Committee for Risk Assessment

RAC

Annex 1

Background document

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

3-Iodo-2propynyl butylcarbamate

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

CLH-O-0000001550-84-03/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

28 November 2012

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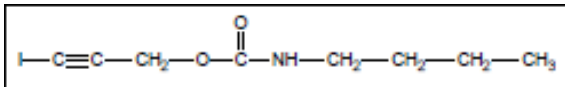
Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	3-Iodo-2-propynyl butylcarbamate
CAS name:	Carbamic acid, N-butyl-, 3-iodo-2-propyn-1-yl ester
IUPAC name:	3-Iodoprop-2-yn-1-yl butylcarbamate
EC number:	259-627-5
CAS number:	55406-53-6
Molecular formula	C8H12INO2
Molecular weight	281.1 g/mol
Smiles notation	O=C(NCCCC)OCC#CI
Structural formula	
Annex VI Index number:	Not listed in Annex VI
Degree of purity:	≥ 98 % (w/w)
Impurities:	None of the impurities are of toxicological, environmental and/or other significance. Therefore, they are not mentioned here. This is in agreement with the provisions of the "CLH report format with explanations".

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	**Not included in Annex VI, Table 3.1**	**Not included in Annex VI, Table 3.2 (CLP)**
Current proposal for consideration by RAC	Acute tox 3 - H331 Acute Tox 4 - H302 Eye Dam.1 - H318 Skin sens.1 - H317 STOT SE3 - H335 Aquatic Acute 1 - H400, M=10 according to Commssion Regulation (EU) No 286/2011(2nd ATP): Aquatic Chronic 1 - H410, M= 1	Xn: R22 Xi: R43 - 41R37 T: R23 N: R50
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	-	-

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

General:

Proposed classification based on DSD criteria (Directive 67/548/EEC) for the technical material IPBC

Class of Danger	T:	Toxic
	N:	Dangerous for the environment
R-Phrases	R22:	Harmful if swallowed
	R23:	Toxic by inhalation
	R37:	Irritating to the respiratory system
	R41:	Risk of serious damage to the eye
	R43:	May cause sensitization by skin contact
	R50:	Very toxic to aquatic organisms

Proposed classification based on CLP criteria (Regulation 1272/2008/EC) for the technical material IPBC

Signal Word	Danger
Classification	Acute Tox 3
	Eye Dam. 1
	Acute Tox 4
	Skin Sens. 1
	STOT SE3
	Aquatic Acute 1

H-Statements	H331: Toxic if inhaled
	H318: Causes serious eye damage
	H302: Harmful if swallowed
	H317: May cause an allergic skin reaction
	H335: May cause respiratory irritation
	H400: Very toxic to aquatic life

according to Commssion Regulation (EU) No 286/2011(2nd ATP):

H410: Very toxic to aquatic life with long-lasting effects

Proposed labelling for the technical material IPBC

Directive 67/548/EEC:

Class of Danger	T, N
R-Phrases	R22-23-37-41-43-50
S-Phrases	S1-2-22-24-26-37/39-38-45-46-61

Regulation 1272/2008/EC

Signal Word: Danger

Pictograms: GHS05, GHS06, GHS09 (CLP, Article 26, 1b)

H-Statements:
H331 Toxic if inhaled
H318: Causes serious eye damage
H302: Harmful if swallowed
H317: May cause an allergic skin reaction
H335: May cause respiratory irritation
H400: Very toxic to aquatic life

according to Commssion Regulation (EU) No 286/2011(2nd ATP):
H410: Very toxic to aquatic life with long-lasting effects

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	-	-	-	conclusive but not sufficient for classification
2.2.	Flammable gases	-	-	-	n.a.
2.3.	Flammable aerosols	-	-	-	n.a.
2.4.	Oxidising gases	-	-	-	n.a.
2.5.	Gases under pressure	-	-	-	n.a.
2.6.	Flammable liquids	-	-	-	n.a.
2.7.	Flammable solids	-	-	-	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	-	-	-	n.a.
2.9.	Pyrophoric liquids	-	-	-	n.a.
2.10.	Pyrophoric solids	-	-	-	n.a.
2.11.	Self-heating substances and mixtures	-	-	-	n.a.
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	n.a.
2.13.	Oxidising liquids	-	-	-	n.a.
2.14.	Oxidising solids	-	-	-	conclusive but not sufficient for classification
2.15.	Organic peroxides	-	-	-	n.a.
2.16.	Substance and mixtures corrosive to metals	-	-	-	n.a.
3.1.	Acute toxicity - oral	H302 Acute Tox 4	-	-	
	Acute toxicity - dermal	-	-	-	conclusive but not sufficient for classification
	Acute toxicity – inhalation	H331 Acute Tox 3	-	-	

		-	-.	-	
3.2.	Skin corrosion / irritation	-	-	-	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	H318 Eye Dam. 1	-	-	
3.4.	Respiratory sensitisation	-	-	-	conclusive but not sufficient for classification
3.4.	Skin sensitisation	H317 Skin Sens. 1	-	-	
3.5.	Mutagenicity	-	-	-	conclusive but not sufficient for classification
3.6.	Carcinogenicity	-	-	-	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	-	-	-	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	STOT SE 3 H335	-	-	
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	conclusive but not sufficient for classification
3.10.	Aspiration hazard	-.	-	-	conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	H400 Aquatic Acute 1	M = 10	-	
		H410*	M = 1*		
5.1.	Hazardous to the ozone layer	-	-	-	conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
n.a.: not applicable
* according to Commssion Regulation (EU) No 286/2011(2nd ATP)

Proposed labelling for technical material IPBC

Signal word: Danger
Hazard statements: H331, H318, H302, H317, H335, H400

Table 4: Proposed classification according to DSD

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification [1)]**	**Reason for no classification [2)]**
Explosiveness	-	-	-	conclusive but not sufficient for classification
Oxidising properties	-	-	-	conclusive but not sufficient for classification
Flammability	-	-	-	conclusive but not sufficient for classification
Other physico-chemical properties	-	-	-	conclusive but not sufficient for classification
Thermal stability	-	-	-	conclusive but not sufficient for classification
Acute toxicity	R22, R23	- -	- -	
Acute toxicity – irreversible damage after single exposure	R41	-	-	
Repeated dose toxicity	-	-	-	conclusive but not sufficient for classification
Irritation / Corrosion	R37	-	-	
Sensitisation	R43	-	-	
Carcinogenicity	-	-	-	conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	-	-	-	conclusive but not sufficient for classification
Toxicity to reproduction – fertility	-	-	-	conclusive but not sufficient for classification
Toxicity to reproduction – development	-	-	-	conclusive but not sufficient for classification

Toxicity to reproduction – breastfed babies. Effects on or via lactation	-	-	-	conclusive but not sufficient for classification
Environment	R50	-	-	

1) Including SCLs
2) Data lacking, inconclusive, or conclusive but not sufficient for classification
n.a.: not applicable

Proposed labelling for technical material containing IPBC

Labelling: Indication of danger: T, N
R-phrases: 22-23-37-41-43-50
S-phrases: S1-2-22-24-26-37/39-38-45-46-61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

In the CA Report for PT8, the following classification and labelling was proposed by RMS DK, Hazard symbol(s): **T**, N

Risk phrases:

- R22 Harmful if swallowed
- **R23 Toxic by inhalation**
- **R37 Irritating to the respiratory system**
- R41 Risk of serious damage to the eye
- **R43 May cause sensitisation by skin contact**
- R50 Very toxic to aquatic organisms

During the commenting period, France proposed that instead of R37/R23 the risk phrase R48/R23 (Toxic: danger of serious damage to health by prolonged exposure through inhalation) should be applied. The following text is from the commenting Table "Response to comments from Member States and applicant on the draft Assessment report on 3-Iodo-2-propynylbutyl carbamate (IPBC)" from 13.04.2007:

FR wrote: "Effects *observed in 13-week study in rats by inhalation* [redacted] *showed epithelial hyperplasia in the central region of the larynx, hyperplasia or squamous metaplasia in the ventrolateral region of the larynx, and necrosis of the underlying cartilage of the larynx at concentrations in the air equal to or greater than 1 mg/m. In spite of the difference in the morphology of the upper respiratory tract of rodents and humans, could a classification R48/23 be proposed?"*

The RMS commented: *"As it is considered as a local and not a systemic effect we would rather propose a R37 instead. However, the final decision must be taken at C&L group in ISPRA. The justification paper regarding the differences between human and rats submitted by the applicant (see text in the end of this document) after the CA had finalised the report would also be submitted to the C&L group to be included for discussion."* The justification referred to by the RMS is attached as Annex II to this CLH Report.

During the commenting period, Germany proposed that additionally the risk phrase R 53 (may cause long-term adverse effects in the aquatic environment) should be applied. The RMS stated in the CA-report in Doc IIIA, section 9, that "*the RMS does not agree to label IPBC with R53 because there is a valid biodegradation test in soil which shows rapid biodegradation*" and that "*the test was done with no pre-exposure of the soil micro-organism and at environmental realistic concentrations of the test substance. The substance is ultimately degraded within 28 days with a half-life of less than 5 days at 12°C.*"

Therefore, the RMS concluded that "*there is still an outstanding question about risk phrase 53*" and that, "*as no common agreement between the Member States could be achieved, this question is sent to the CL group for clarification*." A respective Statement submitted by the Applicant during the evaluation of the PT 8 dossier is attached to the CLH Report as Annex III. The conclusion drawn in the Statement that R 53 is not justified can be translated into CLP: application of chronic category "Chronic (long-term) aquatic hazard" is not triggered.

No REACH registration dossiers were available for IPBC.

2.2 Short summary of the scientific justification for the CLH proposal

In this CLH proposal, the Classification and Labelling as proposed in the CA-report is principally adopted; the proposal made by Germany to apply also R 53 is rejected for the reasons put forward by the RMS DK in the CA-report.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Not included in Annex VI, Table 3.1

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Not included in Annex VI, Table 3.2

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Not applied at present

2.4.2 Current self-classification and labelling based on DSD criteria

The self-classification and labelling applied by most companies is:

Hazard symbol(s): Xn, N

Risk phrases:

- R20 Harmful by inhalation
- R22 Harmful if swallowed
- R41 Risk of serious damage to the eye
- R50 Very toxic to aquatic organisms

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

According to the "CLH Report Format with Explanation", for biocides and pesticides, there is no need for justification (cf. Article 36(3) CLP Regulation).

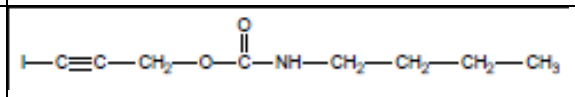
Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	259-627-5
EC name:	3-Iodo-2-propynyl butylcarbamate
CAS number (EC inventory):	55406-53-6
CAS number:	55406-53-6
CAS name:	Carbamic acid, N-butyl-, 3-iodo-2-propyn-1-yl ester
IUPAC name:	3-Iodoprop-2-yn-1-yl butylcarbamate
CLP Annex VI Index number:	Not listed in Annex VI
Molecular formula:	$C_8H_{12}INO_2$
Molecular weight:	281.1 g/mol
Structural formula	
Smiles notation	O=C(NCCCC)OCC#CI

1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
3-Iodo-2-propynyl butylcarbamate	≥ 98 %	-	-

Current Annex VI entry: Not listed in Annex VI

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
-	-	-	-

Current Annex VI entry: Not applicable; none of the impurities are considered to be of potential concern.

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
-	-	-	-	-

Current Annex VI entry: Not applicable; no additives used

1.2.1 Composition of test material

- The purity of the test material (IPBC) in the physico-chemical studies listed in Table 10 below is in the range of 98,3 % to 99.2 % (if indicated in the study report).
- The purity of the test material (IPBC) in the toxicological studies listed in Table 11, 12, 15, 17, 18, 19 and 20 below is in the range of 97 % to 99 %.
- The purity of the test material (IPBC) in the degradation studies provided in Table 21 below is in the range of 97 % to 99.8 %.
- The purity of the test material (IPBC) in the ecotoxicological studies provided in Table 22 below is in the range of 97 % to 99.1 %.

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	Technical: crystalline slightly yellow with a faint odor of iodine Pure: very fine needles, with an off-white color	[redacted]	EPA subdivision D series 63-3 EPA subdivision D series 63-2
Melting/freezing point	65.8 – 66.5 °C	[redacted]	EEC Directive 92/69 A 1 OECD 102
Boiling point	No boiling point	[redacted]	Method: Differential Thermal Analysis (DTA) Decomposition of the test substance starts at 85 °C
Relative density	1.714	[redacted]	Pyknometer method
Vapour pressure	2.36-4.5 x 10^{-3} (at 25 °C)	[redacted]	Vapor pressure balance method EEC Directive 92/69 A 4
Surface tension	69.1 mN/m at 158 mg/L	[redacted]	EEC Directive 92/69 A5 (ring method concentration of test solution: 158 ppm)
Water solubility	168 mg/L (at 20 °C, pH 7)	[redacted]	EEC Directive 92/69 A 6 Flask method No significant influence of the pH value, but an slight increase of the water solubility with temperature rise could be observed.
Partition coefficient n-octanol/water	2.81	[redacted]	OECD 107 Flask shaking method
Flash point	Not relevant, because melting point is > 50 °C.		
Flammability	Not highly flammable Not auto flammable	[redacted]	EEC Directive 92/69 A 10 flammability A 16 auto flammability
Explosive properties	No explosive properties	[redacted]	The oxygen balance (OB%) calculated gives evidence of the oxygen deficiency in case of negative results. An excess of oxygen gives a positive balance and such compounds can function as

			oxidant, whereas the explosive power (energy release) is maximal at equivalence, or zero oxygen balance. For IPBC with an OB of – 113.8 % this is not regarded as critical in terms of explosive properties. In addition, the determination of the flammability of IPBC (according EEC, A10) showed that IPBC could not be ignited and the determination of the auto-flammability (according to guideline EEC, A16) showed no exothermic reaction when heated up to 400°C. These measurements confirm that IPBC has no explosive properties.
Self-ignition temperature	Not relevant See information provided under flammability		
Oxidising properties	No oxidising properties	[redacted]	The oxygen balance (OB%) calculated gives evidence of the oxygen deficiency in case of negative results. An excess of oxygen gives a positive balance and such compounds can function as oxidant, whereas the explosive power (energy release) is maximal at equivalence, or zero oxygen balance. For IPBC with an OB of – 113.8 % this is not regarded as critical in terms of explosive properties. In addition, the determination of the flammability of IPBC (according EEC, A10) showed that IPBC could not be ignited and the determination of the auto-flammability (according to guideline EEC, A16) showed no exothermic reaction when heated up to 400°C. These measurements confirm that IPBC has no explosive properties.
Granulometry	Less than 5% of particles have aerodynamic diameter <_10 µm.	[redacted]	OECD 110
Stability in organic solvents and identity of relevant degradation products	Stable in octanol, petroleum ether and methanol for 9 days when stored at 25 °C	[redacted]	Concentration of the stored solutions: Petroleum ether and methanol: ≥10 % of the saturation level, octanol < 10 % of the saturation level
Dissociation constant	Not applicable, non-ionic material.		
Viscosity	Not relevant IPBC is a solid and not a liquid		

2 MANUFACTURE AND USES

2.1 Manufacture

According to the "CLH Report Format with Explanation", for biocides, "this point does not need to be specified for the CLH proposal". Detailed information is provided in the confidential part of the CA Report.

2.2 Identified uses

- PT06: In-can preservatives
- PT07: Film preservatives
- PT08: Wood preservatives
- PT09: Fibre, leather, rubber and polymerised materials preservatives
- PT10: Masonry preservatives
- PT13: Metalworking preservatives

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
Flammability	Not highly flammable Not auto flammable	[redacted]	EEC Directive 92/69 A 10 flammability A 16 auto flammability
Explosive properties	No explosive properties	[redacted]	Statement
Oxidising properties	No oxidising properties	[redacted]	Statement

IPBC is not highly flammable, has no pyrophoric property and does not undergo spontaneous combustion. IPBC is not explosive and has no oxidizing properties. The oxygen balance (OB%) calculated gives evidence of the oxygen deficiency in case of negative results. An excess of oxygen gives a positive balance and such compounds can function as oxidant, whereas the explosive power (energy release) is maximal at equivalence, or zero oxygen balance. For IPBC with an OB of – 113.8 % this is not regarded as critical in terms of explosive properties. In addition, the determination of the flammability of IPBC (according EEC, A10) showed that IPBC could not be ignited and the determination of the auto-flammability (according to guideline EEC, A16) showed no exothermic reaction when heated up to 400°C. These measurements confirm that IPBC has no explosive properties. Therefore, a classification of IPBC with respect to physical-chemical properties is not justified.

3.1 *General physical-chemical hazards*

3.1.1 Summary and discussion of physical-chemical properties

Not applicable

3.1.2 Comparison with criteria

Not applicable

3.1.3 Conclusions on classification and labelling

A classification with respect to physical-chemical hazards is not required.

4 HUMAN HEALTH HAZARD ASSESSMENT

The information provided in this section is mainly extracted from Doc IIA, Section 3 'Human health effects assessment' of the CA-Report.

Where in Doc IIA detailed information is not provided, additional information has been extracted from Doc IIIA, Section 6. Doc IIIA with the full study summaries from the biocide CA-report has been submitted together with the CLP report to provide necessary details for experts discussion of the proposed classifications.

The following general remarks are made concerning the data evaluated in this chapter:

- Unless otherwise stated, all studies were made according to international accepted guidelines and principles for good laboratory practice (GLP).
- Studies included have reliability scores 1 or 2. Supplementary studies (i.e.: studies with a reliability score of 3 or more) give additional information.
- There were no studies in the open literature that were found to provide sufficient information for the health effects assessment.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Oral route:

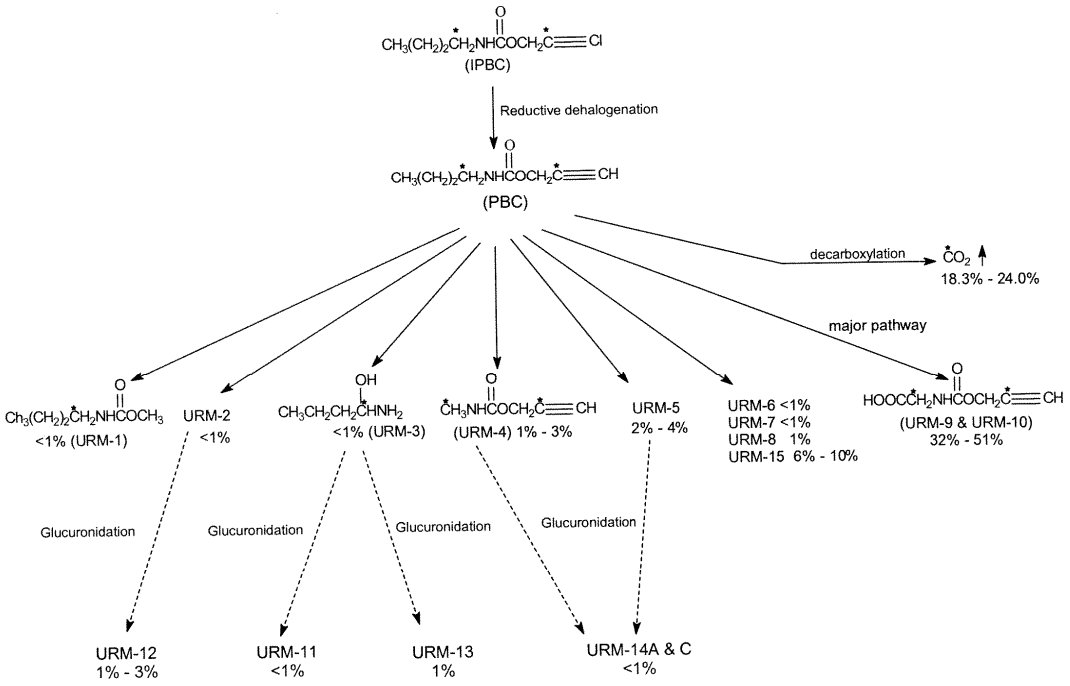
IPBC is rapidly and almost completely absorbed in rats via the oral route (Ampofo, S. (1995); Doc. IIIA, Section A6.2/01). The majority of the administered radioactivity was excreted via urine (57.3% to 70.7%). Faeces was a minor route of excretion in all dose groups (4.4% to 7.4% of the administered 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 blood, carcass, fat, skin, kidney and liver in both sexes of both dosing regimes There was no trend for bioaccumulation observable. Less than 5% of the dose was recovered in carcass and tissues after 14 days.

IPBC was extensively metabolised in the rat. IPBC first underwent reductive dehalogenation of iodine to form PBC as the initial metabolite, which was further metabolised by oxidative dealkylation to form the two distereomeric conformers of propargyl-N-acetic acid carbamate, the major metabolites (32-51 %). In addition, de-carboxylation following reductive dehalogenation yielded carbon dioxide (18.4-24.2 %). Metabolites found in trace amounts included methyl-N-butylcarbamate (<1 %), 1-hydroxybutamide (<1 %) and propargyl-N-methylcarbamate (1-3 %). Several other trace metabolites could not be further characterised. Glucuronidation appeared to be the main secondary metabolism pathway

There were no differences between sexes or applied doses detectable.

In a recently performed internet search no further literature data for toxicokinetics through the oral route could be identified.



Proposed metabolic pathway of 14C-IPBC after oral administration (percentages are based on total dose administered)

Inhalation route:

No toxicokinetic/metabolism study via the inhalation route of exposure is available. Since IPBC is not volatile, exposure via the inhalation route is of low relevance. However, as the substance was rapidly and nearly quantitatively absorbed in the oral toxicokinetic/metabolism study (> 90% within 72 hours: ~57-71% by urinary excretion and ~18-24% by exhaled air), the kinetic behaviour of IPBC after inhalation exposure can be assessed on the grounds of the results obtained in the oral study.

Dermal route:

For IPBC, an *in-vitro* dermal penetration study with human skin is available [redacted] which examines the penetration rates of IPBC for different solvent-based formulations containing IPBC at a concentration of 0.6, 2.3, and 17.1%. The resulting dermal penetration rates including skin residues were 30, 10, and 1.6% of the applied radioactivity, respectively.

The formulation containing 0.6% IPBC is representative for the in use dilution of the solvent based model product (0.7% IPBC) in some scenarios. However, since no dermal absorption values for in use concentrations below 0.5%-0.6% IPBC are available a default value of 100 % has to be used in those cases since dermal absorption is inversely related to the concentration. For the mix/load situation the content of IPBC can be higher and therefore it is justified to use the lower dermal absorption values which correspond to the content of IPBC in the concentrate. However, the worst case dermal absorption value (highest absorption) has been chosen in cases where the concentration of the a.i. lies in an interval between two values. No studies were submitted for the water-based model product; however, it is considered justified that solvent-based products represent a worst-case scenario in terms of dermal adsorption compared to a water-based formulation.

For solid IPBC, the dermal penetration value of 1.6% determined for a solvent-based product containing 17.1% of the active substance is used as worst-case, since no data are available for the technical material itself.

4.1.2 Human information

No information available

4.1.3 Summary and discussion on toxicokinetics

IPBC was completely and readily absorbed via the oral route (<90%). Following absorption, the substance was widely distributed with no trend for bioaccumulation observed. IPBC was extensively metabolised with the major metabolites being the two distereomeric conformers of propargyl-N-acetic acid carbamate. Glucuronidation appeared to be the main secondary metabolism pathway. The majority of the administered radioactivity was excreted via urine (57.3% to 70.7%) with faeces being a minor route (4.4% to 7.4%); radiolabelled carbon dioxide constituted between 18.4 to 24.2% of the administered dose. There were no differences between sexes or applied doses detectable (Ampofo, S. (1995).

In an *in vitro* dermal penetration study with human skin exposed 8 hours for solvent based model products containing 17, 2,4 and 0.6% IPBC followed by skin wash, the absorbed percentages were 1.6, 10, and 30% of the applied doses, respectively. The formulation containing 0.7% IPBC is representative for the in-use dilution of the solvent based model product in some scenarios. However since no dermal absorption values for in use concentrations below 0.5%-0.6% IPBC are available a default value of 100 % has to be used in those cases since dermal absorption is inversely related to the concentration. For the mix/load situation the content of IPBC can be higher. No study were submitted for the water-based model product, however it is considered justified that a solvent based products represents a worst case scenario in terms of dermal absorption compared to a water based formulation [redacted]

For solid IPBC, the dermal penetration value of 1.6% determined for a solvent-based product containing 17.1% of the active substance is used as worst-case, since no data are available for the technical material itself.

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Acute Oral toxicity - Acute Toxic Class Method OECD guideline 423 (adopted 22nd March, 1996) **Species/strain/sex:** Rats/Wistar/(male/female) **Dose levels/ purity**: 200 mg/kg: 3/sex 2000 mg/kg: 3 females (purity 98.3 %) Oral administration by gavage in polyethylene-glycol 400 (PEG 400)	**Oral LD_{50}:** 300 - 500 mg/kg bw	Xn, R22	[redacted]
Acute Dermal Toxicity OECD guideline 402 (adopted 24.02.1987), limit test **Species/strain/sex:** Rats/Wistar/(male/female) 5/sex/group **Dose levels/ purity**: 2000 mg/kg bw (purity 98.3 %) **Exposure duration:** 24 hours	**Dermal LD_{50}:** > 2000 mg/kg bw	No classification warranted	[redacted]
Acute Inhalation Toxicity OECD 403, limit test (In the study, no information is provided on particle-size distribution. RMS concluded in CA-Report that 'therefore, this study is not an OECD TG 403 study strictly spoken'.) **Species/strain/sex:** Rats/Sprague-Dawley/ (male/female) 5/sex/group **Dose levels/ purity**: 6.89 mg/L	**LC_{50}:** > 6.89 mg/L	No classification warranted	[redacted]

(not respirable, purity 99 %) **Exposure duration:** 4 hours			
Acute Inhalation Toxicity US EPA, 81-3"Acute Inhalation Toxicity Study", November 1984 which is comparable to OECD 403 **Species/strain/sex:** Rats/Sprague Dawley/ (male/female) 5/sex/group **Dose levels/ purity**: Dust: 1.7, 0.38, 0.72 mg/L (MMAD 4.3 µm) Liquid aerosol: 3.4, 1.8, 0.45, 0.75 mg/L (MMAD 2.4 µm) (purity 98.2 %) **Exposure duration**: 4 hours	**LC_{50} dust:** 0.67 mg/L (for males and females) LC_{50} liquid Aerosol: 0.63 mg/L for males 0.99 mg/L for females	T, R23	[redacted]
Acute Inhalation Toxicity US EPA, 81-3 "Acute Inhalation Toxicity Study", November 1984 which is comparable to OECD 403 **Species/strain/sex:** Rats/Sprague Dawley/ (male/female) 5/sex/group **Dose levels/ purity**: Dust, micronised (% respirable: 74.4-80.5): 0.16, 0.29, 0.58 mg/L Dust, non-micronised (% respirable: 19.2-26.7): 0.49, 1.19, 2.44 mg/L (Purity 97 %)	**LC_{50}:** From all mortality data: 0.67 mg/L From groups exposed to non-micronised: 0.88 mg/L	T, R23	*[redacted]
Intravenous US EPA **Species/strain/sex:** Rats/Sprague Dawley/ (male/female) 10/sex/group **Dose levels/ purity**: 0, 2, 4, 10, 16 mg/kg bw/d (purity not indicated)	No LD_{50} value can be established No inhibition of RBC cholinesterase activity up to and including the highest dose	n.a.	[redacted]

single dose			
*Non-key study included in the evaluation by the Competent Authority: [redacted]): Acute inhalation toxicity in rats, 4-hour exposure to Omacide® IPBC; [redacted]. (unpublished).			

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

IPBC was moderately toxic to rats via the oral route with an LD_{50} between 300 and 500 mg/kg bw. Clinical signs observed were decreased motility, piloerection, pallor and laboured breathing. Based on the oral LD_{50}-value, classification with Xn; R22 is warranted.

