Committee for Risk Assessment

RAC

Annex 1
Background document
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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It is based on the official CLH report submitted to consultation and additional information (if applicable).

Adopted

14 September 2023

REGULATION (EC) NO 1272/2008 (CLP REGULATION),

ANNEX VI, PART 2

Proposal for Harmonised Classification and Labelling for a biocidal active substance

CLH REPORT

3-iodo-2-propynyl butylcarbamate (IPBC)

EC Number: 259-627-5

CAS Number: 55406-53-6

Index Number: 616-212-00-7

Contact details of dossier submitter: Danish EPA

Version number: 1.1 **Date:** 11 November 2022

TABLE OF CONTENTS

List of tables

ASSESSMENT REPORT

SUMMARY

1. PRESENTATION OF THE ACTIVE SUBSTANCE

1.1 IDENTITY OF THE ACTIVE SUBSTANCE

Table 1 Main constituents

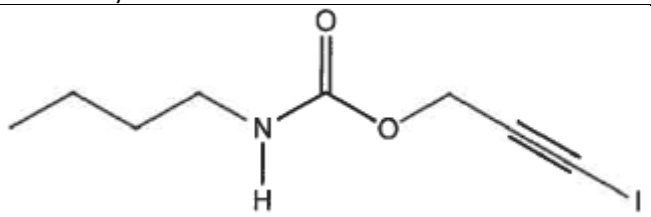
Main constituent(s)	
ISO name	-
IUPAC or EC name	3-iodo-2-propynyl butylcarbamate
EC number	259-627-5
CAS number	55406-53-6
Index number in Annex VI of CLP	616-212-00-7
Minimum purity / content	98.0% w/w
Structural formula	

Table 2 Relevant impurities and additives

Relevant impurities and additives		
IUPAC name or chemical name or EC name	Maximum concentration in % (w/w)	Index number in Annex VI of CLP
-	-	-

1.2 INTENDED USES AND EFFECTIVENESS

Table 3 Use of the active substances

Product type	PT8 Wood preservatives
Intended use pattern(s)	Fungicide for protection of wood against wood rotting fungi and wood discolouring fungi (blue stain) indoors and outdoors. Application techniques include (though are not limited to) vacuum processes, flow-coating (deluging), manual dipping, spraying, and brushing/rolling.
Users	Industrial, professional, non-professional

Table 4 Effectiveness of the active substance

Function	
Organisms to be controlled	Efficacy against (though not limited to) the following organisms has been demonstrated: Wood rotting fungi (basidiomycetes): *Coniophora puteana, Poria placenta*, *Gloeophyllum trabeum*

	Wood discolouring fungi (blue stain): *Aureobasidium pullulans*, *Sydowia polyspora.*
Limitation of efficacy including resistance	Based on the unspecific mode of action of IPBC and an expected single treatment of wood with wood preservatives containing IPBC, the risk of resistance formation due to preservation of wood with IPBC is regarded to be low.
Mode of action	IPBC has a carbamate structure. The target sites of carbamates in fungi are cell membranes (altered permeability) and fatty acids.

2. PROPOSED HARMONISED CLASSIFICATION AND LABELLING OF THE ACTIVE SUBSTANCE ACCORDING TO THE CLP CRITERIA

2.1 PROPOSED HARMONISED CLASSIFICATION AND LABELLING FOR THE ACTIVE SUBSTANCE

Table 5 Proposed harmonised classification and labelling of the substance

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors, ATE values	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Haz-ard state-ment Code (s)		
Current Annex VI entry (ATP06)	616-212-00-7	3-iodo-2-propynyl butyl-carbamate; 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 submitter's proposal	616-212-00-7	3-iodo-2-propynyl butyl-carbamate; 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	

Resulting Annex VI entry if adopted by RAC and agreed by Commis-sion	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 = 0.31 mg/L (dusts or mists) M = 10 M = 10	

Table 6 Reason for not proposing harmonised classification and labelling and the status under CLH public consultation

Hazard class	Reason for not proposing classification and labelling	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not applicable	No
Oxidising gases	Hazard class not applicable	No
Gases under pressure	Hazard class not applicable	No
Flammable liquids	Hazard class not applicable	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances and mixtures	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not applicable	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances and mixtures	Hazard class not applicable	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not applicable	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not applicable	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier (already classified Acute Tox. 4; H302 – no revision proposed)	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Harmonised classification proposed: Acute Tox. 2; H330. Current classification of Acute Tox. 3; H331 no longer supported by eCA DK	Yes
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier (already classified Eye Dam. 1; H318 – no revision proposed)	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class not assessed in this dossier (already classified (Skin Sens. 1; H317 – no revision proposed)	No
Germ cell mutagenicity	Hazard class not assessed in this dossier	No

Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier (already classified (STOT RE 1; H372 (larynx, inhalation) – no revision proposed)	No
Aspiration hazard	Hazard class not applicable	No
Hazardous to the aquatic environment	Acute aquatic toxicity: Hazard class not assessed in this dossier (already classified Aquatic Acute 1; H400, M-factor 10 – no revision proposed) Chronic aquatic toxicity: Harmonised classification proposed: M(Chronic)=10. Current M(Chronic)=1 for Aquatic Chronic 1; H410 no longer supported by eCA DK	Yes
Hazardous to the ozone layer	Hazard class not applicable	No

2.2.1 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The current (first) harmonised classification and labelling of IPBC was adopted by ECHA's Committee for Risk Assessment (RAC) on 28 November 2012. IPBC was included in Annex VI of Regulation (EC) No 1272/2008 with ATP06 of the Regulation.

2.2 PROPOSED CLASSIFICATION AND LABELLING AND PACKAGING FOR THE REPRESENTATIVE PRODUCT(S)

Not applicable for the CLH report.

2.3 DATA SOURCES

The REACH Registered Substance Factsheets for IPBC (https://echa.europa.eu/registration-dossier/-/registered-dossier/23059) were reviewed (final review 02.06.2022) for relevant information.

IPBC is not an active substance used in plant protection products, thus a Rapporteur Member State assessment report (DAR) submitted for EU peer review is not available.

Literature searches

Literature searches with a primary focus on IPBC in relation to human health or the environment were made.

Human health

The literature search for human health (also encompassing non-target animals) involved a search of sources in the Royal Danish Library system. Sources include scientific journals, books, articles, and databases (including Agricola, BIOSIS, CAB Abstracts, CPCI, EMBASE, IPA, PubMed, SCIE, Scopus, and Web of Science, which covers a number of the aforementioned sources). The keywords (IPBC OR 3-iodo-2-propynyl butylcarbamate OR 55406-53-6 (the CAS no. of IPBC)) were combined with (metabol* OR toxic* OR mutage* OR genotox* OR carcinoge* OR reproduct* OR neurotoxi* OR immunotoxi*) (* = wildcard). The search field was unrestricted. The search period was from 2004 (the year the original draft CAR for IPBC in PT8 was submitted to the eCA) to 2022 (inclusive), and was performed on 16.06.2022. There were 574 'hits'. In addition to being covered in the above search, the Web of Science and Scopus databases were searched (on 04.08.2022) as individual searches using the same criteria as above; the Royal Danish Library recommends this approach to ensure accurate and more up-to-date results. The latter searches yielded 36 unique hits, of which 12 were not amongst the 574 hits in the main literature search. The literature searches can be found at the end of 'Appendix V: Overall reference list'.

Two screening steps were applied to identify relevant studies. In Step 1, the title, and if necessary abstract, of hits were reviewed to identify studies of potential relevance. A sizeable proportion of the documents identified addressed issue relating to uses and/or effectivity of IPBC/products containing IPBC. Of the documents addressing biological effects of IPBC, a proportion evaluated effects on the environment; such studies are considered in the literature review for the environment. 14 studies were identified as potentially relevant for human health and non-target animals (they are listed under the 'Human health' subheading of the 'Literature Searches' heading at the end of 'Appendix V: Overall reference list'). In step 2, full texts of the 14 studies were reviewed. The documents addressing effects of IPBC on humans almost exclusively deal with the sensitising potential of IPBC, focusing primarily on contact dermatitis: its relevance and the contribution of different sources of exposure (including industrial, treated articles, and

cosmetics/skin care products). Data from 2 articles reporting the results longitudinal studies of the prevalence of allergy to IPBC (as determined by skin patch testing) were included in the dRAR in order to compare rates with those reported in original CAR for IPBC in PT8. A third relevant study was a brief report of a local lymph node assay (LLNA) with IPBC published in 2004, i.e. shortly after submission of the original draft CAR by the Applicants. See Section A.3.5 Skin sensitisation for further details of the 3 studies. Review of the remaining potentially relevant documents confirmed that they: a) presented information contained in the original CAR for IPBC in PT8, or b) contained information not relevant for inclusion in the Renewal Assessment Report or revised CLH report for IPBC. No documents addressing effects on non-target organisms in the form of pets or domesticated (farm) animals were identified.

Environment

The literature search for the environment has also been performed in The Royal Danish Library system as described above. 4 searches divided by topics were made in June 2022 and in Web of Science and Scopus in August 2022. The 4 topics were endocrine disruption, hazard to the ozone layer, fate and ecotoxicity all with the search criteria that it should be published in 2004 or later. The literature searches can be found at the end of 'Appendix V: Overall reference list'.

Endocrine disruption

The search for endocrine disruption ((IPBC *OR* "3-iodo-2-propynyl butylcarbamate" *OR* "55406-53-6") *AND* "endocrine disrupti*") gave no hits. The same search was performed in Web of Science and Scopus which gave 2 hits, none of which were relevant for the environmental ED assessment.

Ozone depletion

For the topic concerning the ozone depleting potential of IPBC ((IPBC *OR* "3-iodo-2-propynyl butylcarbamate" *OR* "55406-53-6") *AND* (Ozone OR ODP)) the search gave 43 hits, however none relevant. The same search was performed in Web of Science and Scopus which gave 2 hits, none of relevance as they were concerning ozone as bleach in pulp.

Fate

The search for studies relevant to the fate of IPBC ((IPBC OR 3-iodo-2-propynyl carbamate OR 55406-53-6 OR iodocarb) AND (hydroly* OR biodeg* OR aerob* OR phototransf* OR photodeg* OR degrad*)) resulted in 381 studies. To refine the results, the search was made only in the abstracts of studies, which returned 44 results. None of the studies were relevant for the fate assessment of IPBC. The same search was performed in Web of Science and Scopus, which returned 13 hits, 11 of which had no relevance for instance concerning the preservation of properties for materials treated with IPBC or concerning methods for increasing the penetration depth of wood preservatives into wood. The 2 potentially relevant documents were reviewed further, but none of the documents contained information relevant for inclusion in the Renewal Assessment Report or the revised CLH report for IPBC.

Ecotoxicity

The last search was ecotoxicity ((IPBC OR "3-iodo-2-propynyl butylcarbamate" OR "55406-53-6") AND (EC50 OR LC50 OR NOEC OR LOEC) AND ecotox* AND (Chronic OR acute) AND (alga* OR fish OR daphni* OR Microorganism OR Terrestrial OR Groundwater)) which returned 11 hits, 9 of which were not relevant. For the 2 potentially relevant studies, a

further review was carried out. Coors et al. (2012) studied LC_{50} values in fish embryo toxicity tests, however the LC_{50} value found in this study was not for the most sensitive fish or most sensitive organism. The $L(E)C_{50}$ used to determine the environmental classification of IPBC is lower, therefore this study does not contribute with new data relevant for the classification of IPBC. This study is also described in section A.4.2 Effects on environmental organisms. The second potentially relevant study, Tierney et al. (2009) investigates the changes in electro-olfactogram in salmon after exposure to IPBC. The time frame of the study is short (30 minutes exposure and 60 minutes post-exposure) and although an effect is seen at 1µg/L which is lower than the values used for classifying IPBC, this study is not relevant as the classification for Aquatic Acute 1 for fish must be based on a LC_{50} value for a 96 hour test and for the Aquatic Chronic classification, the test should be for chronic effects which is not the case for this study. The same search was performed in Web of Science and Scopus which gave no hits. The search was then altered by removing criteria in the search string in different searches, but this still gave no hits in the search. One additional relevant study appeared in the human health literature search. Tierney et al. (2006) investigated whether the alarm reaction of coho salmon parr was impaired when exposed to IPBC, although this study was assessed to be of no relevance on the same grounds as the Tierney et al. (2009) study.

In summary the literature search showed no additional relevant data for the environmental assessment and classification of IPBC.

A list of references for documents cited in this report is provided in Appendix V: Overall reference list.

3. SUMMARY OF THE HUMAN HEALTH RISK ASSESSMENT

Not applicable for the CLH report.

4. SUMMARY OF THE ENVIRONMENTAL RISK ASSESSMENT

Not applicable for the CLH report.

5. ASSESSMENT OF EXCLUSION CRITERIA, SUBSTITUTION CRITERIA AND POP

Not applicable for the CLH report.

A. Assessment of intrinsic properties and effects of the active substance

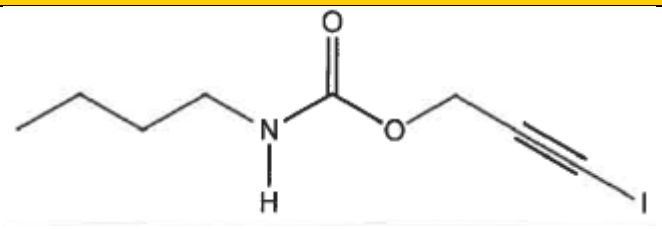
A.1. General substance information

A.1.1. Identity of the substance

Table 7 Summary table on substance identity

Summary table on substance identity	
Common name (ISO name, synonyms)	
Chemical name (EC name, CA name, IUPAC name)	3-iodo-2-propynyl butylcarbamate
EC number	259-627-5
CAS number	55406-53-6
other CAS numbers (e.g. deleted, related, preferred, alternate)	N/A
Molecular formula	$C_8H_{12}INO_2$
Molecular weight or molecular weight range	281.1 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	N/A
Description of the manufacturing process and identity of the source (for UVCB substances only)	N/A
Degree of purity (%)	98.0% w/w

Table 8 Structural formula

Structural formula


A.1.2. Composition of the substance (reference specifications)

Table 9 Main constituents

Main constituent(s)					
Constituent (chemical name)	Typical concentration (%(w/w))	Concentration range (%(w/w))	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	Remarks / Discus-sion
3-iodo-2-propynyl butylcarbamate	≥ 98.0%	-	Acute Tox. 3 (H331) Acute Tox. 4 (H302) STOT RE 1 (H372; larynx) Eye Dam. 1 (H318) Skin Sens. 1 (H317) Aquatic Acute 1 (H400) (M=10) Aquatic Chronic 1 (H410) (M=1)	-	-

For details, refer to the Confidential annex of the CAR.

