COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Last data extracted on 03.09.2019

Substance name: piperonyl butoxide (ISO); 2-(2-butoxyethoxy)ethyl 6-propylpiperonyl ether
CAS number: 51-03-6; (12750-92-4)
EC number: 200-076-7
Dossier submitter: Greece

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2019	France		MemberState	1
Comment received				
FR: In the table 3, we suggest to indicate "not classified" in the column "proposed classification" when "conclusive but not sufficient for classification" is mentioned in the column "reason for no classification" for hazards properties.				

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Germany	Endura S.p.A.	Company-Manufacturer	2
Comment received				
Endura S.p.A. agrees that the sub-acute dermal study may justify EUH066 even though the relevant findings were observed after repeated exposure for 6 h/day under semi-occlusive coverage. These conditions are not relevant for dermal exposure scenarios in real life. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20190829_PBO CLH Endura Comments.pdf				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2019	Germany		MemberState	3
Comment received				
Non-classification is not supported and category 2 is proposed. Carcinogenicity was intensively discussed during the biocide peer review procedure and it was concluded that "PBO should be considered as a potential carcinogen with a threshold mode of action." The following arguments should be in support of Carc. 2 rather than non-classification: - Although the MTD was exceeded in the rat study by Takahashi 1994a, this does not justify exclusion of this study from further WoE analysis. Mortality related to caecal haemorrhage was limited to wk 45-58 and males of the mid dose group (not reported in high dose and females). Hepatic adenoma and carcinoma were observed in this study from the mid-dose level of approx. 1000 mg/kg bw/d with adenoma only in the low dose group (500 mg/kg bw/d). Notably, the highest dose in the rat study Anony-mous-10 was				

500 mg/kg bw/d. Therefore, it should be concluded that hepatic neo-plasia was observed in two species (rather than one species).
- Tumor incidences observed in rat by Takahashi 1994a should be reported. In the independent review prepared for the PBO Task Force by W.H. Butler, visiting the laboratory, the following incidences were confirmed: adenoma in M/F: 0/0, 0/0, 8/1, 13/11; carcinoma in M/F: 0/0, 0/0, 3/0, 7/5 (according to Table II of the report by Butler).
- GST-P positive foci in gpt delta rats were reported by: Matsushita K, Kijima A, Ishii Y, Takasu S, Jin M, Kuroda K, Kawaguchi H, Miyoshi N, Nohmi T, Ogawa K, Umemura T. Development of a Medium-term Animal Model Using gpt Delta Rats to Evaluate Chemical Carcinogenicity and Genotoxicity. At 12000 ppm in feed over 4 weeks, number and size of foci was increased significantly over controls ($n=15$, $p<0.01$). Mu-tation frequencies were unaltered, supporting the suggested non-genotoxic MoA.
- While the involvement of CAR in the MoA was intensively studied, concerns about AhR activation during biocides peer review were not addressed. The data summa-rized by the DS also shows induction of Cyp1a mRNA as well as activity in mouse liver by PBO (Tables 37 and 38). Notably, this induction is still present in CAR/PXR double knock-out mice (Tables 39 and 40). Therefore, the effect of PBO is apparently not limited to CAR activation but likely includes activation of AhR related pathways.
- Induction of Cyp1a and activation of AhR by PBO is supported by findings of: Kawai M, Saegusa Y, Jin M, Dewa Y, Nishimura J, Harada T, Shibutani M, Mitsumori K. Mechanistic study on hepatocarcinogenesis of piperonyl butoxide in mice. Toxicol Pathol. 2009 Oct;37(6):761-9. doi: 10.1177/0192623309344087.
- Therefore, the MoA analysis should be regarded as incomplete and there is good evidence for an alternative MoA which is considered relevant to humans (AhR pathway, OECD AOP No. 41: Sustained AhR Activation leading to Rodent Liver Tumors).

Overall, the German CA considers that there is evidence that hepatic neoplasia is induced in two rather than one species and that there is a plausible alternative mode of action with relevance to humans. Thus, classification as Cat. 2 rather than non-classification appears more appropriate.

Notice: A broader comparison on transcriptional effects of PBO and PB in vivo as provided in the CLH report can be obtained from: Kossler N, Matheis KA, Ostenfeldt N, Bach Toft D, Dhalluin S, Deschl U, Kalkuhl A. Identification of specific mRNA signatures as fingerprints for carcinogenesis in mice induced by genotoxic and nongenotoxic hepatocarcinogens. Toxicol Sci. 2015 Feb;143(2):277-95. doi: 10.1093/toxsci/kfu248.