4.2.1.2 Acute toxicity: inhalation

When IPBC was administered by inhalation to rats in a study performed according to US-EPA TG 81-3 comparable to current provisions of OECD TG 403 ([redacted] Doc. No. 523-002, Doc. IIIA, Section A6.1.3/02), an LC_{50} of about 0.67 mg/L was reported for dust with respirable particle size (MMAD 4,3 µm) and of about 0.78 mg/L for a liquid aerosol with respirable droplet size (MMAD 2,4 µm). In another study performed in accordance with US-EPA TG 81-3 ([redacted] not included in Doc. IIIA, Section A6.1.3.), an LC_{50} of about 0.88 mg/L was reported for dust (non-micronised) with 19.2-26.7% of the particles being of a respirable particle size (MMAD 9.6-14.2 µm) and of about 0.67 mg/L for a combination of micronised and non-micronised dust.

A classification with T; R23 is proposed based on the results from the acute inhalation toxicity study with respirable dust particles, this is supported by the study performed with a test substance with only 19.2-26.7% of the particles being of a respirable particle size of 6 µm (MMAD 9.6-14.2 µm).

Following administration of particles with technical IPBC claimed by the Notifier to be non-inhalable/non-respirable (no details in the study report) an LC50 > 6.89 mg/L was determined [redacted] Doc. IIIA, Section A6.1.3/01). In this study the LC50 indicates that no classification is warranted for this specific test substance; however, the particle size distribution of the tested IPBC in this study was not measured and do therefore not fulfill current guidelines, furthermore OECD recommends a MMAD of 1-4 µm for acute inhalation toxicology studies. The Notifier claims that the particle size of technical IPBC (Troysan Polyphase P-10, 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]

4.2.1.3 Acute toxicity: dermal

When IPBC was administered to rats via the dermal route, no deaths were observed up to and including 2000 mg/kg bw. The LD_{50} was greater than 2000 mg/kg bw. Treated skin areas were partly reddened; partly formation of scale and encrustation was noted up to day 13, but not at day 14 indicating that signs of dermal irritation were reversible. No classification is warranted for acute dermal toxicity.

4.2.1.4 Acute toxicity: other routes

When IPBC was administered i.v. via the lateral tail vein, RBC cholinesterase activity was not reduced up to and including the highest dose level (16 mg/kg bw). The LD_{50} was greater than 16 mg/kg bw; however, the duration of the post-exposure observation period is not stated in the report and was probably only 5 hours.

4.2.2 Human information

No human information is available

4.2.3 Summary and discussion of acute toxicity

Oral: moderate oral toxicity in the rat with an LD_{50} between 300 and 500 mg/kg bw. Clinical signs observed were decreased motility, piloerection, pallor and laboured breathing.

Dermal: low dermal toxicity with an LD_{50} greater than 2000 mg/kg bw. Treated skin areas were partly reddened; partly formation of scale and encrustation was noted up to day 13, but not at day 14 indicating that signs of dermal irritation were reversible.

Inhalation: highly toxic with an LC_{50} of about 0.67 mg/L for dust with respirable particle size (MMAD 4.3 µm) and of about 0.78 mg/L for a liquid aerosol with respirable droplet size (MMAD 2.4 µm); and an LC_{50} of about 0.88 mg/L for dust (non-micronised) with 19.2-26.7% of the particles being of a respirable particle size of 6 µm (MMAD of 9.6-14.2 µm) and of about 0.67 mg/L for a combination of micronised and non-micronised dust. Following administration of particles with technical IPBC (particle size mot measured in this particular study) claimed by the notifier to be non-respirable an LC_{50} > 6.89 mg/L was determined.

RMS proposes classification as toxic with R23: Toxic by inhalation for technical IPBC regardless of the particle size because of several uncertainties.

First of all the particle size of IPBC in the study by [redacted] which is the only study out of three which is not leading to the classification as toxic, was not measured so the actual MMAD and proportion of particle less than 10 µm is uncertain and could be different from the one stated in [redacted] In the study [redacted] measuring the particle size of technical IPBC used in the representative products and products on the market ≤ 5% of the particles were smaller than 10 µm[1]. It should be recognised that in the non-key study the MMAD was 9.6-14.2 µm, 19.2-26.7% of the particles being of a particle size of less than 6 µm (and therefore also less than 10 µm) and lead to an LC_{50} of about 0.88 mg/L and therefore RMS is reluctant to disregard the fact that the MMAD in this study [redacted] is of comparable particle size (10 µm) with 5% of the particles in technical IPBC being used in products on the market.

Applicant disagrees with the proposal from RMS and proposes split entry (please also refer to applicants justification in Annex I)

Based on the results of the above described acute inhalation studies ([redacted] and also considering the results of the 90-day inhalation study by [redacted], the study on particle-size distribution by [redacted] confidential information only provided in the BPD dossier for PT 8) and the recent confirmation by the sponsor of the [redacted] study that no changes were made to the production process between the years 1985 (year of the Gagus

[1] OECD recommends a MMAD of 1-4 µm for acute inhalation studies

study) and 2001 (year of the [redacted] study on particle-size distribution), a proposal for a split-entry classification of IPBC concerning inhalation toxicity has been prepared. It is proposed that IPBC with less than 5% of particles < 10 µm should not be classified for inhalation toxicity, while IPBC with more than 5% of particle < 10 µm should be classified as T, R 23. The detailed argumentation is provided as Annex I.

In conclusion, the applicant proposes to base the classification on the particle size of the tested material of IPBC. IPBC with less than 5% of particles < 10 µm should not be classified for inhalation toxicity, while IPBC with more than 5% of particles < 10 µm should be classified as T, R23. Details of the applicant's proposal are summarized in Annex I.

4.2.4 Comparison with criteria

Based on the results of the acute oral toxicity studies and taking into account the criteria in Table 3.1.1 of the CLP, IPBC is subject to classification and labelling for acute oral toxicity with R22 (Harmful if swallowed) according to Directive 67/548/EEC or Acute Tox. 4, H302 (Harmful if swallowed) according to CLP Regulation 1272/2008/EC.

Based on the results of the acute inhalation studies and taking into account the criteria in Table 3.1.1 of the CLP, IPBC should be classified as R23 (Toxic by inhalation) according to Directive 67/548/EEC and Acute Tox. 3, H331 (Toxic if inhaled) according to CLP Regulation 1272/2008/EC.

Based on a LD_{50} value of > 2000 mg/kg bw found in an acute dermal toxicity study and taking into account the criteria in Table 3.1.1 of the CLP, IPBC is not subject to classification and labelling for acute dermal toxicity according to Directive 67/548/EEC and CLP Regulation 1272/2008/EC.

4.2.5 Conclusions on classification and labelling

Classification/labelling for acute toxicity according to Directive 67/548/EEC:

Xn, R22: Harmful when swallowed.

T; R23: Toxic by inhalation

Classification/labelling for acute toxicity according to CLP Regulation 1272/2008/EC:

Warning, Acute Tox. 4, H302: Harmful when swallowed.

Danger, Acute Tox. 3, H331: Toxic if inhaled

RAC evaluation of acute toxicity
Summary of the Dossier submitter's proposal The dossier submitter (DS) proposed to harmonise the classification as Acute Tox. 4; H302 and Acute Tox. 3; H331 according to CLP, as well as Xn; R22 and T; R23 according to DSD. One acute oral toxicity study was presented in the CLH report. It was performed on rats according to OECD test guideline (TG) 423. The LD_{50} value was between 300 and 500 mg/kg bw and falls within the range of values for classification for acute toxicity category 4; H302 (Harmful if swallowed) according to the Regulation 1272/2008 (CLP) and Xn; R22 (Harmful

if swallowed) according to the Directive 67/548/EEC (DSD).

Three acute inhalation toxicity studies were presented in the CLH report [redacted] The study by [redacted] was performed on technical IPBC with an LC_{50} value > 6.89 mg/l, but there was no information on the particle-size distribution. In 2001, a notifier ([redacted] had claimed that the MMAD of technical IPBC was 79 µm with ≤ 5% of particles being smaller than 10 µm, and later on his sponsor had confirmed that no changes had been made to the production process between years 1985 and 2001. In the CLH report this data was considered uncertain and the applicant's proposal for a split-entry classification in which IPBC with less than 5% of particles < 10 µm should not be classified, while IPBC with more than 5% of particles < 10 µm should be classified for inhalation toxicity was not supported by the dossier submitter. The DS proposed to classify IPBC for acute inhalation toxicity (Acute Tox 3; H331 according to CLP, and T; R23 according to DSD) regardless of particle size, based on two rat studies conducted according to US-EPA TG 81-3 which is comparable to current provisions of OECD TG 403. In the key study by [redacted] the LC_{50} values were 0.67 mg/l for dust with respirable particle size (MMAD 4.3 µm) and 0.78 mg/l for liquid aerosol with respirable droplet size (MMAD 2.4 µm). In the supporting study by [redacted] the LC_{50} values were 0.88 mg/l for non-micronised dust (MMAD 9.6-14.2 µm, 19.2-26.7% of a respirable size of 6 µm) and 0.67 mg/l for a combination of micronized (74.4-80.5% respirable) and non-micronised dust.

In addition, one acute dermal toxicity study [redacted] was presented in the CLH report. The study was performed according to the OECD guideline 402 in which IPBC was administered to rats for 24-hours via the dermal route at up to 2000 mg/kg bw. No deaths were observed. Signs of dermal irritation were reversible. The estimated LD_{50} was greater than 2000 mg/kg bw giving rise to non-classification of IPBC for acute dermal toxicity.

Comments received during public consultation

During PC, comments were received from an association of companies (IPBC Task Force) which proposed a split entry for classification in respect to acute inhalation toxicity (Annex I of the CLH report), in which IPBC with less than 5% of particles < 10 µm should not be classified, while IPBC with more than 5% of particles < 10 µm should be classified for inhalation toxicity. This proposal is similar to the applicant's justification for a split entry in the CAR. One MSCA requested more information on local and systemic toxicity and on particle size in order to conclude on a split entry for this endpoint. Another MSCA commented that the provided information was not sufficient to support a split entry. According to the comment of a third MSCA only the results of the [redacted] study could be used for classification when considering the recommended scale for MMAD values given in the CLP criteria. The MSCA also proposed to compare the available data with the requirements of Pauluhn to conclude whether the conditions for a split-entry approach for acute inhalation toxicity were fulfilled.

Additional key elements

Not needed.

Assessment and comparison with the classification criteria

The LD_{50} value determined in Wistar rats (dose levels 200 and 2000 mg/kg bw) [redacted], [redacted] was between 300 and 500 mg/kg bw falling within the range of 300 < LD_{50} ≤ 2000 mg/kg bw for classification for acute toxicity category 4; H302 (CLP) and 200 < LD50 ≤ 2000 mg/kg bw for classification for Xn; R22 (DSD). RAC therefore supported the conclusion of the dossier submitter that IPBC should be classified as Acute Tox. 4; H302 (Harmful if swallowed) according to the CLP criteria and Xn; R22 (Harmful if swallowed) according to the DSD criteria.

The classification for acute inhalation toxicity is based on the studies by [redacted] and [redacted] 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] 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. 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.

No deaths were observed up to the maximal dose of 2000 mg/kg bw in Wistar rats [redacted] The cut-off value for classification for acute dermal toxicity is 2000 mg/kg bw according to the CLP and DSD criteria. RAC therefore supported the conclusion of the DS that no classification is warranted for acute dermal toxicity.

Supplemental information - In depth analyses by RAC
Not needed.

4.3 Specific target organ toxicity – single exposure (STOT SE)

In the available acute toxicity studies, there was no clear indication for specific target organ toxicity after single exposure and findings made were regarded to be unspecific or to be in the normal range of the species and age of animals used. Clinical signs noted during the acute inhalation studies such as gasping, nasal discharge, rhinorrhea and laboured breathing as well as the findings in the lungs on gross necropsy are suggestive for an irritant effect on the respiratory tract rather than indicative for specific target organ toxicity.

Only in the 90-day repeated dose inhalation toxicity study ([redacted] irritational effects at the larynx were observed, which were considered to be of local nature. The accompanying histopathological findings in the larynx characterized by epithelial hyperplasia in the central region of the larynx, hyperplasia or squamous metaplasia in the ventrolateral region of the larynx, and necrosis of the underlying cartilage of the larynx at concentrations in the air equal to 6.7 mg/m^3 (LOAEC: 6.7 mg/m^3 with a NOAEC: 1 mg/m^3), were considered to be associated with the intrinsic irritating properties of the substance. Despite the differences in the morphology of the upper respiratory tract between rats and humans which may result in a higher susceptibility of the upper respiratory tract in rats and taking into account that rodents are obligatory nose breathers, factors which both result in a higher exposure of the rats' larynx compared to the larynx in humans, the effects in the larynx are regarded by the RMS as relevant for humans. Most importantly, no functional changes or any organ dysfunction have been observed in treated animals as a consequence of the irritational effects in the laryngeal region. As the effects on larynx are considered as local and not systemic effects, a classification as a respiratory irritant has been proposed during the evaluation of the BPD dossier. Further supporting argumentation is provided in Annex II.

Besides local effects directed to the larynx, only changes in the cholinesterase activities were noted in the 13-week inhalation study. Plasma cholinesterase activity was reduced at the highest concentration (6.7 mg/m^3) when compared to the concurrent control. RBC cholinesterase activity was decreased in females at 6.7 mg/m^3 after 2 weeks but not at study termination. Brain cholinesterase activities were decreased in males and females at 6.7 mg/m^3 when compared to concurrent controls (16.8 and 26.1%, respectively) and to historical controls (23.9 and 12.3, respectively). This finding is of unclear relevance since no clear dose-relationship was observed

(small decrease for a large change in dose) and the normal variation seems to be wide. Results indicates that IPBC was not neurotoxic. This was supported by the acute and 90-day neurotoxicity and 104 weeks studies in rats and 78 weeks mice study which all investigated RBC and brain cholinesterase inhibition.

Table 12: Summary table on the 13-week inhalation toxicity study in rats

Method	Results	Remarks	Reference
subchronic (inhalation) 13 weeks (5 days/week; 6 hours/ day whole body) Sprague Dawley rats (both sexes, 15/ group) Dose levels: 0, 0.3, 0.23, 1.16 and 6.7 mg/m3	NOAEL: 1.16 mg/kg bw/d LOAEL: 6.7 mg/kg bw/d There were no clinical signs noted which were attributable to cholinesterase activity. There were no treatment-related mortalities noted. There were no effects on body weight and food consumption noted. Plasma cholinesterase activity was lower when compared to concurrent control at 6.7 mg/m^3. RBC cholinesterase activity was decreased in females at 6.7 mg/m^3 after 2 weeks but not at the end of the study. Brain cholinesterase activities were decreased in females and males at 6.7 mg/m^3. In larynx of the high dose group necrosis in the ventral cartilage, epithelial hyperplasia in ventral region, and squamous metaplasia in ventrolateral region were noted in all animals. In addition, epithelial hyperplasia over the arytenoid projections was noted in all high dosed males and in 5 of the 15 high dosed females. Epithelial ulceration in the ventral region was observed in low incidence in the high dosed males (4 of 15 animals). In some of the high dosed males and females, additionally, atrophy of submucosal glands was noted (3 and 6 animals of 15, respectively). R37; Irritating to respiratory system.	(purity >97 %)	[redacted]

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

No specific target organ toxicity was noted in the acute toxicity studies. In contrast, specific target organ toxicity was observed in the 90-day repeated dose inhalation toxicity study [redacted] which was characterized by local irritation of the larynx. The accompanying histopathological findings in the larynx were regarded to be associated with the irritating nature of IPBC. Most importantly, no functional changes or any organ dysfunction have been observed in treated animals as a consequence of the irritational effects in the laryngeal region. The effects on the larynx are considered as a local and not a systemic effect, and they have been regarded by the RMS to be of relevance for humans despite the differences in the morphology of the respiratory tract between rats and humans which may result in a higher susceptibility of the upper respiratory tract in rats and taking into account that rodents are obligatory nose breathers. For this reason, a classification with R37 ("Irritating to respiratory system") or H335 ("May cause respiratory irritation") has been proposed in the BPD dossier.

4.3.2 Comparison with criteria

Based on the results in the 90-day inhalation study [redacted] reported in table 12 and taking into account the criteria laid down in Table 3.8.1 of the CLP, IPBC is subject to classification and labelling for acute toxicity with R37 (Irritating to respiratory system) according to Directive 67/548/EEC and H335 (May cause respiratory irritation) according to CLP Regulation 1272/2008/EC. This classification is justified as the effects noted in the 13-week inhalation toxicity study were not associated with an functional changes or any organ dysfunction.

4.3.3 Conclusions on classification and labelling

Based on the results of the 90-day repeated dose inhalation toxicity study, IPBC is subject to the following classification:

Classification/labelling for acute toxicity according to Directive 67/548/EEC:

Xi, R37: Irritating to respiratory system

Classification/labelling for acute toxicity according to CLP Regulation 1272/2008/EC:

Warning, STOT SE 3, H335: May cause respiratory irritation.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)
Summary of the Dossier submitter's proposal The dossier submitter proposed to harmonise the classification for IPBC for STOT SE 3; H335 (may cause respiratory irritation) according to CLP, and Xi; R37 (irritating to the respiratory system) according to DSD. The classification proposal was based on a 90-day repeated dose inhalation toxicity study on rats for 5 days/week, 6 hours/day at nominal

concentrations of 0 (control), 0.25 (low dose), 1.25 (medium dose), 6.25 (high dose) mg/m³ corresponding to analytical concentrations of 0, 0.30, 1.16 and 6.70 mg/m^3, respectively [redacted] Histopathological findings in the 90-day inhalation study with IPBC included epithelial hyperplasia in the central region of the larynx, hyperplasia or squamous metaplasia in the ventrolateral region of the larynx, and necrosis of the underlying cartilage of the larynx at concentrations in the air equal to 6,7 mg/m^3. These findings were considered to be associated with the intrinsic irritating properties of the substance. No functional changes or any organ dysfunction were observed as a consequence of the irritating effects in the laryngeal region. The effects in the larynx were considered to be relevant for human although the dossier submitter claimed to be aware of the differences in the morphology of the respiratory tract between rats and humans and to take into account that rodents are obligatory nose breathers. In addition, the severe clinical signs noted during the acute inhalation studies (gasping, nasal discharge, rhinorrhea and laboured breathing) as well as gross necropsy findings in the lungs which were also suggestive for an irritant effect on the respiratory tract according to the dossier submitter.

Comments received during public consultation

One MSCA questioned whether the classification as STOT RE would be more appropriate than STOT SE. Another MSCA commented that the 90-day STOT RE study was not directly relevant for STOT SE, but it could be used as supportive evidence because in the repeated dose inhalation study, irritation occurred normally as an acute effect and was followed by hyperplasia and metaplasia. As there was more supportive evidence in the acute inhalation study in which dyspnoea and rhinorrhea were observed and because the substance had irritating effect on eyes and stomach, the MSCA supported the proposed classification as STOT SE3 ; H335.

Additional key elements

It was requested by RAC members to check the detailed results of acute inhalation studies that would support the classification for STOT SE 3; H335 (may cause respiratory irritation) according to CLP, and Xi; R37 (irritating to the respiratory system) according to DSD. In the CAR the following information is given.

- *The OECD 403 study by [redacted] (dust, nominal tested concentration 6.89 mg/l, was assumed to be nonrespirable, but this was not certain since the particle size distribution of the test substance was not measured at the time the study was performed) at one hour of exposure, all animals exhibited dyspnea, salivation and rhinorrhea until the end of the 4-hour exposure period. Post-exposure, the predominant clinical signs were described as bloody crusts on the nose, rough haircoat, thin, languid, wheezing and urine stains. All clinical signs disappeared by day 4 except for bloody crusts on the nose which disappeared by day 13. The mean body weight of the treated animals declined from day 2 to day 4 post-exposure. After 14 days animals had gained weight similar to control animals. At gross pathology there were no differences between control and treated animals noted.*
- *The OECD 403 study by [redacted] (0.38, 0.72, and 1.7 mg/l IPBC dust and 0.45, 0.75, 1.8, and 3.4 mg formulation/l as liquid aerosol): during the 4-hour exposure period, the most commonly noted signs of toxicity were decreased activity, eye closure and excessive lacrimation. During exposure to the highest concentration, gasping was noted. Up to two hours after removal from the exposure chamber, additional clinical signs were recorded and included laboured breathing, gasping, and rales. Lacrimation, nasal discharge, and salivation persisted throughout the first week of the recovery period, after which these symptoms decreased in incidence and/or became sporadic. Common pathological conditions, including oedema, emphysema, and reddened lungs as well as red facial staining from Harderian gland and yellow/red ano-genital staining, were observed in animals that died between*

test days 1 to 8. These findings were also observed in the premature decedents and were of unclear relevance. Pale lungs and black/red/tan/brown foci in lungs were seen in some of the animals killed at the terminal sacrifice after exposure.

Assessment and comparison with the classification criteria

The CLP criteria for classifying substances as category 3 for respiratory tract irritation are:
(a) respiratory irritant effects (characterised by localised redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included. This evaluation will be based primarily on human data;
(b) subjective human observations could be supported by objective measurements of clear respiratory tract irritation (RTI) (such as electrophysiological responses, biomarkers of inflammation in nasal or bronchoalveolar lavage fluids);
(c) the symptoms observed in humans shall also be typical of those that would be produced in the exposed population rather than being an isolated idiosyncratic reaction or response triggered only in individuals with hypersensitive airways. Ambiguous reports simply of 'irritation' shall be excluded as this term is commonly used to describe a wide range of sensations including those such as smell, unpleasant taste, a tickling sensation, and dryness, which are outside the scope of classification for respiratory irritation;
(d) there are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation;
(e) this special classification would occur only when more severe organ effects including in the respiratory system are not observed.

According to the Guidance on the Application of the CLP Criteria, "Decision on classification of substances" (Section 3.8.2.5), effects leading to STOT SE (category 3) should be confined to changes, whether functional or morphological, occurring in the upper respiratory tract (nasal passages, pharynx and larynx). Localised irritation with associated adaptive responses (e.g., inflammation, epithelial metaplasia, goblet cell hyperplasia, proliferative effects) may occur and are consistent with Category 3 responses.

According to the DSD criteria conditions normally leading to classification with R37 are reversible and usually limited to the upper airways. Positive results from appropriate animal tests may include data obtained in a general toxicity test, including histopathological data from the respiratory system. Data from the measurement of experimental bradypnea may also be used to assess airway irritation.

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; H335 according to CLP, and Xi; R37 according to DSD proposed by the dossier submitter is not warranted. Furthermore, RAC considered that the effects seen at IPBC concentrations of 0.0067 mg/l in the 90-day inhalation study [redacted] and of 0.004 and 0.01 mg/l in the 5-day dose finding study (hyperplasia and metaplasia of the larynx epithelium, and necrosis of the underlying cartilage of the larynx) are not clinical signs of respiratory tract irritation. Consequently, RAC concluded that the classification for STOT SE 3; H335 according to CLP, and Xi; R37 according to DSD is not warranted.

Supplemental information - In depth analyses by RAC
Not needed.

4.4 Irritation

4.4.1 Skin irritation

Table 13: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
EU Method B.4 (Acute Toxicity: Dermal Irritation / Corrosion) OECD Guideline 404 (Acute Dermal Irritation / Corrosion)	Not irritating Erythema score: 0.6 of max. 4 (Time point: 24+48+72h) Oedema score: 0 of max. 4 (Time point: 24+48+72h) Reversibility: yes	Species/strain/sex: rabbit Purity of test material: 98.3%	[redacted]
OECD guideline 402 and followed, in principle, OPPTS 870.1200 and Annex V, Part B.3. to Directive 67/548/EEC Acute dermal study	Treated areas were partly reddened, partly formation of scale and encrustation was noted up to day 12 in males and up to day 13 in females. On day 14, signs of dermal irritation were not observed in both sexes. Erythema score: not determined Oedema score: not determined Reversibility: yes	Species/strain/sex: rat (Wistar (HsdCpd:WU)), 5 per sex Study type: acute dermal toxicity Dose level: 2000 mg/kg bw (limit test) Purity of test material: 98.3%	[redacted] (Non key study)
US EPA guideline 82-3 (compliant with OECD 411) 13 week dermal toxicity study	NOAEL for local effects: 50 mg/kg bw/d (corresponding to 0.28 mg/cm^2 for a 250 g rat) LOAEL for local effects: 200 mg/kg bw/d (corresponding to 1.12 mg/cm^2 for a 250 g rat) Dermal irritation characterized by minimal hyperkeratosis was noted occasionally in single animals at 200 mg/kg bw/d.	Species/strain/sex: Sprague-Dawley, males and females (10/group/sex) Study type: 13-week dermal toxicity study (5 days/week, 6 hours/day) Dose levels: 0, 50, 200, 500 mg/kg bw/day	[redacted] (Non key study)

	At 500 mg/kg bw/d, all animals showed dermal irritation which persisted throughout the treatment period. At this dose level, local reactions were characterized by moderate hyperkeratosis, acanthosis and one incidence of ulcer.	Purity of test material: 97.5%	

4.4.1.1 Non-human information

In a well performed OECD guideline 404 compliant study on the dermal irritation which was selected as the key study, IPBC was slightly irritating to the skin with a mean score of 0.6 for erythema; however, no classification with respect to skin irritation is warranted based on the skin scores obtained in this study.Based on results from older non-key guideline compliant studies, no classification for skin irritancy is warranted either.

In an acute dermal toxicity study [redacted] treated skin areas were partly reddened, and partly formation of scale and encrustation was noted up to day 13, but not at day 14, following administration of 2000 mg/kg bw for 24 hours. In this study, however, an assessment of the skin reaction according Draize was not performed.

In a 13-week dermal toxicity study ([redacted] test substance related changes in the treated skin were 4observed in most animals from the 200 and 500 mg/kg bw/d groups. Skin reactions were characterized by hyperkeratosis noted occasionally in single animals at 200 mg/kg bw/d. At 500 mg/kg bw/d, all animals showed dermal irritation which persisted throughout the treatment period. At this dose level, local reactions were characterized by moderate hyperkeratosis, acanthosis and one incidence of ulcer. In this study, no skin readings of treated test sites according to Draize were performed either and there was no recovery period.

Even though signs of dermal irritation were noted in the acute dermal toxicity study and the 13-week dermal toxicity study, no classification for dermal irritation is proposed since the local effects are only seen in studies where the skin is occluded and only at high doses.

4.4.1.2 Human information

No human information available

4.4.1.3 Summary and discussion of skin irritation

The average scores in the skin irritation test of [redacted] were 0.6 for erythema and zero for oedema, i.e. no skin irritation was observed. Signs of dermal irritation characterized by partial reddening, partial formation of scale and partial encrustation, were noted in an acute dermal toxicity limit test. In a 13-week dermal toxicity study, skin reactions were characterized by hyperkeratosis occasionally noted in single animals at 200 mg/kg bw/d whereas persistent skin reactions such as moderate hyperkeratosis, acanthosis and one incidence of ulcer were observed at 500 mg/kg bw/d.

In the skin irritation study, no classification is warranted on the basis of the skin readings made. Based on the skin reactions observed in the acute dermal study and the subchronic dermal toxicity

study, a classification for dermal irritation is not proposed since the local effects are only seen in studies where the skin was occluded or where the skin was repeatedly treated at high doses.

4.4.1.4 Comparison with criteria

Based on the criteria laid down in Table 3.2.2 of the CLP, the degree of skin irritation noted in the key study of [redacted] do not exceed the trigger for a classification and labelling with respect to skin irritancy (scores for erythema/oedema <2.3).

4.4.1.5 Conclusions on classification and labelling

Based on the results of the skin irritation toxicity study, IPBC is not subjected to classification with respect to skin irritation according to Directive 67/548/EEC and Regulation (E) No. 1272/2008/EC, respectively.

4.4.2 Eye irritation

Table 14: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
Primary Eye Irritation – Rabbit US EPA 81-4	Category 1 (causes serious eye damage) Cornea score: 1.67 of max. 4 (mean) (Time point: 24+48+72h) Iris score: 1.17 of max. 2 (mean) (Time point: 24+48+72h) Conjunctivae score: 2.17 of max. 3 (mean) (Time point: 24+48+72h) Chemosis score: 4 of max. 4 (mean) (Time point: 24+48+72h) Reversibility: no	Species/strain/sex: rabbit Purity of test material: 98%	[redacted]

4.4.2.1 Non-human information

The average scores in the eye irritation test were 1.6 for cornea, 1.17 for iris, 2.17 for conjunctival redness, and 4 for conjunctival chemosis, i.e. severe eye irritation. There were no signs of reversibility during the observation period of 7 days.

