Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Chlorobenzene

EC number: 203-628-5
CAS number: 108-90-7

CLH-O-0000004060-90-03/D

Adopted

14 March 2014

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 some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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Substance name: Chlorobenzene
CAS number: 108-90-7
EC number: 203-628-5
Dossier submitter: Poland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2013	France		MemberState	1
Comment received				
FR agrees with the classification proposal and confirms the classification as acute toxicity in category 4 by inhalation and skin irritation in category 2 according to CLP.				
Dossier Submitter's Response				
Thank you for supporting our CLH proposal for chlorobenzene.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2013	Sweden		MemberState	2
Comment received				
SE supports classification of chlorobenzene (Cas No 108-90-7) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations. Overall, the classification proposal would benefit from a more detailed level of reporting of end point studies (method and results); in its present state it is not quite sufficient. The CLH-report should be a Stand-alone document.				
Dossier Submitter's Response				
Thank you for supporting our CLH proposal for chlorobenzene. During preparation of CLH proposal for chlorobenzene we took into account all available toxicological data of chlorobenzene. In our opinion, based on the information found in CLH proposal for chlorobenzene, it is possible to come to conclusion on classification of chlorobenzene. Additional information concerning Klimisch H.J. (1988) study: Route of administration inhalation: vapour type of inhalation exposure: whole body Analytical verification of test atmosphere concentrations: was determined gravimetrically from the weight loss of the material and the volume of air passing through the generator. Generation of test atmosphere / chamber description - Exposure apparatus: exposure system used in conventional inhalation toxicity studies. Two simple all-glass systems with tubes suitable for the exposure of six to ten animals.				

- Exposure chamber volume: (V=1-2 L). Flow-through exposure tube (glass). - System of generating particulates/aerosols: A glass flask generator was used for generation of a vapor saturated inhalation atmosphere - Temperature, humidity, pressure in air chamber: 20°C, no more data - Duration of observation period following administration: 14 days
RAC's response
Noted, however data on observed effects are limited to table 4 in that publication.

Date	Country	Organisation	Type of Organisation	Comment number
03.10.2013	Belgium		MemberState	3
Comment received				
Chlorobenzene is absorbed via the lung or the GI tract and its distribution is dependent on the fat content of individual organs due to lipophilic character of the substance. Metabolites of chlorobenzene are mainly eliminated in the urine and to smaller extent in the faeces, whereas unmetabolized substance is eliminated with expired air. Metabolism of chlorobenzene was found to be saturated at repeated and high doses.				
Dossier Submitter's Response				
Information about toxinokinetics of chlorobenzene was taken from literature.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2013	Germany		MemberState	4
Comment received				
The DE MSCA supports the classification of chlorobenzene as specified in the proposal: "Acute Tox. 4" (H332: Harmful if inhaled) and "Skin Irrit. 2" (H315: Causes skin irritation).				
Dossier Submitter's Response				
Thank you for supporting our CLH proposal for chlorobenzene.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.09.2013	United Kingdom		National Authority	5
Comment received				
The proposed changes are appropriate. Language and typographical issues throughout the dossier need to be addressed *(ECHA note: The CLH report cannot be updated following the public consultation. There is no possibility of revision at this stage of the process)*				
Dossier Submitter's Response				
Thank you for supporting our CLH proposal for chlorobenzene.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number

06.09.2013	United Kingdom		National Authority	6
Comment received				
n/a				
Dossier Submitter's Response				
Carcinogenicty was not assessed by DS.				
RAC's response				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
06.09.2013	United Kingdom		National Authority	7
Comment received				
n/a				
Dossier Submitter's Response				
Mutagenicity was not assessed by DS.				
RAC's response				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
06.09.2013	United Kingdom		National Authority	8
Comment received				
n/a				
Dossier Submitter's Response				
Toxicity to reproduction was not assessed by DS.				
RAC's response				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2013	Sweden		MemberState	9
Comment received				
Acute Toxicity The SE CA agrees with the rationale for the removal of the reference to minimum classification (*) for Acute Tox 4 and hence supports the proposed classification of chlorobenzene as Acute Tox. 4; H330: Harmful if inhaled. In this proposal, classification was based on the lowest LC50 available from a relevant				

inhalation toxicity study comparable to OECD TG 403. The LC50 in male rats was 13.96 mg/ml/6h and extrapolation to a 4 h exposure period using Haber's modified law resulted in LC50 = 15.5 mg/l/4h (Bonnet et al., 1982). According to CLP classification criteria, if a substance has ATE within limits 10.0 < ATE ≥ 20.0 (vapours, mg/ml) it should be classified in Acute Tox Cat. 4. One additional study with experimental data for acute inhalation toxicity (Klimisch 1988, reliability 2 according to DS) reported LC50 =29.6 mg/l in rats, and one study reported LC50 = 16.1 mg/l based on a PB-PK model using LC50 values retrieved from literature (De Jongh 1998, reliability 3 according to DS) was also presented. The summary and discussion of acute toxicity would benefit from a more detailed reporting of the studies and the results (i.e. experimental details including exposure, dose range, time course of onset of signs of toxicity and whether these were reversible, information on dose response, response data and concentration level for each animal, the likely cause of death, predominant mode of action (systemic versus local toxicity)). In the current proposal no data are presented except for LC50 values which make it difficult to evaluate and compare the included studies.
Dossier Submitter's Response
Thank you for supporting our CLH proposal for chlorobenzene. In our opinion, based on the information found in CLH proposal for chlorobenzene, it is possible to come to conclusion on classification of chlorobenzene.
RAC's response
Agree.

