.63 mg formulation/L: M 0.99 mg formulation/L: F 0.78 mg formulation/L: C Pro-rata correction of the values for the liquid aerosol 0. 25 mg/L: M 0. 40 mg/L: F 0.31 mg/L: C	Anonymous, 1990
Inhalation, Rat, LC_{50} US-EPA TG 81-3; comparable to OECD TG 403,	Rat Sprague-Dawley Male, female 5/sex/group	Technical active substance IPBC (Omacide® IPBC) Purity 97%	Dust, micronised: 0.16, 0.29, 0.58 mg/L	Dust, micronised: LC_{50} could not be calculated, mortality 3/10 at all dose levels.	Anonymous, 1994

adopted May 1981 GLP: Yes Reliability: 2 A large proportion of the non-micronised material was collected at a sieve size with a cut-off size of 9.8 µm. Consequently, the MMAD values calculated for non-micronised IPBC can only be considered approximate.		<u>Dust, micronised</u>: MMAD (± GSD): 3.5 µm (± 1.9 or 2.0) for each group % respirable: 74.4-80.5% <u>Dust, non-micronised</u>: MMAD (± GSD): 9.6 to 14.2 µm (± 2.8 to 3.6) across the 3 groups % respirable: 19.2-26.7%	4 hours, whole body <u>Dust, non-micronised</u>: 0.49, 1.19, 2.44 mg/L 4 hours, whole body	<u>Dust, non-micronised</u> ~ 0.88 mg/L: C <u>From all mortality data:</u> ~ 0.67 mg/L: C	
Acute inhalation toxicity, Limit test OECD TG 403, adopted May 1981; not fully compliant Reliability: 2 GLP: No The actual test substance concentration and particle size were not determined by analysis.	Rat Sprague-Dawley Male, female 5/sex/group	Technical active substance IPBC Purity 99% dust (claimed non-respirable)	Nominal concentrations: 0 and 6.89 mg/L 4 hours, whole body	> 6.89 mg/L (nominal) M/F	Anonymous, 1985

The DS considered the Anonymous 1990 study - performed according to US-EPA TG 81-3 and GLP - as the key study. Two sets of experiments were carried out, one with dust and one with liquid aerosol. With the substance administered as dust (technical active substance IPBC, purity 98.2%, mass median aerodynamic diameter (MMAD) 4.3 µm, concentrations 0.38, 0.72 and 1.7 mg/L), the LC_{50} values obtained were 0.67 mg/L for males/females and 0.68 mg/L for combined sexes. Administered as a liquid aerosol (concentrations 0.45, 0.75, 1.8 and 3.4 mg formulation/L) with respirable droplet size (MMAD 2.4 µm) generated from a liquid formulation containing 40.1% IPBC, the LC_{50} values originally obtained were 0.63 mg/L for males, 0.99 mg/L for females and 0.78 mg/L for the combined sexes. The DS recalculated the LC_{50} values with corrected concentrations using a factor of 0.6, based on an IPBC content of 40.1% in the liquid formulation. The re-evaluated 4h LC_{50} values for male, female, and combined sexes were 0.25, 0.40 and 0.31 mg/L, respectively.

The supportive study of Anonymous 1994 was also performed according to US-EPA TG 81-3 and GLP. In this case the two sets of experiments were carried out with micronised dust or non-micronised dust. Test concentrations for micronised dust were 0.16, 0.29, and 0.58 mg/L with an MMAD of 3.5 µm (± GSD 1.9 or 2.0), where the % of respirable particles was 74.4-80.5%. No LC_{50} could be calculated for the micronised dust, as at all three concentrations the mortality was 3 out of 10 animals (3/5 females, no male mortality occurred). The DS noted that the chosen concentrations were too low and too closely spaced for an appropriate LC_{50} to be calculated. For non-micronised dust, the test concentrations were 0.49, 1.19, and 2.44 mg/L with an approximate range MMAD of 9.6 - 14.2 µm (± GSD 2.8 - 3.6) across the three groups, with a % of respirable particles between 19.2-26.7%. An LC_{50} of ~ 0.88 mg/L was calculated for non–micronised dust for combined sexes, and an LC_{50} of ~ 0.67 mg/L was calculated for a combination

of micronised and non-micronised dust.