4.4.2.2 Human information

No human information is available

4.4.2.3 Summary and discussion of eye irritation

In an US EPA 81-4 compliant eye irritation test EPA, IPBC does exhibit the potential to produce severe eye damage as no reversibility of ocular reactions was observable at the end of the 7-day post-observation period.

4.4.2.4 Comparison with criteria

Based on the criteria laid down in Tables 3.3.1 and 3.3.2 of the CLP, the observed signs of eye irritation and the irreversibility of effects at the end of the observation period trigger a classification and labelling of IPBC with respect to severe eye damage.

4.4.2.5 Conclusions on classification and labelling

Based on the results of the eye irritation study and taking into account the non-reversibility of ocular reactions at the end of the 7-day post-observation period, IPBC is subject to classification with R41 (Risk of serious damage to eyes) according to Directive 67/548/EEC or with Eye Dam. Cat 1 / H 318 (Causes serious eye damage) according to Regulation 1272/2008/EC.

Classification/labelling for acute toxicity according to Directive 67/548/EEC:

Xi, R41: Risk of serious damage to eyes

Classification/labelling for acute toxicity according to CLP Regulation 1272/2008/EC:

Danger, Eye dam. 1, H318: Causes serious eye damage.

RAC evaluation of serious eye damage/eye irritation

Summary of the Dossier submitter's proposal

The dossier submitter proposed to harmonise the classification for IPBC as Eye Dam. 1; H318 according to CLP, and Xi; R41 according to DSD, based on one rabbit study conducted according to US EPA 81-4 ([redacted] The average scores of all animals at 24, 48 and 72 h in the eye irritation test (1.67 for cornea, 1.17 for iris, 2.17 for conjunctival redness and 4 for conjunctival chemosis) were shown in the CLH report. The observation period of the study was 7 days and there were no signs of reversibility during this observation period.

Comments received during public consultation

One MSCA commented that according to the CLP and DSD criteria the scores for cornea and iris damage were below the cut off values for classification as Eye Dam. 1 according to CLP and R41 according to DSD. Several MSCA commented that additional details (e.g. individual scores) are needed to conclude on the eye damage/eye irritation of IPBC. One MSCA agreed with the proposed classification because the effects were not reversible, but not solely because of the scores.

Additional key elements

The dossier submitter provided more details on the study by [redacted] after PC. In the study 6 rabbits (3 per sex) were used and a dose of 80 - 90 mg of test substance was instilled into the right eye of each animals; the left eye served as a control. Post-exposure

period was 7 days. The following average scores (24, 48, 72 h) for the individual animals have been calculated from the study report:

Animal 4204: Corneal opacity: 2.0; Iris: 1.0; Conjunctival redness: 2.0; Chemosis: 4.0
Animal 4205: Corneal opacity: 1.0; Iris: 1.0; Conjunctival redness: 2.0; Chemosis: 4.0
Animal 4206: Corneal opacity: 2.0; Iris: 1.0; Conjunctival redness: 2.0; Chemosis: 4.0
Animal 4207: Corneal opacity: 2.0; Iris: 1.0; Conjunctival redness: 2.0; Chemosis: 4.0
Animal 4208: Corneal opacity: 1.0; Iris: 1.0; Conjunctival redness: 2.0; Chemosis: 4.0
Animal 4209: Corneal opacity: 2.0; Iris: 2.0; Conjunctival redness: 3.0; Chemosis: 4.0
Mean scores (24-72 hours) from six animals: corneal opacity: 1.67; iritis: 1.17; conjunctival redness: 2.17; chemosis: 4.0.

All ocular effects were persistent until the end of the observation time (day 7) in all animals.

Assessment and comparison with the classification criteria

The mean scores for cornea and iris effects described in [redacted] are below the respective cut off values for classification for Eye Dam. 1; H318 (CLP) and Xi; R41 (DSD): corneal opacity ≥ 3 and/or iritis > 1,5 in at least 2 of 3 (or 4 of 6) tested animals calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material. However, the reversibility requirements (at least in 2 of 3 tested animals, a positive response fully reverses within an observation period of 21 days) needed for the classification Eye Irrit. 2; H319 (causes serious eye irritation) are not proven based on the short duration of the study (7 days instead of 21 days required by the CLP criteria). CLP guidance (chapter 3.3.2.3.2.2) states that "in the case of studies with a shorter observation period with irreversible effects, classification based on expert judgment should be considered". To support this judgment, the CAR stated that "the overall incidence and severity of irritation persisted in all animals through day 7 (the last day of the observation period)". This was confirmed verbally during RAC plenary discussions at RAC 22. Based on the above, RAC considers that classification Eye Dam 1; H318 according to CLP and Xi; R41 according to DSD is warranted.

Supplemental information - In depth analyses by RAC

Not needed.

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

According to chapter 3.8.2.2.1, point (d), there are currently no validated animal models dealing specifically with respiratory tract irritation and useful information may be obtained from the single and repeated inhalation toxicity tests. In the acute inhalation toxicity studies, no detailed gross or histopathological examinations were performed. However, clinical signs noted during the acute inhalation studies such as gasping, nasal discharge, rhinorrhea and laboured breathing as well as the findings in the lungs on gross necropsy are considered to be indicative for an irritant effect on the respiratory tract.

In the 90-day inhalation toxicity study (please refer to chapter 4.3), the predominant effect was directed toward the larynx of exposed animals. Histopathological findings were characterized by epithelial hyperplasia in the central region of the larynx, hyperplasia or squamous metaplasia in

the ventrolateral region of the larynx, and necrosis of the underlying cartilage of the larynx at concentrations in the air equal to 6.7 mg/m^3 (LOAEC: 6.7 mg/m^3 with a NOAEC: 1 mg/m^3) which were considered to be associated with the intrinsic irritating properties of IPBC. Although the effects in the larynx were considered as a local and not a systemic effect and despite the differences in the morphology of the upper respiratory tract between rats and humans which may result in a higher susceptibility of the upper respiratory tract in rats and taking into account that rodents are obligatory nose breathers, factors which both result in a higher exposure of the rats' larynx compared to the larynx in humans, these effects were regarded to be of relevance for humans. Most importantly, no functional changes or any organ dysfunction have been observed in treated animals as a consequence of the irritational effects in the laryngeal region. As the effects on larynx are considered as local and not systemic effects, a classification as a respiratory irritant has been proposed during the evaluation of the BPD dossier. Further supporting argumentation is provided in Annex II of the CLH report.

4.4.3.2 Human information

Laryngeal effects during handling of IPBC during production of IPBC are not known.

4.4.3.3 Summary and discussion of respiratory tract irritation

In the repeated dose inhalation toxicity study the predominant effect was characterized by irritation of the larynx. The accompanying histopathological findings in the larynx were regarded to be associated with the irritating nature of IPBC. No functional changes or any organ dysfunction have been observed as a consequence of the irritational effects in the laryngeal region. Although the effects on the larynx are considered as a local and not a systemic effect, they have been regarded to be of relevance for humans by the RMS despite the differences in the morphology of the respiratory tract between rats and humans which may result in a higher susceptibility of the upper respiratory tract in rats and taking into account that rodents are obligatory nose breathers. For this reason a classification with R37 ("Irritating to respiratory system") or H335 ("May cause respiratory irritation") has been proposed in the BPD dossier.

4.4.3.4 Comparison with criteria

Based on the results the 90-day inhalation study by [redacted] reported in table 12 and taking into account the criteria laid down in Table 3.8.1 of the CLP,), IPBC is subject to classification and labelling for acute toxicity with R37 (Irritating to respiratory system) according to Directive 67/548/EEC and H335 (May cause respiratory irritation) according to CLP Regulation 1272/2008/EC. This classification is justified as the effects noted in the 13-week inhalation toxicity study were not associated with an functional changes or any organ dysfunction in treated animals.

4.4.3.5 Conclusions on classification and labelling

Based on the results of the 90-day repeated dose inhalation toxicity study, IPBC is subject to the following classification:

Classification/labeling for acute toxicity according to Directive 67/548/EEC:

Xi, R37: Irritating to respiratory system

Classification/labeling for acute toxicity according to CLP Regulation 1272/2008/EC:

Warning, STOT SE 3, H335: May cause respiratory irritation**.**

4.5 Corrosivity

In the skin irritation studies performed with IPBC, no skin reactions leading to a classification with respect to potential skin irritation or skin corrosion were observed. Thus, IPBC is not considered to be corrosive or irritant to skin. In an eye irritation study, irreversible ocular effects were demonstrated resulting in a classification of IPBC with R41 (Risk of serious damage to eyes) according to Directive 67/548/EEC or Eye Dam. Cat 1 / H 318 (Causes serious eye damage) according to Regulation 1272/2008/EC.

4.5.1 Non-human information

The results of animal studies investigating the potential skin irritancy and corrosion as well as eye irritancy are described in detail in chapter 4.4. According to the results obtained, IPBC does not have to be classified as irritating or corrosive to skin whilst the observable irreversible ocular effects lead to a classification with respect to severe eye damage.

4.5.2 Human information

No studies in are available which studied the potential skin corrosion in human volunteers or in workers.

4.5.3 Summary and discussion of corrosivity

The results of animal studies investigating the potential skin irritancy and corrosion as well as eye irritancy are described in detail in chapter 4.4. According to the results obtained, IPBC does not have to be classified as irritating or corrosive to skin whilst the observable irreversible ocular effects lead to a classification with respect to severe eye damage.

4.5.4 Comparison with criteria

Taking into consideration the provisions of the Directive 67/548/EC as well as the CLP regulation for the classification of a substance with respect to skin irritation or corrosion, the mean values for erythema/eschar or oedema formation did not reach or exceed the triggers warranting a classification of IPBC as corrosive to skin.

4.5.5 Conclusions on classification and labelling

Based on the results obtained in the available skin irritation studies, no classification of IPBC with respect to skin corrosion is warranted.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

Based on the results of the OECD TG 404 study [redacted] on dermal irritation, selected as the key study, the dossier submitter considered IPBC slightly irritating to skin. In addition, in the acute dermal toxicity study ([redacted] conducted according to OECD TG 402, treated skin areas were partly reddened and partial formation of scale and encrustation was noted up to day 13, but not at day 14 following a 24-hour continuous dermal IPBC exposure at 2000 mg/kg bw. It was also stated that the assessment of skin reactions was not performed according to Draize method. In a 13-week dermal toxicity study ([redacted] compliant to OECD TG 411, dermal irritation was observed in some animals occasionally at 200 mg/kg bw/d and in all animals throughout the treatment at 500 mg/kg bw/d. Minimal hyperkeratosis was noted in the 200 mg/kg bw/d animals, and moderate hyperkeratosis, acanthosis and one incidence of ulcer were noted at 500 mg/kg bw/d. Also for this study the assessment of skin reactions was not performed according to Draize method and there was no recovery period. However, no classification for skin irritation was proposed by the DS who took into account that the local effects were only seen in studies where the skin was occluded and only at high doses.

Comments received during public consultation

One MSCA asked to state the number of animals and the dose used in the [redacted] study. If more than 3 animals were used in this study the data should be presented as average scores (across the time points (24-72 hours)) for each individual animal, to enable the CLP criteria to be applied.

Another MSCA argued that the key study should be described in greater detail (number of animals, scores per time point, dose, used vehicle etc.). The MSCA commented that skin occlusion is not a reason for not classifying for skin irritation and that it should be clarified whether the effects occurred early in the repeated dermal study [redacted] indicating irritation, or later being more likely to indicate skin sensitisation.

Besides, a third MSCA questioned whether an additional risk phrase R66 (repeated exposure may cause skin dryness or cracking) according to DSD and EUH066 (repeated exposure may cause skin dryness and cracking) according to CLP should be added considering that hyperkeratosis, acanthosis and ulcer were observed in the 13-week dermal toxicity study [redacted]

Additional key elements

The dossier submitter provided additional details on the skin irritation study by [redacted]) after the public consultation. 3 rabbits were used and a dose of 500 mg of test substance was administered per patch and animal. Post-exposure period was 5 days. The

individual average scores (24, 48, 72 h) for erythema and oedema were (respectively) 0.67, 0.33, 1.0 and 0.0, 0.0, 0.0. The average scores for all animals for 24-72 h was 0.67 (erythema) and 0 (oedema). The skin effects were reversed in 2 animals after 4 days and in 1 animal on day 5.

Assessment and comparison with the classification criteria

According to CLP criteria, individual mean scores of three reading times (24, 48 and 72 hr) should be used in grading skin irritation/corrosion whereas according to DSD criteria, mean scores at each of the reading times (24, 48 or 72 hr) for all animals tested are averaged. Inflammation of the skin is also significant if it persists in at least two animals at the end of the observation time. Particular effects e.g. hyperplasia, scaling, discoloration, fissures, scabs and alopecia should be taken into account. Relevant data may also be available from non-acute animal studies. These are considered significant if the effects seen are comparable to those described above.

RAC emphasizes that the non-key studies, i.e. the acute dermal toxicity study by [redacted] and the 13-week dermal toxicity study by [redacted] are not guideline tests for skin irritation and accordingly, no records of skin reactions were performed on treated test sites. In [redacted] the average scores of 24, 48, 72 h for erythema/eschar or oedema for individual animals were below the cut off value 2.3 for classification (CLP) and the skin effects were reversed by day 5. Also the mean values of scores for either erythema or oedema formation calculated over all the animals tested or for each animal separately were less than 2 so that the criteria for DSD classification are not met. RAC therefore supported the conclusion of the DS that no classification is warranted for skin corrosion/irritation.

RAC didn't agree to add the supplementary hazard statement code EUH066 (CLP) and the additional risk phrase R66 (DSD) proposed by one MSCA during public consultation. Indeed, EUH066 should be applied for substances which may cause concern as a result of skin dryness, flaking or cracking (such as solvents with degreasing/defatting properties) but which do not meet the criteria for skin irritancy based on either:
(1) practical observation after normal handling and use, or
(2) relevant evidence concerning their predicted effects on the skin.

Supplemental information - In depth analyses by RAC

Not needed.

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 15: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
US EPA 81-6 OECD 406 Buehler Test	Not sensitising	Number of animals sensitised/total number of animals: 0/10	[redacted]
OECD 406 US EPA 81-6F Maximisation Test Vehicle; petrolatum	Not sensitising under the conditions of this study; however the requirements of OECD TG 406 are not fulfilled	Number of animals sensitised/total number of animals: 0/20	[redacted]
OECD 406 EC B.6 OPPTS 870.2600 Maximisation Test Vehicle; PEG 400	Sensitising	Number of animals sensitised/total number of animals: 8/10 after 24 hours 9/10 after 72 hours	[redacted]

4.6.1.1 Non-human information

In a recently Guinea Pig Maximisation Test (GPMT) performed according to OECD TG 406 [redacted] 9 of 10 animals showed a positive response to IPBC with 5% IPBC used for challenge as well as 1% and 6% used for intradermal and topical induction, respectively.

In another GPMT [redacted] no skin reactions were observed following challenge; however, this study does not fulfil the requirements of OECD TG 406 as no skin reactions were seen following the topical induction with 3.12% IPBC. In the range finding study, erythema was observed with 6.25% IPBC whereas no skin reactions were observed at 3.12%. Consequently, a concentration higher than 3.12% should have been chosen for the topical induction in the main study. This study is considered unreliable since the low concentration used for topical induction impairs the results of the study. Furthermore it should be noted that the lowest irritating concentration of 6% in the new study ([redacted] is in conflict with the old study [redacted] where 6.25% resulted in severe erythema. It may be noted that different vehicles were used in the two studies.

The applicant argues that in the new study the challenge of 5% was too close to the lowest irritating concentration 6% (two range-finder tests for topical induction were performed), however the study was performed according to OECD and submitted as such.

In a Buehler test also performed according to OECD TG 406 [redacted] IPBC showed no skin sensitising potential; however, the Buehler test is generally not as sensitive as the GPMT. In three non-key studies, IPBC showed positive reactions in two GPMTs (Shimizu, M. *et al.* 2000; Zissu, D. 2002), but no skin sensitising potential in a Buehler test (Cerven, D.R. 1993). However, the GPMT non-key studies of Shimizu, M. *et al. (*2000) and Zissu, D. (2002) lack detailed information on the dose selection for the lowest irritating concentrations for induction and the highest non-irritating concentrations for challenge and are, thus, of limited value as well.

In conclusion, IPBC is considered to be a skin sensitiser and classification with Xi; R43 according to Directive 67/548/EC and as Skin Sens. 1, H317 according to Regulation (EC) No. 1272/2008 is warranted. The skin sensitising potential of IPBC observed in 3 of 4 GPMTs is supported by data from human case reports, see 4.6.1.2.

4.6.1.2 Human information

There are reports available on the sensitisation potential of IPBC in humans. Bryld et al., 1997, reported 3 positive reactions to patch tests with 0.1% IPBC in petrolatum among 311 patients from allergenicity hospitals; contact allergy is likely in at least one case. In a recent study (Bryld et al., 2001), 4 additional patients with IPBC contact allergy were diagnosed among a total number of 3168 persons patch tested with IPBC (0.1% in petrolatum). In another report (Pazzaglia & Tosti, 1999), 3 out of 312 patients showed reactions to patch tests with 0.01 to 0.1% IPBC in petrolatum; one patient had reactions interpreted as allergic. Majoie & van Ginkel, 2000, reported that 5 metalworkers of 23 tested showed positive patch tests to a variety of metalworking fluids containing IPBC at concentrations from 0.5 to 2.5%. Among 4883 persons patch-tested with IPBC (0.1% in petrolatum), 0.3% of the patients had positive skin reactions and 0.5% had a doubtful skin reaction at day 3 (Schnuch et al., 2002).

In conclusion, the human data support the findings from animal studies that IPBC is a skin sensitiser. The applicant argues that no ”useful information could be extracted from the human patch test because the majority of the tested persons had a history of contact dermatitis and might therefore be considered as ”hypersensitive” due to potential pre-sensitisation to other agents. However it should be remembered that the term contact dermatitis includes both irritant contact dermatitis and allergic contact dermatitis and therefore it cannot be concluded that the patients were hypersensitive. The Danish CA evaluates the results from the several positive human patch tests from more than one clinic to be relevant despite the relatively low human incidence rates. It could be argued that persons with contact dermatitis are also a part (and a growing part) of the general population and in that sense a potential occupational worker. In conclusion, the human data are in accordance with the criteria for classification, and that the results are supportive of the positive animal data. On this basis a classification as R43 is warranted.

4.6.1.3 Summary and discussion of skin sensitisation

Among the 3 animal studies submitted as key studies IPBC has shown a clear skin sensitising potential in one Guinea Pig Maximisation Test (GPMT), whereas no skin reactions were observed in another GPMT and in a Buehler tests. However, the negative GMPT study did not fulfil the requirements of OECD TG 406 and the result is considered less reliable. In three non-key studies, IPBC showed no skin sensitisation potential in a Buehler test and positive reactions in two GPMTs the latter of which lack detailed information on the dose selection procedure employed for the identification of appropriate doses for induction and challenge, respectively.. However generally the Buehler tests are not as sensitive as the GPMT and can therefore not overrule the results of the more sensitive GPMT test. The skin sensitising potential of IPBC observed in 3 of 4 GPMTs is supported by data from human case reports where IPBC was demonstrated to induce allergic reactions at low frequencies.

4.6.1.4 Comparison with criteria

The results of the available animals studies and human patch tests demonstrate that IPBC possesses a skin sensitisation potential. All of the Buehler tests are negative, whilst 3 out of 4 GMPT tests are positive. Two of the positive GPMT tests are not evaluable due to methodological deficiencies. . In several human patch tests, less than 1% of the tested collectives reacted positively towards IPBC. Applying the criteria in Tables 3.4.2, 3.4.3 and 3.4.4. of the 2nd ATP to

the CLP (Regulation (EC) No. 286/2011), the one positive GPMT results in a classification in Skin Sens. 1A, whereas the low frequencies observed in the human patch tests (< 1% positive reactions in the tested collectives) suggest a classification in Skin Sens. 1B. Since there is no consistency with regards to incidences in the animal studies and human patch tests and as human data will normally take preference over animal data according to REACh guidance R.8, a classification in Skin Sens. 1 is considered to be appropriate for IPBC.

4.6.1.5 Conclusions on classification and labelling

Based on the results of the available animals studies and human patch tests and applying the criteria laid down in the 2nd ATP to the CLP, , IPBC is subject to classification and labelling with R43 (May cause skin sensitisation by skin contact) according to Directive 67/548/EEC and with Skin Sens. Cat. 1, H317 (May cause an allergic skin reaction) according to CLP Regulation 1272/2008/EC as amended by Regulation (EC) No. 286/2011. The classification into the category in Skin Sens. 1 is considered appropriate considering the positive results in human patch tests, the positive animal studies and taken into consideration that human data will normally take preference over animal data.

Classification/labeling for acute toxicity according to Directive 67/548/EEC:

Xi, R43: May cause skin sensitisation by skin contact

Classification/labeling for acute toxicity according to CLP Regulation 1272/2008/EC:

Warning, Skin Sens. 1, H317: May cause an allergic skin reaction**.**

RAC evaluation of skin sensitisation
Summary of the Dossier submitter's proposal The dossier submitter proposed to harmonise the classification for IPBC as Skin Sens. 1; H317 (may cause an allergic skin reaction) according to CLP, and Xi; R43 (may cause skin sensitisation by skin contact) according to DSD. The proposal was based on three key studies. In two of them, an OECD 406 Buehler Test ([redacted] and an OECD 406 Guinea Pig Maximisation Test (GPMT) [redacted] no sensitisation occurred. However, the study by [redacted] did not fulfil the OECD TG 406 requirements, because no skin reactions were observed following the topical induction with 3.12% IPBC, and that may have influenced the results of this study. In the third key study, an OECD 406 GPMT ([redacted] 8/10 and 9/10 animals were sensitised at 48 hours (reported incorrectly as 24 h in the CLH report) and 72 hours after 5% IPBC challenge exposure (topical induction was performed with 6% IPBC). The DS argued that the challenge concentration of 5% IPBC was too close to the lowest irritating concentration of 6 % IPBC, but the study was performed according to the OECD TG. According to the DS, the Buehler test is not generally as sensitive as the Guinea Pig Maximisation Test (GPMT) and it could not therefore overrule the results of the more sensitive GPMT test. In addition, three non-key studies were mentioned in the CLH report. In two GPMT studies IPBC had shown positive reactions, but no skin sensitising potential had been observed in a Buehler Test according to the CLH report. However, more details on these studies were not presented in the CLH report.

Also five human case reports were briefly summarised in the CLH report that, according to the DS, supported the proposed classification. In these case reports 3/311 (exposed to 0.1% IPBC in petrolatum), 4/3168 (exposed to 0.1% IPBC in petrolatum), 3/312 (exposed to 0.01-0.1% IPBC in petrolatum), 5/23 (exposed to 0.5-2.5% IPBC in metalworking fluids) and 0.3% of 4883 patients (exposed to 0.1% IPBC in petrolatum) had positive skin reactions. It was also noted from these studies that the majority of the test persons had a history of contact dermatitis (as a growing part of the general population does), but the nature of the contact dermatitis was not described further in the CLH report.

Comments received during public consultation

Several MSCAs commented that additional details on studies (e.g. data on positive and negative controls and further information on previous exposures on human) are needed to conclude on the skin sensitization potential of IPBC.

Additional key elements

In the CAR of IPBC, [redacted] reported that the control group consisted of 5 animals. At 48 and 72 hours after challenge, none of these controls exhibited skin reactions or clinical signs. At the end of the study the mean body weight of the treatment group was in the same range as that of the control group animals.

According to the CAR of IPBC, the following induction and challenge doses were used in the GPMT study by [redacted]

- Intradermal induction: 0.1 mL of 0.08% IPBC (in paraffin oil) and 0.1 mL of 0.16% IPBC (emulsified in FCA)
- Topical induction: 0.4 mL of 3.12% IPBC
- Challenge: 0.1 mL of 0.32% IPBC in petrolatum

Assessment and comparison with the classification criteria

RAC considered that the human data with respect to IPBC as skin sensitiser are not convincing because a substantial number of persons were not sensitised (as required by CLP criteria). In addition, human subjects showing positive skin reactions probably have had previous exposures to other chemical substances not related to IPBC.

In order to conclude on Skin Sens. 1; H317 and Xi; R43 based on the positive key study ([redacted] the available information on positive and negative controls was considered by RAC. IPBC produced strong effects up to encrustation after intradermal induction with 1% IPBC. Topical induction with 6 % IPBC was the lowest irritating concentration in range-finder studies. The challenge with the 5 % test item formulation led to skin effects (grade 1) in 80 % of the test item group after 48 h and in 90 % after 72 h. No skin effects were seen in the negative control group. The results with the positive control α-hexylcinnamaldehyde were not reported in the CLH report or in the CAR. RAC agreed that considering only the positive results of the [redacted] study, the criteria were met for Skin Sens. 1A; H317 according to CLP (animal test results in GPMT showing skin effects in more than 60 % of animals by application 1 % intradermal induction dose) and Xi; R43 according to DSD (may cause skin sensitisation by skin contact). However, the results of the other GPMT study ([redacted] and Buehler test [redacted] were negative, although it was stated that the GPMT study did not fulfill the requirements of OECD TG 406 and the Buehler test is not as sensitive as the GPMT study. Due to the weakness of the key study by [redacted] (challenge dose was close to the induction dose), two negative Buehler tests, one less reliable negative GPMT study by [redacted] and a lack of substantial number of sensitised persons in human studies RAC supported the conclusion of the DS that classification of IPBC for Skin Sens. 1; H317 and Xi; R43 is warranted. However, the data were not sufficiently robust for sub-categorisation.

Supplemental information - In depth analyses by RAC

Not needed.

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

In the absence of test guidelines for the testing of the potential respiratory sensitisation, no information is available on this endpoint. However, based on the experience in humans (please refer to chapter 4.6.1.2) and the results of the repeated dose inhalation toxicity study performed with IPBC (please refer to chapter 4.7.1.2), no signs of toxicity or findings indicative for respiratory sensitisation were observed.

4.6.2.2 Human information

There are no humans case reports known to the applicant which would indicate a respiratory sensitisation potential of IPBC (please refer to chapter 4.6.1.2). No such effects reported during manufacture of IPBC.

4.6.2.3 Summary and discussion of respiratory sensitisation

Based on human experience and the results of the available repeated dose toxicity study performed with IPBC via the inhalation route of exposure, a respiratory sensitisation potential of IPBC is not anticipated.

4.6.2.4 Comparison with criteria

Indications for a respiratory sensitisation of IPBC have neither been obtained in humans nor in the available repeated dose inhalation toxicity study. For this reason, a classification as a respiratory sensitizer is not warranted taking into account the criteria laid down in Table 3.4.1 of the 2nd ATP to the CLP.

4.6.2.5 Conclusions on classification and labelling

A classification of IPBC with respect to respiratory sensitisation is not required.