Table 10 Impurities

Impurities					
Constituent (chemical name)	Typical concentra-tion (%(w/w))	Concentration range (%(w/w))	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	Remarks / Discussion
-	-	-	-	-	-

Table 11 Additives

Additives						
Constituent (chemical name)	Function	Typical concentration (%(w/w))	Concentration range (%(w/w))	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	Remarks / Discussion
None	-	-	-	-	-	-

The active substance contains no additives.

A.1.3. Physical and chemical properties of the active substance

No new relevant data on the physical and chemical properties of IPBC have been submitted or identified.

A.1.4. Physical hazards and respective characteristics

No new relevant data on the physical hazards and respective characteristics of IPBC have been submitted or identified that warrant revision of the current EU harmonised classification of IPBC according to Regulation (EC) No 1272/2008 (CLP).

A.1.5. Assessment of physical hazards according to the CLP criteria

No new relevant data on the physical hazards and respective characteristics of IPBC have been submitted or identified that warrant revision of the current EU harmonised classification of IPBC according to Regulation (EC) No 1272/2008 (CLP).

A.1.5.1. Assessment of physical hazards

See the comment under section A.1.5.

A.1.5.2.Explosives

See the comment under section A.1.5.

A.1.5.3. Flammable gases (including chemically unstable gases)

See the comment under section A.1.5.

A.1.5.4. Flammable aerosols and aerosols

See the comment under section A.1.5.

A.1.5.5. Oxidising gases

See the comment under section A.1.5.

A.1.5.6. Gases under pressure

See the comment under section A.1.5.

A.1.5.7. Flammable liquids

See the comment under section A.1.5.

A.1.5.8. Flammable solids

See the comment under section A.1.5.

A.1.5.9. Self-reactive substances

See the comment under section A.1.5.

A.1.5.10. Pyrophoric liquids

See the comment under section A.1.5.

A.1.5.11. Pyrophoric solids

See the comment under section A.1.5.

A.1.5.12. Self-heating substances

See the comment under section A.1.5.

A.1.5.13. Substances which in contact with water emit flammable gases

See the comment under section A.1.5.

A.1.5.14. Oxidising liquids

See the comment under section A.1.5.

A.1.5.15. Oxidising solids

See the comment under section A.1.5.

A.1.5.16. Organic peroxides

See the comment under section A.1.5.

A.1.5.17. Corrosive to metals

See the comment under section A.1.5.

A.1.6. Analytical methods for detection and identification

Not applicable for the CLH report.

A.2. Effects against target organisms

Not applicable for the CLH report.

A.2.1. Intended uses

Not applicable for the CLH report.

Use

IPBC has anti-fungal activity, and has uses that include as a 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.

Mode of action

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.

A.2.2. Summary on efficacy

Not applicable for the CLH report.

A.3. Assessment of effects on Human Health

In this section, summaries and evaluations of studies providing toxicokinetic and toxicological data for IPBC are presented. In relation to toxicological end-points (hazards), studies are only presented for one end-point – acute inhalation toxicity – for which the available data has been (re)assessed, and for which a proposal for (re)classification/labelling according to the criteria of Regulation (EC) No 1272/2008 (CLP) is warranted. For the remaining end-points, the assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. Consequently, opening them for consultation under the CLH process is not warranted and no information is presented for these end-points. One caveate to the latter, is that the RAC Opinion of 28 November 2012 only briefly addressed neurotoxicity (according to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for STOT SE, STOT RE, or reproductive toxicity on the basis of potential neurotoxicity) and did not address immunotoxicity (according to Regulation (EC) No 1272/2008 (CLP), IPBC meets the criteria for classification and labelling for skin sensitisation (Skin Sens. 1; H317: May cause an allergic skin reaction)). In Section A.3.12. Neurotoxicity and A.3.13. Immunotoxicity, neurotoxicological and immunotoxicological data in studies of IPBC included in the original PT8 CAR for IPBC (CA DK, 2008) or cited in the original CLH Report for IPBC (CA DK, June 2011) are identified, as are a number of new studies, that support the RAC Opinion (28 November 2012) in relation to the neurotoxic and immunotoxic potential of IPBC.

The studies presented in Section A.3.2.3. Acute inhalation toxicity have been re-assessed according to currently applicable guidance[1]. The studies were conducted by the IPBC Task Force members; no new studies relevant to acute inhalation toxicity were identified in the open literature.

[1] ECHA's 'Guidance on the data requirements and assessment of applications for renewal of approval of active substances under BPR', November 2020.

A.3.1. Toxicokinetics

Table 12 Summary table of toxicokinetic studies

Summary table of toxicokinetic studies					
Method, Duration of study, Guideline, GLP status, Reliability Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
Toxicokinetic and metabolism in mammals EPA guideline Series 85-1, OECD TG 417, of April 1987 GLP: Yes Reliability: 1 **Key study**	Rat Crl:CD®BR male, female Group A and B: 5 animals/sex Group C and D: 9 animals/sex	a) radiolabelled IPBC: 3-iodo-2-[2-^{14}C]Propynyl-N-[1-^{14}C]-Butyl carbamate Chemical purity: 99.4% Specific activity: 26 µCi/µmol Radiochemical purity: 99.0% b) unlabelled IPBC Chemical purity: 98.3% Vehicle: 0.5% (w/w) aqueous carboxy-methylcellulose Single dose via gavage Group A: single radioactive dose (nominal 125 mg/kg be; actual	IPBC was rapidly and completely absorbed in both sexes at both dose levels: 39% to 75% of the administered radioactivity was detected in the carcass at the 2-h and 4-h sacrifices (Groups C and D), and > 90% was absorbed based on urinary excretion (~ 57 – 71%) and excretion via exhaled air (~ 18 – 24%) within 72 hours (Groups A and B). The majority of the administered radioactivity was excreted via urine (57.3% to 70.7%). A smaller amount was recovered in exhaled air (18.3% to 24.0%), 4.4% to 7.44% of administered radioactivity was recovered	The study complies with the current guideline OECD TG 417 (July 2010) except: 3 instead of 4 rats per sex and timepoint in the tissue distribution study (Group C and D); identication of metabolites ≥ 5% not reported for URM-5 (6 – 7.5% in Group B, and not feasible for URM-15 (6-10%); in tissue	[redacted] (1995) Metabolism of ^{14}C-IPBC in Rats; [redacted] Doc. No. 512-002, Doc. IIIA, Section A6.2/01)

		104 mg/kg bw) Group B: 14-day dosing + single radioactive dose (nominal 20 mg/kg bw/day; actual 20.4 mg IPBC/kg bw/day) Group C: single radioactive dose (nominal 125 mg/kg bw; actual 121 mg/kg bw) Group D: single radioactive dose (nominal 20 mg/kg bw; 19.1 mg/kg bw) Groups A and B: excretion balance (14-day collecting period) Groups C and D: tissue distribution and kinetic (3 animals sacrificed at 2 and 4 hours, and at 5 days, after dosing)	in faeces (Groups A and B). The majority of radioactivity was excreted within 72 hours (77% to 99% of administered radioactivity) (Groups A and B). Radiolabel associated with IPBC was not detected in urine or faeces. 15 radiolabelled metabolites were isolated in the urine and faeces though not all were identified, and a mixture of highly polar metabolites was not characterised (Groups A and B). The data indicate that IPBC is extensively metabolised in the rat; the initial step considered to be reductive dehalogenation yielding iodide and propynyl butylcarbamate (PBC), which is further metabolised by oxidative dealkylation. The major metabolites are two stereo conformers of propargyl-n-acetic acid carbamate, and carbon dioxide. (See the metabolic pathway and quantitative information on metabolites in the study summary / summary of the toxicokinetic information.)	distribution study, no GI tract was collected; total recovery of administered dose was below 90% for one group: Group B, females (81.9%). The deviations are not considered to have implications for the reliability of the study.	

			There were no apparent differences in toxicokinetics between sexes or applied doses.		

A.3.1.1. Short summary and overall relevance of the provided toxicokinetic information

A rat study ([redacted], 1995; Doc. No. 512-002, Doc. IIIA, Section A6.2/01) examined the pharmacokinetics of radiolabelled IPBC administered orally (gavage) at a single nominal dose of 20 or 125 mg/kg bw in 0.5% (w/w) aqueous carboxymethylcellulose.

IPBC was rapidly and almost completely absorbed in rats via the oral route: 39% to 75% of the administered radioactivity was detected in the carcass at the 2-h and 4-h sacrifices, and mean recoveries were 81.9% to 106%.

The majority of the administered radioactivity was excreted via urine (57.3% to 70.7%). Faeces were a minor route of excretion in all dose groups (4.4% to 7.4% of the administered radioactivity), while radiolabelled carbon dioxide constituted between 18.4% to 24.2% of the administered dose. The majority of radioactivity was excreted within 72 hours (77% to 99% of the applied radioactivity).

IPBC was widely distributed. The concentration of radioactivity declined in the tissues with time. The percentage of administered radioactivity after 120-hour was highest in carcass > liver > blood > kidneys/skin/fat in both sexes of both dosing regimens. There was no trend for bioaccumulation observable. Less than 5% of the dose was recovered in carcass and tissues after 14 days.

Radiolabelled IPBC was not detected in urine or faeces suggesting complete degradation. IPBC was extensively metabolised, first undergoing reductive dehalogenation to form PBC and iodide as the initial metabolites. PCB was metabolised by oxidative dealkylation to yield several metabolites, the major being the two distereomeric conformers of propargyl-N-acetic acid carbamate (URM-9 & URM-10), (32% to 51% of the administered dose). Thus PCB, iodide, and the two latter metabolites can be considered 'major metabolites' if this term is defined as metabolites generated at ≥ 10% of the level of the parent compound (as defined in Section 4 of the Introduction to guidance on the BPR, Volumes I-IV, Part A). In addition, de-carboxylation following reductive dehalogenation yielded carbon dioxide, CO_2, (18.4% to 24.2% of the administered dose). A number of compounds were formed through carbon-carbon cleavage of PBC. Metabolites identified in addition to URM-9 and URM-10) were found in trace amounts and included methyl-N-butylcarbamate (URM 1, < 1% of the administered dose), 1-hydroxybutamide (URM 3, < 1%) and propargyl-N-methylcarbamate (URM 4, 1% to 3% of the administered dose). Several other generally trace metabolites could not be further characterised. Glucuronidation appeared to be the main secondary metabolism pathway. Significant amounts of IPBC and/or PBC were found in blood drawn shortly after dosing (2 & 4 h post dose) with percentages ranging from approximately 7.2% to 18.7%.

The proposed metabolic pathway is shown in Figure 1:

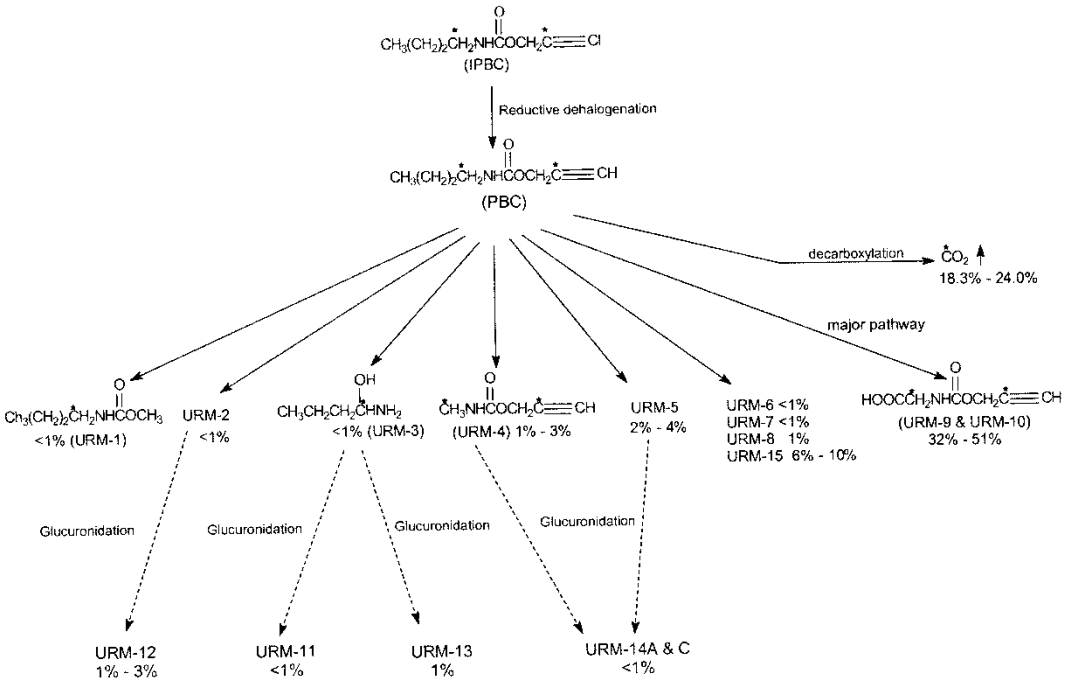


Figure A6.2/01-1: Proposed metabolic pathway of ^{14}C-IPBC after oral administration (percentages are based on total dose administered)

Figure 1 Propose metabolic pathway of IPBC

Since PBC was considered the initial metabolite of IPBC and all metabolites identified do not contain the iodine-moiety, release of iodine from IPBC is inferred. Therefore, it is concluded that iodine is a metabolite of IPBC formed during metabolism of IPBC.

There were no detectable differences between sexes or applied doses.

A.3.1.2. Values and conclusions used for the risk assessment

Not applicable for the CLH report.

A.3.2. Acute toxicity / STOT SE

A.3.2.1. Acute oral toxicity

No new data on acute oral toxicity have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC meets the criteria for classification and labelling for acute oral toxicity (Acute Tox. Cat. 4; H302: Harmful if swallowed).)

A.3.2.1.4. Conclusion on acute oral toxicity related to risk assessment

Not applicable for the CLH report.

A.3.2.2. Acute dermal toxicity

No new data on acute dermal toxicity have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for acute dermal toxicity.)

A.3.2.2.4. Conclusion on acute dermal toxicity related to risk assessment

Not applicable for the CLH report.

A.3.2.3. Acute inhalation toxicity

No new data on acute inhalation toxicity has been generated by the Applicant since the initial active substance approval and its conclusions remain valid. The data peer-reviewed at EU level (during the initial approval) are still considered acceptable. The studies from the initial approval are re-summarised in the table below (with some additional details) and in the 'Short summary' of the information. Data pertaining to exposure to liquid aerosol in one of the original studies has been re-interpreted.