In the third study (Anonymous 1985) animals were administered particles of technical IPBC dust, which were claimed by the Applicant (under biocide approval process) to be non-inhalable/non-respirable. The study was carried out according to the version of OECD TG 403 applicable at the time, with major deviations. Namely, the particle size distribution of the tested IPBC was not measured, and only the nominal, and not the actual test concentration was given. Only one concentration (6.89 mg/L) was used, and a 4h LC_{50} > 6.89 mg/L was estimated.

Based on the recalculated LC_{50} values in the Anonymous 1990 study, the DS proposed classification as Acute Tox. Cat. 2, H330: Fatal if inhaled, with ATE= 0.31 mg/L (dust/mist).

Comments and data received during first consultation

An MSCA commented that in Annex I, the table of the mortality data for the Anonymous 1990 study - referred to in the text in the CLH report - is missing. The DS presented the table in question.

A company commented that IPBC is also used as a fungicide in PT6 in pigment pastes for the paint industry (artist color) and in modelling material for children.

An MSCA agreed with the proposed change of classification to Acute Tox 2; H330, but suggested 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).

An MSCA commented that the acute toxic effect of the unknown ingredients of the mixture used in the liquid aerosol cannot be excluded and the current classification is supported by the acute inhalation toxicity study (Anonymous 1994), where the LC_{50} values suggest the 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 previous harmonised classification, the MSCA did not support the modified classification as Acute Tox. 2 (H330).

The DS replied that the approach taken 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. The DS believed that RAC was not aware (in RAC opinion of November 2012 and due to the way data were presented in the DS's CLH report of June 2011) that the LC_{50} values for the liquid aerosol were not corrected for the concentration of IPBC in the aerosol. Likewise, the DS believed that potential toxic and/or (ant)agonistic effects of other components of the liquid test item were not considered by RAC.

A company-manufacturer clarified that the liquid formulation used in the Anonymous 1990 study containing 40% IPBC also contained 10-15% DMSO which has permeation enhancer properties. Because the 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, the study did not represent the true hazard properties of the pure substance, thus the LC_{50} of the liquid formulation containing up to 15% DMSO reported as 0.78 mg test item/L (equivalent to 0.31 mg IPBC/L) represented an overestimate, and therefore the company-manufacturer disagreed with the classification proposal.

The DS replied that based on the information on the composition of the liquid aerosol formulation, the adjusted LC_{50} value may not be suitable for amending the acute inhalation classification of

IPBC, or for setting an ATE value. 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.

The DS submitted in its response to comments further 2 studies that were not included in the latest CLH dossier:

The additional studies were performed according to OECD TG 403 and GLP. Both studies employed nose-only exposure, and were compliant with the recommended particle size distribution of the test material, i.e. MMAD ranging from 1 to 4 µm with a geometric standard deviation (σg) in the range of 1.5 to 3.0. The purity of the test substance was 99.95%.

Anonymous 2014/1

The study was performed according to OECD TG 403 and GLP. Reliability score was 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 of 2.69 (2.47 – 2.90) µm (mean and range for the 3 groups).

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.

***Table**: Summary of mortality in the Anonymous 2014/1 study*

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, 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

Anonymous 2014/2

The study was performed according to OECD TG 403 and GLP. Reliability score was 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 of 0.05, 0.21, 0.52, 0.53 and 5.03 mg/L (solvent absolute ethanol), with acceptable particle (droplet) size distribution at all exposure concentrations: MMAD of 1.83 (1.23 – 2.30) µm (mean and range for the 5 groups).

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.