4.7 Repeated dose toxicity

Table 16: Summary table of relevant repeated dose toxicity studies

Method	Results	Remarks	Reference
subchronic (oral: gavage) 28 days + 14 days recovery (control and high dose) Wistar rats (both sexes, 5/ group) 0, 10, 30, 100 mg/kg bw/d (m/f) Exposure: 4 weeks (daily for 4 weeks	NOAEL: 10 mg/kg bw/d LOAEL: 30 mg/kg bw/d There were no clinical signs noted. Plasma cholinesterase activity was reduced in the 100 mg/kg bw/d females, however, being reversible. RBC cholinesterase activity was comparable to control up to and including the highest dose. T3, T4, and TSH levels were comparable to concurrent control. Increased absolute and relative liver weights at 30 mg/kg bw/d in males and at 100 mg/kg bw/d in both sexes accompanied with centrilobular cytoplasmatic change in males at 100 mg/kg bw/d was observed. The effects were reversible within 14 days. Increased relative kidney weights at 30 mg/kg bw/d in females was observed and considered of toxicological relevance, since no significant effect were seen on body weight or body weight gain at this dose. At doses >30 mg/kg bw/d increased incidence in alpha-2-microglobulin droplets in males (an effect specific for male rats and not relevant for humans) was observed. Erosions and ulceration in the forestomach at doses >30 mg/kg bw/d were seen, however being reversible during recovery period. There was one incidence of chronic peritonitis in males satellite animals at 100 mg/kg bw/d.	(purity 98.3 %)	[redacted]

subchronic (oral: feeding) 28 days (rangefinder for 104-week feeding study in rats) Wistar rats (both sexes, 10/ group) 0, 60, 125, 250 mg/kg bw/d (m/f) Exposure: 4 weeks (daily for 4 weeks)	NOAEL: n.a. dose-rangefinder LOAEL: n.a. dose-rangefinder There were no clinical signs noted. Reduced body weights, body weight gain and food consumption was noted at dose level >125 mg/kg bw/d. Absolute liver weight was increased in females at 250 mg/kg bw/d. Liver weight after covariance analysis was increased in both sexes at all dose groups, however, without histopathological changes.	(purity 97 %)	[redacted]
Oral feeding dose-rangefinder Rabbit New Zealand White Both sexes 2/group (main groups) 1/sex (additional groups) main groups: 14 days additional groups: 5 and 7 days Dose levels: main groups: 0, 200, 500, 1300, 3000 ppm (0, 5.9, 17.2, 47.1, 115.6 mg/kg bw/d) additional groups: 6000 ppm (64 mg/kg bw/d for males, 30 mg/kg bw/d for females) 10 000 ppm (49 mg/kg bw/d for males and 24 mg/kg bw/d for females)	NOAEL: n.a. dose-rangefinder LOAEL: n.a. dose-rangefinder Reduced food consumption was most likely due to impalatability of the diet which resulted in body weight loss in animals at 6000 and 10 000 ppm as well as reduced test material intake. There were no treatment-related findings up to and including 3000 ppm dose level.	(purity 98.7 %)	[redacted]
Oral feeding study dose-rangefinder 8 weeks Mice CD-1 both sexes (10/group) 0, 50, 250, 500, 1000 mg/kg bw/d	NOAEL: n.a. dose-rangefinder LOAEL: n.a. dose-rangefinder All animals survived. There were no treatment related clinical signs noted.	(purity 97 %)	[redacted]

	Reduced body weights in males at doses > 250 mg/kg bw/dand in females at 1000 mg/kg bw/d . Reduced body weight gain in males at doses > 250 mg/kg bw/d and in females at doses > 500 mg/kg bw/d. Reduced food consumption at 500 and 1000 mg/kg bw/d in both sexes. Darkened livers in both sexes at 1000 mg/kg bw/d. Increased absolute and relative liver weight at doses ≥ 250 mg/kg bw/din males and at ≥ 500 mg/kg bw/din females accompanied by pigmentation of enlarged hepatocytes and of Kupffer cells.		
Inhalation study dose-rangefinder Sprague-Dawley rats both sexes (5/group) 2 weeks (5 days per week, 6 hours per day) whole body exposure Dose levels: 0, 4, 10, 38 and 67 mg/m^3	NOAEL: n.a. dose-rangefinder LOAEL: n.a. dose-rangefinder Study was terminated due to deaths and severity of clinical sings for groups treated with 38 and 67 mg/m^3 after the third exposure. Animals died due to congestion of liver. ≥ 10 mg/m^3: agitated grooming of snout and eyes closed/half closed ≥ 38 mg/m^3: noisy respiration, sneezing, brown staining around snout, jaws, and forepaws as well as gasping, red ears, red limbs, discharges from nostrils Body weight loss or reduced body weight gain as well as reduced food consumption at concentrations > 10 mg/m^3. Increased absolute and relative liver weight at dose levels at 10 mg/m^3. Histopathology of liver was not performed. No information about liver weight at doses > 38 mg/m^3. Hyperplasia and metaplasia of the larynx epithelium and necrosis of the underlying cartilage at dose levels of 4	(purity >97 %)	[redacted]

	and 10 mg/m^3. No effects on lungs or nasal passages.		
Inhalation study dose-rangefinder (5 days) Sprague-Dawley rats both sexes 5/group whole body exposure Dose levels: 0, 0.3, 1.0, 3.8 mg/m^3	NOAEL: n.a. dose-rangefinder LOAEL: n.a. dose-rangefinder No mortalities, no clinical signs No effects on body weight gain and food consumption At 3.8 and 1 mg/m^3: Histopathological changes in the larynx included epithelial hyperplasia of the ventral region and hyperplasia or squamous metaplasia in the ventrolateral regions, with necrosis of the underlying cartilage.	(purity >97 %)	[redacted]
Subchronic (oral: gavage) 90 days Sprague Dawley rats (both sexes, 10/ group) Dose levels: 0, 10, 20, 35, 80 mg/kg bw/d	NOAEL: 35 mg/kg bw/d LOAEL: 80 mg/kg bw/d One mortality due to gavaging accident. Immediately after dosing, salivation and breathing sounds in some animals at 35 and 80 mg/kg bw/d. Reduced body weight and body weight gain in males at 80 mg/kg bw/d. No effects on body weights in females. There were isolated findings of reduced food consumption in males at 80 mg/kg bw/d. Food conversion ratio was reduced in males at the 80 mg/kg bw/d dose level. Reduced iron concentration in both sexes at 80 mg/kg bw/d . Increased absolute and relative liver and kidney weights in females and increased relative liver weight in males at 80 mg/kg bw/d dose level. Single incidences in gastric irritation at 80 mg/kg bw/d.	(purity 98 %)	[redacted]
subchronic (oral: gavage) 13 weeks 5 days/week + 28 days recovery (high dose) Sprague Dawley rats (both sexes, 10/ group)	NOAEL: 20 mg/kg bw/d LOAEL: 50 mg/kg bw/d Salivation and burrowing was noted immediately after dosing at 50 and 125 mg/kg	(purity 98 %)	[redacted]

Satellite group 0, 20, 50, 125 mg/kg bw/d (m/f)	bw/d. No treatment related mortalities. Occasionally, reduced body weights in the 125 mg/kg bw/d males. Overall body weight gains were comparable to controls in all groups. No effects on cholinesterase activity (not specified whether RBC or plasma); brain cholinesterase activity was not determined. Increased absolute and relative liver weight in females at 50 mg/kg bw/d and in both sexes at 125 mg/kg bw/d accompanied by hepatocyte enlargement. Hepatocyte enlargement was not observed after recovery. Hyperkeratosis and acanthosis in forestomach in all treatment groups, however, without a clear dose-response relationship and reversibility after recovery.		
subchronic (oral: feeding) 3 months Rabbit New Zealand White both sexes 5/group 0, 13, 75, 150 mg/kg bw/d (m/f) (0, 500, 2000, 4000 ppm)	NOAEL: 13 mg/kg bw/d LOAEL: 75 mg/kg bw/d There were no clinical signs and mortalities noted which were related to treatment. Body weight gain and food consumption was reduced in animals treated with 4000 ppm especially during the first week of treatment. Gamma-glutamyl-transferase activity was increased in females dosed with 4000 ppm. Absolute liver weight was increased (considered of biological significance) in females at 2000 ppm and statistical significant relative liver weight ≥ 2000 ppm. In animals at 2000 and 4000 ppm, hepatocyte hypertrophy and brown pigment in the liver were noted.	(purity 98.7 %)	[redacted]

subchronic (dermal) 13 weeks 5 days/week (6 hours/ day) Sprague Dawley rats (both sexes, 10/ group) 0, 50, 200, 500 mg/kg bw/d (m/f)	NOAEL: Local effects: 50 mg/kg bw/d Systemic effects: 500 mg/kg bw/d LOAEL: Local effects: 200 mg/kg bw/d Systemic effects: - There were no treatment related clinical signs noted. Dermal irritation was occasionally noted in single animals at 200 mg/kg bw/d. At 500 mg/kg bw/d all animals showed dermal irritation which persisted throughout the treatment period. There were no effects on body weight and food consumption noted. Minimal hyperkeratosis was noted in the 200 mg/kg bw/d animals. Moderate hyperkeratosis, acanthosis and one incidence of ulcer were noted at 500 mg/kg bw/d.	(purity 97.5 %)	[redacted]
subchronic (inhalation) 13 weeks (5 days/week; 6 hours/ day) Sprague Dawley rats (both sexes, 15/ group) Dose levels: 0, 0.3, 0.23, 1.16 and 6.7 mg/m3	NOAEL: 1.16 mg/kg bw/d LOAEL: 6.7 mg/kg bw/d There were no clinical signs noted which were attributable to cholinesterase activity. There were no treatment-related mortalities noted. There were no effects on body weight and food consumption noted. Plasma cholinesterase activity was lower when compared to concurrent control at 6.7 mg/m^3. RBC cholinesterase activity was decreased in females at 6.7 mg/m^3 after 2 weeks but not at the end of the study. Brain cholinesterase activities were decreased in females and males at 6.7 mg/m^3. In larynx of the high dose group necrosis in the ventral cartilage, epithelial	(purity >97 %)	[redacted]

	hyperplasia in ventral region, and squamous metaplasia in ventrolateral region were noted in all animals. In addition, epithelial hyperplasia over the arytenoid projections was noted in all high dosed males and in 5 of the 15 high dosed females. Epithelial ulceration in the ventral region was observed in low incidence in the high dosed males (4 of 15 animals). In some of the high dosed males and females, additionally, atrophy of submucosal glands was noted (3 and 6 animals of 15, respectively). R37; Irritating to respiratory system.		

4.7.1 Non-human information

The toxicity of IPBC has been investigated in several studies using the oral route (gavage and feeding), the dermal route and following administration via inhalation. The results of the studies are summarised in Table 17.

4.7.1.1 Repeated dose toxicity: oral

When IPBC was administered by gavage to rats, post-dose salivation immediately after dosing was noted in most studies at doses equal to or greater than 30 mg/kg bw/d. Post-dose salivation is often observed in gavage studies. IPBC is an irritating substance and post-dose salivation could be a result of the irritating properties of IPBC and/or application of IPBC via gavage. When IPBC was administered via the diet no treatment-related clinical signs were noted indicating that post-dose salivation might be a result of the dosing procedure in the gavage studies and not a result of increased cholinergic activity.

In rats, brain and RBC cholinesterase activities were not reduced up to and including the highest dose levels administered. Plasma cholinesterase activity was reduced at doses equal to or greater than 50 mg/kg bw/d being reversible within 14 days. In mice and rabbits, plasma and RBC cholinesterase activity was not reduced up to and including the highest dose. These data further support the view that clinical signs observed in gavage studies might be a result of the irritating properties of IPBC. Results indicated that IPBC was not neurotoxic when administered via the oral route. This was supported by the acute and 90-day neurotoxicity studies in rats.

In rats, rabbits and mice treated with IPBC in the diet, food consumption was reduced at doses equal to or greater than 80 mg/kg bw/d and reduced body weights and/or body weight gains were observed at doses equal or greater than 40 mg/kg bw/d. In gavage studies, reduced body weight, body weight gain was observed at 80 mg/kg bw/d.

The administration of IPBC via the oral route (gavage and via the diet) caused local erosions, ulceration, and/or inflammation of the stomach (fore-stomach and/or glandular stomach). These findings, which were observed at dose levels from about 20 to 30 mg/kg bw/d were reversible within 28 days after the treatment with IPBC had stopped. No lesions in the mouth cavity or esophagus were noted. The effects observed in the stomach and fore-stomach are most likely due to the intrinsic irritating properties of IPBC.

At doses equal to or greater than 30 to 40 mg/kg bw/d, increased absolute and relative liver weights were observed in rats sometimes accompanied by hepatocellular changes. In a rat study with a 14-day recovery period, increased liver weights and histological changes in hepatocytes were reversible (see [redacted] Increased relative kidney weight has been observed in female rats at dose levels from 30 mg/kg bw/d and is considered of toxicological relevance, since no significant effect were seen on body weight or body weight gain at this dose.

In a two-year feeding study with rats, an increased incidence in foamy macrophages aggregates was noted in the lungs in males at 40 and 80 mg/kg bw/d.

In mice treated for 78-weeks with IPBC in the diet, there was an increased incidence in enlarged thyroids at the highest dose (150 mg/kg bw/d). At histopathology, the following findings were observed: foci of small vacuolated cells most likely of follicular origin and general follicular enlargement in both sexes in all treated dose groups. The findings indicated that follicles stored colloid and could not release it, resulting in apparent follicular enlargement. These findings were not considered to be indicative of a break of the normal pituitary, thyroid, hypothalamic circuit because no adenoma (as expected in the case of a break of pituitary, thyroid, hypothalamic circuit) were observed. This is further supported by the lack of changes in T_4, T_3, and TSH levels in rats ([redacted] The toxicological significance of the findings in thyroids remains unclear.

IPBC was not carcinogenic in rats and mice up to and including the highest dose levels (80 and 150 mg/kg bw/d for rats and mice. In the mouse carcinogenicity study, an increased incidence of hepatocellular adenomas in high dose males (11/50) is not considered to be of biological relevance.

4.7.1.2 Repeated dose toxicity: inhalation

The toxicity of IPBC via inhalation was studied in 3 studies with rats: 2 range-finding sub-acute studies and one 90-day sub-chronic study. Clinical signs (indicative of irritation), reduced body weight gain and food consumption, and increased absolute and relative liver weight were noted in a 2-week dose range-finding study at concentrations in the air from 10 mg/m^3. No such effects were noted in the 13-week inhalation study.

In the 13-week study, plasma cholinesterase activity was reduced at the highest concentration (6.7 mg/m^3) when compared to concurrent controls. RBC cholinesterase activity was decreased in females at 6.7 mg/m^3 after 2 weeks but not at study termination. Brain cholinesterase activities were decreased in males and females at 6.7 mg/m^3 when compared to concurrent controls (16.8 and 26.1%, respectively) and to historical controls (23.9 and 12.3, respectively). This finding is of unclear relevance since no clear dose-relationship was observed (small decrease for a large change in dose) and the normal variation seems to be wide Results indicated that IPBC was not neurotoxic. This was supported by the acute and 90-day neurotoxicity and 104 weeks studies in rats and 78 weeks mice study which all investigated RBC and brain cholinesterase inhibition.

The predominant histopathological findings were epithelial hyperplasia in the central region of the larynx, hyperplasia or squamous metaplasia in the ventrolateral region of the larynx, and necrosis of the underlying cartilage of the larynx at concentrations in the air equal to 6.7 mg/m^3 (LOAEC: 6.7 mg/m^3 with a NOAEC: 1 mg/m^3). These histopathological changes, which may be associated with the intrinsic irritating properties of IPBC, are considered by the RMS as being of relevance to humans although realising the difference in morphology of the upper respiratory tract of rodents and humans which may result in a higher susceptibility of the upper respiratory tract in rats and that rodents are obligatory nose breathers, factors which both result in a higher exposure of the rats' larynx compared to the larynx in humans. No functional changes or any organ dysfunction have been observed in treated animals as a consequence of the irritational effects in the laryngeal

region. As the effects on the larynx are considered as local and not systemic effects, a classification of IPBC as a respiratory irritant is proposed.

4.7.1.3 Repeated dose toxicity: dermal

The toxicity of IPBC via dermal application has been studied in a 13-week study in rats. Dermal irritation, which persisted throughout the treatment period, was observed at the highest dose level (500 mg/kg bw/d). At 200 mg/kg bw/d, dermal irritation was only noted occasionally in single animals. At termination, mild hyperkeratosis was noted at 200 mg/kg bw/d while at 500 mg/kg bw/d hyperkeratosis was more severe and resulted in ulceration. No adverse systemic effects were observed.

4.7.1.4 Repeated dose toxicity: other routes

No information available

4.7.1.5 Human information

No information available

4.7.1.6 Other relevant information

No information available

4.7.1.7 Summary and discussion of repeated dose toxicity

Oral: In rats, post-dose salivation was observed immediately after dosing by gavage from 30 mg/kg bw/d, but not when IPBC was administered via the diet indicating that post-dose salivation might be a result of the dosing procedure in the gavage studies and not a result of increased cholinergic activity. In rats, brain and RBC cholinesterase activities were not reduced up to and including the highest dose levels administered. Plasma cholinesterase activity was reduced at doses equal to or greater than 50 mg/kg bw/day being reversible within 14 days. Results indicated that IPBC was not neurotoxic when administered via the oral route. This was supported by the acute and 90-day neurotoxicity studies in rats In rats, rabbits and mice treated with IPBC via the diet, food consumption was reduced from 80 mg/kg bw/d (dietary, gavage) and body weights and/or body weight gains from 40 mg/kg bw/d (dietary) or 80 mg/kg bw/d (gavage).

In rats, local erosions, ulceration, and/or inflammation of the stomach (fore stomach and/or glandular stomach) were observed from about 20 to 30 mg/kg bw/d (dietary, gavage). Increased liver weights, sometimes accompanied by hepatocellular changes, and increased kidney weight (females only) were observed from 30 to 40 mg/kg bw/d. Increased incidence in foamy macrophages aggregates was noted in the lungs of male rats from 40 mg/kg bw/d in the 2-year rat study. In the 78-week mice study, an increased incidence in enlarged thyroids accompanied by foci of small vacuolated cells most likely of follicular origin and general follicular enlargement was noted at 150 mg/kg bw/d; the toxicological significance of these findings in thyroids remains unclear. IPBC was not carcinogenic in rats and mice up to and including the highest dose levels (80 and 150 mg/kg bw/d for rats and mice, respectively).

Dermal: Dermal irritation persisting throughout the treatment period, and hyperkeratosis and ulceration was observed at 500 mg/kg bw/d; at 200 mg/kg bw/d mild hyperkeratosis. No adverse systemic effects observed.

Inhalation: Decreased RBC cholinesterase activity observed in females at 6.7 mg/m^3 (after 2 weeks but not at study termination) and decreased brain cholinesterase activities in females and in males at 6.7 mg/m^3. The finding is of unclear relevance since no clear dose-relationship was observed (small decrease for a large change in dose) and the normal variation seems to be wide. Results indicated that IPBC was not neurotoxic. This was supported by the acute and 90-day neurotoxicity and 104 weeks studies in rats and 78 weeks mice study (all investigating RBC and brain cholinesterase inhibition). Histopathological findings were epithelial hyperplasia in the central region of the larynx, hyperplasia or squamous metaplasia in the ventrolateral region of the larynx, and necrosis of the underlying cartilage of the larynx at 6.7 mg/m^3 (NOAEC 1.16 mg/m^3). No functional changes or any organ dysfunction have been observed in treated animals as a consequence of the irritational effects in the laryngeal region. As the effects on larynx are considered as a local and not a systemic effect a classification of IPBC as a respiratory irritant is proposed although acknowledging the difference in morphology of the upper respiratory tract of rodents and humans which may result in a higher susceptibility of the upper respiratory tract in rats and considering that rodents are obligatory nose breathers.

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

In the available repeated dose toxicity studies following oral administration liver and kidney were the target organs in rats observed as organ weight changes and in the liver accompanied with hepatocellular changes. In the subchronic inhalation toxicity study, the larynx has been demonstrated to be affected. This effect has been regarded to be of local rather than of systemic nature. No functional changes or any organ dysfunction have been observed as a consequence of the irritational effects in the laryngeal region. The local irritation in the larynx led to the conclusion that IPBC is a local irritant in the upper respiratory tract of rats. This effect is regarded as of relevance for humans although realising the difference in morphology of the upper respiratory tract of rodents and humans which may result in a higher susceptibility of the upper respiratory tract in rats and that rodents are obligatory nose breathers, factors which both result in a higher exposure of the rats' larynx compared to the larynx in humans.

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

Based on the available data and the effects observed in the 90-day repeated dose inhalation toxicity study, IPBC is subject to classification and labelling for specific target organ toxicity with R37 (Irritating to respiratory system) according to Directive 67/548/EEC. Neither the effects in the oral nor in the dermal repeated dose toxicity studies trigger a classification and labelling of IPBC with respect to specific target organ toxicity after repeated administration as no functional changes or any organ dysfunction have been observed as a consequence of the irritational effects in the laryngeal region.

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

Based on the results of the 90-day repeated dose inhalation toxicity study and considering the local effects observed at the larynx, IPBC is subject to the following classification:

Classification/labelling for acute toxicity according to Directive 67/548/EEC:

Xi, R37: Irritating to respiratory system

Classification/labelling for acute toxicity according to CLP Regulation 1272/2008/EC:

Warning, STOT SE 3, H335: May cause respiratory irritation**.**

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

The dossier submitter did not propose a classification for repeated dose toxicity. Specific target organ toxicity after repeated exposure of IPBC was investigated in oral (feeding and gavage studies), dermal and inhalation studies.

A) Oral route:

IPBC administration via gavage in in Sprague Dawley rats (OECD 408) induced salivation immediately after dosing at 35 and 80 mg/kg bw/d in some rats ([redacted] and at 50 and 125 mg/kg bw/d ([redacted] Salivation was considered to be a result of irritating properties of IPBC and/or application of IPBC via gavage. Administration of IPBC via gavage caused hyperkeratosis and acanthosis in fore-stomach of all treated rats (20, 50 and 125 mg/kg bw/d) without a clear dose-response relationship and reversibility after recovery [redacted] Erosions and ulceration were seen in the fore-stomach at doses >30 mg/kg bw/d) being reversible during recovery period in a 28-day study on Wistar rats (OECD 407) [redacted] Also single incidences in gastric irritation at 80 mg/kg bw/d were reported ([redacted] The observed effects in the stomach and fore-stomach were considered to be results of irritating properties of IPBC.

Reduced body weights, body weight gain and food consumption were noted at >125 mg/kg bw/d in a 28-day oral feeding dose-range finding study for a carcinogenicity/chronic toxicity study in rats [redacted] In an 8-week oral feeding dose-range finding study in CD-1 mice body weights were decreased at >250 and at 1000 mg/kg bw/d in males and females, respectively, body weight gains were reduced at >250 and at >500 mg/kg bw/d in males and females, respectively, and food consumption was decreased at 500 and 1000 mg/kg bw/d in both sexes. ([redacted] In the oral gavage study in rats reduced body weight, body weight gain and isolated findings of reduced food consumption were reported in males at 80 mg/kg bw/d. ([redacted] In the 13-weel oral gavage study reduced body weight gains were noticed occasionally at 125 mg/kg bw/d [redacted] In the oral 14-day feeding dose range finding study of New Zealand White rabbits the reduced body weight and test material intake at 6000 and 10000 ppm were considered to result from the un-palatability of the diet ([redacted] In the subchronic 90-day oral feeding study (OECD TG 409) with New Zealand White rabbits, the body weight gain and food consumption were reduced at 150 mg/kg bw/d [redacted]

In the 28-day oral gavage study absolute and relative liver weights were increased at 30 mg/kg bw/d in males and at 100 mg/kg bw/d in both sexes. At 100 mg/kg bw/d, hepatic centrilobular cytoplasmic change in males was observed. These effects were reversible within 14 days [redacted] Absolute liver weights were increased in a 4-week dose range finding study in female rats at 250 mg/kg bw/d and after covariance analysis liver weights were statistically significantly increased in both sexes in all dose groups (60, 125, 150 mg/kg

bw/d), but no histopathological changes were observed [redacted] Darkened livers in both sexes at 1000 mg/kg bw/d were reported in the 8-week oral feeding dose range finding study in mice by [redacted] Increased absolute and relative liver weights at ≥250 mg/kg bw/d in males and at ≥ 500 mg/kg bw/d in females were accompanied by pigmentation of enlarged hepatocytes and Kupffer cells. At 80 mg/kg bw/d increased absolute and relative liver weights in females and increased relative liver weights in males were observed in a 90-day oral gavage study in rats ([redacted] Increased absolute and relative liver weights in females at 50 mg/kg bw/d and in both sexes at 125 mg/kg bw/d were accompanied by hepatocyte enlargement in a 13-week oral gavage study in rats. Hepatocyte enlargement was not observed after recovery ([redacted] Absolute and relative liver weights of rabbits were increased in females at 75 mg/kg bw/d in a 3-month oral feeding study. At 75 and 125 mg/kg bw/d, hepatocyte hypertrophy and brown pigment were noted in the liver [redacted]

In a 28-day oral gavage study in rats relative kidney weights were increased in females at 30 mg/kg bw/d. That was considered of toxicological relevance since no significant effects were seen on body weight or body weight gain at this dose. [redacted] In a 90-day oral gavage study in rats absolute and relative kidney weights were increased in females at 80 mg/kg bw/d ([redacted]

In addition, some results of carcinogenicity studies were discussed for STOT RE. In a 104-week oral feeding study in Sprague-Dawley rats body weight and body weight gain were reduced in males and females at 40 and 80 mg/kg bw/d, and food consumption was reduced in males at 80 mg/kg bw/d. ([redacted] and [redacted] At interim sacrifice (after 52 weeks) mean absolute liver weight was increased in females at 40 and 80 mg/kg bw/d and in males at 80 mg/kg bw/d. This was not noted at terminal sacrifice. At termination, there was an increased incidence in depressed foci in stomach in both sexes at 40 and 80 mg/kg bw/d. At interim sacrifice, there was an increased incidence in stomach erosions in females at 80 mg/kg bw/d. In the fore-stomach, inflammation and epithelial hyperplasia were noted in both sexes at 40 and 80 mg/kg bw/d. There was an increased incidence in lobular degeneration of the salivary gland in both sexes at 40 and 80 mg/kg bw/d and males had an increased incidence in fibro-adenoma in this organ at 80 mg/kg bw/d. An increased incidence in foamy macrophages aggregates was noted in male lungs at 40 and 80 mg/kg bw/d. Plasma cholinesterase activity was reduced in females at 80 mg/kg bw/d.

In an oral 78-week feeding study in CD-1 mice the body weight and body weight gain were reduced at 150 mg/kg bw/d ([redacted] and [redacted] There was an increased incidence in enlarged thyroids in males at 150 mg/kg bw/d and an increased incidence of non-neoplastic changes in thyroids in both sexes at ≥20 mg/kg bw/d. The toxicological significance of these findings in the thyroid remained unclear for the authors. Males had an increased incidence in pneumonitis at 150 mg/kg bw/d. Also, there was a slight increase in the incidence of hepatocellular adenomas in males at 150 mg/kg bw/d (11/50), but this finding was not considered to be of biological significance because the incidence was close to the historical control range.

B) Inhalation route

In the 90-day OECD 413 study in Sprague-Dawley rats by [redacted] plasma cholinesterase activity was reduced at the highest concentration (6.7 mg/m^3) when compared to concurrent controls. RBC cholinesterase activity was decreased in females at 6.7 mg/m^3 after 2 weeks but not at study termination. Brain cholinesterase activities were decreased in males and females at 6.7 mg/m^3 when compared to concurrent controls (16.8 and 26.1%, respectively) and to historical controls (23.9 and 12.3, respectively). There

were histopathological changes in the larynx at 6.7 mg/m^3, necrosis in the ventral cartilage, epithelial hyperplasia in the ventral region, and squamous cell metaplasia in the ventrolateral region.

C) Dermal route

The toxicity of IPBC via dermal application has been studied in a 13-week study in Sprague-Dawley rats (OECD 411) ([redacted] Dermal irritation was observed at the highest dose (500 mg/kg bw/d). At 200 mg/kg bw/d, dermal irritation was only noted occasionally in single animals. Minimal hyperkeratosis was noted at 200 mg/kg bw/d while moderate hyperkeratosis, acanthosis and one incidence of ulcer were reported at 500 mg/kg bw/d.

Comments received during public consultation

One MSCA commented that in the study of [redacted] an increase in relative kidney weight, increased incidence in alpha-2-microglobulin droplets, erosion and ulceration in the fore-stomach were observed at 30 mg/kg/d and above, not only above 30 mg/kg/d. In the study by [redacted] the reduced body weight and body weight gain in males were observed at 250 mg/kg/d and above, not only above 250 mg/kg/d. Reduced body weight gain was observed in females at 500 mg/kg/d and above, not only above 500 mg/kg/d. In the repeated dose oral gavage study reduced food consumption was observed at 80 mg/kg/d.