Table 13 Summary table of animal studies on acute inhalation toxicity

Summary table of animal studies on acute inhalation toxicity*						
Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/group	Test substance (including purity), form (gas, vapour, dust, mist) and particle size (MMAD) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value 4h LC_{50}	Remarks (e.g. major deviations)	Reference
Acute inhalation toxicity Inhalation, Rat, LC_{50} US-EPA TG 81-3; comparable to OECD TG 403, adopted May 1981 GLP: Yes Reliability: 1 **Key study**	Rat Sprague-Dawley CD® Male, female 5 animals /sex/ group 7 groups	Technical active substance IPBC (Troysan Polyphase P-100) Purity 98.2% <u>Dust</u>: 1.7, 0.38, 0.72 mg/L (exposure groups' mean MMAD 4.3 µm, range 3.9 – 4.5 µm)	During the dust exposure period, the most commonly noted signs of toxicity were decreased activity, eye closure and excessive lacrimation; at the high exposure level gasping was noted, and mortality occurred. During the liquid aerosol exposure	<u>Dust</u>: 0.67 mg/L for males and for females; 0.68 mg/L for combined sexes <u>Liquid Aerosol</u>: 0.63 mg formulation/L for males; 0.99 mg	The liquid aerosol was generated using a liquid formulation comprising 40.1% IPBC. As the composition of the formulation is not known, pro-rata correction to estimate the toxicity of IPBC liquid aerosol may not be acceptable. Changes to the	[redacted], 1990 Doc. No. 523-002, Doc. IIIA, Section A6.1.3/02

		Technical active substance IPBC (Troysan Polyphase P-100) as a liquid formulation comprising 40.1% IPBC <u>Liquid aerosol</u>: 3.4, 1.8, 0.45, 0.75 mg formulation/L (exposure groups' mean MMAD 2.4 µm, range: 1.9 – 2.9 µm) 4 hours, whole body	similar responses were noted; mortality occurred at the 2 highest exposure levels. Responses noted during the first 2 hours post-exposure included laboured breathing, gasping, rales, lacrimation, nasal discharge, and salivation.	formulation/L for females; 0.78 mg formulation/L for combined sexes. Pro-rata correction of the values for the liquid aerosol yields values for IPBC of 0.40, 0.25, and 0.31 mg/L for males, females, and combined sexes, respectively.	version (Sept. 2009) of OECD TG 403 applicable at the time of renewal of IPBC do not have implications for the reliability of the study.	
Acute inhalation toxicity, Limit test OECD TG 403, adopted May 1981; not fully compliant Reliability: 2 GLP: No Supportive study	Rat Sprague-Dawley Male, female 5/group	Technical active substance IPBC Purity 99% dust (claimed non-respirable) 4 hours, whole body Nominal concentrations: 0 and 6.89 mg/L	At 1 h, all animals exhibited dyspnoea, salivation and rhinorrhoea; these symptoms persisted throughout the exposure period. All animals also showed lacrimation during the last 1.5 h of exposure. During the 14-day post-exposure period, some of the predominant clinical signs were bloody	> 6.89 mg/L (nominal) for males and for females	The actual test substance concentration and particle size were not determined by analysis, thus strictly speaking, the study is not an OECD TG 403 study. Changes to the version (Sept. 2009) of OECD TG 403 applicable at the time of renewal of IPBC	[redacted], 1985 Doc. No. 523-001, Doc. IIIA, Section A6.1.3/01

			crusts on nose, eyes, mouth, chest, and ears as well as rough hair coat, languid, wheezing, and urine stains. The majority of clinical signs had disappeared by day 4 post-exposure except for bloody crust around the nose. Four of the males were normal in appearance by day 13 post-exposure. All (4) surviving females were normal in appearance by day 11 post-exposure; one female was found dead on day 5 post-exposure.		do not have implications for the reliability of the study.	
Acute inhalation toxicity Inhalation, Rat, LC_{50} US-EPA TG 81-3; comparable to OECD TG 403, adopted May 1981 GLP: Yes Reliability: 2 Supportive	Rat Sprague-Dawley Male, female 5/sex/group (purity 97%)	Technical active substance IPBC (Omacide® IPBC) Purity 97% <u>Dust, micronised</u>: 0.16, 0.29, 0.58 mg/L MMAD (± GSD): 3.5 µm (± 1.9 or 2.0) for each group	During exposure, exaggerated respiratory movements, partial closing of eyes, wetness around the snout and mouth were seen in all rats; erythema of the ears and restless behaviours were seen in rats exposed to micronised IPBC. During the	From all mortality data: LC_{50} of ~ 0.67 mg/L From groups exposed to non-micronised: LC_{50} of ~ 0.88 mg/L The LC_{50} for micronised IPBC could not be calculated	A large proportion of the non-micronised material collected in the particle size sample was collected at a sieve size with a cut-off size of 9.8 µm. Consequently, the MMAD values calculated calculated for non-micronised IPBC can only be	[redacted], 1994 Doc. No. 523-003, Doc. IIIA, Section A6.1.3/03

study		% respirable: 74.4-80.5% <u>Dust, non-micronised</u>: 0.49, 1.19, 2.44 mg/L 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	observation period, abnormalities to respiration, brown staining, yellow staining in urogenital region, partial closing of eyes, secretion from eyes, peripheral vasodilation, dry/loose flaky skin, swollen stomach, swollen limbs, and death were seen. The persistence of clinical signs showed no obvious correlation with exposure level	from the available mortality data as there was no dose-related trend in mortality in the 3 dosage levels evaluated.	considered approximate, with implications for the accuracy of the 4h LC_{50} values calculated. The lack of a dose-respond relationship for mortality seen for the 3 doses of micronised material indicates that the dose range used was inadequate. Changes to the version (Sept. 2009) of OECD TG 403 applicable at the time of renewal of IPBC do not have implications for the reliability of the study.	

* Refer to Appendix VII for information regarding the Study summary for the studies in this table.

No human data on acute inhalation toxicity is available. No other data on acute inhalation toxicity is available.

A.3.2.3.1. Short summary and overall relevance of the provided information on acute inhalation toxicity

Information on acute inhalation toxicity evaluate on first authorisation

The following information was included in the original PT8 CAR for IPBC. Some details have been added or removed to aid clarity, however the analysis and conclusions are unaltered.

When IPBC was administered by inhalation to rats in a key study ([redacted], 1990, Doc. No. 523-002, Doc. IIIA, Section A6.1.3/02) performed according to US-EPA TG 81-3, comparable to the provisions of version of OECD TG 403 applicable at the time[2], a 4h LC_{50} of 0.67 mg/L for both males and for females (0.68 mg/L for the combined sexes) was reported for dust with respirable particle size (MMAD 4.3 µm) and of 0.63 mg/L for males and 0.99 mg/L for females (0.78 mg/L for the sexes combined) for a liquid aerosol with respirable droplet size (MMAD 2.4 µm) generated from a liquid formulation containing 40.1% IPBC. In a supportive study ([redacted], 1994, Doc. No. 523-003, not included in Doc. IIIA, Section A6.1.3) also performed in accordance with US-EPA TG 81-3[3], a 4h LC_{50} of ~ 0.88 mg/L (combined sexes) was reported for dust (non-micronised) with 19.2 - 26.7% of the particles being of a respirable size (MMAD 9.6 – 14.2 µm), and a 4h LC_{50} of ~ 0.67 mg/L for a combination of micronised and non-micronised dust[4]. Classification with T; R23 (Acute Tox. 3; H331 in the GHS) was proposed based on the results from the acute inhalation toxicity study with respirable dust particles, and was considered supported by the study performed with a test substance with only 19.2 – 26.7% of particles being of a respirable particle size of < 6 µm (MMAD 9.6 – 14.2 µm).

Following administration of particles of technical IPBC dust claimed by the Applicant to be non-inhalable/non-respirable (no details in the study report) in a second key study ([redacted], 1985, Doc. No. 523-001, Doc. IIIA, Section A6.1.3/01) made according to, though not fully compliant with, the version of OECD TG 403 applicable at the time[5], a 4h LC_{50} > 6.89 mg/L was estimated[6]. In this study the LC_{50} indicates that no classification was warranted for this specific test substance. However, the particle size distribution of the tested IPBC was not measured, thus the study does not fulfil the provisions of OECD TG 403. The Applicant claimed that the particle size of technical IPBC (Troysan Polyphase P-100, purity 98%) used in the representative products and products on the market are not-respirable with ≤ 5% of the particles being smaller than 10 µm and a MMAD of 79 µm ([redacted], 2001, Doc. No. 111-001).

IPBC was considered to be highly toxic, with a 4h LC_{50} (rat) of:

0.67 mg/L for males and for females (0.68 mg/L combined sexes) for dust with respirable particle size (MMAD 4.3 µm)

0.63 mg/L for males and 0.99 mg/L for females (0.78 mg/L combined sexes) for a liquid aerosol with respirable droplet size (MMAD 2.4 µm)

[2] Changes to the version (Sept. 2009) of OECD TG 403 applicable at the time of renewal of IPBC do not have implications for the reliability of the study.

[3] Comparable to the provisions of version of OECD TG 403 applicable at the time; changes to the version (Sept. 2009) of OECD TG 403 applicable at the time of renewal of IPBC do not have implications for the reliability of the study.

[4] Notes at the time of renewal: Technical problems encountered with the dust generator in the studies with non-micronised IPBC mean that MMAD values calculated from these data can only be considered approximate, with implications for the accuracy of the 4h LC_{50} values calculated. The LC_{50} for micronised IPBC could not be calculated from the available data.

[5] Changes to the version (Sept. 2009) of OECD TG 403 applicable at the time of renewal of IPBC do not have implications for the reliability of the study.

[6] Note at the time of renewal: The value is based on the nominal exposure concentrations; actual test substance concentration was not determined by analysis.

~ 0.88 mg/L (combined sexes) for dust (non-micronised; MMAD of 9.6 - 14.2 µm, 19.2 – 26.7% of particles of a respirable size of ≤6 µm)

~ 0.67 mg/L (combined sexes) for a combination of non-micronised and micronised dust.

Following administration of technical IPBC of unconfirmed particle size (though claimed by the Applicant to be non-respirable), a 4h LC_{50} (rat) > 6.89 mg/L (for males and for females) was estimated.

Therefore, the Applicant proposed the followed approach for inhalation toxicity:

- in the case the product contains no significant amounts of respirable particles, classification with "T" is not warranted as concluded from the study of [redacted] (1985)

- in the case the product contains significant amount of respirable particles, classification with "T" could be proposed as concluded from the study of [redacted] (1990).

Thus, the Applicant proposed to base the classification on the particle size of the IPBC material. In contrast, the eCA proposed classification as toxic with R23 (Acute Tox. 3; H331: Toxic by inhalation, in the GHS) for technical IPBC regardless of the particle size because of several uncertainties. Firstly in the study by [redacted] (1985), the only acute inhalation toxicity study not leading to classification as toxic, the particle size of IPBC was not measured. The actual MMAD and proportion of particle less than 10 µm in the IPBC used is thus uncertain and could differ to that stated in the study of [redacted] (2001) used to support the study of [redacted] (1985). Furthermore, the study of [redacted] (2001), which measured the particle size of technical IPBC used in the representative products and products on the market, found only ≤ 5% of the particles to be smaller than 10 µm, which is well below the requirement of the applicable version of OECD TG 403. It should also be noted that in the non-key study of [redacted] (1994), the MMAD of the non-micronised dust was 9.6 – 14.2 µm, with 19.2 – 26.7% of the particles being < 6 µm (and therefore also less than 10 µm), and a 4h LC_{50} of ~ 0.88 mg/L was estimated.

The RAC Opinion on IPBC (28 November 2012) concluded the following (p. 5): "The classification for acute inhalation toxicity is based on the studies by [redacted] (1990) and [redacted] (1994). The LC_{50} values obtained from these studies are within the range 0.5 < LC_{50} ≤ 1.0 mg/l, corresponding to acute toxicity category 3; H331 for dust/mists (CLP) and 0.25 < LC_{50} ≤ 1.0 mg/l/4hr corresponding to T; R23 for aerosols and particulates (DSD). However, one study ([redacted], 1985) showed much higher LC_{50} values. This study was discarded because there was no information on the particle size distribution. RAC considers that there is not enough information in order to attribute specific toxicological effects between different forms of IPBC. In addition, the difference in LC_{50} values between micronised and non-micronised dusts was not significant. The RAC therefore supported the conclusion of the dossier submitter that IPBC should be classified as Acute Tox. 3; H331 (Toxic if inhaled) according to the CLP criteria and T; R23 (Toxic if inhaled) according to the DSD criteria."

Re-evaluation of the information on acute inhalation toxicity on first renewal

As noted above, the RAC Opinion on IPBC (28 November 2012) discounted the study of [redacted](1985) due to the lack of information on particle size distribution, and noted that the difference in LC_{50} values between micronised and non-micronised dusts was not significant[7]. The RAC also considered that there was not enough information to attribute specific toxicological effects between different forms of IPBC, as tested in the study of [redacted], (1990).

[7] The status of the study has been revised from 'Key' to 'Supportive'.

On re-evaluating the key study of [redacted] (1990) (Doc. No. 523-002, Doc. IIIA, Section A6.1.3/02) in connection with the renewal of IPBC in PT8, the eCA determined that the 4h LC_{50} values reported for the liquid aerosol are for the liquid formulation (which contained 40.1% IPBC) as opposed to being for technical IPBC. The eCA notes that the abstract of the study of [redacted] (1990) states that it was "… *designed to assess the toxic effects and determine the median lethal concentration of Troysan Polyphase P-100* [technical IPBC]*, when administered by inhalation using a powder and a liquid formulation to Sprague-Dawley CD® rats* …" This objective, reiterated at the beginning of the Conclusion section, is considered to indicate that the purpose of testing the liquid formulation was to determine the toxicity of IPBC liquid aerosol. This interpretation is supported by testing of the liquid aerosol at a range of concentrations in order to identify a LC_{50} value. Accordingly, the eCA considers that it is unlikely that the unknown co-formulant(s) in the liquid formulation was/were a substance(s) likely to significantly enhance the toxicity of IPBC liquid aerosol[8]. Consequently, pro-rata correction of the IPBC exposure/4h LC_{50} data for the liquid formulation (i.e. in the manner done if a vehicle has been employed) is considered justifiable. Pro-rata correction (using a factor of 0.6, based on an IPBC content of 40.1% in the liquid formulation) of the 4h LC_{50} values for male, female, and the combined sexes of Sprague-Dawley CD exposed to the liquid aerosol of IPBC yields 4h LC_{50} values for IPBC of 0.25, 0.40 and 0.31 mg/L, respectively. In considering the reliability of the 4h LC_{50} value for dust and the liquid aerosol from the study of [redacted] (1990) it should be noted that the MMAD for the liquid aerosol (mean and range of group means: 2.4 µm, 1.9 – 2.9 µm) is within the requirement (MMAD of 1 – 4 µm) of OCED TG 403, whereas the corresponding values for the dust (4.3 µm, 3.9 – 4.5 µm) are slightly outside the required range.