***Table**: Summary of mortality in the Anonymous 2014/2 study*

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. Additionally, 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) in the highest dose 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

Conclusion of the DS based on the new evidence

In both of the newly submitted studies the values for males, females, and the combined sexes fell within the range > 0.05 to ≤ 0.5 mg/L that characterises Category 2 for acute inhalation toxicity for dust or mist, i.e. Acute Tox. 2, H330 – Fatal if inhaled. The DS considered the two studies 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'. According to the DS, the most appropriate ATE is 0.17 mg/L (dusts and mists) obtained for male CRL:(WI) Wistar strain rats in Study 1 (Anonymous 2014/1).

Comments received during targeted (second) consultation

The targeted consultation was held on the two additional studies presented by the DS.

An MSCA commented that in light of the additional studies the CA supports the modified classification as Acute Tox. 2 (H330).

A company-manufacturer stated that the two new studies do not belong to the IPBC data set used for the approval of IPBC as biocidal product and were not available for the renewal of IPBC as PT8 under the Biocide Product Regulation. Furthermore, from an animal welfare perspective the studies would not have been necessary. The company-manufacturer questioned the reliability of the study for the following reasons: missing information on how the "achieved concentrations" were determined, objection to the use ethanol as vehicle in the second study, no vehicle control group, and IPBC concentration, homogeneity, and stability in the vehicle not performed.

Assessment and comparison with the classification criteria

There are three inhalation studies described in the CLH dossier (Anonymous 1990, Anonymous 1994, Anonymous 1985) and two other inhalation studies were submitted by the DS during the consultation (Anonymous 2014/1 and Anonymous 2014/2).

The **Anonymous 1990 study** was performed according to US-EPA TG 81-3 and GLP, employing 4-hour whole body exposure. Two sets of experiments were done, one with dust and one with liquid aerosol. With the substance (technical active substance IPBC, purity 98.2%, MMAD 4.3 µm, concentrations 0.38, 0.72 and 1.7 mg/L) administered as dust, the LC_{50} values obtained were 0.67 mg/L for males/females and 0.68 mg/L for combined sexes. Administered as a liquid aerosol (concentrations 0.45, 0.75, 1.8 and 3.4 mg formulation/L) with respirable droplet size (MMAD 2.4 µm) generated from a liquid formulation containing 40.1% IPBC, the LC_{50} values originally obtained were 0.63 mg/L (males), 0.99 mg/L (females) and 0.78 mg/L (combined sexes). The DS recalculated the LC_{50} values with the corrected concentrations based on an IPBC content of 40.1% in the liquid formulation. The re-evaluated 4h LC_{50} values were 0.25 mg/L (males), 0.40 mg/L (females) and 0.31 mg/L (combined sexes). A comment from a company manufacturer during consultation revealed that the formulation also contained up to 15% DMSO, which enhances permeation through membranes. Therefore, DMSO may have enhanced the absorption of IPBC through the skin, orally from fur cleaning, and via the lung during whole body exposure. In consequence, the LC_{50} of the liquid formulation containing up to 15% DMSO represents an overestimation of unknown proportions, rendering this part of the study unreliable.

The **Anonymous 1994 study** was also performed according to US-EPA TG 81-3 and GLP, employing 4-hour whole body exposure. In this case the two sets of experiments were carried out with micronised dust or non-micronised dust. Test concentrations for micronised dust were 0.16, 0.29, and 0.58 mg/L with an MMAD of 3.5 µm (± GSD 1.9 or 2.0), where the % of respirable particles was 74.4-80.5%. No LC_{50} could be calculated for the micronised dust, as at all 3 concentrations mortality was seen in 3 out of 10 animals. For non-micronised dust, the test concentrations were 0.49, 1.19, and 2.44 mg/L with an approximate range of MMAD 9.6 - 14.2 µm (±GSD 2.8 - 3.6) across the 3 groups, with a percentage of respirable particles of 19.2-26.7%. An LC_{50} of ~ 0.88 mg/L was calculated for non–micronised dust for combined sexes, and a 4h LC_{50} of ~ 0.67 mg/L was calculated for a combination of micronised and non-micronised dust.