Another MSCA commented that it would be worth considering classification for STOT RE 1; H371 (resp. R48/23) based on the high incidence (all animals in the high dose group), severity and potential irreversibility of the necrotic damage to the larynx. The MSCA added that the CLP regulation does not specify that STOT RE classifications should only be applied in the presence of systemic effects. In addition, oral studies by i.e., [redacted] provide indication for damage in the fore-stomach (erosions, ulceration, hyperkeratosis and acanthosis) of rats exposed to ≥30 mg/kg IPBC. According to the MSCA it should be discussed whether these effects would warrant classification for repeated toxicity as well.

One MSCA commented that quantitative changes (body weight, liver weight, cholinesterase activity etc) are needed to decide whether effects are biologically relevant and relevant for classification. In addition, histological changes should be specified in the text. Also data to conclude that IPBC was not neurotoxic when administered via the oral route was missing. According to the MSCA the severity of liver effects (weight and histopathological changes) after oral administration should be further discussed to conclude whether the effects are severe enough for classification as STOT RE 2; H373 (CLP) and Xn; R48/22 (DSD).

Additional key elements

Copied from the DAR:

[redacted]

In this 13-week OECD TG 413 study, there were no changes in organ weights. Histopathological examination of the organs showed no changes in treated animals when compared to controls except for larynx and lungs of the high dosed animals. In lungs an increased incidence in the aggregation of macrophages was noted in the high dosed males (6.7 mg/m^3) (7 of 15 animals compared to 4 of 15 animals in the concurrent control).

RBC and brain cholinesterase activities were within the range of normal biological variation.

Histopathological findings in the larynx of the high dose group (6.7 mg/m^3) included necrosis in the ventral cartilage, epithelial hyperplasia in ventral region, and squamous metaplasia in ventrolateral region in all animals. In addition, epithelial hyperplasia over the

arytenoid projections in all high dosed males and in 5 of the 15 high dosed females was noted. Epithelial ulceration in the ventral region was observed in low incidence in the high dosed males (4 of 15 animals). In some of the high dosed males and females, additionally, atrophy of submucosal glands was noted (3 and 6 animals of 15, respectively).

Assessment and comparison with the classification criteria

RAC did not agree with the DS proposal on the absence of classification, and supported classification for STOT RE 1; H372 (larynx) in accordance with CLP and T; R48/23 in accordance with DSD. This classification is based on the high incidence (all rats in the high dose group) of the effects in larynx (necrosis in the ventral cartilage, epithelial hyperplasia in ventral region and squamous metaplasia in ventrolateral region) found in the 90-day inhalation study [redacted] The effective dose for larynx toxicity was 0.0067 mg/l which is below the cut-off level for classification for STOT RE 1 (0.02 mg/l).

Therefore, RAC concluded that classification as STOT RE 1; H372 (larynx) (CLP) and T; R48/23 (DSD) is justified.

RAC also assessed the available oral and dermal repeated dose toxicity studies but concluded that the observed effects do not warrant a classification for STOT RE.

Supplemental information - In depth analyses by RAC
Not needed

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

In the available repeated dose toxicity studies following oral administration liver and kidney were the target organs in rats observed as organ weight changes and in the liver accompanied with hepatocellular changes. In the subchronic inhalation toxicity study, the larynx has been demonstrated to be affected. This effect has been regarded to be of local rather than of systemic nature. Most importantly, no functional changes or any organ dysfunction have been observed as a consequence of the irritational effects in the laryngeal region. The local irritation in the larynx led to the conclusion that IPBC is a local irritant in the upper respiratory tract of rats affording a classification as a respiratory irritant. It should be noted that there are differences in the morphology of the upper respiratory tract of rodents and humans which may result in a higher susceptibility of the upper respiratory tract in rats and considering that rodents are obligatory nose breathers, factors which both result in a higher exposure of the rats' larynx compared to the larynx in humans.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

Systemic effects were neither observed in the repeated dose toxicity studies nor in the carcinogenicity studies performed with IPBC which would fulfil the criteria for specific target organ toxicity after repeated exposure. Most importantly, in the 90-day inhalation toxicity study, the predominant effect was a local irritation of the larynx which was not associated with functional changes or any organ dysfunction. Furthermore, no severe effects on clinical pathology or on (histo)pathological examination were observed.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

Based on the findings made in the available repeated dose toxicity studies and taking into account the dose/concentration guidance values according to paragraphs 3.9.2.9.6 and 3.9.2.9.7 (Table 3.9.2 and 3.9.3) of the CLP, a classification of IPBC with respect to STOT RE is not required.

4.9 Cell mutagenicity (Mutagenicity)

Table 17: Summary table of relevant in vitro and in vivo mutagenicity studies

Method	Results	Remarks	Reference
Bacterial reverse mutation assay (e.g. Ames test) (gene mutation) S. *typhimurium* TA 1535, TA 1537, TA 98, TA 100 and TA 102 (met. act.: with and without) Doses: 0-5000 µg/plate OECD Guideline 471 (Bacterial Reverse Mutation Assay) EC B.14	Test results: negative for S. *typhimurium* TA 1535, TA 1537, TA 98, TA 100 and TA 102 (all strains/cell types tested); met. act.: with and without cytotoxicity: Bacteriotoxic effects starting at 40 µg/plate	(purity 98.3 %)	[redacted]
In vitro mammalian chromosome aberration test (chromosome aberration) Chinese hamster lung fibroblasts (V79) (met. act.: with and without) Doses: 0 to 20 ug/ml: OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test) OECD 476 OPPTS 870.5300	Test results: negative with metabolic activation equivocal without metabolic activation cytotoxicity: yes without metabolic activation: > 2 µg/mL with metabolic activation: $\geq$ 16 µg/mL	(purity 98.3 %)	[redacted]
Mammalian cell gene mutation assay (gene mutation at HPRT locus) Chinese hamster lung fibroblasts (V79) (met. act.: with and without) Doses: The cell cultures were evaluated at the following concentrations: without S9 mix: 0.01 to 15 µg/mL with S9 mix: 0.5 to 96 µg/mL OECD Guideline 476 (In vitro Mammalian Cell	Test results: negative for Chinese hamster lung fibroblasts (V79)(all strains/cell types tested); met. act.: with and without. cytotoxicity: yes without metabolic activation: $\geq$ 6 µg/mL without metabolic activation: $\geq$ 48 µg/mL	(purity 98.3 %)	[redacted]

Gene Mutation Test) OPPTS 870.5300			
Micronucleus assay (chromosome aberration) Mouse (ICR) male/female (5/sex/group) Dose levels: 0, 28, 55, 110 mg/kg bw (i.p.) one application Sampling time: 24, 48, and 72 hours after i.p. Injection According to US EPA 84-2 Comparable to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)	Test results: Genotoxicity: Negative at all sampling times (male/female) One male of the 110 mg/kg bw was found dead on day 2.	(purity 97.5 %)	[redacted]
Micronucleus assay (chromosome aberration) mouse (CD-1) male/female (5/sex/group) oral: gavage one application Dose levels: 0, 200, 660, 2000 mg/kg bw ; positive control Sampling time: 30, 48, and 72 hours after oral gavage According to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)	Test results: Genotoxicity: Negative at all sampling times (male/female) positive control showed significant increase in micronucleus frequency	(purity 99%)	[redacted]

4.9.1 Non-human information

4.9.1.1 In vitro data

IPBC was not genotoxic *in vitro* up to and including cytotoxic concentrations in *Salmonella typhimurium* bacteria or in Chinese hamster V79 cells. There was an indication of clastogenic activity *in vitro* at cytotoxic concentrations in V79 cells without metabolic activation only.

4.9.1.2 In vivo data

IPBC did not induce micronuclei *in vivo* in mice bone marrow up to and including the MTD. Another non-key *in vivo* micronucleus study which was negative in higher doses further supports the absence of cytogenetic effects *in vivo*. Furthermore, the available oral toxicokinetics study

demonstrated that IPBC is rapidly absorbed and almost quantitatively bioavailable which indicates that IPBC could be able to reach the target in the *in vivo* MNT studies.

4.9.2 Human information

No information available

4.9.3 Other relevant information

No information available

4.9.4 Summary and discussion of mutagenicity

IPBC was not genotoxic *in vitro* up to and including cytotoxic concentrations in *Salmonella typhimurium* bacteria or in Chinese hamster V79 cells. There was an indication of clastogenic activity *in vitro* in cytotoxic concentrations in V79 cells without metabolic activation whereas clear negative results were obtained in the presence of metabolic activation. IPBC did not induce micronuclei *in vivo* in mice bone marrow up to and including the MTD. Another non-key *in vivo* micronucleus study which was negative in higher doses further supports the absence of cytogenetic effects *in vivo*. Including the result from the toxicokinetics/metabolism study and the two negative cancer studies in the assessment of genotoxicity, the overall weight of evidence indicates that IPBC is not a genotoxic substance.

4.9.5 Comparison with criteria

The weight of evidence from the available well-conducted *in vitro* and *in vivo* genotoxicity studies indicates that IPBC is not a genotoxic substance and, thus, does not fulfil the criteria for a classification as a category 1A, 1B or 2 germ cell mutagen as laid down in Table 3.5.1 of the CLP

4.9.6 Conclusions on classification and labelling

Taking into account the results of the available *in vitro* and *in vivo* mutagenicity studies, IPBC does not need to be classified and labelled as mutagenic according to Directive 67/548/EEC or the CLP Regulation (EC) No. 1272/2008.

RAC evaluation of germ cell mutagenicity
Summary of the Dossier submitter's proposal Three studies performed by [redacted] were referred to by the DS in the CLH report with regard to cell mutagenicity: a bacterial reverse mutation assay (conducted according to OECD TG 471) with *Salmonella typhimurium* bacteria, an in vitro mammalian chromosome aberration test with Chinese hamster V79 lung fibroblasts (conducted according to OECD TG 473) and a mammalian cell gene mutation assay with Chinese hamster V79 lung fibroblasts (conducted according to OECD TG 476). Furthermore, results of a micronucleus assay (chromosome aberration) test with mice strain ICR (comparable to OECD TG 474) ([redacted] and of a micronucleus assay (chromosome aberration) test with mice strain CD-1 (conducted according to OECD TG 474) ([redacted] are provided in the CLH report. All these tests were negative except one equivocal result from the in vitro mammalian chromosome aberration test which gave an indication of clastogenic

activity at cytotoxic concentrations in V79 cells without metabolic activation only. No classification is proposed based on the overall weight of evidence of the results.

Comments received during public consultation

One MSCA asked to include the source of metabolic activation, whether appropriate controls (positive and negative) were used and to specify the doses used (not only min-max). It was stressed that without this information it was difficult to conclude whether the studies were indeed performed according to guidelines.

Additional key elements

Not needed.

Assessment and comparison with the classification criteria

IPBC was not genotoxic in vitro up to and including cytotoxic concentrations in *Salmonella typhimurium* bacteria (160 µg/plate) with and without S9 or in Chinese hamster V79 cells (up to 20 µg/ml in one test with and without S9 and in another test up to 15 µg/ml without S9 and up to 96 µg/ml with S9). However, there was an indication of clastogenic activity in vitro in the first test but at cytotoxic concentrations in V79 cells without metabolic activation only. In vivo, IPBC did not induce micronuclei in mouse bone marrow up to and including the MTD concentration.

Data indicates that IPBC is not mutagenic in vitro or in vivo. According to the CLP classification criteria for Mutagenicity Category 2 there should be positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, positive evidence obtained from somatic cell mutagenicity tests in vivo, in mammals; or other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays. Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification for Category 2 mutagens. According to the DSD criteria, there should be in vivo evidence of mutagenicity for Mutagenicity Cat 3 classification. Considering these criteria for the classification and labelling outlined in paragraph 3.5.2 of the CLP regulation and according to the Directive 67/548/EEC, IPBC does not meet the criteria for classification as a mutagen. RAC therefore supported the conclusion of the DS that no classification is warranted for mutagenicity.

Supplemental information - In depth analyses by RAC

Not needed.

4.10 Carcinogenicity

Table 18: Summary table of relevant carcinogenicity studies

Method	Results	Remarks	Reference
Oral feeding 104 weeks with interim kill after 52 weeks Sprague-Dawley rats; both sexes 65/group 15/group sacrificed at interim kill Dose levels 0, 20, 40, 80 mg/kg bw/d (daily)	NOAEL: 20 mg/kg bw/d LOAEL: 40 mg/kg bw/d There were no treatment related mortalities or clinical signs noted. Body weight and body weight gain in both sexes at 40 and 80 mg/kg bw/d were reduced. Food consumption was reduced in the 80 mg/kg bw/d males. Ophthalmoscopy was unremarkable. There were no treatment-related effects on haematology, clinical chemistry, or urinary parameters noted. Plasma cholinesterase activity was reduced at 80 mg/kg bw/d in females. There was no effect on RBC and brain cholinesterase activity. At interim kill mean absolute liver weight was increased in females at 40 and 80 mg/kg bw/d and in males at 80 mg/kg bw/d. This was not noted at terminal kill. At termination, in the 40 and 80 mg/kg bw/d dose levels, there was an increased incidence in depressed foci in stomach in both sexes. At interim kill, there was an increased incidence in stomach erosions in the 80 mg/kg bw/d females. In forestomach, inflammation and epithelial hyperplasia were noted at 40 and 80 mg/kg bw/d in both sexes. In both sexes at 40 and 80 mg/kg bw/d, there was an increased incidence in lobular degeneration of the salivary	(purity 97 %)	[redacted]

	gland. Additionally, males at 80 mg/kg bw/d had an increased incidence in fibro-adenoma in this organ. In lungs an increased incidence in foamy macrophages aggregates was noted in males at 40 and 80 mg/kg bw/d. IPBC was not carcinogenic in rats.		
Oral feeding 78 weeks Mice (CD-1); both sexes 50/group 15/group sacrificed at interim kill Dose levels 0, 20, 50, 150 mg/kg bw/d (daily)	NOAEL: --- LOAEL: 20 mg/kg bw/d There were no treatment related mortalities and clinical signs noted. Body weight and body weight gain in the 150 mg/kg bw/d animals was reduced. There were no treatment related effects on food consumption. Differential blood counts as well as plasma, RBC and brain cholinesterase activities were comparable to concurrent controls. There was an increased incidence in enlarged thyroids in the 150 mg/kg bw/d males. There was an increased incidence of non-neoplastic changes in thyroids of both sexes at ≥ 20 mg/kg bw/d. The toxicological significance of this finding remained unclear. Males treated with 150 mg/kg bw/d had an increased incidence in pneumonitis when compared to concurrent control. Hepatocellular adenomas were observed in an increased incidence in males at 150 mg/kg bw/d (11/50); however, this finding is not considered to be of biological relevance to human. IPBC was not carcinogenic in mice.		[redacted]

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

IPBC was not carcinogenic in rats and mice up to and including the highest dose levels tested (80 and 150 mg/kg bw/day for rats and mice, respectively).

4.10.1.2 Carcinogenicity: inhalation

No information available

4.10.1.3 Carcinogenicity: dermal

No information available

4.10.2 Human information

No information available

4.10.3 Other relevant information

No information available

4.10.4 Summary and discussion of carcinogenicity

In the two year carcinogenicity study in rats, there were no neoplams observed after one year as well as after two years which showed a treatment related increased. In females, the incidence of mammary fibroadenomas was increased at 20 mg/kg bw/day. The incidence of pituitary adenoma was increased at 40 mg/kg bw/day in females. In the absence of a dose-response relationship, these findings were considered to be incidental.

A consideration of the overall tumour incidence in the control and high dose groups did not indicate a treatment related increase in the number of tumours in either sex of rats. Thus, IPBC is not considered to be carcinogenic in rats up to and including the highest dose level tested (80 mg/kg bw/d).

In the 78 weeks carcinogenicity study in mice, a statistically significantly higher incidence in hepatocytic adenoma was observed in males at the high dose level of 150 mg/kg bw/day (11/50) when compared to the concurrent control (4/50) or to historical control data (1 to 8/50). However, statistical significance was judged at the 95% probability level. The appropriate p value for significance in analysing common neoplasms (historical control incidence >1%) is considered to be $p<0.01$ rather than $p<0.05$. Thus, there is no statistically significantly increase in the incidence in hepatocellular adenomas. Furthermore, there was no statistically significantly increase in the incidence of hepatocellular carcinoma or in foci of cellular alteration. Additionally, there was no evidence of progression to malignant hepatocellular tumours and no effect on tumour multiplicity observable. Hepatocytotoxicity or genotoxicity was not observed. In females, the incidence of hepatocellular adenoma and/or carcinoma was comparable to controls. The finding of hepatcellular adenoma in this sensitive strain of mice is considered to be of no biological relevance to humans due to the well known sensitivity of the strain of mice used and as the MTD was

exceeded in the high dose group of male mice (body weight development reduced by 23%). Thus, IPBC is not carcinogenic to mice under the conditions of this study.

4.10.5 Comparison with criteria

In the available rodent carcinogenicity studies which were performed to protocols comparable to OECD guidelines 453 and 451, IPBC was not carcinogenic in rats and mice up to and including the highest dose levels (80 and 150 mg/kg bw/d for rats and mice, respectively). In the carcinogenicity study performed in mice, an increased incidence of hepatocellular adenomas in the high dose group of males was not considered to be of biological relevance to humans as hepatocellular adenomas occur frequently in susceptible strains of mice and as an exceedance of the MTD had been observed. Based on the findings made in the available rodent carcinogenicity studies and taking into account the criteria laid down in Table 3.6.1 of the CLP for the classification of a substance as carcinogenic into category 1A, 1B or 2, IPBC does not fulfil the criteria for a carcinogenic substance.

4.10.6 Conclusions on classification and labelling

Based on the results obtained in the rat and mouse carcinogenicity studies, IPBC revealed no specific carcinogenic effects in rodents. Therefore, a classification and labelling of IPBC as carcinogenic according to the provisions of Directive 67/548/EEC (DPD) or Regulation (EC) No. 1272/2008 (CLP) is not required..

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

No classification for carcinogenicity was proposed by the dossier submitter. Two oral feeding carcinogenicity studies were presented in the CLH report. In the 104-week study (with an interim kill after 52 weeks) with Sprague-Dawley rats (0, 20, 40 and 80 mg/kg bw/d) ([redacted] 1988; [redacted] males had an increased incidence in fibro-adenoma in the salivary gland at 80 mg/kg bw/d. In females, the incidence of mammary fibroadenomas was slightly increased at 20 mg/kg bw/day only. The incidence of pituitary adenomas was increased at 40 mg/kg bw/day in females. In the absence of a dose-response relationship, these findings were considered to be incidental. In the 78-week study with CD-1 mice (0, 20, 50 and 150 mg/kg bw/d) [redacted] an increased incidence in hepatocellular adenomas was observed in males at 150 mg/kg bw/d. The findings were not considered to be of biological relevance to human by the DS due to the well-known sensitivity of the strain of mice used and as the MTD was exceeded in the high dose group of male mice.

Comments received during public consultation

One MSCA commented that detailed incidence data for each group was missing and therefore the dose-response for hepatocellular adenomas could not be assessed with respect to other signs of non-specific toxicity at doses significantly exceeding the MTD. Further discussion on the argument that CD-1 mice are specifically susceptible for liver tumours at doses exceeding the MTD was proposed. Also other MSCAs commented that further information regarding the incidence of observed tumours in all dose groups (hepatocellular adenomas of the mouse study, mammary and salivary gland fibroadenomas and pituitary adenomas of the rat study) and historical controls would be useful.

Additional key elements

In the CAR for IPBC, fibroplasia of the salivary gland is reported. The term fibroadenoma as used in the CLH report seems to be less appropriate than fibroplasia.

Assessment and comparison with the classification criteria

No human data are available with respect to carcinogenicity. Regarding to the animal data, in Sprague-Dawley rat females ([redacted] 1988; [redacted] no neoplasms have been observed after one year as well as after two years of treatment. The incidence of mammary fibroadenomas was slightly increased (i.e. 20/50) in the low dose group of 20 mg/kg bw/day only. At 40 mg/kg bw/day and 80 mg/kg bw/day the incidences of mammary fibroadenomas (i.e. 12/50 and 13/50, respectively) were comparable to the control (i.e. 12/50). Thus, no dose-response relationship was evident. The same conclusion can be drawn with respect to pituitary adenomas, which were slightly increased at 40 mg/kg bw/day in females (39/50) but not at the doses of 20 and 80 mg/kg bw/day (33/50 and 29/50, respectively) comparing to the control group (32/50). The LOAEL is 40 mg/kg bw/day in both sexes based on reduced mean body weight and body weight gain in both sexes and increased incidence of histopathological changes in stomach, forestomach and salivary glands at this dose.

According to the DS, hepatocellular adenomas recorded in the CD-1 mice carcinogenicity study ([redacted] shall be regarded as non-specific, high-dose toxicity effects in sensitive species. In the dose groups treated with 20 mg/kg bw/day and 50 mg/kg bw/day, no significant increase in incidence (i.e. 3/50 and 5/50 in males; 1/50 and 1/50 in females, respectively) of hepatocellular adenoma was observed when compared to the controls (i.e. 4/50 in males and 0/50 in females). In males at 150 mg/kg bw/day a higher incidence in hepatocellular adenoma (11/50) was observed when compared to controls (4/50). Nevertheless, at 150 mg/kg bw/d, the body weight gain was reduced by 23% and 20% in males and females, respectively, which demonstrates that the MTD was exceeded at the high dose level. According to the study summary "Spontaneous Neoplastic Lesions in the CrI:CD-1(ICR) Mouse in Control Groups from 18 Month to 2 year Studies" (Charles River Laboratories, 2005) even up to 28% of male mice can be subject to spontaneous hepatocellular adenoma but the average amount of impacted mice from 52 studies and 2941 animals used in total was 10.47%. The incidence in hepatocellular adenoma observed in this study (11/50, 22%) is only slightly outside the observed historical control range (i.e. 1 to 8/50, 2 to 16%) for this type of neoplasm, as indicated in RCOM. No statistically significant increase in the incidence of hepatocellular carcinomas or in foci of cellular alteration was observed. LOAEL is estimated at 20 mg/kg bw/day, based on histopathological non-neoplastic changes in thyroids. In addition, hepatocytotoxicity or genotoxicity was not observed.

According to the Directive 67/548/EEC, a substance should not be classified in any of the categories for carcinogenicity
- if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man,
- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories,
- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.

For the CLP Category 2 classification outlined in the paragraph 3.6.2 of the CLP Regulation, there should be limited evidence of carcinogenicity: "*a positive association observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence*".

According to RAC, the causal interpretation could not be confirmed and there is a reasonable confidence for a chance finding based on the following factors (which, according to the CLP, should be taken into account when assessing the overall level of concern): the background incidence was high for all of the observed tumors, there was no multi-site responses; and the lesions were not progressed to malignancy; the responses were seen in single sex and single species and there was no evidence of mutagenic activity in vivo.

Increased tumor incidence of IPBC was limited to hepatocellular adenomas in males (11/50, 22%) at the highest dose tested (MTD) in this particularly sensitive mouse strain (Charles River Laboratories, 2005) (1 to 8/50 in historical controls) without any supplementary evidence and for a slight increase of benign mammary fibroadenomas in females within the low dose group where the incidence of these adenomas was also within the historical control range.

RAC therefore supported the conclusion of the DS that no classification is warranted for carcinogenicity as criteria outlined in the paragraph 3.6.2 of the CLP Regulation and the criteria according to Directive 67/548/EEC are not met.

Supplemental information - In depth analyses by RAC
Not needed.

4.11 Toxicity for reproduction

Table 19: Summary table of relevant reproductive and developmental toxicity studies

Method	Results	Remarks	Reference
Rabbit New Zealand White female 16 to 18/group Dose levels: 0, 10, 20, 40 mg/kg bw/d Exposure period: Day 7 to 19 of pregnancy OECD Guideline 414 (Prenatal Developmental Toxicity Study) US EPA 83-3	$NOAEL_{maternal}$: 10 mg/kg bw/d $NOAEL_{development}$: 40 mg/kg bw/d $LOAEL_{maternal}$: 20 mg/kg bw/d $LOAEL_{development}$: 40 mg/kg bw/d One female at 20 and 4 females at 40 mg/kg bw/day were sacrificed due to body weight loss and refusal to eat. Necropsy revealed severe irritations (ulceration and redness) in glandular stomach of these animals. Food consumption was reduced during the first week of treatment at 20 and 40 mg/kg bw/day. After treatment had stopped food consumption was increased. Body weight gain tended to be lower in all dose groups without being statistically significant. After treatment had stopped body weight gain of the treated animals tended to be higher. There were no treatment related effects on mean number of live foetuses, mean pre-and post-implantation loss, mean foetal weight and sex ratio noted. Foetal examination revealed no changes between control and treated groups. IPBC was not teratogenic.	(purity >97 %)	[redacted]

Female rat (Sprague-Dawley) 24/group oral: gavage Dose levels: 0, 25, 75, 250 mg/kg bw/d Exposure period: Day 6 to 15 of pregnancy OECD Guideline 414 (Prenatal Developmental Toxicity Study) US EPA 83-3	$NOAEL_{maternal}$: 25 mg/kg bw/d $NOAEL_{development}$: 75 mg/kg bw/d $LOAEL_{maternal}$: 75 mg/kg bw/d $LOAEL_{development}$: 250 mg/kg bw/d There were no mortalities noted. Clinical signs were post-dose salivation and aggressive behaviour at 75 and 250 mg/kg bw/d. Body weight gain and food consumption was reduced at 75 and 250 mg/kg bw/d. Mean absolute and relative liver weight was increased at 250 mg/kg bw/d. Pregnancy data and the incidences in major anomalies and in minor external and visceral anomalies were comparable to controls. Mean female foetal weight was decreased at 250 mg/kg bw/d. Male foetal weight was comparable to controls. At 250 mg/kg bw/d, there was increased incidence in minor rib defects and incomplete or non-ossification. The incidence in not ossified 5^{th} sternebrae was increased at 250 mg/kg bw/d. The retardation of ossification was considered to be the result of maternal toxicity.	(purity >97 %)	[redacted]
rat (Sprague-Dawley) both sexes, 25/group oral: gavage Dose levels: First generation: 0, 10, 30, 100 mg/kg bw/d Second generation: 0, 10, 30, mg/kg bw/d Exposure period: F_0: 10 weeks before mating F_1: 13 weeks before mating	NOAEL Parental: 10 mg/kg bw/d Reproduction: 30 mg/kg bw/d Developmental: 10 mg/kg bw/d One incidence of incomplete parturition at 30 and 4 incidences at 100 mg/kg bw/d in F_0 females. Post-dose salivation at doses $\geq$ 30 mg/kg bw/d.	(purity >97 %)	[redacted]

According to: OECD Guideline 415 (One-Generation Reproduction Toxicity Study) US EPA 83-3 Comparable to OECD 416 (except two dose levels for second generation)	Occasionally, hunched posture and forepaw paddling at 30 and 100 mg/kg bw/d in F_0 animals and at 30 mg/kg bw/d in F_1 animals. Reduced body weight gain in F_0 males at 100 mg/kg bw/d. Reduced food consumption and body weight gain during first week of lactation in F_0 females at 100 mg/kg bw/d. Acanthosis and hyperkeratosis in stomach in F_1 parents at 30 mg/kg bw/d (not examined in F_0 animals). Reduced fertility/mating index in F_0 parents at 100 mg/kg bw/d. Reduced live birth index in F_1 pups at 100 mg/kg bw/d; reduced viability index 1 and cumulative survival index in F_1 pups at 30 and 100 mg/kg bw/d. Reduced mean birth pup body weight in F_1 females at 100 mg/kg bw/d; reduced mean pup body weight at day 4 and 21 post partum in both sexes of F_1 100 mg/kg bw/d , and at day 21 post partum in F_2 females at 30 mg/kg bw/d. Increased incidence of pups without milk in stomach and/or bitten or cannibalised pups at 30 and 100 mg/kg bw/d.		
Rat (Sprague-Dawley) both sexes, 25/group oral: feeding Dose levels: 0, 120, 300, 750 ppm equivalent to males: 0, 8.4 – 10.7, 20.7 – 26.1, 50.5 – 62.8 mg/kg bw/d females: 0, 8.0 – 17.1, 20.2 – 39.6, 49.8 – 101.2 mg/kg bw/d	NOAEL Parental: 750 ppm Reproduction: 750 ppm Developmental: 750 ppm No treatment related mortalities. Body weight gain and food consumption tended to be lower in both generations in the 750 ppm males. In females, body weight gain was slightly reduced in F_0 females at 750 ppm during	(purity >97 %)	[redacted]

(The stability of the active substance in the feed has not been determined at the time of this study) Exposure period: F_0: 14 weeks before mating F_1: 13 weeks before mating According to: US EPA 83-4 Comparable to OECD Guideline 416 (Two-Generation Reproduction Toxicity)	gestation; food consumption was comparable between groups. There were no effects on fertility and pup development noted.		

