Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

3-iodo-2-propynyl butylcarbamate (IPBC)

EC number: 259-627-5

CAS number: 55406-53-6

ECHA/RAC/CLH-O-CLH-O-0000001550-84-03/F

Adopted

28 November 2012

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CLH-O-0000001550-84-03/F

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

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

Substance Name: **3-iodo-2-propynyl butylcarbamate (IPBC)**

EC number: **259-627-5**

CAS number: **55406-53-6**

The proposal was submitted by **Denmark** and received by the RAC on **29 June 2011.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification

	CLP	**DSD**
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	**Not included in Annex VI, Table 3.1**	**Not included in Annex VI, Table 3.2 (CLP)**
Proposal by dossier submitter for consideration by the RAC	Acute Tox. 3 - H331 Acute Tox. 4 - H302 Eye Dam. 1 - H318 Skin Sens. 1 - H317 STOT SE 3 - H335 Aquatic Acute 1 - H400, M=10 Aquatic Chronic 1 - H410, M= 1	T; R23 Xn; R22 Xi; R37-41 R43 N; R50
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by the dossier submitter	Acute Tox. 3 - H331 Acute Tox. 4 - H302 Eye Dam. 1 - H318 Skin Sens.1 - H317 STOT SE 3 - H335 Aquatic Acute 1 - H400, M=10 Aquatic Chronic 1 - H410, M= 1	T; R23 Xn; R22 Xi; R37-41 R43 N; R50

PROCESS FOR ADOPTION OF THE OPINION

Denmark has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **29/07/2011.** Parties concerned and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **12/09/2011**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **José Luis Tadeo**
Co-rapporteur, appointed by the RAC: **Normunds Kadikis.**

The opinion takes into account the comments provided by MSCA and parties concerned in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **28 November 2012** Comments received are compiled in Annex 2.

This RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that IPBC should be classified and labelled as follows[1]:

[1] Note that not all hazard classes have been evaluated

Classification & labelling in accordance with CLP

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
616-212-00-7	3-iodo-2-propynyl butylcarbamate	259-627-5	55406-53-6	Acute Tox. 3 Acute Tox. 4 STOT RE 1 Eye Dam. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H331 H302 H372 (larynx) H318 H317 H400 H410	GHS06 GHS08 GHS05 GHS09 Dgr	H331 H302 H372 (larynx) H318 H317 H410		M = 10 M = 1	

Classification & labelling in accordance with DSD

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
616-212-00-7	3-iodo-2-propynyl butylcarbamate	259-627-5	55406-53-6	T; R23-R48/23 Xn; R22 Xi; R41 R43 N; R50	T; N R: 22-23-41-43-48/23-50 S: (1/2-)26-39-45-63	N; R50: C ≥ 2.5 %	

SCIENTIFIC GROUNDS FOR THE OPINION

General comment

IPBC is a biocide without a current Annex VI entry under CLP. The current CLH proposal for 3-iodo-2-propynyl butylcarbamate is based on the classification and labelling proposal in the MSCA Report for Product Type 8 under the Biocidal Products Directive 98/8/EC submitted by Denmark as a reporting member state in 2004. The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by Denmark.

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 4; H302 (Harmful if swallowed) according to the Regulation 1272/2008 (CLP; DSD Xn; R22, Harmful if swallowed).

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. [redacted] had claimed as the notifier that the MMAD of technical IPBC was 79 µm with ≤ 5% of particles being smaller than 10 µm; later on his sponsor confirmed that no changes had been made to the production process between the 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 DS. 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 the 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 Public Consultation (PC), comments were received from an association of companies, the 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. This latter MSCA also proposed to compare the available data with the requirements of Pauluhn [2008][1] to conclude whether the conditions for a split-entry approach for acute inhalation toxicity were fulfilled.

Assessment and comparison with the classification criteria

The LD_{50} value determined in Wistar rats (dose levels 200 and 2000 mg/kg bw) [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). The 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. The RAC therefore supported the conclusion of the dossier submitter that IPBC should be classified as Acute Tox. 3; H331 (Toxic if inhaled) according to the CLP criteria and T; R23 (Toxic if inhaled) according to the DSD criteria.

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. The RAC therefore supported the conclusion of the DS that no classification is warranted for acute dermal toxicity.

Specific target organ toxicity – single exposure (STOT SE)

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 to be slightly irritating

[1] Pauluhn, J. (2008): Inhalation toxicology: Methodological and regulatory challenges; Experimental and Toxicological Pathology, 60, p.111-124

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 an appropriate method. In a 13-week dermal toxicity study [redacted] according to OECD TG 411, dermal irritation was observed occasionally in some animals 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. Similarly for this study the assessment of skin reactions was not performed according to an appropriate 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 proposed to the Dossier Submitter 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.