As part of its re-evaluation of the supportive study of [redacted] (1994) (Doc. No. 523-003, Doc. IIIA, Section A6.1.3/03), the eCA noted the study author's statement that the LC_{50} for micronised IPBC could not be calculated from the available mortality data due to no dose-related trend in mortality in the 3 dosage levels evaluated[9]. The eCA does, however, consider the data to indicate that micronised IPBC was more acutely toxic on inhalation than equivalent or higher levels of non-micronised IPBC. Exposure to 0.29 or 0.58 mg/L micronised IPBC resulted in the death of 3 of 5 females (1 on each of days 1, 2 and 3), and 3 of 5 females (all on day 1), respectively; no males died at these exposure levels. In contrast, exposure to 0.49 mg/L non-micronised IPBC resulted in the death of 1 female on day 4 and 1 male on day 5. When considering that the 4h LC_{50} of 0.88 mg/L for the non-micronised IPBC was derived from a dust with respirable fraction in the range 19.2 – 26.7%, the mortality data for micronised IBPC with a respirable fraction in the range 74.4 – 80.5% suggest that a 4h LC_{50} significantly below 0.88 mg/L could be predicted (especially for female rats) had an adequate upper dose been tested. In this regard, the 4h LC_{50} value based on all mortality data (non-micronised and micronised exposure) was 0.67 mg/L.

A.3.2.3.2. Comparison with the CLP criteria

The text cited below is from the Guidance on the application of CLP Criteria (July 2017).

[8] The Conclusion section of [redacted] (1990) notes the finding that the 4h LC_{50} for the liquid formulation was only slightly lower than that of the IPBC dust – despite the IPBC content of the liquid formulation being 60% lower – may be attributable to toxicity of other ingredients in the liquid formulation. However, it is also notes that the difference may have been attributable to particle size/lung deposition differences, or the liquid formulation being more easily absorbed that the dust.

[9] The eCA agrees with this statement, though considers that to properly explain the finding it should have been expanded to note that the dose range for the micronised IPBC was narrow (a factor of 3.6), such that the highest dose tested was too low to result in a mortality rate adequate to permit calculation of a LC_{50}.

Acute toxicity hazard categories and acute toxicity estimates (ATE) defining the respective categories

Exposure Route	*Category 1*	*Category 2*	*Category 3*	*Category 4*
Dusts and mists (mg/l)	*ATE ≤ 0.05*	*0.05 < ATE ≤ 0.5*	*0.5 < ATE ≤ 1.0*	*1.0 < ATE ≤ 5.0*

A 4h LC_{50} value for IPBC in 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 requires the classification for acute inhalation toxicity, Category 2; H330: Fatal if inhaled. The ATE (dust/mist) is 0.31 mg/L.

A.3.2.3.3. Conclusion on classification and labelling for acute inhalation toxicity

According to Regulation (EC) No 1272/2008 (CLP), IPBC dust/mist requires classification and labelling for acute inhalation toxicity (Acute Tox. Cat. 2, H330: Fatal if inhaled), which is a revision of the current EU harmonised classification of Acute Tox. Cat. 3; H331: Toxic if inhaled.

A.3.2.3.4. Conclusion on acute inhalation toxicity related to risk assessment

Not applicable for the CLH report.

A.3.2.4. Specific target organ toxicity – single exposure Category 1 and 2 (STOT SE 1 and 2)

No new data on Specific Target Organ Toxicity STOT SE 1 and 2 have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for STOT SE 1 or 2.)

A.3.2.5. Specific target organ toxicity – single exposure Category 3 (STOT SE 3)

No new data on Specific Target Organ Toxicity STOT SE 3 have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC meets the criteria for classification for STOT SE 3, however, classification for STOT SE 3 (respiratory track irritation) is not warranted as classification of IPBC for acute inhalation toxicity is required.)

The above conclusion is consistent with the RAC Opinion on IPBC (28 November 2012), which states (pp. 14-15): "The RAC concluded that since dyspnoea, salivation, lacrimation and rhinorrhea were observed in the acute inhalation toxicity studies at toxic concentrations (LC_{50} values between 0.5 and 1 mg/l) and the criteria for classification for acute inhalation toxicity are met, the classification for STOT SE 3 proposed by the DS is not warranted."

A.3.2.5.4. Overall conclusion on acute toxicity related to risk assessment

Not applicable for the CLH report.

A.3.3. Skin corrosion and irritation

No new data on skin corrosion and irritation have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classified for skin corrosion/irritation.)

A.3.3.4. Overall conclusion on skin irritation and corrosivity related to risk assessment

Not applicable for the CLH report.

A.3.4. Serious eye damage and Eye irritation

No new data on serious eye damage and eye irritation have been submitted or identified to

warrant revision of the current EU harmonised classification* of IPBC. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC meets the criteria for classification and labelling for serious eye damage (Eye Damage Cat. 1; H318: Causes serious eye damage).)

A.3.4.4. Overall conclusion on eye irritation and corrosivity related to risk assessment

Not applicable for the CLH report.

A.3.5. Skin sensitisation

No new data on skin sensitisation have been submitted or identified[#] that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. RAC concluded that data was not sufficiently robust for sub-categorisation for skin sensitisation (Skin Sens.). New data (see below) generated since the RAC Opinion are considered to support this position. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC meets the criteria for classification and labelling for skin sensitisation (Skin Sens. 1; H317: May cause an allergic skin reaction).)

As noted in relation to the literature review for human health in Section 2.3. Data Sources, new documents identified that addressed effects of IPBC on humans almost exclusively deal with the sensitising potential of IPBC, focusing primarily on contact allergy: its relevance and the contribution of different sources of exposure. Martin-Gorgojo & Johansen 2013 detected 55 cases – equivalent to 0.55% – of contact allergy in 9755 subjects (6449 women, 3306 men) tested with IPBC (initially 0.1% in petrolatum; raised to 0.2% in 2004) during the period 2000 – 2011. A significant rising trend during the period 2000 – 2011 was evident, though with no statistically significant changes during the period 2006 – 2011. The intensity of positive reactions was rated as +, ++ or +++; 74.6% of the positive reactions were rated '+' and 1.8 were rated '+++'. The IPBC contact allergy was significantly more prevalent among male patients, occupational, related to hand eczema, and more frequent among patients over 40 years old. A significant relationship between IPBC and thiuram mix allergy was found. The higher – though generally stable – frequency of positive reactions in the period 2006 – 2011 was attributed to the change (in 2005) of the patch test concentration from 0.1% to 0.2% IPBC. The intensity of positive reactions was considered concordant with a concomitant series covering the period 1998 – 2008. The authors considered IPBC to be among the less frequent allergens. Gimenez-Arnau et al. 2017 evaluated data collected by the European Surveillance System on Contact Allergies (ESSCA) network between 2009 and 2012 from 12 European countries. Sensitization rates to 0.1% IPBC in petrolatum among 7956 subjects, and to 0.2% in petrolatum among 12360 subjects were 0.11 and 1.21%, respectively. The RAC Opinion on IPBC (28 November 2012) noted that the value of data patch test studies in relation to classification of IPBC for skin sensitisation is limited as it can be expected that a substantial number of the subjects were not sensitised (as required by CLP criteria), and that subjects showing positive skin reactions probably have had previous exposures to other chemical substances not related to IPBC. Overall, the findings of the studiesof Martin-Gorgojo & Johansen (2013) and Gimenez-Arnau et al. (2017) are considered consistent with the information for skin sensitisation in the original CLH report.

As noted in relation to the literature review for human health in Section 2.3. Data Sources, a brief report (Siebert**,** 2004; Doc. No. 592-016, Doc. IIIA, Section A6.1.5/04) of a local lymph node assay (LLNA) with IPBC was published shortly after submission to the eCA of the original draft CAR; it was not addressed in the original CAR for IPBC or in the original

CLH report for IPBC. The LLNA was stated to have been conducted according to the applicable OECD TG 429 (version of April 2002), though the brief report provides only limited information[10] on: a) the manner in which the study was performed, b) its findings, and c) the laboratory conducting the study. Consequently, the reliability score of the study is 3 (unacceptable). In summary, IPBC concentrations of 0.1, 1, 5 and 10% had a Stimulation index (SI) (mean ± SD) of 0.7 ± 0.3, 3.4 ± 1.4, 4.2 ± 1.8, and 12.0 ± 3.4, respectively. The EC3 value (theoretically derived by linear interpolation) was 0.87%. Due to the aforementioned inadequacies, the study is not considered sufficiently reliable for use in relation to the classification of IPBC.

A.3.5.4. Overall conclusion on skin sensitisation related to risk assessment

Not applicable for the CLH report.

A.3.6. Respiratory sensitisation

No new data on respiratory sensitisation have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for respiratory sensitisation.)

A.3.6.4. Overall conclusion on respiratory sensitisation related to risk assessment

Not applicable for the CLH report.

A.3.7. Repeated dose toxicity/STOT RE

The repeated dose toxicity of IPBC has been investigated in short-term-, sub-chronic-, and long-term (chronic) repeated dose toxicity studies using the oral route (gavage or feeding), the dermal route, and following exposure via inhalation.

A.3.7.1. Short term repeated dose toxicity

A.3.7.1.1 Short-term oral toxicity

No new data on short-term oral toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for oral toxicity.

A.3.7.1.2. Short-term dermal toxicity

No new data on short-term dermal toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for dermal toxicity.

[10] Important information missing from the brief study report (and expected to be included in the Test report for a LLNA study according to OECD TG 429, version of July 2010) includes – though is not limited to – purity and impurities of the IPBC test substance; strain, sex, age, body weight and number of mice in each treatment group; quantity of test material dilutions (and of positive and negative controls) applied to the ears; preparation of the single-cell suspension of lymph node cells; eventual deviations from the study protocol. It is not stated if the study was conducted according to GLP. The study did not undergo peer-review.

A.3.7.1.3. Short-term inhalation toxicity

No new data on short-term oral toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for inhalation toxicity.

A.3.7.1.4. Overall conclusion on short-term repeated dose toxicity related risk assessment

Not applicable for the CLH report.

A.3.7.2. Sub-chronic repeated dose toxicity

A.3.7.2.1. Sub-chronic oral toxicity

No new data on sub-chronic oral toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for oral toxicity.

A.3.7.2.2. Sub-chronic dermal toxicity

No new data on sub-chronic dermal toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for dermal toxicity.

A.3.7.2.3. Sub-chronic inhalation toxicity

No new data on sub-chronic inhalation toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for inhalation toxicity.

A.3.7.2.4. Overall conclusion on sub-chronic repeated dose toxicity related risk assessment

Not applicable for the CLH report.

A.3.7.3. Long-term repeated dose toxicity

A.3.7.3.1. Long-term oral toxicity

No new data on long-term (chronic) oral toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for oral toxicity.

A.3.7.3.2. Long-term dermal toxicity

No new data on long-term dermal toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for dermal toxicity.

A.3.7.3.3. Long-term inhalation toxicity

No new data on long-term inhalation toxicity have been submitted or identified that have implications for the current EU harmonised classification of IPBC for inhalation toxicity.

A.3.7.3.4. Overall conclusion on long-term repeated dose toxicity related risk assessment

Not applicable for the CLH report.

A.3.7.4. Specific target organ toxicity – repeated exposure (STOT RE)

No new data on Specific Target Organ Toxicity STOT RE 1 and 2 have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC meets the criteria for classification and labelling for STOT RE 1 (larynx).)

A.3.8. Genotoxicity / Germ cell mutagenicity

No new data on genotoxicity / germ cell mutagenicity have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for mutagenicity.)

A.3.8.2.4. Overall conclusion on genotoxicity related to risk assessment

Not applicable for the CLH report.

A.3.9. Carcinogenicity

No new data on carcinogenicity have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for carcinogenicity.)

A.3.9.4. Overall conclusion on carcinogenicity related to risk assessment

Not applicable for the CLH report.

A.3.10. Reproductive toxicity

A.3.10.1. Sexual function and fertility

No new data on toxicity to sexual function or fertility have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for toxicity to

sexual function or fertility.)

A.3.10.1.3. Overall conclusion on sexual function and fertility related to risk assessment

Not applicable for the CLH report.

A.3.10.2. Developmental toxicity

No new data on developmental toxicity have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for developmental toxicity.)

A.3.10.2.3. Overall conclusion on effects on development related to risk assessment

Not applicable for the CLH report.

A.3.10.3. Effects on or via lactation

No new data on toxic effects on or via lactation have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. The assessments of the Committee for Risk Assessment (RAC), as provided in its Opinion on IPBC of 28 November 2012, are considered to remain valid. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for toxic effects on or via lactation.)

A.3.10.3.3. Overall conclusion on effects on or via lactation related to risk assessment

Not applicable for the CLH report.

A.3.10.5. Overall conclusion on reproductive toxicity related to risk assessment

Not applicable for the CLH report.

A.3.11. Aspiration hazard

No new data on aspiration toxicity have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for aspiration toxicity.)

A.3.12. Neurotoxicity

No new data on neurotoxicity have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC does not meet the criteria for classification for STOT SE, STOT RE, or reproductive toxicity on the basis of potential neurotoxicity.)

In the original PT8 CAR (2008) for IPBC the studies providing information relevant for the evaluation of neurotoxicity were not collected and evaluated in a single section[11]. In the RAR for IPBC in PT8, the studies in question are addressed in Section A.3.12. 'Neurotoxicity', which also evaluates additional relevant information on neurotoxicity (including from studies of reproductive toxicity) present in studies submitted as part of the original application for approval, though not considered in detail in the original PT8 CAR. As part of the application for renewal of approval of IPBC in PT8, the Applicant submitted an expert rule-based (Quantitative) Structure Activity Relationship ((Q)SAR) analysis using Derek Nexus 6.1.0 (Derek KB 2020 1.0) software of the neurotoxicity of IPBC ([redacted], 2021; Doc. No. 581-013). The Applicant also submitted an Expert Evaluation of the neurotoxicity of IPBC ([redacted] 2021; Doc. No. 581-012).

A.3.12.1. Short summary and overall relevance of the provided information on neurotoxicity

The neurotoxicity potential of IPBC was investigated in detail via review of relevant data in the repeated-dose toxicity studies. Clinical signs as well as acetylcholinesterase activity in plasma, RBC, and the brain were investigated as parameters for neurotoxicity. Mechanistic *in vivo* and *in vitro* studies conducted to investigate the ability of IPBC to inhibit the acetylcholinesterase enzyme were considered. (See the relevant footnote in Section A.3.12. for the identity of the relevant studies.)