4.11.1 Effects on fertility

4.11.1.1 Non-human information

In a 2-generation reproductive toxicity study, rats were treated via gavage at 0, 10, 30, and 100 mg/kg bw/d. Due to severity of clinical signs at 100 mg/kg bw/d, treatment with this dose level was not continued for the F_1 animals. Post-dose salivation was observed at doses equal to or greater than 30 mg/kg bw/d. Body weight gain and food consumption were reduced at 100 mg/kg bw/d during pre-mating period in males and during the first week of lactation in females. Acanthosis and hyperkeratosis were observed in F_1 parental animals at 30 mg/kg bw/d (not examined in F_0 parental animals). A reduced fertility/mating index was observed in F_0 parents at 100 mg/kg bw/d. Reduced live birth index was noted in F_1 pups at 100 mg/kg bw/d, and reduced viability index 1 and cumulative survival index in F_1 pups at 30 and 100 mg/kg bw/d. Mean birth pup body weight was reduced in F_1 females at 100 mg/kg bw/d, mean pup body weight at day 4 and 21 post partum in both sexes of F_1 100 mg/kg bw/d, and mean pup body weight was statistically significantly reduced on day 21 post partum in F_2 females at 30 mg/kg bw/d. An increased incidence of pups without milk in stomach and/or bitten or cannibalised pups was noted at 30 and 100 mg/kg bw/d. Effects in pups were noted only at dose levels, which also resulted in maternal toxicity. IPBC was not toxic to reproduction at dose levels at which maternal toxicity was not observed. It should be noted that this study has a deviation according to OECD TG 416 as at least three dose levels are required; in this study, the second generation was administered 2 dose levels only as a consequence of a discontinuation of the high dose level of 100 mg/kg bw/d.

In a second 2-generation reproductive toxicity study, rats were treated with 0, 120, 300, and 750 ppm in the diet (equivalent to 0, 8.4 – 10.7, 20.7 – 26.1, 50.5 – 62.8 mg/kg bw/d in males and to 0, 8.0 – 17.1, 20.2 – 39.6, 49.8 – 101.2 mg/kg bw/d in females). There were no clinical signs and treatment-related mortalities noted. Body weight gain and food consumption tended to be lower at 750 ppm in males. In females, body weight gain was slightly reduced in F_0 females at 750 ppm during gestation; food consumption was comparable between groups. There were no effects on fertility and pup development noted. Under the conditions of this study, IPBC was not toxic to reproduction. However, the stability of the active substance in the feed has not been determined at the time of this study. An attachment to the study report contained results from subsequently analyses of what was called ”dietary remains” from the study. This analytical report showed a considerable decline in the stability of IPBC in the diet over one month, especially for the

high concentrations. Therefore, this study is not considered adequate for the evaluation of a reproductive toxic potential of IPBC and can only be used as a supporting study.

4.11.1.2 Human information

No information available

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

In a study with rabbits performed in accordance with OECD TG 414 (1981) following oral administration of dose levels of 0, 10, 20 and 40mg/kg bw/d via gavage, there was one premature death at the 20 mg/kg bw/d and four at the 40 mg/kg bw/d dose level; animals were sacrificed due to body weight loss and refusal to eat. Irritation (redness, ulceration) of the glandular stomach was observed and is considered to be the most likely cause of reduced food consumption and subsequent body weight loss. There were no treatment-related effects on pregnancy data or foetal development including teratogenicity. IPBC was not teratogenic in rabbits.

In a study with rats performed in accordance with OECD TG 414 (1981) following oral administration of dose levels of 0, 25, 75 and 250mg/kg bw/d via gavage, clinical signs noted were post-dose salivation and aggressive behaviour from 75 mg/kg bw/d. Body weight gain and food consumption was reduced at doses equal to or greater than 75 mg/kg bw/d. Absolute and relative liver weights were increased at 250 mg/kg bw/d. There were no treatment-related effects on pregnancy data, or increased incidences in major and minor anomalies (external and visceral). The incidence in minor rib defects and in incomplete or non-ossification was increased at 250 mg/kg bw/d, which is considered to be a result of observed maternal toxicity at this dose level. Mean female foetal weight was decreased at 250 mg/kg bw/d. IPBC was not teratogenic in rats.

4.11.2.2 Human information

No information available

4.11.3 Other relevant information

No information available

4.11.4 Summary and discussion of reproductive toxicity

Teratogenicity: Maternal toxicity was noted in rabbits (premature deaths, body weight loss, refusal to eat, redness and ulceration of the glandular stomach) from 20 mg/kg bw/d and in rats (clinical signs, reduced body weight gain and food consumption) from 75 mg/kg bw/d). There were no treatment-related effects on pregnancy data or foetal development, including

teratogenicity, in rats up to 75 mg/kg bw/d and in rabbits up to 40 mg/kg bw/d . In rats at 250 mg/kg bw/d, mean foetal weight was decreased in females and the incidence in minor rib defects and incomplete or non-ossification was increased.

Fertility: When IPBC was administered to rats by gavage, parental toxicity (characterized by clinical signs, reduced body weight gain and food consumption, and acanthosis and hyperkeratosis) was observed from 30 mg(kg bw/d. IPBC was toxic to reproduction (reduced fertility/mating index in F_0 parents at 100 mg/kg bw/d) only at dose levels, which also resulted in maternal toxicity and there was no indication in this study that IPBC causes selective impairment of reproduction at systemically non-toxic dose levels. Effects in pups (characterized by reduced live birth index, viability index 1 and cumulative survival index in F_1 pups at 30 and 100 mg/kg bw/d; reduced pup weights in F_1 at 100 mg/kg bw/d and in F_2 females at 30 mg/kg bw/d; increased incidence of pups without milk in stomach and/or bitten or cannibalised pups at 30 and 100 mg/kg bw/d), were also noted only at dose levels, which also resulted in maternal toxicity. It should be noted that this study has a deviation according to OECD TG 416 as at least three dose levels are required. Inthis study, the second generation was administered 2 dose levels only and the high dose level of 100 mg/kg bw/d was discontinued due to overt signs of toxicity F1 parental animals.

When IPBC was administered to rats in the diet, parental effects (slightly reduced body weight gain) was noted at 750 ppm. There were no effects on fertility and pup development. However, no analytical data were available with respect to concentration or stability of the active substance in the feed and therefore, this study is not considered adequate for the evaluation of a reproductive toxic potential of IPBC.

4.11.5 Comparison with criteria

In the available reproductive and developmental toxicity studies, IPBC did not affect fertility and did not cause developmental toxicity in the absence of parental or maternal toxicity. In rabbits, no developmental toxicity or teratogenic effects were observed. Taking into account the results obtained in these studies and considering the criteria laid down in Table 3.7.1 of the CLP regulation for the classification of a substance as reprotoxic into category 1A, 1B or 2, IPBC does not possess a significant potential with respect to toxicity to reproduction in rats and to the development of rats and rabbits.

4.11.6 Conclusions on classification and labelling

Based on the results obtained in the reproductive and developmental toxicity studies where no selective toxicity to the reproduction of rats or to the development of rats and rabbits was observed in the absence of parental or maternal toxicity, IPBC does not need to be classified and labelled with respect to developmental or reproduction toxicity (sexual function, fertility and lactation) according to Directive 67/548/EEC and Regulation (EC) No. 1272/2008/EC.

RAC evaluation of reproductive toxicity
Summary of the Dossier submitter's proposal No classification for reproductive toxicity was proposed by the dossier submitter because reproductive toxicity occurred only at dose levels which also resulted in parental toxicity. Fertility Two studies were presented in the CLH report for effects on fertility: One key study on rats (two-generation reproductive study comparable to OECD TG 416 except that two dose levels, 10 and 30 mg/kg bw/d were administered for the second generation (F_2) due to severity of clinical signs observed at 100 mg/kg bw/d) ([redacted] and an additional rat study

(comparable to OECD TG 416 without analytical data available with respect to concentration or stability of the active substance in the feed) (The DS reported reduced fertility/mating index in F_0 parents was observed at doses which also caused parental toxicity (clinical signs, reduced body weight gain and food consumption). In the additional study there were no effects on fertility, but this study was not considered adequate for the evaluation of a reproductive toxic potential of IPBC due to missing analytical data for IPBC.

Development
Two OECD TG 414 studies using rabbits (or rats were presented in the CLH report for developmental toxicity. Parameters for developmental toxicity were reported also in the two-generation reproductive study on rats (The DS concluded on the absence of treatment related effects for mean number of live foetuses, mean pre- and post-implantation loss, mean foetal weight and sex ratio in Mean female foetal weight was decreased and there was an increased incidence in minor rib defects and incomplete or no ossification at 250 mg/kg bw/d in

In the two-generation reproductive study on rats live birth index was reduced in F1 pups at 100 mg/kg bw/d, viability index 1 and cumulative survival index were reduced in F_1 pups at 30 and 100 mg/kg bw/d. Mean birth pup body weight was reduced in F_1 females at 100 mg/kg bw/d. Mean pup body weight was reduced at day 4 and 21 post-partum in both sexes of F_1 animals at 100 mg/kg bw/d, and at day 21 post-partum in F_2 females at 30 mg/kg bw/d. An increased incidence of pups without milk in stomach and/or bitten or cannibalised pups was noted at 30 and 100 mg/kg bw/d. Effects in pups were noted only at dose levels, which also resulted in maternal toxicity.

Comments received during public consultation

Some MSCAs commented that the CLH report did not provide sufficient detailed information to serve as a base for conclusive assessment of reproductive toxicity. Incidence data for parental toxicity, changes in fertility parameters and developmental toxicity for each dose group would be needed in order to be able to conclude whether the observed effects were biologically relevant and whether reproductive toxicity was due to parental toxicity. One MSCA required additional details on the stage or period of pregnancy at which females were sacrificed in the study by They also pointed out that the NOAEL for development could not be the same as the LOAEL for development and questioned the absence of significant effects on body weight in the 40 mg group while four animals were sacrificed due to excessive body weight loss.

Additional key elements

The following tables are extracted from the CAR:

CAR Table A6.8.2/01-2: Multigeneration Reproduction Toxicity Study in Rats: Parental effects (Twoney, 1996)

Parameter	Generation	Dose level [mg/kg bw/day]									
		0		10		30		100		Dose-response +/-	
		m	f	m	f	m	f	m	f	m	f
Number of animals per group		**25**	**25**	**25**	**25**	**25**	**25**	**25**	**25**		

Clinical Observations	Incidence											
pre/post-dose salivation		F_0	0	0	0	0	all	5	all	all	+	+
paddling with fore paws			0	0	0	0	all	all	all	all	+	+
hunched posture with holding abdomen			0	0	0	0	all	0	all	all	+	+
post-dose salivation		F_1	0	0	0	0	all	all	--	--	+	+
paddling with fore paws			0	0	0	0	all	all	--	--	+	+
hunched posture with holding abdomen			0	0	0	0	0	0	--	--	-	-
Mortality	Incidence	F_0	0	0	0	0	0	1	0	5	-	+
		F_1	0	1	0	1	0	2	--	--	-	-
Body weight gain	[g]											
day 1 to 106		F_0	349	--	353	--	355	--	312	--	+	/
pre-mating day 1 to 71			--	171	--	175	--	177	--	161	/	-
pregnancy day 0 to 20[1)]			--	138	--	136	--	143	--	138	/	-
lactation day 1 to 7[2)]			--	30	--	33	--	35	--	21	/	+
lactation day 7 to 14[2)]			--	16	--	15	--	15	--	22	/	+
lactation day 14 to 21[2)]			--	-12	--	-7	--	-10	--	-3	/	+
day 25 to 165		F_1	529	--	552	--	550	--	--	--	--	/
pre-mating day 25 to 95			--	257	--	262	--	252	--	--	/	--

pregnancy day 0 to 20			--	148	--	147	--	152	--	--	/	-
lactation day 1 to 7[2)]			--	23	--	15	--	18	--	--	/	-
lactation day 7 to 14[2)]			--	16	--	19	--	17	--	--	/	-
lactation day 14 to 21[2)]			--	-15	--	-11	--	-11	--	--	/	-
Food consumption	[g]											
week 1 to 14		F_0	ne	--	ne	--	ne	--	ne	--	-	/
pre-mating week 1 to 10			--	ne	--	ne	--	ne	--	ne	/	-
pregnancy			--	ne	--	ne	--	ne	--	ne	/	-
post-partum day 1 to 7			--	40	--	40	--	39	--	32**	/	+
post-partum day 7 to 14			--	68	--	70	--	66	--	52***	/	+
week 19 to 35		F_1	ne	--	ne	--	ne	--	--	--	-	/
pre-mating week 19 to 27			--	ne	--	ne	--	ne	--	--	/	-
pregnancy			--	ne	--	ne	--	ne	--	--	/	-
post-partum			--	ne	--	ne	--	ne	--	--	/	-
Liver weight		F_0										
absolute	[g]		19.83	17.11	20.05	17.54	20.61	15.91*	21.47	15.49**	-	+
relative	[g/kg]		32.21	47.11	32.33	49.41	33.12	44.06	37.68**	44.80	+	-
Liver weight		F_1										
absolute	[g]		19.60	16.96	19.42	16.59	19.95	17.06	--	--	-	-
relative	[g/kg]		32.43	40.93	31.25	38.73	32.38	42.04	--	--	-	-
Ovaries weight		F_0										
absolute	[g]		--	0.101	--	0.097	--	0.110	--	0.117*	/	+

relative	[g/kg]		--	0.279	--	0.272	--	0.305	--	0.341***	/	+
Ovaries weight		F_1										
absolute	[g]		--	0.130	--	0.112	--	0.122	--	--	/	-
relative	[g/kg]		--	0.315	--	0.260**	--	0.299*	--	--	/	+
Heart weight		F_0										
absolute	[g]		nd	nd	nd	nd	nd	nd	nd	nd	-	-
relative	[g/kg]		nd	nd	nd	nd	nd	nd	nd	nd	-	-
Heart weight		F_1										
absolute	[g]		1.79	1.38	1.63	1.37	1.73	1.28	--	--	-	-
relative	[g/kg]		3.10	3.36	2.74*	3.36	2.83*	3.23	--	--	+	-
Histopathology												
Stomach	Incidence	F_0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	-	-
diffuse acanthosis with hyperkeratosis	minimal	F_1	0/10	0/10	0/10	0/10	3/10	5/10	--		+	+
	slight		0/10	0/10	0/10	0/10	4/10	2/10	--	--	+	+
	moderate		0/10	0/10	0/10	0/10	3/10	0/10	--	--	+	-
Sperm characterisation		F_0	ne	--	ne	--	ne	--	ne	--	-	
		F_1	ne	--	ne	--	ne	--	--	--	-	

Abbreviations

1) day of pregnancy

2) day post-partum

* significantly different from control, $p<0.05$

** significantly different from control, $p<0.01$

*** significantly different from control, $p<0.001$

Nd not determined

CAR Table A6.8.1/04-3: Teratogenicity study in rats: Foetal Examination (on litter basis) [redacted]

Parameter	**0 mg/kg bw/d**		**25 mg/kg bw/d**	**75 mg/kg bw/d**	**250 mg/kg bw/d**	**dose-response + / -**
	historical	study				
External and visceral examinations						
Total number of foetuses (litters) examined	5048 (343)	357 (23)	355 (24)	349 (24)	373 (24)	
Major anomalies [mean %]	0.0 - 1.2	1.2	0.0	0.5	1.7	-
Minor anomalies [mean %]	0.0 – 1.5	0.3	0.3	0.8	0.9	-
Skeletal examinations						
Total number of foetuses (litters) examined	3102 (456)	179 (23)	177 (24)	175 (24)	187 (24)	
Major anomalies [mean %]	0.0 – 0.5	0.5	0.0	0.0	0.0	-
Minor anomalies [mean %]	0.0 – 19.5	16.0	9.9	11.8	25.0*	+
Combined examination						
Major anomalies [mean %]	0.0 – 1.2	1.2	0.0	0.5	1.7	-
Foetal variants						
All foetuses with normal sternebrae	--	72.7	82.2	73.8	47.3**	+
Sternebrae 5th not ossified [mean%]	10.5 – 30.4	21.6	12.6	21.5	44.1**	+
Metacarpals –one or more not ossified	2.4 – 55.3	39.2	38.5	32.6	47.7	-

Uni – or bilateral: vestigial 14th	1.2 – 25.4	12.0	19.8	21.7	23.7	**- ***

Mean%: sum of % of affected foetuses per litter/number of litters.

CAR Table A6.8.1/04-1: Teratogenicity study in rats: Maternal effects [redacted]

	Dose level [mg/kg bw/day]					
Parameter	**0**		**25**	**75**	**250**	**dose-response + / -**
	Hist. ctrl	study				
Number of dams in group		24	24	24	24	
Pregnancy index [%]	95.3	95.8	100	100	100	-
aggressive behaviour at dosing [number of animals]	--	0	0	24	24	+
post-dose salivation [number of animals]	--	0	0	24	24	+
Mortality of dams [%]		0	0	0	0	
Abortions		0	0	0	0	
Body weight gain						
day 0-6 [g]		33	32	32	34	-
day 6-9 [g]		**15**	**16**	**11**	**1****	**+**
day 9-12 [g]		22	20	17**	20	-
day 12-15 [g]		22	21	21	23	-
day 15-20 [g]		76	79	83	76	-
day 6-15 [g]		**59**	**57**	**49****	**44****	**+**

Food consumption						
day 0-6 [g/rat/day]		25.4	26.3	25.9	26.5	-
day 6-9 [g/rat/day]		**25.2**	**25.7**	**21.5****	**17.8****	**+**
day 9-12 [g/rat/day]		29.7	30.8	34.9**	27.1	-
day 12-15 [g/rat/day]		29.4	30.6	30.7	27.4	-
Liver weight						
absolute [g]		**18.0**	**18.6**	**18.8**	**21.0****	**+**
Relative [g/kg]		**43.8**	**46.2**	**46.8**	**53.6****	**+**
Necropsy findings in dams dead before end of test		n.a.	n.a.	n.a.	n.a.	-

* statistically significant from control, $p<0.05$

Assessment and comparison with the classification criteria

There is no human data available.

In a two-generation reproductive toxicity study [redacted] Sprague-Dawley rats were treated via gavage at 0, 10, 30, and 100 mg/kg bw/d. Due to the severity of clinical signs at 100 mg/kg bw/d, treatment with this dose level was discontinued for the F_1. Exposure period was 10 weeks before mating for F_0 and 13 weeks before mating for F_1.

Effects of parental toxicity were characterized by reduced body weight gain in F_0 males at 100 mg/kg bw/d, reduced food consumption and body weight gain during the first week of lactation in F_0 females at 100 mg/kg bw/d as well as acanthosis and hyperkeratosis in stomach in F_1 parents at 30 mg/kg bw/d (not examined in F_0 animals). Diffuse acanthosis with hyperkeratosis in stomach were noted at 30 mg/kg bw/day in F1 males (minimal 3/10, slight 4/10 and moderate 3/10, respectively) and F1 females (minimal, slight and moderate: incidence of 5/10, 2/10, 0/10, respectively) compared to the respective control groups (males and females: 0/10). Pre- and/or post-dose salivation was noted in all males at 30 and 100 mg/kg bw/day as well as in 5 females at 30 mg/kg bw/day and in all females at 100 mg/kg bw/day. There was also an occasional hunched posture and forepaw paddling at 30 and 100 mg/kg bw/d in F_0 animals and at 30 mg/kg bw/d in F_1 animals. One female given 30 mg/kg bw/day and four females given 100 mg/kg bw/day were sacrificed due to elongated/difficult parturition. One female at 100 mg/kg bw/day was sacrificed with masses on the forelimb.

There were no treatment related effects on copulation/pregnancy incidences noted up to and including 100 mg/kg bw/d in the F_0 generation or in the F_1 generation up to and including 30 mg/kg bw/d. A reduced fertility/mating index was observed in F_0 parents at 100 mg/kg

bw/d. A reduced live birth index was noted in F_1 pups at 100 mg/kg bw/d, and reduced viability index and cumulative survival index in F_1 pups at 30 and 100 mg/kg bw/d. Mean birth pup body weight was reduced in F_1 females at 100 mg/kg bw/d. Besides, there was an increased incidence with pups without milk in stomach and/or bitten or cannibalised pups at 30 and 100 mg/kg bw/d in the F_1 pups. However, this was not noted in pups of the F_2 generation at 30 mg/kg bw/d. The live birth index and the pup viability during the first 4 days of lactation was reduced in the F_1 pups at 100 mg/kg bw/d which was considered to be the result of parental toxicity at that dose. Reduced live birth index and pup viability was not observed at the lower doses. The following NOAELs were estimated: NOAEL parental: 10 mg/kg bw/d; NOAEL reproduction: 30 mg/kg bw/d; NOAEL developmental: 10 mg/kg bw/d.

A teratogenicity study on New Zealand White rabbits (females; dose levels: 0, 10, 20, 40 mg/kg bw/d; exposure period: days 7 to 19 of pregnancy) showed no treatment related effects on mean number of live foetuses, mean pre-and post-implantation loss, mean foetal weight and sex ratio noted ([redacted] Foetal examination revealed no changes between control and treated groups. The following NOAELs and LOAELs were estimated: NOAEL maternal: 10 mg/kg bw/d; NOAEL development: 40 mg/kg bw/d; LOAEL maternal: 20 mg/kg bw/d; LOAEL development: 40 mg/kg bw/d.

A teratogenicity study on Sprague-Dawley rats (females, dose levels: 0, 25, 75, 250 mg/kg bw/d; exposure period: day 6 to 15 of pregnancy) revealed mean female foetal weight decrease at 250 mg/kg bw/d and increased incidence in minor rib defects and incomplete or non-ossification ([redacted] but it was considered to be the result of maternal toxicity. Statistically significant reduced body weight gain is noted at 75 and 250 mg/kg bw/d as well as increase in absolute and relative liver weight at 250 mg/kg bw/d. Besides, strongly pronounced agressive behaviour at dosing and post-dosing salivation were described at 75 and 250 mg/kg bw/d. The following NOAELs and LOAELs were estimated: NOAEL maternal: 25 mg/kg bw/d; NOAEL development: 75 mg/kg bw/d; LOAEL maternal: 75 mg/kg bw/d; LOAEL development: 250 mg/kg bw/d.

For the Category 2 classification criteria outlined in the CLP the classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity. However, the developmental toxicity can also occur as a non-specific secondary mechanism like via maternal stress and the disruption of homeostasis. The adverse reproductive effects observed only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would normally not lead to classification, unless other information is available, e.g. toxicokinetics data indicating that humans may be more susceptible than animals suggesting that classification is appropriate. In addition, when a substance causes maternal death or severe inanition or when dams are prostrate and incapable of nursing pups during treatments, it is reasonable to assume that developmental toxicity is produced solely as a secondary non-specific consequence of maternal toxicity and the developmental effects are discounted. Also, classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity.

According to the Directive 67/548/EEC the classification into Category 3 may be based on the results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2. Moreover, since adverse pre- and post-natal effects may be secondary to maternal toxicity, reduced food or water intake, maternal stress, lack of maternal care, specific dietary deficiencies, poor animal husbandry, intercurrent infections, etc., it is important that the effects observed should occur in well conducted studies and at dose levels which are not associated with marked maternal toxicity.

Taking into account the overall weight of evidence RAC therefore supported the conclusion of the DS that no classification is warranted for reproductive toxicity. According to RAC, there was no evidence of selective impairment of fertility or development in the tested species at systemically non-toxic dose levels. The effects on reproductive toxicity could be considered as secondary to maternal toxicity. In conclusion, RAC agreed that no classification for reproductive toxicity is justified as both CLP (outlined in the paragraph 3.7.2 of the CLP Regulation) and DSD criteria are not met.

Supplemental information - In depth analyses by RAC
Analyses

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Table 20: Summary table of relevant neurotoxicity studies

Method	Results	Remarks	Reference
Acute oral neurotoxicity study with gavage administration 14 days post-exposure Sprague-Dawley rats, both sexes 30/group	Dose levels: 0, 100, 300 and 1000 mg/kg bw LOAEL: Systemic 300 Neurotoxicity > 1000 NOAEL: Systemic toxicity: 100 Neurotoxicity: 1000	(purity >99%)	[redacted]
Oral feeding 90 days recovery 28 days satellite animals Sprague Dawley rats, both sexes, 36/group, satellite animals:12/group	Dose levels: 0, 10, 50 and 120 mg/kg bw/d LOAEL: Systemic toxicity: 50 Neurotoxicity: > 120 NOAEL: Systemic toxicity: 10 Neurotoxicity: 120	(purity >99%)	[redacted]

The results from the available acute and subchronic neurotoxicity study demonstrated that IPBC is not neurotoxic and no treatment-related findings were made on neuropathological examination either. This is further supported by the findings in the 104 weeks studies in rats and 78 weeks mice study (all investigating RBC and brain cholinesterase inhibition), where no signs indicative for a potential neurotoxic effect of IPBC were found.

4.12.1.2 Immunotoxicity

No information available. The clinical pathology parameters investigated in the available repeated dose toxicity studies do not provide indication for a potential immunotoxic effect of IPBC.

4.12.1.3 Specific investigations: other studies

No information available

4.12.1.4 Human information

No information available

4.12.2 Summary and discussion

No information available

4.12.3 Comparison with criteria

The results of the available acute and subchronic neurotoxicity studies as well as of the combined chronic toxicity/carcinogenicity studies indicate that IPBC seems not to possess a neurotoxicty and/or immunotoxicity potential. No specific study investigating immunotoxicity are available.

4.12.4 Conclusions on classification and labelling

Based on the available data IPBC does not have to be classified and labelled with respect to adverse effects on the nervous or immune system as the target organs.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 21: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Test type: Hydrolysis EG guideline C7. 92/69	Half-life, DT50 (25 °C): The test substance IPBC is	Purity 98.3%	[redacted]

Test substance concentration: Not indicated Temperature: 50°C (pH 4, 7 and 9) = Pretest 65°C (pH 9) = Main test 80°C (pH 9) = Main test	not degradable at pH 4 and pH 7 DT50 values at pH 9: 5.6 h = 0.2 days (80°C) 31 h = 1.3 days (65°C) 282 h = 11.8 days (50°C) Calculated: 12942 h = 539 days (25°C)		
Test type: Hydrolysis EPA Subdivision N, No. 161-1 Test substance concentration: 5 mg/L	Half-life, DT50 (25 °C): pH5: 267 d pH7: 248 d pH9: 229 d	Radiochemical purity > 98%	[redacted]
Test type: Photolysis OECD Guideline for testing of chemicals (Draft), August 2000 Test substance concentration: 1.977 mg/L	IPBC was stable within 3 days of continuous irradiation	Purity 99.8%	[redacted]
Test type: ready biodegradability OECD guideline 301F Test parameter: CO2 evolution Inoculum Type: Activated sludge Concentration: 30 mg dry material per litre Adaption: No Additional substrate: No Test substance concentration: 50 mg/L	Degradation: Incubation period: 28d Degree [%]: 0	Purity 99 %	[redacted]
Test type: inherent biodegradability OECD guideline 302B Test parameter: DOC Inoculum Type: Activated sludge Concentration: - Adaption: No	Degradation: Incubation period: 28d Transfor-mation of IPBC to PBC within 2 hours	Purity 99.2%	[redacted]

Additional substrate: No Test substance concentration: 0.02/ 1.0 mg/L			
Test type: anaerobic degradation in water/ sediment EPA Pesticide Assess. Guide, Subdiv. N, series 162-3 Test parameter: $^{14}CO_2$ evolution ^{14}C-IPBC removal Inoculum Type: No, natural inoculum was used Concentration: No Adaption: No Additional substrate: No Test substance concentration: 0.94 – 1.04 ppm	Degradation: Incubation period: 118 – 244d Degree [%]: DT_{50} 1.5 h (IPBC) 11.5 d (PBC)	Purity: > 97% Radiochemical purity: 99.4%	[redacted]
Test type: Aerobic degradation in soil EPA Pesticide Assess. Guide, Subdiv N, series 162-1 Test parameter: IPBC dissipation; metabolite formation; CO_2 evolution; bound residues Inoculum Type: No, natural inoculum was used Concentration: No Adaption: No Additional substrate: No Test substance concentration: 0.87 – 1.03 ppm	Degradation: Incubation period: 14 – 245d Degree [%]: <u>IPBC,</u> DT_{50} 2.13 h (22°C) 8.6 h (5°C) <u>PBC,</u> DT_{50} 4.3 d (22°C)	Purity: 99% Radiochemical purity: 99.4%	[redacted]

5.1.1 Stability

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.