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

Assessment and comparison with the classification criteria

According to the 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 the DSD criteria, mean scores at each of the reading times (24, 48 or 72 h) for all animals tested are averaged.

According to DSD 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.

The RAC emphasized 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. The RAC therefore supported the conclusion of the DS that no classification is warranted for skin corrosion/irritation.

The RAC did not agree to add the supplementary hazard statement code EUH066 (CLP; DSD, R66) 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.

Eye corrosion/irritation

Summary of the Dossier submitter's proposal

The DS proposed to harmonise the classification for IPBC as Eye Dam. 1; H318 according to CLP, (DSD: Xi; R41), 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 (DSD:,R41). Several MSCAs 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.

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, DSD Xi; R41): 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 met 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 Competent Authority Report (CAR) for IPBC (March 2004, Section 6.1.4/02, Annex point IIA, VI.6.1.4) 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, the RAC considers that classification for Eye Dam 1; H318 according to CLP (DSD, Xi; R41) is warranted.

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.

Assessment and comparison with the classification criteria

The RAC considered that the human data supporting IPBC as a 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 Sensitization based on the positive key study [redacted] the available information on positive and negative controls was considered by the 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. The 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 fulfil the requirements of OECD TG 406 and the Buehler test is generally recognised in the scientific literature as being less sensitive than the GPMT. 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 the RAC supported the conclusion of the DS that classification of IPBC for Skin Sens. 1; H317 (DSD Xi; R43) is warranted. However, the data were not sufficiently robust for sub-categorisation.

Repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

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 for 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 was proposed by the DS 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.

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 outlined in paragraph 3.5.2 of the CLP regulation and according to the DSD, when considering the available in vitro and in vivo data, IPBC does not meet the criteria for classification as a mutagen. The RAC therefore supported the conclusion of the DS that no classification is warranted for mutagenicity.

Carcinogenicity

Summary of the Dossier submitter's proposal

No classification for carcinogenicity was proposed by the dossier submitter. Two oral dietary 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] males had an increased incidence in fibro-adenoma in the salivary gland at 80 mg/kg bw/d. In females, the incidence of mammary fibro-adenomas 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.

Assessment and comparison with the classification criteria

No human data are available with respect to carcinogenicity. With regard to the animal data, in female Sprague-Dawley rats [redacted] no neoplasms were observed after one year and 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, fore-stomach and salivary glands at this dose.

According to the DS, hepatocellular adenomas recorded in the CD-1 mice carcinogenicity study [redacted] are 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 of hepatocellular adenoma (11/50) was observed when compared to controls (4/50). Nevertheless, at 150 mg/kg bw/d, 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" ([redacted] 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 of hepatocellular adenomas 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 the RCOM. No statistically significant increase in the incidence of hepatocellular carcinomas or in foci of cellular alteration was observed. The 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 CLP, the placing of the substance in Category 2 can be done on the basis of limited evidence obtained from animal studies. The evidence of carcinogenicity in experimental animals is limited if e.g.: (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence

only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

According to the DSD, 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.
According to the 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 tumours, there were no multi-site responses; the lesions did not progress to malignancy, the responses were seen in a single sex and a single species and there was no evidence of mutagenic activity in vivo.

The increased tumor incidence following IPBC exposure was limited to hepatocellular adenomas in males (11/50, 22%) at the highest dose tested (MTD) in this particularly sensitive mouse strain ([redacted] 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.

The RAC therefore supported the conclusion of the DS that no classification is warranted for carcinogenicity according to the criteria outlined in paragraph 3.6.2 of the CLP Regulation and the DSD criteria.

Reproductive toxicity

Summary of the Dossier submitter's proposal

No classification for reproductive toxicity was proposed by the DS 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 [redacted] 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) and an additional rat study [redacted] 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 [redacted] and rats [redacted] were presented in the CLH report to cover developmental toxicity. Parameters for developmental toxicity were reported also in the two-generation reproductive study on rats [redacted] 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 [redacted] 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 [redacted]

In the two-generation reproductive study on rats [redacted] the 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 the stomach and/or bitten or cannibalised pups was noted at 30 and 100 mg/kg bw/d. However, these 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 sufficiently detailed information to serve as a basis for conclusive assessment of reproductive toxicity. They noted that 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 or not and whether the reproductive effects were 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 [redacted] 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.

Assessment and comparison with the classification criteria

The RAC noted that no human data was 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 the stomach of F_1 parents at 30 mg/kg bw/d (not examined in F_0 animals). Diffuse acanthosis with hyperkeratosis in the 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 were 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 aggressive 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 such as through 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 DSD 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.

According to the 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 is considered to be secondary to maternal toxicity. In conclusion, the RAC agreed with the DS that no classification for reproductive toxicity is justified as

both the CLP (outlined in the paragraph 3.7.2 of the CLP Regulation) and DSD criteria are not met.