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Germany	Endura S.p.A.	Company-Manufacturer	4
Comment received				
Endura S.p.,A. strongly supports to not classify PBO as Cat 2 for carcinogenicity. The CLH report recognises the Mode of Action (MoA) studies and concludes that liver adenomas in male mice observed after chronic PBO administration are not relevant for humans. The MoA involves CAR/PXR activation by PBO that occurs in murine, but not in human hepatocytes. Therefore, PBO should not be classified as Carc 2. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20190829_PBO CLH Endura Comments.pdf				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number

21.08.2019	Germany		MemberState	5
Comment received				
The German CA agrees that the available data do not trigger classification with regard to germ cell mutagenicity.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2019	Germany		MemberState	6
Comment received				
The German CA agrees that the available data do not trigger classification with regard to reproductive toxicity.				

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Sweden		MemberState	7
Comment received				
Effects on sexual function and fertility For transparency, the Swedish CA considers that below findings noted in the 24-month dietary study (Anonymous – 10, 1987) also should be included in the assessment of male reproductive toxicity: • Statistically significantly increased dose-dependent incidence of smaller seminal vesicles was seen in 5%, 6.67%, 15%, 16.67% and 20% for the control group 1, control group 2, 30, 100 and 500 mg/kg bw/day; • Statistically significantly increased incidences of bilateral testicular atrophy was reported in 18%, 15%, 33.3%, 46.67% and 43.33% for the control group 1, control group 2, 30, 100 and 500 mg/kg bw/day. Adverse effects on or via lactation The Swedish CA notes that an assessment of effects of piperonyl butoxide on or via lactation is lacking under heading 4.11 Reproductive toxicity. If criteria are not fulfilled this should also be stated by the DS in the CLH proposal.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2019	Germany		MemberState	8
Comment received				
The proposal for EUH066 is in agreement with the outcome of the discussion in the biocide review procedure and is supported.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2019	Germany		MemberState	9
Comment received				
The proposal for STOT SE3, H335 is in agreement with the outcome of the discussion in the biocide review procedure and is supported.				

Date	Country	Organisation	Type of Organisation	Comment number

30.08.2019	Sweden		MemberState	10
Comment received				
The Swedish CA supports the classification of piperonyl butoxide as STOT SE 3, for respiratory tract irritation (RTI) effects. Since classification as STOT SE 3 in the current proposal is mainly based on human data, a more detailed description and discussion of the available epidemiological data would strengthen the CLH argumentation				

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Germany	Endura S.p.A.	Company-Manufacturer	11
Comment received				
Endura S.p.A. agrees that the acute inhalation study may justify H335. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20190829_PBO CLH Endura Comments.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
25.07.2019	Finland		MemberState	12
Comment received				
Health effects following single exposure to piperonyl butoxide have been investigated in epidemiological studies and in two inhalation toxicity studies in rats. In humans, bronchospasm, cough/choke and dyspnea have been reported to be more likely if the exposure included piperonyl butoxide. According to other literature, pyrethrin-based products may exacerbate symptoms in asthmatics. The DS considers that these findings are probably related to the synergistic properties of piperonyl butoxide. In an acute inhalation toxicity study in rats, nasal discharge and labored breathing accompanied by red foci in the lungs were observed. In a 3-month inhalation toxicity study in rats, red nasal discharge and histopathological alterations in the larynx including slight squamous metaplasia with minimal hyperkeratosis and moderate inflammation were noted at 0.512 mg/l. No other effects on respiratory system were observed. Classification in STOT SE Category 3 (transient target organ effects, including respiratory tract irritation) is primarily based on human data. There are no validated animal models that deal specifically with respiratory tract irritation, but the CLP Regulation states that clinical findings and histopathology indicating respiratory irritant effects in animals can be used as part of weight of evidence evaluation. Considering all the available data on piperonyl butoxide, respiratory irritation has been observed in both human epidemiological data and animal studies, and in the absence of other more severe effects in the respiratory system. Therefore, classification as STOT SE Category 3 is justified. FI CA supports the proposed classification of STOT SE 3; H335 for piperonyl butoxide.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Belgium		MemberState	13
Comment received				
Based on the available results in the CLH dossier, we support the proposed environmental classification for piperonyl butoxide as Aquatic Acute 1, 400 and Aquatic Chronic 1, H410. In view of above classification and toxicity bands the proposed M-factors are also				

supported:
Macute = 1 : most sensitive species : invertebrates (Crassostrea virginica) with 96hEC50 = 0.23 mg/L
Mchronic = 1 : not rapidly degradable substance, most sensitive species : invertebrates (Daphnia magna) with 21dNOEC= 0.030 mg/L.

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Germany	Endura S.p.A.	Company-Manufacturer	14
Comment received				
Endura S.p.A. agrees that the available information justifies H400 and Acute M-factor = 1. Endura S.p.A. agrees that the available information justifies H410 and Chronic M-factor = 1. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20190829_PBO CLH Endura Comments.pdf				

PUBLIC ATTACHMENTS
1. 20190829_PBO CLH Endura Comments.pdf [Please refer to comment No. 2, 4, 11, 14]