The **Anonymous 1985 study**, employing 4-hour whole body exposure, was a non-GLP study, administering particles of technical IPBC dust claimed by the Applicant to be non-inhalable/non-respirable. The study was carried out according to OECD TG 403 with major deviations, namely the particle size distribution of the tested IPBC was not measured, and only the nominal and not the actual test concentration was given. Only one concentration (6.89 mg/L) was used, and a 4h LC_{50} > 6.89 mg/L was estimated.

The **Anonymous 2014/1 study** was performed according to OECD TG 403 and GLP, employing 4-hour nose-only exposure. The mean achieved atmosphere concentrations of IPBC dust of were 0.050, 0.205 and 0.494 mg/L, with acceptable particle size distribution at all exposure concentrations: MMAD 2.69 (2.47 – 2.90) µm (mean and range for the 3 groups). The calculated 4h LC_{50} and 95% confidence limits for the IPBC test material were 0.17 (0.05 – 0.42) mg/L (males), 0.33 mg/L (females) and 0.23 (0.13 – 0.45) mg/L (combined sexes).

The **Anonymous 2014/2 study** was performed according to OECD TG 403 and GLP, employing 4-hour nose-only exposure. The mean achieved atmosphere concentrations of IPBC as a liquid aerosol, using absolute ethanol as solvent were 0.05, 0.21, 0.52, 0.53 and 5.03 mg/L, with acceptable particle (droplet) size distribution at all exposure concentrations: MMAD 1.83 (1.23 – 2.30) µm (mean and range for the 5 groups). The calculated 4h LC_{50} and 95% confidence limits

for the IPBC test material were 0.365 (0.256 – 0.514) mg/L (males), 0.303 mg/L (females) and 0.337 (0.267 – 0.418) mg/L (combined sexes). Historical inhalation toxicity data to support the lack of acute inhalation toxicity of the vehicle (absolute ethanol) were not presented, and the homogeneity, concentration and stability of the IPBC test material in liquid test formulations prepared by dissolving IPBC in absolute ethanol were not determined.

Conclusion of RAC

The LC_{50} values in the older studies, which used whole body exposure, vary between 0.67 mg/L (Anonymous 1990, males/females, dust, and Anonymous 1994 combined sexes, non-micronised+micronised dust) and > 6.89 mg/L (Anonymous 1985). The part of the Anonymous 1990 study administering liquid aerosol containing up to 15% DMSO represents an overestimation of the absorption of IPBC, rendering this part of the study unreliable. The LC_{50} values in two of the older studies warrant classification as Acute Tox. 3, as the values are between 0.5 and 1 mg/L.

The two recent studies on the other hand employed nose-only exposure, which is the preferred mode of exposure in the OECD TG 403. In these studies, the LC_{50}-values were in the range of 0.17 mg/L (males) and 0.33 mg/L (females) for dust, and 0.303 mg/L (females) and 0.365 mg/L (males) for liquid aerosol. All the values obtained are in the range for Category 2 ($0.05 < LC_{50} \leq 0.5$ mg/L) for acute inhalation toxicity.

Therefore, on the basis of the Anonymous 2014/1 study, with the Anonymous 2014/2 study as supporting evidence, RAC concludes that classification of IPBC as **Acute Tox 2, H330 (Fatal if inhaled) with an ATE of 0.17 mg/L (dusts or mists) is warranted.**

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

3-iodo-2-propynyl butylcarbamate (IPBC) is currently listed in Annex VI of the Regulation (EC) 1272/2008 (CLP) with harmonised classification and labelling regarding environmental hazards as Aquatic Acute 1 (H400), with an M-factor of 10, and Aquatic Chronic 1(H410), with an M-factor of 1.

No new relevant acute/short term toxicity data to aquatic organisms was submitted during renewal of IPBC under the BPR. However, the DS indicated that in the previous evaluation the "Iodine-moiety" degradation product(s) had not been indicated and considered. Therefore, in contrast to the previous 2012 RAC opinion, the DS proposed that for the purpose of classification and labelling IPBC should be considered as not rapidly degradable after taking into account the iodine degradation product(s). The reason for the DS's proposal to revise the conclusion on the degradability of IPBC was that indicated "Iodine-moiety" degradation products are/is hazardous to the aquatic environment and therefore IPBC cannot be considered as rapidly degradable.