In rat and rabbit studies on sexual function and fertility ([redacted], 1996; Doc. No. 553-003, Doc. IIIA, Section A6.8.2/01, and [redacted], 1987; Doc. No. 553-002, Doc. IIIA, Section A6.8.2/05), and in rat and rabbit studies on developmental toxicity ([redacted], 1994; Doc. No. 551-008, Doc. IIIA, Section A6.8.1/04, and [redacted], 1994; Doc. No. 551-006, Doc. IIIA, Section A6.8.1/02), clinical signs suggestive of neurotoxicity were limited to post-dose salivation, aggressive behaviour (1 study), and occasional hunched posture or forepaw padding (1 study) in adult rats administered IPBC by gavage. Post-dosing salivation following gavage is likely to be a result of the irritating properties of IPBC, and potentially also the gavage process itself, rather than increased cholinergic activity; a position supported by the lack of reports of salivation in rats, mice and rabbits fed

[11] Information in Section 3.8 'Neurotoxicity' was limited to: "Results indicated that IPBC was not neurotoxic; please refer to chapter 3.5." The introduction to Chapter 3.5 'Short-Term Repeated Dose, Subchronic and Chronic toxicity' noted that the results of studies [relevant for evaluation of neurotoxicity] were summarised in Table 3.8 'Summary of neurotoxicity'. The two studies presented in the table (a rat acute dose range-finding study with 14-days post-exposure ([redacted], 2001; Doc. No. 541-001 to 541-003, Doc. IIIA, Section A6.9/02 to 04), and a 13-week dietary neurotoxicity study in the rat ([redacted], 2001; Doc. No. 542-001 to 542-004, Doc. IIIA, Section A6.9/06 to 09) were reviewed under the heading 'Oral administration of IPBC' of Chapter 3.5. However, under the heading 'Administration of IPBC via inhalation' of Chapter 3.5, the neurotoxicity findings of a 13-week rat inhalation toxicity study ([redacted], 1994; Doc. No. 535-001, Doc. IIIA, Section A6.4.3/01) were identified, and were considered supported by a 104-week (oral) toxicity study in the rat ([redacted], 1989; Doc. No. 537-001, Doc. IIIA, Section A6.7/01 and [redacted], 1988; Doc. No. 537-002, Doc. IIIA, Section A6.7/02) and a 78-week (oral) toxicity study in the mouse ([redacted], 1989; Doc. No. 555-001 to 555-004, Doc. IIIA, Section 6.7/04/05/06/07). In addition, Section 3.2 'Acute toxicity' of the original CAR included a study that examined the neurotoxicity of single doses of IPBC administered *i.v.* to the rat ([redacted], 1988; Doc. No. 541-006, Doc. IIIA, Section A6.11/01). Section 3.9 'Human data' presented human health data from two occupational health surveys ([redacted] (2003) and [redacted] (2003); Doc. No. 574-001 and 574-002, Doc. IIIA, Section A6.12.1/01/02; and, ([redacted] 1992; Doc. No. 592-013, Doc. IIIA, Section A6.12.3/01). An *in vitro* study ([redacted], 1989; Doc. No. 541-005, Doc. IIIA, Section A6.9) measuring acetyl cholinesterase activity in rat and human plasma and erythrocytes after addition of IPBC to blood samples was submitted as part of the initial application for approval of IPBC in PT8 though was not addressed in the CAR. Not all the above studies were considered in relation to neurotoxicity in the original CLH Report for IPBC (CA DK, June 2011).

comparable or higher doses of IPBC. No signs of developmental neurotoxicity were reported in a two-generation reproduction toxicity study in which rats were administered oral doses of up to 30 mg/kg bw/day (with up to 100 mg/kg bw/day administered to F_0 parents) ([redacted], 1996; Doc. No. 553-003, Doc. IIIA, Section A6.8.2/01), or in pre-natal developmental toxicity studies in which rats and rabbits were administered oral doses of up to 250 mg/kg bw/day or 40 or mg/kg bw/day, respectively ([redacted], 1994; Doc. No. 551-008, Doc. IIIA, Section A6.8.1/04, and [redacted], 1994; Doc. No. 551-006, Doc. IIIA, Section A6.8.1/02).

In the expert rule-based (Quantitative) Structure Activity Relationship ((Q)SAR) analysis of the neurotoxicity of IPBC using Derek Nexus software ([redacted], 2021; Doc. No. 581-013) none of the eight alerts for neurotoxicity were triggered[12]. The software also includes two alerts for cholinesterase inhibition (organophosphorus ester and N-methyl or N,N-dimethyl carbamate), neither of which were triggered.

Regarding the potential for cholinesterase inhibition by IPBC, the Applicant's Expert Evaluation of the neurotoxicity of IPBC ([redacted] 2021; Doc. No. 581-012) noted that evaluation of structure–activity relationships of the carbamate insecticides has revealed general similarities with those of the organophosphates (OPs). The anticholinesterase activity of a carbamate is primarily a function of the reactivity of the carbonyl carbon (rather than the phosphorus of OPs) and of the ability of the carbamate to diffuse into the active site cleft of the cholinesterase and form Michaelis complexes (steric properties). The steric properties of a carbamate modulate the access of the carbamate to the catalytic serine of the cholinesterase. Bulky substituents – such as the butyl group (a component of the IPBC molecule) reduce access to the catalytic site and thus limit anticholinesterase activity.

In conclusion, the neurotoxicity studies in rodents are considered to provide sufficient data to evaluate the potential neurotoxicity of IPBC. No clear signs of neurotoxicity are considered evident. The animal data are supported by the (Q)SAR analysis of the neurotoxicity of IPBC, by evaluations of the structure–activity relationships of the carbamate insecticides in the published literature, and by the limited human data for IPBC.

A.3.12.2. Comparison with the CLP criteria

According to the note to Table 3.8.1 'Categories for specific target organ toxicity – single exposure', and the note to Table 3.9.1 'Categories for specific target organ toxicity – repeated exposure' in Sections 3.8.1. and 3.9.1, respectively, of Regulation (EC) No 1272/2008 (CLP), neurotoxicity can be considered a specific target organ toxicity (when not judged to be a secondary toxic effect), and trigger classification for STOT SE and/or STOT RE. As IPBC is not considered to demonstrate acute or chronic neurotoxicity (or developmental neurotoxicity), it is not considered to require classification for STOT SE or STOT RE (or reproductive toxicity) on the basis of potential neurotoxicity.

A.3.12.3. Conclusion on neurotoxicity related to risk assessment

Not applicable for the CLH report.

[12] Eight alerts for neurotoxicity are incorporated in Derek Nexus 6.1.0: gamma-diketone or precursor, acrylamide or glycidamide, nitroimidazole, carbon disulphide or precursor, pyrethroid, 1-methyl-1,2,3,6-tetrahydropyridin, lead or lead compound, organophosphorus ester.

A.3.13. Immunotoxicity

No new data on immunotoxicity have been submitted or identified that warrant revision of the current EU harmonised classification* of IPBC. (* According to Regulation (EC) No 1272/2008 (CLP), IPBC meets the criteria for classification and labelling for skin sensitisation (Skin Sens. 1; H317: May cause an allergic skin reaction).)

Immunotoxicity – with the exception of skin sensitisation – was not specifically addressed in the original PT8 CAR (2008) for IPBC, and no data was specifically cited (combined chronic toxicity/carcinogencity studies were referred to) in relation to immunotoxicity in the original CLH Report for IPBC (June 2011). As part of the application for renewal of approval of IPBC in PT8, a detailed assessment of information related to immune parameters in studies peer-reviewed at EU level during the initial approval was performed ([redacted], 2021, Doc. No. 581-011) according to the Guidance on BPR Volume III Parts B+C Version 4.0 December 2017. Data on IPBC from standard repeated-dose toxicity tests (28-day and 90-day), plus data from chronic toxicity/carcinogenicity and multi-generation and reproductive toxicity studies, were evaluated with the aim of assessing the immunotoxic potential of the active substance with emphasis on: a) morphological changes to lymphoid organs and tissues including bone marrow (e.g. changes in thymus, spleen, lymph nodes, and/or bone marrow), b) weight changes of lymphoid organs, c) changes in haematology parameters (e.g. white blood cell number, differential cell counts of lymphocytic, monocytic and granulocytic cells), and d) changes in clinical chemistry parameters (e.g. serum protein levels, immunoglobulin concentrations if determined). No data for IPBC from animal studies specifically on immunotoxicity, or for *in vitro* immunotoxicity, was submitted as part of the initial approval application.

A.3.13.1. Short summary and overall relevance of the provided information on immunotoxicity

A total of 11 studies (9 key studies, 2 supportive studies), including a 2-year rat study and a 78-week mouse study in which animals were fed IPBC at doses up to 80 or 150 mg/kg bw/day, respectively, and a two-generation reproduction toxicity study in the rat in which IPBC was fed at doses up to 30 mg/kg bw/day, that were all included in the initial application for approval were evaluated.

No alteration in the immune system organs (thymus, spleen, lymph nodes, bone marrow) in terms of gross pathology and histopathology were observed (in the rat, mouse, and rabbit) under treatment with IPBC. Furthermore, treatment with IPBC had no effects on the weights of the lymphoid organs. Additionally, the total- and differential white blood cell counts (lymphocytic, monocytic, and granulocytic cells) were not considered affected by IPBC treatment in all 9 of the studies in which the parameter was investigated. A decrease in the number of WBC in female rats at the high dose, and a decrease in the number of lymphocytes in the mid- and high dose groups after 45 days treatment in a 3-month study ([redacted], 1997; Doc. No. 533-003, Doc. IIIA, Section A6.4.1/03) were not considered treatment-related due to the lack of a dose-response relationship and absence of temporal consistency. Changes to haematological parameters in a 2-year rat study ([redacted], 1989; Doc. No. 537-001, Doc. IIIA, Section A6.7/01) were not considered treatment-related due to the lack of a dose-response relationship and absence of temporal consistency and/or small magnitude.

Clinical chemistry parameters were reported in 8 of 11 studies, with no toxicologically relevant changes in serum protein (albumin, globulins) levels considered evident in the studies. An increase in albumin level in male and female rats at the high dose in a 13-week study ([redacted], 2002; Doc. No. 533-005, Doc. A6.4.1/01) were considered to be incidental due to the low magnitude. An increase in total protein and globulin in female

rats at the high dose after 45 days treatment in a 3-month study ([redacted], 1997; Doc. No. 533-003, Doc. IIIA, Section A6.4.1/03) were not considered toxicologically relevant due to the lack of a dose-response relationship and absence of temporal consistency.

In conclusion, no indications for disturbance of proper functioning of the immune system due to administration of IPBC (via oral, dermal or inhalation route) were evident in studies evaluated. Therefore, it can be reasonably concluded that IPBC does not raise concern for immunotoxicity (other than for skin sensitisation as addressed in Section A.3.5). Consequently, further testing (as described in the Guidance on BPR,) is not warranted[13]. The limited human data presented as part of the original application for approval of IPBC in PT8 do not raise any concerns in relation to immunotoxicity.

A.3.13.2. Comparison with the CLP criteria

The conclusion on classification and labelling can be found in Section A.3.5 Skin sensitisation.

A.3.13.3. Conclusion on immunotoxicity related to risk assessment

Not applicable for the CLH report.

A.3.14. Endocrine disruption

Not applicable for the CLH report.

A.3.15. Further Human data

No new human data have been submitted or identified that have implications for the current EU harmonised classification of IPBC.

A.3.16. Other data

Phototoxicity

Not relevant*. (* According to Section 2.1.13.1 'Phototoxicity – additional study of Part A (Information Requirements)' of Volume III of the Guidance on the BPR (Version 1.2, May 2018), *in vitro* toxicity testing is required when the active substance absorbs electromagnetic radiation in the range 290 – 700 nm. IPBC does not absorb light at wavelengths above 290 nm.)

[13] According to the Guidance on BPR, additional investigations (e.g. T-cell function test, host resistant models) should be conducted in case the screening parameters (morphological changes to lymphoid organs and tissues, changes in haematology and of clinical chemistry) indicate concerns AND if the results of such additional investigations can be interpreted in relation to the risk assessment for the substance.

A.4. Environmental effects assessment

A.4.1. Fate and distribution in the environment

A.4.1.1. Degradation

A4.1.1.1 Abiotic degradation

Hydrolysis

No new data was submitted on hydrolysis for the renewal of IPBC in PT8. The studies submitted for the initial approval under the directive in 2008 are considered valid under the Biocidal Product Regulation 528/2012 and are summarised in the table below:

Table 14 Summary table – Hydrolysis

Summary table - Hydrolysis							
Method, Guideline, GLP status, Reliability, Key/ supportive study	pH	Temp. [°C]	Initial TS concentration, C_0[mol/l]	Half-life, DT50 [d]	Coefficient of correlation, r^2	Remarks	Reference
EG guideline C7. 92/69, GLP: Yes, Reliability: 1, key study	Pre-test: pH 4, 7 and 9 Main test: pH 9	Pretest: 50 °C Maintest: 65 °C 80 °C	Not indicated	The test substance IPBC is not degradable at pH 4 and pH 7 pH 9: 12942 h = 539 days (25 °C) 282 h = 11.8 d (50°C) 31 h = 1.3 d (65°C) 5.6 h = 0.2 d (80°C)	 0.998 0.993 0.999	Reaction rate constant (K_h) pH 9: 0.0025 h^{-1} (50 °C) 0.0224 h^{-1} (65 °C) 0.125 h^{-1} (80 °C)	[redacted], 2001: Doc. No.: 711-004; IUCLID section, A10.1.1.1.a/ 01
EPA Subdivision N, No. 161-1, GLP: Yes, Reliability: 1, key study	pH 5, 7 and 9	25 ± 1°C	5 mg/L	pH 5: 267 d pH 7: 248 d pH 9: 229 d	0.657 0.7 0.796	Reaction rate constant (K_h) pH 5: 0.0026 d^{-1} pH 7: 0.00279 d^{-1} pH 9: 0.00302 d^{-1} (25°C)	[redacted], 1994: Doc. No.: 711-003; IUCLID section A10.1.1.1.a/ 02

Value used in Risk Assessment	
Value/conclusion	Stable to hydrolysis
Justification for the value/conclusion	IPBC was found to be hydrolytically stable (DT_{50} 267 days at pH 5, 248 days at pH 7 and 229 – 539 days at pH 9) in aqueous solution at relevant pH. Recalculated to 12 °C the DT50 of hydrolysis would be: pH 9 at 12 °C = 648 d = 1525 d

Phototransformation in water

No new data was submitted on phototransformation in water for the renewal of IPBC in PT8. The studies submitted for the initial approval under the directive in 2008 are considered valid for renewal under the Biocidal Product Regulation 528/2012 and are summarised in the table below:

Table 15 Summary table – Photolysis in water

Summary table – Photolysis in water								
Method, Guideline, GLP status, Reliability, Key/ supportive study	Initial molar TS concentration	Total recovery of test substance [% of appl. AS]	Photolysis rate constant (kcp)	Direct photolysis sunlight rate constant (kpE)	Reaction quantum yield (φcE)	Half-life (t1/2E)	Remarks	Reference
OECD Guideline for testing of chemicals (Draft), August 2000, GLP: Yes, Reliability: 1, key study	1.977 mg IPBC/L	Sterilised buffer: 100.0-102.0 pond water: 100.6 - 104.7	IPBC was stable within 3 days of continuous irradiation	-	-	-		[redacted], 2005, Doc. No.: 712-001, IUCLID section A10.1.1.1.b/03
Guideline: no, publication, GLP: No, Reliability: 2, key study	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Ca. 25% decomposition after 17 days in irradiated ethanol solution		Lee, D. et al. (1991): Doc. No.: 792-005, IUCLID section, A10.1.1.1.b/02/01 and Lee, D. et al. (1991): Doc. No.: 792-004, IUCLID section A10.1.1.1.b/02

According to Lee, D. *et al*. (1991), IPBC is subject to photolytic degradation on wood surfaces:

- In irradiated ethanol solutions, approximately 25 % of the initial IPBC was degraded within 17 days of exposure.