According to [redacted] 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.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

Not relevant since studies on biodegradation (screening tests as well as simulations tests) are available.

5.1.2.2 Screening tests

According to the standard tests on ready and inherent biodegradation (see Table 21), IPBC is not readily but is primary biodegradable according to Zahn-Wellens test.

5.1.2.3 Simulation tests

In additional tests it was shown that IPBC is rapidly transformed in the environment to PBC (propargyl butyl carbamate, CAS No. 76114-73-3), constituting the major degradation product of IPBC. PBC has a substantially lower toxicity to the environment than IPBC (see Table 22 below).

- A modified Zahn-Wellens test was conducted, in which IPBC and the degradation product PBC were analytically monitored in the sludge and water phase at different time points. The test shows, that IPBC is rapidly transformed under the conditions of the test into the major metabolite PBC (within 2 hours) by the elimination of iodine. Two doses were tested (high dose of 1 mg/L and low dose of 0.02 mg/L). In the tested high dose, 99% of IPBC was degraded to PBC after 2 hours; after 4 hours no IPBC was detected (LOQ: 0.01 mg/L). A PBC content of 87% of the expected amount was measured 2 and 4 hours after application of IPBC which shows that IPBC is completely transformed to PBC. At later time points continuous degradation of PBC was observed. On day 21 the PBC concentration was below the LOQ (0.01 mg/L). IPBC was not detected at all in the sludge phase and PBC only to a minor extend (0.5%) leading to the conclusion that both substances were not absorbed to the sludge phase, but almost completely dissolved in the aqueous phase. In the tested low dose, IPBC could neither be determined in the aqueous phase nor in the sludge phase after 2 hours. PBC could not be determined due to technical reasons because of interferences at the low concentration level.

- Also in a water sediment study, which was performed under anaerobic (worst case) conditions, it was found that the degradation of IPBC to PBC is quite fast (DT_{50} 1.5 h for the whole system at 22°C and 3.3 hours at 12°C). DT_{90} was 5.0 hours for the whole system at 22°C and 11.0 hours at 12°C. Based on the measured concentrations in the study, the DT_{50} values for the water and sediment phase can be calculated: For the water phase, a DT_{50} of 1.4 hour and for the sediment phase a DT_{50} of 2.2 hours was estimated assuming a pseudo first order degradation kinetics. The distribution between water and sediment indicates that 78% remained in the water phase and less than 10% in the sediment. Non-extractable residues were 3.9 – 6.3% after 162/119 days. The mineralization was 42% in nonsterile static samples after 93 days, 21% in nonsterile enclosed samples after 119 days and 10% in nonsterile continuous N_2 flow samples after 120 days.

  In the sterile system (total system) the DT_{50} was 13.3 hours at 22°C and 30 hours at 12°C. The DT_{90} total system (sterile) was 44.3 hours at 22°C and 99 hours at 12°C. No mineralization was found in the sterile system.

  The initial degradation product of IPBC was PBC accounting for > 97 % (of the applied radioactivity) one day after treatment. PBC was further degraded to 2-propenyl-butyl carbamate and two non-identified compounds prior to complete mineralisation to the ultimate degradation products CO_2 and CH_4. Residue levels of 2-popenyl-butyl carbamate in sediment and water of non-sterile static systems peaked at 8.0 and 34.7 % of the applied radioactivity, respectively, at day 59. Total residue levels of either of the non-identified metabolites accounted for less than 3 % at any sampling interval.

  Under sterile conditions PBC was again the major degradation product accounting for maximum values of >80 % of applied radioactivity in the total system 29 days after treatment.

  For PBC the DT_{50} total system (non-sterile) was 11.5 days at 22°C and 26 days at 12°C. The DT_{90} was 38.4 days at 22°C and 86 days at 12°C. The distribution between water and sediment was as follows: Surface water up to ca. 89% after 8 hours and in the sediment up to ca. 13-21% after 4 hours/Day 1.

  The degradation product 2-PBC was found as an intermediate product before the complete mineralisation to the ultimate degradation products CO_2 and CH_4. 2-PBC was found in a concentration > 10%; however this metabolite is only found under anaerobic conditions and since the estimated toxicity based on QSAR (EPIWIN) was found to be comparable to that of IPBC no experimental ecotoxicological data of this metabolite was required in this case. Distribution of 2-PBC in water/sediment shoved that up to ca. 35% was found in surface water at day 59 and ca. 9% at day 59 and 93.

  Bound residues remained below 10%. Material balance values declined with time probably due to the formation of $^{14}CH_4$. Thus, the terminal degradation products of IPBC in anaerobic aquatic systems appear to be CO_2 and CH_4.

  In an aerobic soil degradation study, it could be shown that IPBC is rapidly degraded with a DT_{50} of 8.6 h at 5°C and a DT_{50} of 2.1 h at 22°C. Recalculated to 12°C, the DT_{50} was 5 hours. PBC was the major soil metabolite formed accounting for a maximum value of 95.0 % of applied radioactivity 12 hours after treatment. After a short lag period, PBC was also rapidly degraded. PBC was readily mineralised in non-sterile samples maintained at

22°C with a DT_{50} value of 4.3 days corresponding to a DT_{50} value of 10 days recalculated to 12°C. One minor metabolite was detected which did not exceed 5 % (of applied radioactivity).

CO_2 accounted for up to 75.3 % of applied radioactivity after 21 days of incubation in nonsterile samples incubated at 22°C. Bound residues reached a maximum value of 21.4% after approx. 7 days.

- The degradation of IPBC in soil was primarily microbial mediated but non-biological mechanisms may contribute to the degradation process. Due to their fast degradation in soil, neither IPBC nor PBC are likely to accumulate in soil. Both substances are completely mineralised to CO_2.

5.1.3 Summary and discussion of degradation

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 environmental compartments soil, water-sediment and STP, a fast transformation of IPBC to PBC occurs. This includes both biotic and non-biological processes. PBC is further metabolised. The final degradation products are CO_2 and CH_4 (anaerobic conditions). The metabolite 2-PBC was found in a concentration > 10%; however this metabolite is only found under anaerobic conditions and since the estimated toxicity based on QSAR (EPIWIN) was found to be comparable to that of IPBC no experimental ecotoxicological data of this metabolite was required in this case.

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

Soil:	IPBC, DT_{50} = 2.1 h at 22 °C;	PBC, DT_{50} = 4.3 days at 22 °C
Water:	IPBC, DT_{50} = 1.4 h at 22 °C;	PBC, DT_{50} = 14.2 days at 22 °C
Sediment:	IPBC, DT_{50} = 2.2 h at 22 °C;	PBC, DT_{50} = 14.3 days at 22 °C

The following DT_{50} values are based on 12 °C (using Arrhenius equation)

Soil:	IPBC, DT_{50} = 4.7 h at 12 °C;	PBC, DT_{50} = 9.5 days at 12 °C
Water:	IPBC, DT_{50} = 3.1 h at 12 °C;	PBC, DT_{50} = 31.2 days at 12 °C
Sediment:	IPBC, DT_{50} = 4.9 h at 12 °C;	PBC, DT_{50} = 31.4 days at 12 °C

The indicated half-life for PBC is based on data from the water/sediment system study that included differentiated water / sediment data. Another transformation product formed is iodine.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

IPBC has moderate K_{OC} values ranging from 61 to 309 with a geometric mean of 113.25 (log 2.1). However it is questionable whether the batch equilibrium method is applicable for IPBC because in soil studies IPBC is transformed in only a few hours time. When the Koc value for IPBC is estimated by QSAR, a value of 365 (log. 2.6) is obtained. This value was considered to support the experimental value sufficiently. IPBC adsorption is not closely correlated with soil organic matter content, clay content or cation exchange capacity. In the above cited adsorption study, PBC was detected as the (only) metabolite.

The adsorption coefficient of PBC was calculated with PCKOC (v 1.66) to be 198.1.

5.2.2 Volatilisation

The calculated Henry's Law constant of $3.38*10^{-3}$ $Pa*m^3*mol^{-1}$ indicates that volatilisation from surface waters is not expected to be an important process.

5.2.3 Distribution modelling

The Henry's Law constant was calculated and resulted in a value of 3.38*10-3 Pa*m3*mol-1.

5.3 Aquatic Bioaccumulation

No studies are available on the aquatic bioaccumulation of IPBC.

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

- The Log K_{OW} of IPBC at 25°C following the OECD 107 Guideline is 2.81. This indicates that IPBC has a low potential for bio-concentration and therefore bio-accumulation is not expected.
- Additionally, IPBC degrades rapidly in the environment: Under non-sterile anaerobic aquatic conditions, DT50 and DT90 values of 1.5 and 5.0 hours were determined, respectively. This is another indicator for a low bio-concentration potential.
- IPBC is not a surface active substance: its surface tension is 69 mN/m, which is above the trigger value of 50 mN/m. Only if the surface tension is below a value of 50 mN/m, an in-depth consideration of the bio-concentration potential is needed.
- The main degradation product of IPBC is PBC, which has a half-life of 11.5 days under anaerobic aquatic conditions. Thus, PBC is not persistent in aquatic systems. The criterion

for identification of persistence is a half-life in freshwater greater than 40 days, according to the TGD on Risk Assessment.

- According to the formula provided in the TGD on Risk Assessment, a BCF_{fish} of 48.8 for IPBC can be deduced from the log K_{ow} of 2.81, which is below the trigger value of 100. Therefore IPBC has no potential for bio-concentration in aquatic organisms.

5.3.1.2 Measured bioaccumulation data

No information available

5.3.2 Summary and discussion of aquatic bioaccumulation

The Log K_{OW} of IPBC at 25°C following the OECD 107 Guideline is 2.81. This indicates that IPBC has a low potential for bio-concentration and therefore bio-accumulation is not expected. Moreover, IPBC degrades rapidly in the environment to PBC. This is a further indication for a low bio-concentration and bio-accumulation potential. Like IPBC, the degradation product PBC dissipates rapidly in the environment. Therefore, no accumulation is expected (see Doc. IIIA, Section A7.4.2 of the PT8 CA-Report).

5.4 Aquatic toxicity

For all of the three species (fish, invertebrates and algae), valid acute toxicity tests with IPBC and PBC are available. In addition, long-term tests for fish and invertebrates are provided for IPBC.

Table 22: Summary of relevant information on aquatic toxicity

Method	Results	Remarks	Reference
IPBC data			
Test type: Acute toxicity to fish EPA-FIFRA 72-1 *Pimephales promelas* (Fathead Minnow) Design: Flow-through Duration: 96 hours	NOEC: 0.096 mg/L LC_{50}: 0.200 mg/L LC_{100}: 0.360 mg/L	Purity: 97.5%	[redacted]
Test type: Acute toxicity to fish EPA-FIFRA 72-3 *Cyprinodon variegatus* (Sheepshead Minnow)	NOEC: 0.14 mg/L (based on lethargy effects) LC_{50}: 0.410 mg/L LC_{100}: 1.100 mg/L	Purity: 97.3%	[redacted]

Design: Flow-through Duration: 96 hours			
Test type: Acute toxicity to fish EPA-FIFRA 72-1 *Lepomis macrochirus* (Bluegill Sunfish) Design: Flow-through Duration: 96 hours	NOEC: 0.14 mg/L LC_{50}: 0.230 mg/L LC_{100}: 0.320 mg/L	Purity: 97.7%	[redacted]
Test type: Acute toxicity to fish 92/69/EEC, C1 (1992) & OECD 203 *Danio rerio* formerly *Brachydanio rerio* (Zebra fish) Design: static Duration: 96 hours	NOEC: 0.26 mg/L LC_{50}: 0.430 mg/L LC_{100}: 0.710 mg/L	Purity: 98.3%	[redacted]
Test type: Acute toxicity to fish EPA-FIFRA 72-1 *Oncorhynchus mykiss* (Rainbow trout) Design: Flow-through Duration: 96 hours	NOEC: 0.046 mg/L LC_{50}: 0.072 mg/L LC_{100}: 0.120 mg/L	Purity: 97.5%	[redacted]
Test type: Acute toxicity to fish EPA-FIFRA 72-1 *Oncorhynchus mykiss* (Rainbow trout) Design: Flow-through Duration: 96 hours	NOEC: 0.049 mg/L LC_{50}: 0.067 mg/L LC_{100}: 0.120 mg/L	Purity: 97.7%	[redacted]
Test type: effects on reproduction and growth rate of IPBC on fish EPA-FIFRA 72-4 *Pimephales promelas*	NOEC: 0.0084 mg/L LOEC: 0.019 mg/L	Purity: 97.3%	[redacted]

(Fathead Minnow) Design: Flow-through Duration: 35 days			
Test type: Acute toxicity to invertebrates EPA-FIFRA 72-2 *Daphnia magna* Design: Flow-through Duration: 48 hours	EC0: 0.076 mg/L EC_{50}: 0.16 mg/L EC_{100}: 0.28 mg/L	Purity: 97.5%	[redacted]
Test type: effects on reproduction and growth rate of IPBC on *Daphnia magna* EPA-FIFRA 72-4 & OECD 202 *Daphnia magna* Design: Flow-through Duration: 21 days	LOEC: 0.099 mg/L NOEC: 0.050 mg/L EC_{50}: 0.133 mg/L	Purity: 97%	[redacted]
Test type: growth inhibition effects of IPBC on algae 92/69/EEC, C3 (1992) & OECD 201 *Scenedesmus subspicatus* Design: static Duration: 72 hours	NOE_rC: 0.0046 mg/L E_bC_{50}: 0.0220 mg/L E_rC_{50}: 0.0530 mg/L	Purity: 99.1%	[redacted]
Test type: growth inhibition effects of IPBC on algae EPA-FIFRA 122-2 *Selenastrum capricornutum* Design: static Duration: 120 hours	NOE_rC: < 0.089 mg/L E_bC_{50}: 0.100 mg/L	Purity: 97.5%	[redacted]
PBC data			
Test type: Acute toxicity to fish EPA-FIFRA 72-1 Oncorhynchus mykiss (Rainbow trout) Design: Flow-through **Duration: 96 hours**	NOEC: 30 mg/L LC_{50}: 85 mg/L LC_{100}: 150 mg/L	Purity: 99.6%	[redacted]
Test type: Acute toxicity to invertebrates	EC_0: 17 mg/L EC_{50}: 60 mg/L	Purity: 99.8%	[redacted]

EPA-FIFRA 72-2 *Daphnia magna* Design: Flow-through Duration: 48 hours	EC_{100}: 150 mg/L		
Test type: growth inhibition effects of IPBC on algae TSCA 797.1050 *Selenastrum capricornutum* Design: static Duration: 96 hours	NOE_rC: 21.2 mg/L E_bC_{50}: > 41.3 mg/L E_rC_{50}: > 41.3 mg/L	Purity: 99.4%	[redacted]

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

The acute studies on fish indicate that IPBC is toxic to freshwater fish. The LC_{50} values range from 0.067 mg IPBC/L [redacted] to 0.430 mg IPBC/L [redacted] with *Oncorhynchus mykiss* (Rainbow trout) being the most sensitive species.

In the acute toxicity study of PBC to fish the LC_{50} is 85 mg/L [redacted]

5.4.1.2 Long-term toxicity to fish

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

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

In the acute toxicity study on *Daphnia magna*, an EC_{50} value of 0.160 mg IPBC/L [redacted] is reported, which represents the lowest value from three valid acute studies with this organism.

In the acute toxicity study of PBC to *Daphnia magna* the EC_{50} is 60 mg/L [redacted]

5.4.2.2 Long-term toxicity to aquatic invertebrates

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

5.4.3 Algae and aquatic plants

For freshwater algae, the EC_{50} values based on biomass ranged from 0.0220 (E_rC_{50} of 0.0530 mg IPBC/L) ([redacted] to 0.100 mg IPBC/L ([redacted] The NOEC of 0.0046 mg IPBC/L ([redacted] represents the lowest value from all available studies.

For freshwater algae, the EC_{50} value based on biomass and growth rate for PBC is < 41.3 mg/L and the NOEC value is 21.2 mg/L

These E(L)C50 values and also the NOEC value of the algae study indicate that PBC is by several orders of magnitude less toxic to aquatic organisms than the active substance IPBC. Thus, the data on acute basis clearly reveal that PBC has a substantially lower toxicity to aquatic organisms than IPBC. The data on acute toxicity of PBC to aquatic organisms reveal algae (*Selenastrum capricornutum*) to be the most sensitive species with an EC_{50} and NOEC value of 41.3 and 21.2 mg PBC/L, respectively [redacted]

5.4.4 Other aquatic organisms (including sediment)

The EC_{50} of IPBC concerning respiration inhibition is calculated to be 44 mg IPBC/L [redacted]. This value is the lowest from three valid respiration inhibition studies with activated sludge. In the study on microbial activity with *Pseudomonas putida*, an EC_{50} of 91 mg IPBC/L [redacted] was determined. Thus, the EC_{50} of 44 mg IPBC/L represents the lowest value from all available studies.

Table 23: Summary of relevant information on microbial inhibition

Method	Results	Remarks	Reference
Test type: Inhibition to microbial activity (key –study) EU 88/302/EEC, Part C11 Activated sludge Design: static Duration: 3 hours	EC_{50}: 44 mg/L	Purity: 98.3%	[redacted]
Test type: Inhibition to microbial activity (non-key –study) OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test" Activated sludge Design: static Duration: 3 hours	EC_{50}: 121 mg/L	Purity: 98%	[redacted]
Test type: Inhibition to microbial activity (non-key –study)	EC_{50}: 160 mg/L	Purity: 99%	[redacted]

OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test" Activated sludge Design: static Duration: 3 hours			
Test type: Inhibition to microbial activity (key-study) As described in the German Water Hazard Classification Scheme and ISO 10712 *Pseudomonas putida* Design: static Duration: 16 hours	EC_{50}: 91 mg/L	Purity: not indicated	[redacted]

Studies on sediment organisms are not available.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Comparison with the "old" criteria for environmental hazard according to CLP-Regulation 1272/2008/EC.

Aquatic toxicity (acute toxicity)

For fish:
96 h, LC50 (*Oncorhynchus mykiss*): 0.067 to 0.072 mg/L
For algae:
72 h, E_bC_{50} (*Scenedesmus subspicatus*): 0.022 mg/L
72 h, E_rC_{50} 0.053mg/L
For daphnia:
48 h, EC50 (*Daphnia magna*): 0.160 mg/L

The results for acute aquatic toxicity are below the value of < 1 mg/L and therefore fulfil the criteria for classification and labelling of IPBC as "Very toxic to aquatic life " (Acute Category 1). Since the lowest valid LC50 and EC50 values in fish and algae are between 0.01 and 0.1 mg/L, the assignment of a multiplying (M) factor of 10 is required for IPBC.

An application of chronic (long-term) aquatic hazard (category chronic 1) does not apply since IPBC is considered to be rapidly degradable, the log Pow of IPBC is 2.81 which is below the trigger value of 4 and the BCF_{fish} of 48.8, calculated based on the log Pow value according to the formula provided in the TGD, is below the trigger value of 100 as defined in the TGD and far below the trigger value of 500 for experimentally derived BCF values as given in Table 4.1.0 of the CLP-Regulation.

In the statement of the applicant provided in Annex III to the CLH Report) saying that R53 (may cause long-term adverse effects in the aquatic environment) is not justified an argumentation is

provided which shows that IPBC has to be considered as rapidly degradable and that IPBC has no potential for bio-concentration in aquatic organisms.

Please find under the point below "*Comparison with the "new" criteria for environmental hazard according to CLP-Regulation 1272/2008/EC and Commission Regulation (EU) No. 286/2011 of 10 March 2011" an argumentation according to the CLP criteria.* The criteria to consider a substance as rapidly degradable have not been changed under the "new" Regulation 286/2011.

Comparison with the "new" criteria for environmental hazard according to CLP-Regulation 1272/2008/EC and Commission Regulation (EU) No. 286/2011 of 10 March 2011.

Aquatic toxicity (long-term toxicity)

For fish:	
35 days, NOEC (*Pimephales promelas*):	0.0084 mg/L
For algae:	
72 h, NOEC (*Scenedesmus subspicatus*):	0.0046 mg/L
For daphnia:	
21 days, NOEC (*Daphnia magna*):	0.050 mg/L

The results for long-term aquatic toxicity of IPBC are below the trigger value for rapidly degradable substances of < 0.01 mg/L and therefore fulfil the criteria for classification and labelling of IPBC as "Very toxic to aquatic life with long lasting effects " (Category Chronic 1). Since the lowest NOEC values in fish (0.0084 mg/L) and algae (0.0046 mg/L) are between 0.001 and 0.01 mg/L and considering that IPBC is rapidly degradable the multiplying (M) factor is 1.

Criteria for classification of a substance as rapidly degradable and their applicability to IPBC:

According to Commission Regulation (EU) No. 286/2011 (2nd ATP) there are three criteria for substances to be considered as rapidly degradable (point 4.1.2.9.5):

"*Substances are considered rapidly degradable in the environment if one of the following criteria holds true:*

(a) if, in 28-day ready biodegradation studies, at least the following levels of degradation are achieved:

(i) tests based on dissolved organic carbon: 70 %;
(ii) tests based on oxygen depletion or carbon dioxide generation: 60 % of theoretical maximum.

These levels of biodegradation must be achieved within 10 days of the start of degradation which point is taken as the time when 10 % of the substance has been degraded, unless the substance is identified as an UVCB or as a complex, multi-constituent substance with structurally similar constituents. In this case, and where there is sufficient justification, the 10-day window condition maybe waived and the pass level applied at 28 days; or

(b) if, in those cases where only BOD and COD data are available, when the ratio of BOD5/COD is≥ 0,5; or

(c) if other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level > 70 % within a 28-day period."

While the first criteria (ready biodegradability according to the results from a ready test) is not fulfilled and the second one does not apply, the third criteria is fully complied with, i.e. other convincing scientific evidence is available which demonstrates that the substance can be degraded in the aerobic aquatic environment to a level of > 70% within a 28-day period. The corresponding data are summarised below:

Degradation of IPBC:

Ready biodegradation tests

IPBC does not fulfil the criteria for ready biodegradability according to results from tests according to OECD 301 F, OECD 301 B and Directive 92/69/EEC, C.4-e. These activated sludge studies provide only a first approach to estimate the potential biodegradability of a substance and do not allow a final conclusion on the degradability of a substance. Under point 4.1.2.9.2 of Regulation (EU) No. 286/2011 it is stated "*However, a fail in the screening test does not necessarily mean that the substance will not degrade rapidly in the environment."*

Higher tier studies show that IPBC degrades rapidly in the environmental compartments soil and water.

- **Soil degradation study**

  In an aerobic soil study, IPBC and its degradation product PBC were rapidly degraded at 22 °C with a DT_{50} of 2.1 h and 4.3 days, respectively. The material balance shows that at sampling day 21, 75.3% of the applied IPBC had been degraded (via PBC) to CO_2. Consequently, IPBC and PBC must be regarded as rapidly degradable in soil. Point (d) of Annex II.4 (Annex II: Rapid Degradation, Annex II.4 Decision scheme) of the "Guidance to Regulation (EC) No 1272/2008 on Classification, Labeling and Packaging of substances and mixtures" applies to IPBC since IPBC is demonstrated to be ultimately degraded in a soil simulation test with a half life of < 16 days (corresponding to a degradation of > 70% within 28 days). 75.3% of IPBC had been degraded to CO_2 after 21 days.

- **Water sediment study**

  The DT_{50} of IPBC and PBC at 22 °C were determined to be 1.4 h and 11.5 days, respectively. One day after test start, no IPBC could be detected because IPBC had been transformed to PBC. Although the ultimate degradation of PBC could not be demonstrated, it is accepted that an anaerobic study presents a worst case situation and that under aerobic conditions a much faster degradation would occur, similar to the soil study. This argument is valid because it is generally accepted that when a substance has been shown to be degraded rapidly in a soil simulation study (as done for IPBC), it is most likely also rapidly degradable in the aquatic environment. In Annex II.2.3.6 (Annex II.2.3.6 Soil and Sediment degradation data) of the "Guidance to Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures" it is stated that "*It has been agreed that for many non-sorptive substances more or less the same degradation rates are found in soil and in surface water. Thus, when a substance has been shown to be degraded rapidly in a soil simulation test, it is most likely also rapidly degradable in the aquatic compartment. It is therefore proposed that an experimentally determined degradation in soil is sufficient documentation for a rapid degradation in surface water".*

- **Inherent biodegradation test**

A rapid degradation of IPBC to PBC was also demonstrated in an inherent biodegradation test. The modified Zahn-Wellens test (OECD guideline 302 B) shows that IPBC is completely transformed to PBC within 2 hours. A continuous degradation of PBC was shown so that the PBC concentration was below the LOQ (0.01 mg/L) on day 21.

Bioaccumulation potential of IPBC and PBC

According to the EC working document on aquatic ecotoxicology and the TGD on Risk Assessment, substances exhibiting a log P_{ow} greater than or equal 3 should be investigated with regard to their bioaccumulation potential. The log P_{ow} of IPBC (log P_{ow}: 2.81) is below the trigger value of 3. Furthermore the BCF_{fish} of 48.8 for IPBC deduced from the log P_{ow}, according to the formula provided in the TGD is below the trigger value of 100. Therefore IPBC has no potential for bio-concentration in aquatic organisms. The calculated log P_{ow} value of the degradation product PBC provided by Danish EPA is 1.64 (estimated) which gives no rise for a bioaccumulation potential of the degradation product PBC.

Conclusion: IPBC is a substance to be considered as rapidly degradable in the environment and IPBC has no potential for bio-concentration in aquatic organisms.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Based on the available data IPBC has to be classified and labelled for aquatic toxicity with R50 (Very toxic to aquatic organisms) according to Directive 67/548/EEC and with H400 (Very toxic to aquatic life), M-factor = 10, according to CLP Regulation 1272/2008/EC and with H410 (Very toxic to aquatic life with long lasting effects), M-factor = 1, according to Commission Regulation (EU) No. 286/2011.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

The dossier submitter (DS) proposed to harmonise the classification for IPBC as Aquatic Acute 1, H400 (M=10) and Aquatic Chronic 1, H410 (M=1) according to CLP, and R50 (very toxic to aquatic organisms) according to DSD.

Degradation

Degradation was studied in two hydrolysis tests, a photolysis test, a ready and inherent biodegradability test and an anaerobic (water/sediment) and an aerobic (soil) degradation test.

According to the information presented in the dossier, IPBC can be considered hydrolytically stable and is not affected by direct or indirect photolysis in the aquatic environment, but it degraded rapidly in the atmosphere by reaction with OH radicals, although the presence of this compound in air is not expected due to its low vapour pressure.

IPBC is not readily biodegradable under test conditions (OECD TG 301F), however a modified Zahn-Wellens test (OECD TG 302B) shows that IPBC is rapidly transformed under the conditions of the test into the major metabolite PBC (within 2 hours) by the elimination of iodine.

Although no valid screening tests for freshwater were available, in the anaerobic water-sediment study IPBC was rapidly degraded to PBC (maximum 95%) in non-sterile

medium with $DT50_{whole\ system}$ of 3.3 h, $DT50_{water\ phase}$ of 1.4 h and $DT50_{sediment}$ of 2.2 h at 12ºC. Non-extractable residues were 3.9 – 6.3% after 162/119 days and the mineralization was 10% after 120 days. This conclusion was in agreement also with a sterile system although in this case no mineralization was found.

Two different degradation products appeared in this anaerobic water/sediment test, PBC with a $DT50_{whole\ system}$ of 26 days at 12ºC (89/13 % water/sediment) and 2-PBC which was found as an intermediate product before the complete mineralisation to the ultimate degradation products CO_2 and CH_4.