Therefore, the DS proposed to retain classification as Aquatic Acute 1, M = 10 without any changes. The DS proposed Aquatic Chronic 1 with an M-factor of 10, based on IPBC being considered as not rapidly degradable.

Degradation

Biodegradability

No new data was submitted on ready/inherent biotic degradation in water for the renewal of IPBC. Based on a ready biodegradability test (OECD TG 301F), IPBC was considered as not readily biodegradable. The indicated mean biodegradation after 28 days was 24-26 %. Nevertheless, based on modified "Zahn-Wellens / EMPA Test" (OECD TG 302), IPBC was considered by DS as primarily biodegradable, however it was not possible to conclude on the inherent biodegradability. IPBC rapidly transformed (within 2 hours) to propynyl-butylcarbamate (PBC) by releasing the iodine-moiety.

Hydrolysis

No new data was submitted on hydrolysis for the renewal of IPBC. IPBC was found to be hydrolytically stable in aqueous solution at relevant pH. One study indicates a DT_{50} of 267 days at pH 5, 248 days at pH 7, and 229 days at pH 9 (at temperature 25 ± 1°C). Another study indicates that IPBC is not degradable at pH 4, pH 7, orpH9 DT_{50} of 539 days (at temperature 25 °C) was derived.

Photolysis

No new data was submitted on phototransformation in water for the renewal of IPBC. IPBC was considered by the DS to be stable to direct and indirect photolysis in the aquatic environment.

Simulation studies

New data was submitted on aerobic degradation in water for the renewal of IPBC. In a new study following OECD TG 308, the route and rate of degradation of [^{14}C]IPBC was investigated in two different aquatic systems (river and pond). A mean DT_{50} of 1.42 days at 12°C was determined, but the $^{14}CO_2$ formation was at a level of 49.3% and 70.6% AR (mean = 59.95% AR) at 28 days for the river and pond systems, respectively. Two metabolites were further investigated in the study:

- propynyl-butylcarbamate (PBC) with DT_{50} of 14.56 days at 12 °C; and
- 2-propenyl-butylcarbamate (2-PBC) with DT_{50} of 13,75 days at 12 °C.

However, the iodine-moiety metabolites have not been investigated in this study, although iodine-moieties are released during the first degradation step of IPBC into PBC.

In addition, the DS provided an anaerobic water-sediment study. The DT_{50} value for the total system was 3.3 hours at 12°C. IPBC was predominantly found in the water phase. PBC was found to be a major metabolite with a DT_{50} of 26 days at 12°C. Under sterile conditions in a water/sediment system, the DT_{50} of IPBC was 13.3 hours at 22°C, indicating that the IPBC was primarily degraded microbially in the anaerobic system. The study had issues with recovery and with proving the final conversion into of CO_2 into CH_4.

Overall, the DS concluded that IPBC primarily degraded in the aquatic environment with a half-life of < 16 days. However, it could not be demonstrated that all degradation products did not fulfil the criteria for classification as hazardous to the aquatic environment. Therefore, the DS proposed to consider IPBC as not rapidly degradable according to the CLP criteria.

Aquatic Bioaccumulation

No new information regarding aquatic bioaccumulation has been provided by the DS in the CLH report.

Aquatic Toxicity

The DS indicated that for all of the three species (fish, invertebrates, and algae), valid acute and chronic toxicity tests with IPBC were available. As no new data was submitted for freshwater organisms for the renewal of IPBC, a literature review was performed and one new acute toxicity study for zebra fish (*Danio rerio*) embryos was provided by the DS. The 96-h LC50 was 0.349 mg/L derived as the mean of the results from 2 independent tests. DS indicated that in the previous CLH report the provided studies were showing lower LC50 values with the most sensitive fish being Rainbow trout (*Oncorhynchus mykiss*) with an LC50 of 0.067 mg/L (EPA-FIFRA 72-1), and the most sensitive species being the algae *Scenedesmus subspicatus* with an ErC50 of 0.0530 mg/L and a EbC50 of 0.0220 mg/L. As these values show a more sensitive EC50 or LC50, the classification was set from the lowest value, the results from the zebra fish embryo study does not affect the Aquatic Acute classification.