- Results on the decomposition of IPBC in wood suggest that photodegradation is likely to occur in a thin layer of the wood surface. After 25 to 50 days of irradiation, the recovery rate of IPBC decreased to approximately 40 to 50 %. IPBC was converted to PBC by photolytic cleavage of the carbon-iodine bond and release of the iodine.

- According to [redacted] (2005) the results of a photodegradation study in sterilised aqueous buffer solution at pH 7 and natural pond water at a pH value of about 8.5 made in according to the OECD guideline show that IPBC was stable within 3 days of continuous irradiation (corresponding to 6.1 days natural summer sunlight at latitude 50°N). Since IPBC was stable during the incubation period no half-lives and no quantum yield could be calculated. The results of the study demonstrate that IPBC is stable to direct and indirect photolysis in the aquatic environment. The study by [redacted] (2005) was selected as the key study for the endpoint photolysis in water.

Value used in Risk Assessment	
Value/conclusion	Stable to photolysis
Justification for the value/conclusion	IPBC is stable to direct and indirect photolysis in the aquatic environment as demonstrated for sterilised buffer and natural pond water at 25°C for up to 3 days.

Photodegradation in air

Not relevant for the CLH report

Estimated photooxidation in air

Not relevant for the CLH report

A4.1.1.2 Biotic degradation, initial studies

A4.1.1.2.1 Biodegradability (ready/inherent)

No new data was submitted on ready/ inherent biotic degradation in water for the renewal of IPBC in PT8. The studies submitted for the initial approval under the directive in 2008 are considered valid for renewal under the Biocidal Product Regulation 528/2012 and are summarised in the table below:

Table 16 Summary table - biodegradation studies (ready/inherent)

Summary table - biodegradation studies (ready/inherent)											
Method, Guideline, GLP status, Reliability, Key/ supportive study	Test type[1]	Test parameter	Inoculum			Addition-al substrate	Test sub-stance concentr.	Degradation		Remarks [positive control]	Reference
			Type	Concen-tration	Adap-tation			Incubat-ion period	Degree [%]		
Manometric respirometry test, OECD guideline 301F, GLP: Yes, Reliability: 1, key study	ready	CO_2 evolution	Acti-vated sludge	30 mg dry material per litre	No	No	50 mg/L	28 d	24-26		[redacted], 2002, Doc. No.: 713-002; IUCLID section 10.1.1.2.a/01
Modified "Zahn-Wellens / EMPA Test", OECD guideline 302B, GLP: Yes, Reliability: 1, key study	inherent	Analysis of IPBC and PBC	Acti-vated sludge	High dose: 1.0 mg/L Low dose: 0.02 mg/L	No	No	0.02/1.0 mg/L	28 d	transfor-mation of IPBC to PBC within 2 hours		[redacted], 2004, Doc. No.:713-004, IUCLID section 10.1.1.2.b/01
1 Test on inherent or ready biodegradability according to OECD criteria											

According to the above cited standard tests on ready and inherent biodegradation, IPBC is not readily but is primary biodegradable according to Zahn-Wellens test. It was not possible to conclude on the inherent biodegradability from [redacted] (2004).

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.

In the degradation process IPBC ($C_8H_{12}INO_2$) breaks down into PBC ($C_8H_{13}NO_2$) by releasing the iodine-moiety. See section *A.4.5.3. Conclusion on classification and labelling for environmental hazards and comparison with the CLP criteria* on the rapid degradability assessment of IPBC and section *A.4.2.3.1 Freshwater compartment* for iodine/iodide/iodate ecotoxicity.

Value used in Risk Assessment	
Value/conclusion	IPBC is not readily degradable, it is primarily degradable. For the rapid degradability assessment, see section *A.4.5.3. Conclusion on classification and labelling for environmental hazards and comparison with the CLP criteria*.
Justification for the value/conclusion	The assessment of biodegradability is based on results performed according to the OECD test guidelines 301F and 302B

A4.1.1.3 Rate and route of degradation including identification of metabolites and degradation products

A4.1.1.3.1 Biological sewage treatment

Data on the biological sewage treatment from the STP simulation test is not included as it is not relevant in the CLH report

A4.1.1.3.2 Biodegradation in freshwater

Aerobic aquatic degradation

Data waiving	
Information requirement	Aerobic aquatic degradation
Justification	A test on aerobic aquatic degradation e.g. acc. to OECD 309 is not required since a water/sediment study under aerobic conditions according to OECD 308 is available (see below).

Water/sediment degradation test

New data was submitted on aerobic degradation in water for the renewal of IPBC in PT8. The study was evaluated in accordance to current guideline under the Biocidal Product Regulation 528/2012 and are summarised in the table below:

Table 17 Summary table – fresh water/sediment degradation

Summary table – fresh water/sediment degradation									
Method, Guideline, GLP status, Reliability, Key/supportive study	**Test type[1]**	**Exposure**	**Test system**		**Test substance concentration**	**Incubation period**	**Degradation (DT50)**	**Remarks**	**Reference**
			Water	Sediment					
Anaerobic aquatic metabolism study, EPA Pesticide Assess. Guide, Subdiv N, series 162-3, GLP: Yes, Reliability: 2, key study	anaerobic	Water/ sediment	--	--	0.94 – 1.04 ppm	118-244 d	DT_{50} 1.5 h (IPBC) 11.5 d (PBC)	--	[redacted], 1992 Doc. No.: 715-001; IUCLID section 10.1.3.2.b/01
IPBC – Degradation/Metabolism of [^{14}C]IPBC in Two Aquatic Systems under Aerobic Conditions OECD Guideline 308, GLP: Yes, Reliability 1, key study	aerobic	Water/ sediment	Water	Sediment	0.200-0.203 mg/L	56 d	IPBC (River): 0.657 d (total system) 0.661 d (water phase) IPBC (Pond): 0.682 d (total system) 0.704 d (water phase)	--	[redacted], 2018 Doc. No.: 714-001, IUCLID section 10.1.3.2.b/02
Assessment of degradation kinetics of IPBC and its metabolites in water/sediment systems under laboratory conditions according to the recommendations of the FOCUS report on degradation kinetics (2006, 2014), GLP: no, Reliability 1, key study	--	--	--	--	--	--	IPBC (total system): 0.8 d (Pond) 0.7 d (River) 0.7 d geomean PBC (total system): 6.5 d (Pond) 8.1 d (River) 7.2 d geomean 2-PBC (total system): 5.3 d (Pond) 8.8 d (River) 6.8 d geomean	--	[redacted], 2018 Doc. No.: 781-005, IUCLID section 10.1.3.2.b/03
[1] Test according to OECD criteria									

An aerobic water-sediment study according to OECD-guideline 308 was performed for IPBC. In this study the route and rate of degradation of [^{14}C]IPBC was investigated in two different aquatic sediment systems: a river and a pond system. [^{14}C]IPBC was applied at a rate ranging from 139.9 to 142.1 µg test item per river and pond system sample, corresponding to a water concentration ranging from 199.9 to 203.0 µg/L. The aquatic sediment systems were incubated under aerobic conditions in the laboratory in the dark at 20.8 ± 0.2 °C.
Duplicate samples were taken for analysis immediately after application (time 0), and after 0.08 (2 hours), 0.17 (4 hours), 0.29 (7 hours), 0.96 (23 hours), 7, 14, 28 and 56 days of incubation for both the river and pond systems. IPBC was predominantly detected in the water phase. In sediment extracts, parent was only detected at the 23-hour (0.96 DAT) sampling interval at a relative abundance of 0.3% and 0.2% AR for the river and pond system, respectively.
The amount of test item in the total river system decreased from 99.8% AR on day 0 to 73.9% AR after 7 hours (0.29 DAT) and to 36.7% AR after 23 hours (0.96 DAT), thereafter remaining <LOD at subsequent intervals through the end of the 56-day incubation period. The corresponding values for the total pond system were 98.0% AR at time 0, decreasing to 72.0% AR after 7 hours (0.29 DAT) and to 39.7% AR after 23 hours (0.96 DAT), thereafter remaining <LOD at subsequent intervals until the end of the 56-day incubation period.
In the river and pond systems, two major metabolites (M1 and M2) were observed. M1 was identified as propynyl-butylcarbamate (PBC) and M2 as 2-propenyl-butylcarbamate (2-PBC). As previously mentioned iodine is released during the first degradation step of IPBC into PBC, however the iodine containing metabolites are not mentioned in this study.
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 CO_2.
The degradation rates in the total system are for IPBC in the range of 0.657-0.682 days. For the major metabolite PBC the DT_{50} values in the total systems range between 5.8-12.6 days and for 2-PBC between 4.7-16.3 days.
Based on the results of the water-sediment study an assessment of degradation kinetics was performed and the following DT_{50}-valus were determined:

IPBC: 0.8 d (Pond), 0.7 d (River), 0.7 d geomean
PBC: 6.5 d (Pond), 8.1 d (River), 7.2 d geomean
2-PBC: 5.3 d (Pond), 8.8 d (River), 6.8 d geomean

In [redacted] 1992 (Doc. No: 715-001), the degradation of IPBC in an anaerobic water/sediment system was investigated. The DT_{50} value for the total system was 1.5 hours at 22°C corresponding to a DT_{50} value of 3.3 hours at 12°C (found using the Arrhenius equation). IPBC was predominantly found in the water phase. PBC was found to be a major metabolite. With a DT_{50} of 11.5 days at 22°C corresponding to 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 is 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.

Value used in Risk Assessment	
Value/conclusion	IPBC 0.7 d (20.8 °C)1.4 d (12 °C) PBC: 7.2 d (20.8 °C)14.6 d (12 °C) 2-PBC: 6.8 d (20.8 °C) 13.7 (12 °C)
Justification for the value/conclusion	The rate and route of degradation of [^{14}C]IPBC was investigated in two different aquatic systems (a river and a pond) under aerobic conditions. The study was performed according to the current guideline OECD 308 and the degradation rates of [^{14}C]IPBC and its major metabolites PBC and 2-PBC were determined. These values were the basis for the assessment of degradation kinetics in which the above mentioned DT_{50}-values were calculated. The iodine species metabolites were not investigated in these studies.

A4.1.1.3.3 Biodegradation in seawater

Not relevant for the CLH report

A4.1.1.3.4 Higher tier degradation studies in water or sediment

Not relevant for the CLH report

A4.1.1.3.5 Biodegradation during manure storage

Not relevant for the CLH report

A4.1.1.3.6 Biotic degradation in soil

A4.1.1.3.6.1 Laboratory soil degradation studies

Not relevant for the CLH report

A4.1.1.3.6.2 Higher tier degradation studies in soil

Not relevant for the CLH report

A4.1.1.3.7 Short summary and overall relevance of the provided information on degradation and conclusion on rapid degradation for classification and labelling purposes

IPBC is hydrolytically stable and is stable to direct and indirect photolysis in the aquatic environment. It degrades quickly in the atmosphere by reaction with OH radicals. It is not readily but primary biodegradable according to Zahn-Wellens test. In the water-sediment compartment a fast transformation of IPBC to PBC occurs. The estimated toxicity based on QSAR (EPIWIN) for the metabolite 2-PBC was found to be comparable to that of IPBC and therefore, no experimental ecotoxicological data of this metabolite was required in this case.

The following DT_{50} values for the different environmental compartments are determined:

Table 18 DT_{50} values for 20.8 °C

	temperature	**DT_{50}**		
		IPBC	PBC	2-PBC
Soil	n.r.	n.r.	n.r.	n.r.
Water	20.8 °C	0.7 d	7.2 d	6.8 d

n.r.: not relevant for the CLH report

The following DT_{50} values used in the risk assessment are based on 12 °C (using Arrhenius equation):

Table 19 DT_{50} values for 12 °C

	temperature	**DT_{50}**		
		IPBC	PBC	2-PBC
Soil	n.r.	n.r.	n.r.	n.r.
Water	12 °C	1.42 d	14.56 d	13.75 d

n.r.: not relevant for the CLH report

The indicated half-life for PBC/2-PBC is based on data from the water/sediment system study that included differentiated water / sediment data.

A.4.1.2. Distribution

Not relevant for the CLH report

A4.1.2.1 Adsorption onto/desorption from soils

Not relevant for the CLH report

A4.1.2.2 Higher tier soil adsorption studies

Not relevant for the CLH report

A4.1.2.3 Volatilisation

Not relevant for the CLH report

A.4.1.3. Bioaccumulation

Not relevant for the CLH report

A.4.1.3.1 Short summary and overall relevance of the provided information on bioaccumulation and conclusion on bioaccumulation potential for classification and labelling purposes

Not relevant for the CLH report

A.4.1.4. Monitoring data

Not relevant for the CLH report

A.4.2. Effects on environmental organisms

No new data on the effects on environmental organisms have been submitted that warrant revision of the current EU harmonised classification of IPBC concerning ecotoxicity endpoints (Aquatic Acute 1 and Aquatic Chronic 1). A literature review has been performed as described in section 2.3 Data sources. Relevant studies are presented below.

- # In the literature search on ecotoxicity data for IPBC, one study with relevance was discovered. In the study by Coors et al. (2012) mixture toxicity of wood preservative products in the fish embryo toxicity test is investigated. IPBC is also tested separately. This study is an acute toxicity test for zebra fish (*Danio rerio*) embryos and after the study was published, an OECD Guideline (OECD 236) was developed for this test method. As the study is a fish study running for 96 hours and the target value is a LC_{50} value, this study could be relevant to consider for the Aquatic Acute classification. The LC_{50} found for zebra fish embryos for IPBC in Coors et al. is 0.349 mg/L derived as the mean of the results from 2 independent tests. The data submitted for the IPBC dossier include studies showing lower LC_{50} values with the most sensitive fish being Rainbow trout (*Oncorhynchus mykiss*) with an LC_{50} of 0.067 mg/L (EPA-FIFRA 72-1), and the most sensitive species being the algae *Scenedesmus subspicatus* with an E_rC_{50} of 0.0530 mg/L and a E_bC_{50} of 0.0220 mg/L. As these values show a more sensitive EC_{50} or LC_{50}, the classification is set from the lowest value, the results from the zebra fish embryo study does not affect the Aquatic Acute classification.

A.4.2.1. Atmosphere

Not applicable for CLH report.

A.4.2.2. Toxicity to sewage treatment plant (STP) microorganisms

Not relevant for the CLH report

A.4.2.3. Aquatic compartment

According to the Guidance on the BPR (Volume IV: Environment, Part A: Information Requirements, Version 1.2; May 2018) for wood preservatives (Product type 8), acute and long term toxicity tests on aquatic organisms are required for fish, invertebrates and algae.