Date	Country	Organisation	Type of Organisation	Comment number
03.10.2013	Belgium		MemberState	10
Comment received				
According to the CLP Guideline, the substance can be classified as Acute Tox. 4 for inhalation route (for vapours) if: 10.0 < ATE ≤ 20.0. From the supporting study by Bonnet et al. (1982), LC50 of 15.6 mg/l was calculated and hence the classification as Acute Tox. 4 is considered to be appropriate. Therefore removal of the reference indicating minimum classification for Acute Tox. 4 for this route is considered to be justified.				
Dossier Submitter's Response				
Thank you for supporting our CLH proposal for chlorobenzene.				
RAC's response				
Agree				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2013	Germany		MemberState	11
Comment received				
Acute toxicity (inhalation): Based on the 4h LC50 value in two rat studies of 15.5 mg/L (Bonnet et al. 1982) and 16.1 mg/L (De Jongh et al. 1998) chlorobenzene, we agree that the reference indicating minimum classification (*) is no longer necessary. The quality of the data from the study by De Jongh et al. (1998) was classified by the submitter as category 3 (not reliable), but at the same time the study was declared by the submitter as key study. The submitter has not provided any explanation for these judgements. Please provide an explanation for the limitation of the data from the De Jongh et al. (1998) study and the suitability for the proposal for classification of chlorobenzene for this endpoint.				

According to CLP regulation requirements chlorobenzene should be classified as "Acute Tox. 4" with hazard statement H332 (Harmful if inhaled).
Dossier Submitter's Response
Thank you for supporting our CLH proposal for chlorobenzene. In case of study performed by De Jongh, the study was not followed the OECD guideline 403 (Acute Inhalation Toxicity). There is no information about the sex of animals used in test. Taking into consideration all the above mentioned information, in our opinion, the results of the De Jongh study can be used to support the classification of chlorobenzene for Acute Tox. 4; H332.
RAC's response
It is considered that the proposed reliability score of 3 seems conclusive having read the information from the Swedish CA; still the question remains why this study was identified as a key study.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2013	Sweden		MemberState	12
Comment received				
SE agrees with the rationale for classification into the proposed hazard class and differentiation Skin Irrit. 2; H315 based on a new evaluation of existing skin corrosion/irritation data by the dossier submitter. Three animal studies are presented within the proposal: Suberg 1983 (reliability 1 according to DS), company data from BASF 1960 (reliability 2 according to DS), and Irish 1962 (reliability 4 according to DS; only secondary literature). In the Suberg-study the irritant/corrosive effects of chlorobenzene was tested on rabbit skin according to OECD TG 404 and evaluation was performed according to Draize scoring system. 2 out of 3 animals had erythema score 3 (mean value: 2.7) at 24 h, 48 h, and 72 h, and 3 out of 3 animals had oedema score 1 at 24 h, 48 h, and 72 h. The skin findings were reversible within 6 days after patch removal. The results fulfill the criteria for classification in Skin irritation 2 category for erythema score ≥2.3 - ≤4 in at least 2 of 3 tested animals from gradings at 24, 48 and 72 h after patch removal. As weight of evidence for skin irritation a third study (non-assignable) indicates slight reddening of the skin from application of chlorobenzene (Irish, 1962). In addition, a report on dermal exposure of chlorobenzene on human volunteers for 1 h demonstrate burning pain, hyperemia, whealing, and erythema formation at application site with minimal local vesticulation 12 h postexposure. In contrast, the skin findings from the BASF-study in rabbit (BASF method, comparable to OECD TG 404, with acceptable restrictions) did not meet the criteria for Skin irritation 2 where erythema mean score was 1.85 and edema mean score was 0.5 at 24h and 48h. Moreover, the effects were fully reversible. It should be noted that this study included only two animals per time point and that the original BASF scoring system has been converted to the Draize scoring system. The overall conclusion is that chlorobenzene is a skin irritant.				
Dossier Submitter's Response				
Thank you for supporting our CLH proposal for chlorobenzene.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
03.10.2013	Belgium		MemberState	13

Comment received
Classification as Skin Irrit. 2: H315 is supported by us basing on the evidence presented in the study of Suberg et al. (1983a).
Dossier Submitter's Response
Thank you for supporting our CLH proposal for chlorobenzene.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2013	Germany		MemberState	14
Comment received				
We agree that, based on the results of the rabbit skin irritation study (Suberg, H. 1983) chlorobenzene is irritant to shaved rabbit skin. According to CLP regulation requirements chlorobenzene should be classified as "Skin Irrit. 2" with hazard statement H315 (Causes skin irritation).				
Dossier Submitter's Response				
Thank you for supporting our CLH proposal for chlorobenzene.				
RAC's response				
Noted.				