Overall DS did not propose to change the current harmonized classification as Aquatic Acute 1, H400, with an M-factor of 10.

Regarding chronic toxicity, the DS indicated that no new studies on chronic endpoints were submitted for the renewal of IPBC and provide available data for chronic toxicity of IPBC.

Test method	Test organism	Long-term result (endpoint)	Reference / Purity / Klimisch score
Fish			
EPA-FIFRA 72-4, comparable to OECD 210, GLP	*Pimephales promelas*	35 d-NOEC = 0.0084 mg/L	1992, Doc. No. 826-001, IUCLID Section, 9.1.6 / 97.3% / 1
Aquatic invertebrates			
EPA-FIFRA 72-4, OECD 202, GLP	*Daphnia magna*	21 d-NOEC = 0.050 mg/L	1991, Doc. No. 827-001, IUCLID Section, 9.1.6 / 97 % / 1
Algae / other aquatic plants			
92/69/EEC, C3 (1992), OECD 201, GLP	*Scenedesmus subspicatus*	72 h-NOEC = 0.0046 mg/L 72 h-EC_{10} = 0.013 mg/L (calculated from growth rate)	2001, Doc. No. 823-003, IUCLID Section, 9.1.3 / 99,1 % / 1
EPA-FIFRA 122-2, comparable to OECD 201, GLP	*Selenastrum capricornutum*	120 h-NOEC <0.089 mg/L	1994, Doc. No. 823-001, IUCLID Section, 9.1.3 / 97-98 %/ 3

The DS considered that available aquatic chronic toxicity data indicated algae (*Scenedesmus subspicatus*) to be the most sensitive species with a NOEC of 0.0046 mg/L. Therefore, the DS proposed to retain classification as Aquatic Chronic 1. However, the DS noted that the decision on IPBC degradability was a decisive factor in adjusting the M-factor. The first step in the degradation of IPBC is dehalogenation which forms the metabolite PBC and releases the iodine moiety (iodate, iodide, and iodine). Iodine has a harmonized classification as Aquatic Acute 1, H400. For iodide and iodate there are no harmonized classifications. However, the DS noted that for all iodine species the most acutely sensitive species was *Daphnia magna* with LC50 values of 0.83 mg/L, 58.5 mg/L, and 0.59 mg/L for iodide, iodate, and iodine, respectively. Therefore, in addition to the iodine, iodide will also fulfil the criteria for classification as hazardous to the aquatic environment. Hence, the DS considered that it could not be demonstrated that all degradations products of IPBC would not fulfil the criteria for classification as hazardous to the aquatic environment. Consequently, the DS considered that IPBC should be treated as not rapidly degradable according to the CLP criteria and an M-factor of 10 should apply, based on the lowest NOEC of 0.0046 mg/L for *Scenedesmus subspicatus*.

Comments received during consultation

Two Member States (MS), one National Authority (NA), and one Company-Manufacturer (IND) commented on the environmental part of DS's proposals. None of them expressed any objection to remain classification as Aquatic Acute 1, with an M-factor of 10.

Both commenting MSs agreed to the proposal to change the chronic M-factor to 10. Additionally, one MS noted that in the new aerobic water/sediment study the geometric mean values were derived from two points. However, the geometric mean value should be determined from 4 or more data points. Therefore, the corresponding worst case DT_{50} should be used instead of geometric mean. The DS agreed that the DT_{50} should be based on the worst case and not on the geometric mean. The MS also asked why the information on the soil degradation studies was considered not relevant by the DS for the CLH report. The DS indicated that as a new surface water/sediment simulation test (according to OECD TG 308) has been provided in the dossier, degradation in soil was considered as not necessary. Another MS noted that acute aquatic toxicity data were relevant for the CLH report and should be added to support the conclusion. The DS agreed that acute aquatic toxicity data might be relevant as supporting information. However, as no new data on acute aquatic toxicity was provided for the renewal of IPBC, the DS referred to the previous CLH-report (June 2011) in which all available data could be found. The remaining part of comments from the MS were non-critical editorial elements and the DS agreed with them.