For all of the three species (fish, invertebrates and algae), valid acute and long term toxicity tests with IPBC are available. Only the

key studies which provided the lowest endpoint were included in IUCLD and summarised in the tables below.

No new data was submitted for freshwater organisms for the renewal of IPBC in PT8. The studies submitted for the initial approval under the directive in 2008 are considered valid for renewal under the Biocidal Product Regulation 528/2012 and are summarised in the tables below.

A.4.2.3.1 Freshwater compartment

Acute/short-term toxicity (freshwater)

Data on acute/short term toxicity of IPBC to aquatic organisms is not relevant for the CLH report.

Data on the acute/short term toxicity for iodine, iodide and iodate are presented in the following table. Data are from Appendix 1, Chapter 5 in the List of Endpoints in the Iodine CAR (2013). These are not new data, however as they are relevant for the current assessment they are included. See section *A.4.5.3. Conclusion on classification and labelling for environmental hazards and comparison with the CLP criteria* for further details on the impact of the ecotoxicity data on iodine, iodide and iodate.

Table 20 Summary table of acute/short-term aquatic toxicity of iodine, iodide and iodate

Acute/short-term aquatic toxicity of iodine, iodide and iodate			
Species	Time-scale	Endpoint	Toxicity
Fish			
Oncorhynchus mykiss	96 hours	LC_{50} (iodide)	3780 mg/L
		LC_{50} (iodate)	220 mg /L
		LC_{50} (iodine)	1.67 mg/L
Invertebrates			
Daphnia magna	48 hours	LC_{50} (iodide)	0.83 mg/L
		LC_{50} (iodidate)	58.5 mg/L
		LC_{50} (iodine)	0.59 mg/L
Algae			
Desmodesmus subspicatus	72 hours	E_rC_{50} (iodine)	1.3 mg /L
		E_bC_{50} (iodine)	0.62 mg/L

From the data presented in the summary table on acute/short-term aquatic toxicity of iodine, iodide and iodate, it is seen that for all iodine species, the most sensitive species is Daphnia magna with LC50 values of 0.83 mg/L, 58.5 mg/L and 0.59 mg/L for iodide, iodate and iodine, respesctively.

Chronic/long-term toxicity (freshwater)

No new studies on chronic endpoints were submitted for the renewal in PT8.

Table 21 Summary table – chronic/long-term aquatic toxicity of IPBC

Summary table – chronic/long-term aquatic toxicity								
Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material	Exposure		Results	Remarks	**Reference**
				Design	Duration	LOEC/NOEC /EC10[specify the value]		
Fish								
EPA-FIFRA 72-4, comparable to OECD 210, GLP: Yes, Reliability: 1, key study	*Pimephales promelas* (Fathead Minnow)	Larval growth (length and weight) / Early life stage test	Technical active substance IPBC Purity 97.3%	Flow-through	35 days	LOEC: 0.019 NOEC: 0.0084		[redacted], 1992 Doc. No. 826-001 IUCLID Section, 9.1.6
Invertebrates								
EPA-FIFRA 72-4, OECD 202, GLP: Yes, Reliability: 1 key study	*Daphnia magna*	Mortality, reproduction and growth effects	Technical active substance IPBC Purity 97%	Flow-through	21 days	LOEC: 0.099 mg/L NOEC: 0.050 mg/L	LC_{50}: 0.133 mg/L	[redacted], 1991 Doc. No. 827-001 IUCLID Section, 9.1.6
Algae (growth inhibition)								
92/69/EEC, C3 (1992),	*Scenedesmus*		Technical active substance IPBC	Static	72 hours	NOEC 0.0046	EC10 0.013	[redacted], 2001

OECD 201, GLP: Yes, Reliability: 1 key study	*subspicatus*		Purity 99.1%			mg/L	mg/L [1] 0.0058 µg/L [2]	Doc. No. 823-003 IUCLID Section, 9.1.3
EPA-FIFRA 122-2, comparable to OECD 201, GLP: Yes, Reliability: 3, supportive study	*Selenastrum capricornutum*		Technical active substance IPBC Purity 97 - 98%	Static	120 hours	< 0.089 mg/L		[redacted], 1994 Doc. No. 823-001 IUCLID Section, 9.1.3

[1] Calculated from growth rate

[2] Calculated from biomass

Long-term exposure (35 days) of fish (*Pimephales promelas*) to IPBC resulted in an NOEC value of 0.0084 mg IPBC/L.

Long-term exposure (21 days) of daphnids to the active substance IPBC resulted in an NOEC of 0.050 mg IPBC/L.

The NOEC value of 0.0046 mg/L from the algae study with *Scenedesmus subspicatus* is the most sensitive endpoint for the active substance IPBC.

Value used in Risk Assessment	
Value/conclusion	NOEC of 0.0046 mg IPBC/L
Justification for the value/conclusion	The data on acute and chronic toxicity of IPBC to aquatic organisms reveal algae (*Scenedesmus subspicatus*) to be the most sensitive species. The lowest NOEC of 0.0046 mg IPBC/L was used to derive the PNEC for the Risk Assessment.

A.4.2.3.2 Sediment compartment (freshwater)

Not relevant for the CLH report

A.4.2.3.3 Marine compartment

Not relevant for the CLH report

A.4.2.3.4 Sea sediment compartment

Not relevant for the CLH report

A.4.2.3.5 Higher tier studies on aquatic organisms

Not relevant for the CLH report

A.4.2.4. Terrestrial compartment

Not relevant for the CLH report

A.4.2.5. Groundwater

Not relevant for the CLH report

A.4.2.6. Birds and mammals

Not applicable for CLH report.

A.4.2.7. Primary and secondary poisoning

Not applicable for CLH report.

A.4.3. Endocrine disruption

Not applicable for CLH report.

A.4.4. Derivation of PNECs

Not applicable for CLH report.

A.4.5. Overall summary of acute and chronic aquatic toxicity data and Comparison with the CLP criteria

A.4.5.1. Acute aquatic hazard

Not relevant for the CLH report.

A.4.5.2. Long-term aquatic hazard (including information on bioaccumulation and degradation)

Table 22 Summary of key information on chronic/ long-term aquatic toxicity relevant for chronic classification

Method	Species	Test material	Results[1]	Remarks	Reference
Fish					
Early-life stage toxicity test	Fathead minnow (*Pimephales promelas*)	Technical active substance IPBC (Tryosan Polyphase P-100)	NOEC: 0.0084 mg/L		[redacted], 1992 Doc. No. 826-001 Doc. IIIA, Section A7.4.3.2/01 IUCLID Section, 9.1.6.1
Invertebrates					
Acute immobilisation test	*Daphnia magna*	Technical active substance IPBC (Troysan Polyphase P100)	NOEC: 0.050 mg/L		[redacted], 1991 Doc. No. 827-001 Doc. IIIA, Section A7.4.3.4/01 IUCLID Section, 9.1.6.2
Algae					
Acute/Chronic toxicity	*Scenedesmus subspicatus*	Technical active substance Purity 99.1%	E_bC_{50}: 0.022 mg/L E_rC_{50}: 0.053 mg/L NOEC:		[redacted], 2001 Doc. No. 823-003 IUCLID

			0.0046 mg/L		Section, 9.1.3

A.4.5.3. Conclusion on classification and labelling for environmental hazards and comparison with the CLP criteria

IPBC is classified according to Annex VI of the CLP Regulation as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410).

M-factor

The M-factor for the environmental hazard classification Aquatic Acute is set based on toxicity data. According to ECHA's *Guidance on the Application of the CLP Criteria*, version 5.0, table 4.1.3, page 509, the M-factor for a substance with the lowest value of acute toxicity of $0.01<L(E)C_{50}\leq 0.1$, which is the relevant range for IPBC, is 10. DK CA agrees with the M-factor for the Aquatic Acute classification.

The M-factor the for Aquatic Chronic classification is set using data on the active substance's degradability and data on ecotoxicity. There is a factor 10 difference in the M-factor depending on whether the substance is rapidly degradable or not. To determine this, the decision scheme in ECHA's *Guidance on the Application of the CLP Criteria*, version 5.0, page 570 is used. For the classification of IPBC in the CLH report of 2011, the Commission Regulation (EU) No. 286/2011 section 4.1.2.9.5, was followed and criteria c) was fulfilled, concluding that IPBC was rapidly degradable. In the *Guidance on the Application of the CLP Criteria* from ECHA (July 2017), the decision scheme includes an additional criteria on the classification of the metabolites compared to 286/2011.

A substance is considered not rapidly degradable (giving an M-factor 10 times higher than for rapidly degradable compounds with the same level of toxicity to aquatic organisms) unless a, b or c from the decision scheme is fulfilled. Point c resembles what was previously considered fulfilled, as the substance was demonstrated to be primarily degraded in the aquatic environment with a half-life of <16 days.

The impact of the ecotoxicity of the metabolites with iodine on rapid degradability

The formulation in c) in the Guidance is: "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**". The criteria only concerns the ecotoxicity of the metabolites, not the fate, therefore the ecotoxicity of the metabolites of IPBC is investigated. The two previously mentioned metabolites PBC and 2-PBC are not hazardous to the aquatic environment, however other metabolites are formed, when IPBC is degraded.

As presented in section *A.3.1.1 Short summary and overall relevance of the provided toxicokinetic information* the first step in the degradation of IPBC ($C_8H_{12}INO_2$) is dehalogenation which forms the metabolite PBC ($C_8H_{13}NO_2$) and releases the iodine moiety. According to the Iodine CAR (2013), iodine will appear as different species depending on the environmental compartment and the conditions in the compartment. The two most environmentally relevant species are iodate (IO_3^-) and iodide (I^-). Iodine (I_2) is also relevant and will be investigated further.

Looking into the environmental classification on iodine, iodide and iodate, the harmonised classification for iodine is stated in the publicly available Iodine CAR (2013). Iodine is classified Aquatic Acute 1 ; H400. No harmonised classification is available for iodide and iodate, but ecotoxicity data for both are available as presented in current CLH report, section *A.4.2.3.1 Freshwater compartment*. The most sensitive species to both iodide and iodate in an acute toxicity test is Daphnia magna with an LC_{50} value of 0.83 mg iodine/L and 58.5 mg iodine/L respectively. According to the *Guidance on the Application of the CLP Criteria* a substance with

an LC_{50} or EC_{50} ≤ 1 mg/L should be classified Category Acute 1. This leads to the conclusion that iodide fulfils the criteria for Category Acute 1 classification and iodate does not.

Returning to the criteria c) in the rapid degradability decision scheme, stating that degradation products must not fulfil the criteria for classification as hazardous to the environment, if the criteria should be fulfilled, two results from the iodine/iodide/iodate assessment are relevant:

1: Iodine species (including iodide/iodate) are metabolites of IPBC

2: At least one metabolite has a classification as hazardous to the environment (iodine and iodide)

As both points are fulfilled the criteria for hazardous to the aquatic environment, criteria c) is not fulfilled.

Note, that the decision scheme in *Commission Regulation (EU) No. 286/2011* and in *Guidance on the Application of the CLP Criteria* are not identical, so criteria a), b) and c) in 286/2011 do not correspond directly to a), b) and c) in the Guidance. The following steps in the decision scheme to show rapid degradability, are not fulfilled either. Therefore IPBC is considered not rapidly degradable, and the M-factor will have to be adjusted accordingly.

The degradability of IPBC was discussed during the finalisation of the CLH report from 2011 where DE commented on the M-factor. In the RAC Opinion on IPBC (28 November 2012), the RAC argued with a weight of evidence approach, as the aerobic soil study showed rapid degradation of IPBC, which was in agreement with results from other studies and an expert judgement, and therefore concluded, that IPBC was rapidly degradable. The degradation of the metabolites was not considered during this evaluation.

Although IPBC was considered rapidly degradable, the degradation of the metabolites are the decisive factor for the intention to adjust the M-factor.
In conclusion the Danish EPA suggests maintain the M-factor of 10 for the Aquatic Acute classification and to adjust the M-factor from 1 to 10 for the Aquatic Chronic classification.

A.5. Assessment of additional hazards

A.5.1. Hazardous to the ozone layer

Not relevant for the CLH report.

A.5.1.1. Short summary and overall relevance of the provided information on ozone layer hazard

Not relevant for the CLH report.

A.5.1.2. Comparison with the CLP criteria

Not relevant for the CLH report.

Conclusion on classification and labelling for hazardous to the ozone layer

Not relevant for the CLH report.

A.6. Additional Labelling

No new data have been submitted or identified that warrant revision of the classification and labelling* of IPBC. (* According to Regulation (EC) No 1272/2008 (CLP), mixtures (all physical states) containing IPBC at a concentration ≥ 0.1% but < 1.0% are required to bear the supplemental hazard (warning) statement EUH208: 'Contains 3-iodo-2-propynyl butylcarbamate (IPBC). May produce an allergic reaction.'

No additional labelling is necessary with regards to physical-chemical hazards or environmental hazards.

A.7. Assessment of exclusion criteria, substitution criteria and POP

A.7.1. Exclusion criteria

Not relevant for the CLH report.

A.7.2. Substitution criteria

Not relevant for the CLH report.

A.7.3. Assessment of long-range environmental transportation and impact on environmental compartments

Not relevant for the CLH report.

B. Exposure assessment and effects of the active substance in the biocidal product(s)

Not applicable for the CLH report.

C. Risk characterisation of the biocidal product(s)

Not applicable for the CLH report.

D. Appendices

APPENDIX I: LIST OF ENDPOINTS

Not applicable for the CLH report.

APPENDIX II: HUMAN EXPOSURE CALCULATIONS

Not applicable for the CLH report.

APPENDIX III: ENVIRONMENTAL EMISSION (AND EXPOSURE) CALCULATIONS

Not applicable for the CLH report.