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 as STOT SE 3; H335 (may cause respiratory irritation) according to CLP, DSD Xi; R37, irritating to the respiratory system). Their 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 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.

Assessment and comparison with the classification criteria

According to the CLP Guidance (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.

The RAC considered that the effects seen at IPBC concentrations of 0.0067 mg/l in the 90-day inhalation study [redacted] and at 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. The RAC concluded that since dyspnoea, salivation, lacrimation and rhinorrhea were observed

in the acute inhalation toxicity studies at toxic concentrations (LC_{50} values between 0.5 and 1 mg/l) and the criteria for classification for acute inhalation toxicity are met, the classification for STOT SE 3 proposed by the DS is not warranted. .

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:

Reduced body weights, body weight gain and food consumption were noted at high doses in several studies in mice, rats and rabbits [redacted]; [redacted] and [redacted] In the oral 14-day feeding dose range finding study in 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]

The observed effects (e.g. hyperkeratosis, acanthosis, erosions, ulceration) in the stomach and/or fore-stomach following oral IPBC administration [redacted] 1984; [redacted] and [redacted] were considered to be results of irritating properties of IPBC. Post-dose salivation observed directly after dosing in the gavage studies on rats [redacted] was considered to be a result of the dosing procedure and/or irritating properties of IPBC.

Liver weights (absolute and/or relative) were increased in many studies and were sometimes accompanied by hepatocellular changes, [redacted] and [redacted] In a rat study with a 14-day recovery period, increased liver weights and histological changes in hepatocytes were reversible [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] Also 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 a 104-week oral study in rats, there was an increased incidence in lobular degeneration of the salivary gland at 40 and 80 mg/kg bw/d in both sexes an increased incidence in fibro-adenoma in males in this organ at 80 mg/kg bw/d. Also an increased incidence in foamy macrophages aggregates was noted in male lungs at 40 and 80 mg/kg bw/d and plasma cholinesterase activity was reduced in females at 80 mg/kg bw/d at termination.

In an oral 78-week feeding study in CD-1 mice [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 higher doses,. In the study by [redacted] the reduced body weight and body weight gain in males were observed at 250 mg/kg/d and higher doses. Reduced body weight gain was observed in females at 500 mg/kg/d and higher dosis. 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 indications 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).

Assessment and comparison with the classification criteria

The 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 (DSD T; R48/23). This classification is based on the high incidence (all rats in the high dose group) of the effects in larynx (necrosis of the ventral cartilage, epithelial hyperplasia in the ventral region and squamous metaplasia in the 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, the RAC concluded that classification as STOT RE 1; H372 (larynx) (CLP) and T; R48/23 (DSD) is justified. The 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.

Environmental hazards

Summary of the Dossier submitter's proposal

The 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 (DSD, R50 - very toxic to aquatic organisms).

Degradation

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

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

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

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, IPBC was 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, with a DT50 of 9.57 days at 12ºC. CO_2 which accounted for up to 75.3 % of applied radioactivity after 21 days of incubation 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

An experimental BCF was not available but a calculated BCF value was provided in the dossier. The BCF_{fish} was calculated using a log K_{ow} of 2.81 (pH 4 to 7) yielding a value of 48.8, which shows a low potential for bioaccumulation.

Aquatic toxicity

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

assessing acute toxicity to microalgae were also used in calculating NOErC values for chronic toxicity.

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 based on measured concentrations. These two values were used as key studies for classification. Regarding the PBC metabolite, 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 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 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 the additional proposed environmental classification and labelling with R53 according to the 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 proposed that IPBC be should be classified as Aquatic Chronic 1 with an M factor of 1, this latter due to rapid degradability.

Assessment by RAC and comparison with the classification criteria

Degradation
There are different studies for IPBC which can be used in the 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 and that the concentration of the test substance applied (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. It can be used as additional information under certain circumstances.

The anaerobic water-sediment study showed that IPBC primarily degrades under the 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 in addition to the inherent test it can be also be used as additional information.

In an aerobic soil degradation study, IPBC was rapidly degraded primarily by microorganisms with a 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, with a DT_{50} of 9.57 days at 12°C. CO_2 and accounted for up to 75.3% of the applied radioactivity after 21 days of incubation 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, the RAC proposed that IPBC be considered as **rapidly degradable according to the CLP criteria and readily degradable according to the DSD criteria** because there is enough scientific evidence available to demonstrate that the substance can be degraded rapidly in the environment.

Bioaccumulation
In the current CLP criteria (2^{nd} 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 E/LC_{50} value which corresponds to an ErC50 of 0.053 mg/l for *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 should be classified 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 to be 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.

The RAC therefore agrees with the DS 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 (DSD: **N; R50 with specific concentration limits**C ≥ 2.5 %).

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by the RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information).