The NA noted that in previous RAC opinion, soil simulation data was considered as there were uncertainties regarding available aquatic fate data. However, as a new OECD TG 308 study is now available, which is considered reliability 1, this study should take precedence over soil data. Nevertheless, the NA noted that information on ultimate degradation (as mineralisation) was unclear due to unclear levels of iodine species. The NA agreed that hazard information on iodine species might need to be considered. However, in the CLH report no long-term endpoints for iodine species were provided. Thus, the NA referred to the REACH registration dossier for iodine where a NOEC of 0.025 mg/L is given for algae.

In answer to these comments, the DS justified that in the new OECD TG 308 study two systems was investigated (river and pond). In these systems, a mean DT50 of 1.42 days (at 12°C) was determined, but the $^{14}CO_2$ formation was at a level of 49.3% for the river and 70.6% AR for the pond systems after 28 days. 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, assessment of the fate of iodine in a single study may not bring substantial information. As a conservative approach, the DS has considered that 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. The DS has accepted the provided a NOEC of 0.025 mg/L as additional supporting information.

Additionally, the NA mentioned that in terms of chronic toxicity data for IPBC EC_{10} endpoint of 0.013 mg/L was available for the algal study (2001) which should be used in preference to the NOEC endpoint. Thus, long-term toxicity value for fish *Pimephales promelas* NOEC of 0.0084 mg/L would be most sensitive endpoint for IPBC. As *P. Promelas* was not the most acutely sensitive fish species the NA requested consideration of the surrogate approach with the acute *Oncorhynchus mykiss* endpoint for completeness.

In answer to these comments, the DS indicated that it would not change the overall conclusion for classification category or the M-factor.

The company/manufacturer did not agree with DS proposal to change M-factor from 1 to 10. They basically referred to the previous RAC opinion and pointed that the degradation products did not have an impact on the environmental hazard classification of IPBC. The toxicity of the

degradation products PBC and 2-PBC regarding aquatic organisms is 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.

In response, the DS noted that the comment 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.

Assessment and comparison with the classification criteria

Degradation

RAC acknowledges that based on a ready biodegradability test according to OECD TG 301F, IPBC 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 ^{0}C. 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 CO_2 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. It is hydrolytically stable and 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 is no scientific evidence to demonstrate that ultimate biodegradation (i.e. full mineralisation) has been achieved at level > 70 % within a 28-day period. In addition, it cannot be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

Therefore, RAC agrees with the DS and considers IPBC as not rapidly degradable according to the CLP criteria.

Aquatic Bioaccumulation

An experimental BCF is not available and the calculated BCFfish was obtained using a log Kow of 2.81 (pH 4 to 7) yielding a value of 48.8, which shows a low potential for bioaccumulation.

Therefore, RAC agrees with the DS that IPBC has a low potential for bioaccumulation according to the CLP criteria.

Aquatic Toxicity

RAC acknowledges that valid acute and chronic toxicity data is available for all three species (fish, invertebrates and algae). 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.

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 agrees with the DS to 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*.

Aquatic Chronic toxicity

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), IPBC 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 LC_{50} 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 agrees with the DS that IPBC warrants classification as Aquatic Chronic 1 (H410), with M factor of 10.

Conclusion on classification

Overall, IPBC is considered as not rapidly degradable and does not fulfil the criteria for bioaccumulation. Based on the available and reliable information, RAC considers that IPBC warrants classification as:

Aquatic Acute 1 (H400), M = 10

Aquatic Chronic 1 (H410), M = 10

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter and additional information (if applicable).

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).

Annex 3 Records of the targeted consultation following the submission of additional information on acute inhalation toxicity for 3-iodo-2-propynyl butylcarbamate; 3-iodoprop-2-yn-1-yl butylcarbamate