In an aerobic soil degradation study, it could be shown that IPBC is rapidly degraded primarily by microorganisms with a DT_{50} of 5 h at 12 ºC. PBC was the major soil metabolite formed accounting for a maximum value of 95.0% of applied radioactivity 12 hours after treatment. After a short lag period, PBC was also rapidly degraded, DT50 of 9.57 days at 12ºC. CO_2 accounted for up to 75.3 % of applied radioactivity after 21 days of incubation in nonsterile samples incubated at 22ºC. Bound residues reached a maximum value of 21.4% after approx. 7 days.

Based on both studies (anaerobic water/sediment and soil tests) the DS proposed to confirm IPBC as well as PBC as rapidly degradable substances in water.

Bioaccumulation
Experimental BCF was not available and therefore, a calculated BCF value was provided in the dossier. The BCF_{fish} was calculated using the log K_{ow} of 2.81 (pH 4 to 7) according to the TGD in Risk assessment and a value of 48.8 can be deducted, which shows a low potential for bioaccumulation.

Aquatic toxicity
Six acute toxicity studies in fish, one in invertebrates and two in algae were reported by the DS. In addition, one long-term toxicity study in fish (35 days, *Pimephales promelas*), one in aquatic invertebrates and two in algae were provided.

Three acute studies on IPBC's main degradation product (PBC) were also available.

The algae (*Scenedesmus subspicatus*) is the most sensitive taxonomic group in acute and chronic tests for IPBC, with ErC_{50} value of 0.053 mg/l and NOErC of 0.0046 mg/l (ErC_{10} = 0.013 mg/L) based on measured concentrations. These two values were used as key studies for classification. Regarding the PBC, it shows a lower toxicity than the parent compound, with values of EC_{50}/LC_{50} from 41.3 to 85 mg / L for the three trophic levels.

Comments received during public consultation

Germany and the Netherlands proposed to add H410 (CLP) to the environmental labelling, and Germany requested to complement the H-statement H410 with M-factor 10 according to CLP and R50 with R53 according to DSD. Germany and Sweden did not agree with the DS on that IPBC would be rapidly biodegradable since it does not pass the ready test and according to Germany the variable measured in the inherent biodegradability test was not DOC as had been incorrectly stated in table 21 of the CLH report.

The DS provided their responses to the public consultation comments and did not agree with German and Swedish proposal because of the "ready" biodegradability is only one criterion to demonstrate that a substance is "rapidly" degradable. According to CLP (2^{nd} ATP- 4.1.2.9.5) a substance can be considered rapidly degradable if (c) other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level of > 70% within a 28-day period.

According to the DS, two different tests, anaerobic water-sediment and aerobic soil studies

confirm that IPBC degrades rapidly in natural environments and therefore it can be classified as "rapidly" degradable.

After considering the comments received during PC, the DS agreed with Germany that inherent biodegradation cannot be proven because the DOC information was lacking. Also, the DS did not agree with the proposal to complete proposed environmental classification and labelling for the risk phrase R53 according to DSD, since R53 should be assigned to substances which are not readily degradable. There are three criteria for ready degradability (5.2.1.3 of Annex 6 of 2001/59/EC). The first and the second criteria (a and b) are based on tests of ready and inherent degradation, which are not fulfilled by IPBC. However, the third criterion (c) "if other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level of > 70 % within a 28-day period", is fully met by IPBC in anaerobic water-sediment and aerobic soil studies.

After considering the comments received during PC, the DS agreed that in the label for the IPBC, the statement H410 should be included as the classification of Aquatic Chronic 1 is established. However, the DS did not agree to conclude this classification with an M-factor of 10, because they believed that the substance is rapidly degradable and therefore an M= 1 should be considered (please see the DS's reply to the comments in Annex 2 to the opinion, i.e. RCOM).

Assessment and comparison with the classification criteria

Degradation

There are different studies for IPBC which can be used in assessment of the degradation as an intrinsic property of the substance.

The reported ready biodegradability test (OECD TG 301B) shows that the substance is not readily biodegradable, although the concentration of the test substance (50 mg/l) is close to the inhibition concentration for microorganisms (EC_{20} = 57 mg/l).

The inherent biodegradability test (OECD 302B) shows that IPBC is rapidly transformed under the conditions of the test into the major metabolite PBC (within 2 hours) by the elimination of iodine, however this test is not suitable for the assessment of rapid degradation due to the lack of DOC data and the optimised conditions in the test that stimulate adaptation of microorganisms increasing the biodegradation potential, although it can be used as additional information.

The anaerobic water-sediment study showed that IPBC primarily degrades at test conditions with a half-life of a few hours, however, anaerobic studies should not be used for classification purposes as recommended in The Guidance on Application of the CLP Criteria *(EC) No 1272/20088 (p. 484)*, although as well as the inherent test it can be used as additional information.

In an aerobic soil degradation study, it could be shown that IPBC is rapidly degraded primarily by microorganisms with DT_{50} of 5 h at 12ºC. PBC was the major soil metabolite formed accounting for a maximum value of 95% of applied radioactivity 12 hours after treatment. After a short lag period, PBC was also rapidly degraded, DT_{50} of 9.57 days at 12°C. CO_2 accounted for up to 75.3% of applied radioactivity after 21 days of incubation in nonsterile samples incubated at 22ºC. The results of the aerobic soil degradation test, i.e. the observed degradation, can be considered when assessing the rapid degradation of the substance, and it is in agreement with CLP (2^{nd} ATP-4.1.2.9.5) and The Guidance on Application of the CLP Criteria (EC) No 1272/2008 (p.484).

The degradation products do not have an impact on the environmental hazard classification of IPBC.

According to the Guidance of application of CLP (p. 482) the evaluation of data on fulfilment of this criterion should be conducted on a case-by-case basis by expert judgement. In general, only data from aquatic biodegradation simulation tests are considered directly applicable. However, simulation test data from other environmental compartments could be considered as well.

Therefore, taking into account all the reported information and expert judgement, RAC proposed that IPBC be considered as **rapidly degradable according to the CLP criteria and readily degradable according to the DSD criteria** because there are enough available convincing scientific evidence to demonstrate that the substance can be degraded rapidly in the environment.

Bioaccumulation
In the current CLP criteria (2nd ATP) bioaccumulation is important only if the surrogate approach is applied for assessing long-term hazards. For IPBC chronic adequate toxicity data is available for all trophic levels and therefore, bioaccumulation data is not used in classification according to CLP. However, under the DSD bioaccumulation should be used for assessing long-term adverse effects but in this case does not meet the criteria for classification, since the measured log K_{ow} for IPBC is 2.81.

Aquatic toxicity
Under CLP, the acute toxicity category should be based in the lowest ErC_{50} of 0.053 mg/l which corresponds to *Selenastrum capricornutum*, this value is ≤ 1 mg/l, therefore IPBC should be classified as Acute category 1 (H400), with a M-Factor of 10, since the LC_{50} is between 0.01 and 0.1 mg/l.

Regarding chronic toxicity, IPBC classifies as Chronic category 1 (H410) with an M-Factor of 1, since the lowest NOEC value is between 0.001 and 0.01 (i.e. NOErC for *Scenedesmus subspicatus* = 0.0046 mg/l*)* and it is considered as a rapidly degradable substance.

Under DSD, the key study for acute toxicity has an EC_{50} value of 0.053 mg/l (*Selenastrum capricornutum*), which is below the classification criterion of 1 mg/l, therefore IPBC should be classified as N; R50. IPBC is considered as rapidly degradable substance and it fulfils the criteria of ready degradability according to the DSD. Therefore, classification for long-term adverse effects (R53) under DSD is not justified.

RAC agreed with the DS proposal. RAC proposed to classify IPBC according to the CLP criteria as hazardous to the aquatic environment, **Acute Category 1 (H400)** with an M-Factor 10 and in addition to add **Chronic Category 1 (H410)** with an M-Factor 1 and according to the DSD criteria as **N; R50 with specific concentration limits** N; R50 C ≥ 2.5 %.

Supplemental information - In depth analyses by RAC

Biotransformation products:
Three different biotransformation products were identified:

PBC appears as the major metabolite of IPBC, with a maximum value of 95.0% in the soil degradation study. It can be considered to be rapidly degradable, it shows no potential for bioconcentration (log K_{ow} 1.64) and has a lower acute toxicity (LC_{50} from 41.3 to 85 mg/l). Therefore the classification of the parent compound is more restricted than the PBC.

Iodine is currently under discussion for inclusion in Annex I of the Biocides Directive 98/8/EC. SE is carrying out the assessment and according to the information included in the

dossier, the Swedish proposal is N, R50 (DSD) and Aquatic Acute 1; H400 M = 1 (CLP (2nd ATP)), therefore iodine does not have impact on classification of IPBC.

2-PBC was found at a concentration > 10% in one degradation study; however this metabolite is only found under anaerobic conditions and according to the report the estimated toxicity based on QSAR (EPIWIN) was found to be comparable to that of IPBC. No experimental ecotoxicological data of this metabolite was supplied. There are not available data to carry out classification assessment of this metabolite.

6 OTHER INFORMATION

No information available

7 REFERENCES

The Reference list of all documents cited in this report is attached as Annex IV.

8 ANNEXES

ANNEX I

Proposal for split-entry classification of IPBC concerning inhalation toxicity: attached as a separate document

ANNEX II

(copied from the commenting table "Response to comments from Member States and applicant on the draft assessment report on 3-Iodo-2-propynyl butyl carbamate (IPBC) - comments concerning Mammalian toxicology only" from 13.04.2007)

Additional information submitted by applicant after CA had finalized the evaluation; it concerns the human relevance of the larynx effect seen in rats

"The applicant disagrees with the RMS: The laryngeal lesions observed in the rats exposed to IPBC are typical of the exposure-induced non-specific lesions observed in the upper respiratory tract of rodents exposed to a variety of materials. For example, similar lesions have even been observed with aerosolized glycerol (Renne et al., 1992). Lesions in nasal passages and laryngeal region of rodents are considered to be related to air flow characteristics and regional epithelial sensitivity (Chevalier and Dontenwill, 1972; Gopinath et al., 1987; Lewis, 1991; Morgan and Monticello, 1990; Renne and Miller, 1996; Miller and Renne, 1996; Harkema, 1999).

The thin epithelium covering the larynx in the rat is susceptible to injury by inhaled particles deposited by impaction due to the high velocity of air flow through the larynx with its small diameter. Because the epithelium is thin, damage to the epithelium may extend to the underlying delicate laryngeal cartilage. Damage to the epithelium is manifest by reparative hyperplasia as a protective mechanism. This may progress to metaplasia if the damage is sufficiently severe as seen in the 6.7 mg/m^3 exposure group. The underlying cartilage is slow to repair and damage is evident as necrosis.

Extensive research has been conducted on the upper respiratory tract region of rodents and humans that provides an extensive body of knowledge for understanding why rodents are hyper-sensitive to upper respiratory tract injury from inhaled materials as compared to humans (Miller, 1995; Harkema, 1999). Most of the attention has been directed to the nasal passages and have provided increased insight into why the nasal passages of rats are generally more sensitive to injury than the nasal passages of humans. Indeed, these differences have been recognized by regulatory agencies such as the US EPA in establishing Reference Inhalation Concentrations (RfCs) for various chemicals. For example, the LOAEL or NOAEL values determined in rats were adjusted upward to create human equivalent LOAEL and NOAEL values for hydrogen sulfide and hydrogen chloride (IRIS, 2003). These adjustments take into account the fact that the human must inhale a higher concentration of the chemical than does the rat to achieve equivalent local tissue doses.

Although less attention has been directed to comparing the rat and human larynx the data available point to the need for making similar adjustments, as for nasal passages, when extrapolating from laboratory animal species to humans. Proctor (1989) was one of the pioneers who emphasized the importance of understanding species differences. He noted, "We are in the paradoxical situation of having a special need to carry out investigations in the living human, but in many instances are faced with the impossibility of doing so. While we are forced to seek much of our information on the upper airways from non-human investigations, we must be especially cautious about extrapolating conclusions applicable to the health of humans."

Proctor (1989) called attention to a number of the factors influencing species differences in the deposition of inhaled materials. Humans breathe through both their nose and mouth whereas rats are obligate nose breathers. This results in differences in the two species in the air flow and degree of turbulence produced as the inhaled air mass proceeds from the nose and/or mouth to

the nasal and oral pharynx to the glottis and larynx and on to the trachea. Proctor (1989) provided a schematic figure showing the main lines of inspiratory air flow in humans and rats to make the point. In the human, the pattern is similar to an upside down "L" with the nares at the tip of the "L," the nasopharynx at the junction between horizontal flow and vertical flow down past the glottis. In the rat there is essentially a straight horizontal line of flow from the nares to the glottis and larynx. Thus, the rat has inspiratory flow lines with minimal turbulence as compared to humans. This favors deposition by impaction in the nasal passages and the larynx of the rat as compared to the human. As Proctor (1989) noted, "The significant differences and their probable effect on particle deposition are self-evident." He went on to note – "We should recognize the fact that in measuring the fate of inhaled materials during their inspiration through the upper air ways, research in animals may lead to misleading information. Not only are the main lines of inspiratory airflow very different, but animals rarely employ oronasal breathing, do not indulge in conversation, and do not blow their noses."

The admonishments of Proctor have been borne out by recent work modeling upper respiratory tract dosimetry for inhaled particles in humans and rats. Asghanan and Miller (2003) have extended earlier work (Anjilud and Asgharian, 1995; Asgharian, Hofmann and Bergmann, 2001) and calculated that the Human Equivalent Concentration would have to be 2 to 4 times greater than the Rat Exposure Concentration for particles 0.3 to 5 µm in aerodynamic diameter to achieve equivalent tracheobronchial deposition. A similar or larger factor likely applies to the larynx. For example, Raabe et al (1977, 1988) exposed rats to monodisperse particles ranging in aerodynamic size from less than 0.2 µm to 3.05 µm. They found with the 3.05 µm particles the following deposition: nasopharynx – 34.8%; larynx – 3.4%; tracheobronchial – 5.4%; and pulmonary – 4.9%. The authors attributed the high fractional deposition of the large particles to their inertial properties.

ANNEX III

Statement of the European Union IPBC Task Force on the proposal of Germany to apply R53 to IPBC in addition to the classification and labelling proposed in the CA report on IPBC Dossier (submitted 2004 for PT8): attached as a separate document

ANNEX IV

References

Author(s)	**Section No./ Reference No.**	**Year**	**Title Source (laboratory) Report No. GLP; (un)published Doc. No.**	**Data protection**	**Owner**
[redacted]	A6.3.1/ 05	1987	Iodopropynylbutyl carbamate (IPBC) 8 week dietary dose range finding study in mice [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	200	Repeated dose toxicity 90-day oral toxicity study in rats with	Yes (Data on	DOW Benelux

	01	2	IPBC technical (Protram TM 98) [redacted] GLP, unpublished [redacted]	existing a.s. submitted for the first time for entry into Annex I.)	B.V.
[redacted]	[redacted]	1992	Anaerobic aquatic metabolism study of P-100 [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1992	Aerobic soil metabolism study of P-100 [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1994	Acute toxicity of Omacide IPBC to the fathead minnow (Pimephales promelas) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1994	Acute toxicity of Omacide IPBC to the rainbow trout, Oncorhynchus mykiss [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1994	Acute toxicity of Omacide IPBC to the daphnid, Daphnia magna [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1994	Growth and reproduction test with Omacide IPBC and the freshwater alga, Selenastrum capricornutum [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals

Bryld, L.E. Agner, R. Rastogi, S.C.	A6.12.6 /01	1997	Iodopropynyl butylcarbamate: a new contact allergen Contact Dermatitis vol. 36, pp. 156-158, 1997 Report No.: Not applicable Not GLP, published Doc. No.: 592-003	No	N.R.
Bryld, L.E. Agner, T. Menné, T.	A6.12.6 /04	2001	Allergic contact dermatitis from 3-iodo-2-propynyl-butylcarbamate (IPBC) - an update Contact dermatitis, 2001, Vol. 44, pp. 276-278 Report No.: Not applicable Not GLP, published Doc. No.: 592-009	No	N.R.
[redacted]	[redacted]	1988	3-iodo-2-propynyl butyl carbamate (IPBC) chronic dietary toxicity study in rats [redacted] GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	2001	[redacted] Particle size distribution of TROYSAN Polyphase P-100 [redacted] GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation Confidential business information!
[redacted]	[redacted]	1985	Acute inhalation limit test in rats 3-iodo-2-propynyl butyl carbamate [redacted] Not GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1995	Review and interpretation of selected thyroid and forestomach lesions in the carcinogenicity study of 3-iodo-2-propynyl butyl carbamate (IPBC) in sprague-dawley rats [redacted] Not GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1984	90-Day subchronic oral toxicity test in rats [redacted]	Yes (Data on existing a.s.	TROY Corporation

			[redacted] GLP, unpublished [redacted]	submitted for the first time for entry into Annex I.)	
[redacted]	[redacted]	2005	Statement on the explosive properties of 3-Iodopropynylbutyl Carbamate (IPBC) [redacted] Not GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	IPBC Task Force (ARCH, DOW, ISP, LANXESS, TROY)
[redacted]	[redacted]	2005	Statement on the oxidising properties of 3-Iodopropynylbutyl Carbamate (IPBC) [redacted] Not GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	IPBC Task Force (ARCH, DOW, ISP, LANXESS, TROY)
[redacted]	[redacted]	2002	Ready biodegradability of IPBC in a manometric respirometry test [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	2002	Toxicity of IPBC to activated sludge in a respiration inhibition test; [redacted] GLP; (unpublished); [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	2001	Preventol MP 100 - Salmonella/Microsome test plate incorporation and preincubation method [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	2001	Preventol MP 100 - In vitro chromosome aberration test with chinese hamster V79 cells [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH

[redacted]	[redacted]	2001	Preventol MP 100 - V79/HPRT-Test in vitro for the detection of induced forward mutations [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	2002	Toxicity of IPBC to activated sludge in a respiration inhibition test; [redacted] GLP; (unpublished); [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	DOW Benelux B.V.
[redacted]	[redacted]	1990	TROYSAN Polyphase P-100 - Acute inhalation toxicity study in the rat [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1995	The in vitro percutaneous absorption through human abdominal epidermis of [14C]-IPBC (3-Iodo-2-Propynyl-N-Butyl-Carbamate) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1994	Acute inhalation toxicity in rats 4-hour exposure to Omacide IPBC [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	2000	Preventol MP 100 - Physicochemical properties [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	200	Preventol MP 100 - Water solubility	Yes (Data on	LANXESS Deutschland

		0	[redacted] GLP, unpublished [redacted]	existing a.s. submitted for the first time for entry into Annex I.)	GmbH
[redacted]	[redacted]	2000	Preventol MP 100 - Partition coefficient (n-octanol/water) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	2001	Preventol MP 100 - Abiotic degradation [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	1994	Omacide IPBC - 2-week repeat dose inhalation toxicity study in rats [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1994	Omacide IPBC - 5-day repeat dose inhalation toxicity study in rats [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1994	Omacide IPBC - 13-week inhalation toxicity study in rats [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	2000	Preventol MP 100 - Acute oral toxicity study in male and female wistar rats [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	2000	Preventol MP 100 - Acute dermal toxicity study in male and female wistar rats [redacted]	Yes (Data on existing a.s. submitted for the first time	LANXESS Deutschland GmbH

			GLP, unpublished	for entry into Annex I.)	
		1993	TROYSAN Polyphase P-100 - The guinea pig maximization test GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
		2000	Acute skin irritation test (patch test) of Preventol MP 100 in rabbits GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
		2004	Determination of the flammability of IPBC technical GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	IPBC Task Force (ARCH, DOW, LANXESS, TROY)
		2004	Determination of the relative self-ignition temperature of IPBC technical GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	IPBC Task Force (ARCH, DOW, LANXESS, TROY)
		1991	TROYSAN Polyphase P-100 - Acute toxicity to sheepshead minnow (Cyprinodon variegatus) under flow-through conditions GLP, unpublished	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
		1992	TROYSAN Polyphase P-100 - Toxicity to fathead minnow (Pimephales promelas) embryos and larvae	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation

			GLP, unpublished [redacted]		
[redacted]	[redacted]	1984	In vivo micronucleus assay in mice 3-iodo-2-propynyl butyl carbamate (IPBC) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1988	Polyphase cholinesterase inhibition study in rats [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	2002	IPBC – Acute toxicity to bacteria (Pseudomonas putida) [redacted] GLP; (unpublished) [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1997	Product chemistry determinations of IPEX 1000 (Color, Physical State) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	DOW Benelux B.V.
[redacted]	A6.7/01	1989	3-iodo-2-propynyl butyl carbamate (IPBC) 104 week dietary carcinogenicity study in rats (Volume 1 and 2) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	A6.7/04	1989	IPBC 78 week dietary carcinogenicity study in mice Volume 1 to 3 (803 pages) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation

[redacted]	[redacted]	2001	Preventol MP 100 - Acute Fish Toxicity [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	2000	Preventol MP 100 – Toxicity to bacteria [redacted] GLP; (unpublished) [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	2000	Preventol MP 100 - Vapor pressure, Physical-chemical properties [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	2000	Preventol MP 100 - Surface tension, physical-chemical properties [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	1987	TROYSAN Polyphase two generation oral (dietary administration) reproduction toxicity study in the rat (one litter per generation) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
Pazzaglia, M. Tosti, A.	A6.12.6/06	1999	Short Communications - Allergic contact dermatitis from 3-iodo-2-propynyl-butylcarbamate in a cosmetic cream Contact Dermatitis, Vol. 41, pp. 290, 1999 Report No.: Not applicable Not GLP, published Doc. No.: 592-006	No	N.R.
[redacted]	[redacted]	2001	Toxicity of Polyphase P-100 to Scenedesmus subspicatus in a 72-hour algal growth inhibition test - (Included the Analytical Report - Determination of the	Yes (Data on existing a.s. submitted for the first time	TROY Corporation

			Concentrations of the test item in test medium) [redacted] GLP, unpublished [redacted]	for entry into Annex I.)	
[redacted]	[redacted]	2005	Aqueous Photolysis of IPBC and Determination of the Quantum Yield [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	IPBC Task Force (ARCH, DOW, ISP, LANXESS, TROY)
[redacted]	[redacted]	1994	Physical and chemical properties of 3-iodo-2-propynylbutylcarbamate (Omacide IPBC) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1993	Omacide IPBC - Micronucleus cytogenetic assay in mice [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1992a	(Propargyl Butyl Carbamate) - Acute Toxicity to rainbow trout (Oncorhynchus mykiss) under flow-through condition [redacted] GLP; (unpublished) [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1992b	(Propargyl Butyl Carbamate) - Acute Toxicity to daphnids (Daphnia magna) under flow-through conditions [redacted] GLP; (unpublished) [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	199	Hydrolysis of 14C-3-iodo-2-propynyl-n-butylca	Yes (Data on	ARCH

[redacted]	[redacted]	4	rbamate (14C-IPBC) [redacted] GLP, unpublished [redacted]	existing a.s. submitted for the first time for entry into Annex I.)	Chemicals
[redacted]	[redacted]	1990	[redacted] Melting Point of TROYSAN Polyphase P100 3-Iodo-2-Propynyl Butyl Carbamate [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
Shimizu, M. Yamano, T. Noda, T.	A6.8.1	2000	Allergenicity evaluation of chemicals for use in household products (IV) - Contact allergenicity of three halide bactericides, 3-iodo-2-propynyl butylcarbamate (IPBC), p-chlorophenyl-3-iodopropargylformyl (CPIP) and BECDIP in Guinea pigs Seikatsu Eisei, Vol. 44, No. 3, pp. 129-138, 2000 Report No.: Not applicable Not GLP, published Doc. No.: 592-008	No	N.R.
[redacted]	[redacted]	2002	Final Report: IPBC Determination of the Vapour Pressure [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	DOW Benelux B.V.
Schnuch, A. Geier, J. Brasch, J. Uter, W.	A6.12.6/05	2002	The preservative iodopropynyl butylcarbamate: frequency of allergic reactions and diagnostic considerations Contact Dermatitis 2002, 46, 153-156 Report No.: ISSN 0105-1873 Not GLP, published Doc. No.: 592-010	No	N.R.
[redacted]	[redacted]	1996	A 2-week range-finding study of TROYSAN Polyphase P100 in the rabbits via dietary administration [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1997	A subchronic (3-month) toxicity study of TROYSAN Polyphase P100 in the rabbits via dietary	Yes (Data on existing a.s.	TROY Corporation

			administration [redacted] GLP, unpublished [redacted]	submitted for the first time for entry into Annex I.)	
[redacted]	[redacted]	1986	Iodopropynylbutyl carbamate (IPBC) 4 week dieatry dose range finding study in rats [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	2004	Inherent Biodegradability of IPBC in a modified "Zahn-Wellens /EMPA Test" [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	IPBC Task Force (ARCH, DOW, LANXESS, TROY)
[redacted]	[redacted]	1990	Analysis of Polyphase P100 - Octanol/Water Partition coefficient (63-11) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1991	91-day dermal toxicity study in rats with TROYSAN Polyphase P-100 [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1990	TROYSAN Polyphase P-100 - Acute toxicity to bluegill sunfish (Lepomis macrochirus) under flow-through conditions [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	1990	TROYSAN Polyphase P-100 - Acute toxicity to rainbow trout	Yes (Data on	TROY Corporation

			(Oncorhynchus mykiss) under flow-through conditions [redacted] GLP, unpublished [redacted]	existing a.s. submitted for the first time for entry into Annex I.)	
[redacted]	[redacted]	2001	Preventol MP 100 - 3-iodo-2-propynyl-n-butyl carbamate (IPBC) - Study for subacute oral toxicity in rats (gavage study over 4 weeks and 2 weeks recovery period) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	1994	Omacide IPBC - Oral (Gavage) rabbit developmental toxicity study [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1994	Omacide IPBC - Oral (Gavage) rat development toxicity (Teratogenicity) study [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	1996	Omacide IPBC - Oral (Gavage) rat one generation (expanded to two generation) reproductive toxicity study (3 Volumes) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals
[redacted]	[redacted]	2001	Preventol MP 100 - Study for the skin sensitization effect in guinea pigs (Guinea pig maximization test according to Magnusson and Kligman) [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	LANXESS Deutschland GmbH
[redacted]	[redacted]	199	TROYSAN Polyphase P-100 -	Yes	TROY

	/01	1	Chronic toxicity to the water flea, Daphnia magna, under flow-through test conditions [redacted] GLP, unpublished [redacted]	(Data on existing a.s. submitted for the first time for entry into Annex I.)	Corporation
[redacted]	[redacted]	1997	Growth and Reproduction Toxicity test with Propargal Butyl Carbamate and the Freshwater Alga, Selenastrum capricornutum [redacted] GLP; (unpublished) [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	TROY Corporation
[redacted]	[redacted]	2001	Acute oral neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) administered by gavage in CD rats - Volume 1 of 3 [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals TROY Corporation
[redacted]	[redacted]	2001	Acute oral neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) administered by gavage in CD rats - Volume 2 of 3 [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals TROY Corporation
[redacted]	[redacted]	2001	Acute oral neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) administered by gavage in CD rats - Volume 3 of 3 [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	ARCH Chemicals TROY Corporation
[redacted]	[redacted]	2001	13-week dietary neurotoxicity study with 3-iodopropynylbutyl carbamate (IPBC) in CD rats Volume 1 of 4 [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into	ARCH Chemicals TROY Corporation

			[redacted] GLP, unpublished [redacted]	Annex I.)	
[redacted]	[redacted]	1998	Primary eye irritation - IPEX 1000 [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	DOW Benelux B.V.
[redacted]	[redacted]	1998	Dermal sensitization test - Buehler Method - IPEX 1000 [redacted] GLP, unpublished [redacted]	Yes (Data on existing a.s. submitted for the first time for entry into Annex I.)	DOW Benelux B.V.
Zissu, D.	A6.1.5	2002	The sensitizing potential of various biocides in the guinea pig maximization test Contact Dermatitis 2002, 46, 224-227 Report No.: Not applicable Not GLP, published Doc. No.: 592-012	No	N.R.