APPENDIX IV: LIST OF TERMS AND ABBREVIATIONS

Stand. term / Abbreviation	**Explanation**
AR	applied radioactivity
ATE	acute toxicity estimate
ATP	Adaptation to Technical Progress
BPR	Biocidal Products Regulation
bw	body weight
°C	degrees Celsius (centigrade)
CAR	Competent Authority Report
CAS (No.)	Chemical Abstracts Service (unique identification number)
Cat.	category
CLH	Harmonised Classification and Labelling
CLP	Classification, Labelling and Packaging
d	day(s)
DAR	Draft Assessment Report
DAT	days after treatment
DK CA	Danish Competent Authority
DT_{50}	period required for 50 percent dissipation
EC	European Commission
EC3	estimated concentration three (EC3) (estimated concentration of a test substance needed to produce a SI of three in a LLNA)
EC_{50}	median effective concentration
E_bC_{50}	the concentration of test substance which results in a 50 percent reduction in biomass growth (E_bC_{50}) relative to the control
E_rC_{50}	the concentration of test substance which results in a 50 percent reduction in growth rate (E_rC_{50}) relative to the control
eCA	Evaluating Competent Authority
ECHA	European Chemical Agency
EC name	European Community name
EPA	Environmental Protection Agency
EU	European Union
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	gram(s)
GHS	Global Harmonisation System
GLP	good laboratory practice
h	hour(s)
IPBC	3-iodo-2-propynyl butylcarbamate
ISO	International Organization for Standardization
IUCLID	International Uniform Chemical Information Database

Stand. term / Abbreviation	**Explanation**
IUPAC	International Union of Pure and Applied Chemistry
iv, i.v.	intravenous
kg	kilogram
l, L	litre
LC_{50}	lethal concentration, median
LLNA	Local Lymph Node Assay
LOEC	lowest observable effect concentration
µm	micrometre (micron)
mg	milligram
min	minute(s)
mL	millilitre
mm	millimetre
MMAD	mass median aerodynamic diameter
mol	mole(s)
µmol	micromole
n.a. (N.A.)	not applicable
n	number of observations
nm	nanometre
No., no.	number
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
ODP	ozone depletion potential
OP	organophosphate
2-PBC	2-propenyl-butylcarbamate
PBC	propynyl butylcarbamate
POP	persistent organic pollutant
PT	product type
(Q)SAR	quantitative structure-activity relationship
RAC	Risk Assessment Committee (of ECHA)
SI	stimulation index (in LLNA)
STP	sewage treatment plant
STOT SE	Specific Target Organ Toxicity Single Exposure
STOT RE	Specific Target Organ Toxicity Repeated Exposure
TG	technical guideline, technical group
URM	urinary metabolite
US	United States

Stand. term / Abbreviation	**Explanation**
UVBC	Substances of unknown or variable composition, complex reaction products or biological materials
w/w	weight per weight
%	percent
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

APPENDIX V: OVERALL REFERENCE LIST (INCLUDING DATA OWNER AND CONFIDENTIALITY CLAIM)

Note: Microbial Control (previously Nutrition & Biosciences (Switzerland) GmbH; previously Specialty Electronic Materials Switzerland GmbH; previously Dow Benelux B.V. ARXADA (previously Lonza Ltd, previously ARCH Chemicals).

Author(s)	**Year**	**Section No / Reference No. (BPR)**	**Title, Source** (where different from company), **Company, Report No., GLP** (where relevant) **(Un)Published**	**Data Protection Claimed** (Yes/ No)	**Owner**	**Applicability**	
						CAR	**CLH**
[redacted]	2001	3.14	Particle size distribution of Troysan Polyphase P-100 Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No. 111-001	Yes	TROY Chemical Corporation B.V.	X	
Siebert	2004	8.3	The sensitising potential of iodopropynyl butylcarbamate in the local lymph node assay. Contact Dermatitis (2004) **51**(5-6): 318-9. Not GLP Published	No	n.a.	X	X
[redacted]	1985	8.7.2	Acute inhalation limit test in rats 3-iodo-2-propynyl butyl carbamate Source: [redacted] Report No.: [redacted] Not GLP Unpublished Doc. No.: 523-001	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1990	8.7.2	TROYSAN Polyphase P-100 - Acute inhalation toxicity study in the rat Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 523-002	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1994	8.7.2	Acute inhalation toxicity in rats – 4-hour exposure to Omacide IPBC Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No. 523-003	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1995	8.8.1	Metabolism of 14C-IPBC in rats Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 512-002	Yes	TROY Chemical Corporation B.V.	X	

[redacted]	2002	8.9.2 8.13.3	Repeated dose toxicity 90-day oral toxicity study in rats with IPBC technical (Protram TM 98) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 533-005	Yes	Nutrition & Biosciences (Switzerland) GmbH	X	X
[redacted]	1997	8.9.2 8.13.8	A subchronic (3-month) toxicity study of TROYSAN Polyphase P100 in the rabbits via dietary administration Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 533-003	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1989	8.9.3 8.13.3	3-iodo-2-propynyl butyl carbamate (IPBC) 104 week dietary carcinogenicity study in rats (Volume 1 and 2) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 537-001	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1988	8.9.3	3-iodo-2-propynyl butyl carbamate (IPBC) chronic dietary toxicity study in rats Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 537-002	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1994	8.9.2 8.13.3	Omacide IPBC - 13-week inhalation toxicity study in rats Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 535-001	Yes	Lonza Ltd.	X	X
[redacted]	1994	8.10.1 8.13.3	Omacide IPBC - Oral (Gavage) rabbit developmental toxicity study Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 551-006	Yes	Lonza Ltd.	X	X
[redacted]	1994	8.10.1 8.13.3	Omacide IPBC - Oral (Gavage) rat development toxicity (Teratogenicity) study Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 551-008	Yes	Lonza Ltd.	X	X
[redacted]	1996	8.10.2 8.13.3	Omacide IPBC - Oral (Gavage) rat one generation (expanded to two generation) reproductive toxicity study (3 Volumes) Source: [redacted] Report No.: [redacted]	Yes	Lonza Ltd.	X	X

			GLP Unpublished Doc. No.: 553-003				
[redacted]	1987	8.10.2	TROYSAN Polyphase two generation oral (dietary administration) reproduction toxicity study in the rat (one litter per generation) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 553-002	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1989	8.11.2 8.13.3	IPBC 78 week dietary carcinogenicity study in mice Volume 1 to 3 (803 pages) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 555-001	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1989	8.11.2	IPBC 78 week dietary carcinogenicity study in mice Volume 2 to 3 (803 pages) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 555-002	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1989	8.11.2	IPBC 78 week dietary carcinogenicity study in mice Volume 2 continued to 3 (803 pages) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 555-003	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1989	8.11.2	IPBC 78 week dietary carcinogenicity study in mice Volume 3 to 3 (803 pages) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 555-004	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	2003	8.12.1	ARCH letter to SCC - Health data (Cholinesterase levels - Rocherster) Source: [redacted] Report No.: [redacted] Not GLP Unpublished Doc. No.: 574-001	Yes	Lonza Ltd.	X	X
[redacted]	2003	8.12.1	Medical surveillance program - Carbamates - IPBC Source: [redacted] Report No.: [redacted] Not GLP Unpublished Doc. No.: 574-002	Yes	Lonza Ltd.	X	X
Martin-Gorgojo & Johansen	2013	8.12.6	Contact dermatitis caused by iodopropynyl butylcarbamate in Denmark. Contact Dermatitis	No	n.a.	X	X

			(2013) **69**(2): 78-85. Not GLP Published				
Gimenez-Arnau et al.	2017	8.12.6	Contact allergy to preservatives: ESSCA results with the baseline series, 2009-2012. J. Eur. Acad. Dermatol. Venereol. (2017) **31**(4): 664-671. Not GLP Published	No	n.a.	X	X
[redacted]	2001	8.13.2	Acute oral neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) administered by gavage in CD rats - Volume 1 of 3 Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 541-001	Yes	Lonza Ltd. TROY Chemical Corporation B.V.	X	X
[redacted]	2001	8.13.2	Acute oral neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) administered by gavage in CD rats - Volume 2 of 3 Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 541-002	Yes	Lonza Ltd. TROY Chemical Corporation B.V.	X	X
[redacted]	2001	8.13.2	Acute oral neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) administered by gavage in CD rats - Volume 3 of 3 Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 541-003	Yes	Lonza Ltd. TROY Chemical Corporation B.V.	X	X
[redacted]	2001	8.13.2	13-week dietary neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) in CD rats Volume 1 of 4 Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 542-001	Yes	Lonza Ltd. TROY Chemical Corporation B.V.	X	X
[redacted]	2001	8.13.2	13-week dietary neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) in CD rats Volume 2 of 4 Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 542-002	Yes	Lonza Ltd. TROY Chemical Corporation B.V.	X	X
[redacted]	2001	8.13.2	13-week dietary neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) in CD rats Volume 3 of 4	Yes	Lonza Ltd. TROY Chemical Corporation B.V.	X	X

			Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 542-003				
[redacted]	2001	8.13.2	13-week dietary neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) in CD rats Volume 4 of 4 Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 542-004	Yes	Lonza Ltd. TROY Chemical Corporation B.V.	X	X
[redacted]	1988	8.13.2	Polyphase cholinesterase inhibition study in rats Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 541-006	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1989	8.13.2	In vitro examination of acetylcholinesterase inhibition in rat blood Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 541-005	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	2021	8.13.2	Toxicological analysis of 3-iodo-2-propynyl butylcarbamate (IPBC, CAS no. 55406-53-6) using Derek Nexus Source: [redacted] Report No.: [redacted] Not GLP Unpublished Doc. No.: 581-013	Yes	IPBC Task Force (LANXESS, Lonza, Nutrition & Biosciences , TROY)	X	X
[redacted]	2021	8.13.2	Expert Evaluation Neurotoxicity - IPBC – [redacted] Source: [redacted] Report No.: [redacted] Not GLP Unpublished Doc. No.: 581-012	Yes	IPBC Task Force (LANXESS, Lonza, Nutrition & Biosciences, TROY)	X	X
[redacted]	2021	8.13.4	Expert Evaluation on Immunotoxicity - IPBC – [redacted] Source: [redacted] Report No.: [redacted] Not GLP Unpublished Doc. No.: 581-011	Yes	IPBC Task Force (LANXESS, Lonza, Nutrition & Biosciences , TROY)	X	X
[redacted]	2001	9.1.3	Toxicity of Polyphase P-100 to Scenedesmus subspicatus in a 72-hour algal growth inhibition test – (Included the Analytical Report – Determination of the Concentrations of the test item in test medium) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 823-003	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1994	9.1.3	Growth and	Yes	Lonza Ltd.	X	X

			reproduction test with Omacide IPBC and the freshwater alga, Selenastrum capricornutum Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 823-001				
[redacted]	1992	9.1.6.1	TROYSAN Polyphase P-100 – Toxicity to fathead minnow (Pimephales promelas) embryos and larvae Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 826-001	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	1991	9.1.6.2	TROYSAN Polyphase P-100 – Chronic toxicity to the water flea, Daphnia magna, under flow-through test conditions Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 827-001	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	2001	10.1.1.1	Preventol MP 100 - Abiotic degradation Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 711-004	Yes	LANXESS Deutschland GmbH	X	X
[redacted]	1994	10.1.1.1	Hydrolysis of 14C-3-iodo-2-propynyl-n-butylcarbamate (14C-IPBC) Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 711-003	Yes	Lonza Ltd.	X	X
Lee, D.-H. Tsunoda, K. Takahashi, M.	1991	10.1.1.1	Photostability of organoiodine wood preservatives I. Progressive degradation and loss in fungal inhibition rate through photoirradiation Source: Mokuzai Gakkaishi, Vol. 37, No. 1, p. 76-81 (1991) Not GLP Published Doc. No.: 792-005	No	N.R.	X	X
Lee, D.-H. Tsunoda, K. Takahashi, M.	1991	10.1.1.1	Photostability of organoiodine wood preservatives II. The photolytic process of preservatives Source: Mokuzai Gakkaishi, Vol. 37, No. 3, p. 261-265 (1991) Not GLP Published Doc. No.: 792-004	No	N.R.	X	X
[redacted]	2005	10.1.1.1	AQUEOUS PHOTOLYSIS OF IPBC AND DETERMINATION OF	Yes	IPBC Task Force (LANXESS,	X	X

			THE QUANTUM YIELD Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 712-001		Lonza, Nutrition & Biosciences, TROY)		
[redacted]	2002	10.1.1.2	Ready biodegradability of IPBC in a manometric respirometry test Source: [redacted] Report No.: [redacted] 831172 GLP Unpublished Doc. No.: 713-002	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	2004	10.1.1.2	Inherent Biodegradability of IPBC in a modified "Zahn-Wellens /EMPA Test" Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 713-007	Yes	IPBC Task Force (LANXESS, Lonza, Nutrition & Biosciences, TROY)	X	X
[redacted]	1992	10.1.3.2	Anaerobic aquatic metabolism study of P-100 Source: [redacted] Report No.: [redacted] GLP Unpublished Doc. No.: 715-001	Yes	TROY Chemical Corporation B.V.	X	X
[redacted]	2018	10.1.3.2	IPBC - Degradation/Metabolism of [14C]IPBC in Two Aquatic Systems under Aerobic Conditions Source: [redacted] Report No.: [redacted] GLP Unpublished Doc No.: 781-005	Yes	IPBC Task Force (LANXESS, Lonza, Nutrition & Biosciences, TROY)	X	X
[redacted]	2018	10.1.3.2	Assessment of degradation kinetics of IPBC and its metabolites in water/sediment systems under laboratory conditions according to the recommendations of the FOCUS report on degradation kinetics (2006, 2014) (model calculation) Source: [redacted] Report No.: [redacted] Not GLP Unpublished Doc No.: 781-005	Yes	IPBC Task Force (LANXESS, Lonza, Nutrition & Biosciences, TROY)	X	X

Literature Searches

Human Health

Royal Danish Library literature sea

Web of Science database literature s

Scopus database literature search for

Identity of the 14 studies identified as potentially relevant in Step 1 of the literature review for human health (and non-target animals):

Benoit-Marand et al. (2010)_In vivo inhib. of dopamine uptake by D2 antagonists.pdf
Gimenez-Arnau et al. (2017)_Contact allergy to preservatives.pdf
Gradin et al. (2021)_Quant. sens. pot. using dose-resp. adapt. of GARDskin.pdf
Hoffmann et al. (2018)_Non animal methods to predict skin sens.pdf
Hwang et al. (2021)_Skin irrit. & inhal. tox._human epidermis & airway models.pdf
Jagielski et al. (2017)_in vivo acivity against Prototheca spp. in cows.pdf
Johnson (2017)_IPBC safety in cosmetics_mini review.pdf
Kim et al. (2021)_Combined inhalation of biocides in household products.pdf
Martin-Gorgojo & Johansen (2013)_IPBC & contact dermatitis in Denmark.pdf
Olsén & Olsén (2020)_IPBC exposure, reprod. behav. & milt volumes in trout.pdf
Sasseville (2004)_Hypersensitivity to preservatives.pdf
Schmidt et al. (2022)_Mutation and gene flow in bacteria.pdf
Siebert (2004)_Sensitizing potential of IPBC in LLNA.pdf
Vanhoutte et al. (2019)_allergic reactions to IPBC and-or (free) iodine.pdf

Environment

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Web of Science database literature s

Scopus database literature search for

The potentially environmentally relevant studies from the literature research:

Coors et al. (2012) - Mixture toxicity of wood preservative products in the fish embryo toxicity test.pdf
Tierney et al. (2006) - Alarm reaction in salmon parr impaired by IPBC.pdf
Tierney et al. (2009) - Changes in juvenile coho salmon electro-olfactogram exposed to pesticides.pdf

APPENDIX VI: CONFIDENTIAL INFORMATION

Not applicable for the CLH report.

APPENDIX VII: STUDY SUMMARIES

Relevant study summaries are provided in the Annex 1 to the CLH report.