Committee for Risk Assessment

RAC

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

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CLH-O-0000004060-90-03/D

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:

Chemicals name: Chlorobenzene

EC number: 203-628-5

CAS number: 108-90-7

The proposal was submitted by **Poland** and received by the RAC on **21 August 2013.** All classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS); the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer given.

PROCESS FOR ADOPTION OF THE OPINION

Poland 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 **21 August 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **7 October 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Agnes Schulte**

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **14 March 2014** and the comments received are compiled in Annex 2.

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

OPINION OF THE RAC

The RAC adopted the opinion on Chlorobenzene that should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					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)**	
Current Annex VI entry	602-033-00-1	chlorobenzene	203-628-5	108-90-7	Flam. Liq. 3 Acute Tox. 4* Aquatic Chronic 2	H226 H332 H411	GHS02 GHS07 GHS09 Wng	H226 H332 H411		
Dossier submitters proposal	602-033-00-1	chlorobenzene	203-628-5	108-90-7	**Modify** Acute Tox. 4 **Add** Skin. Irrit. 2	**Retain** H332 **Add** H315	**Retain** GHS07 Wng			
RAC opinion	602-033-00-1	chlorobenzene	203-628-5	108-90-7	**Modify** Acute Tox. 4 **Add** Skin Irrit. 2	**Retain** H332 **Add** H315	**Retain** GHS07 Wng	**Retain** H332 **Add** H315		
Resulting Annex VI entry if agreed by COM	602-033-00-1	chlorobenzene	203-628-5	108-90-7	Flam. Liq. 3 Acute Tox. 4 Skin Irrit. 2 Aquatic Chronic 2	H226 H332 H315 H411	GHS02 GHS07 GHS09 Wng	H226 H332 H315 H411		

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

RAC general comment

The current harmonised classification and labelling for chlorobenzene in Annex VI to the CLP Regulation, includes classification as Acute Tox. 4*, H332. Some entries of the C&L inventory propose a classification as Skin Irrit. 2, Eye Irrit. 2, Eye Dam. 1 or Acute Tox. 4 (H302). Chlorobenzene was indicated to be classified as a skin irritant in one registration dossier, while two other registration dossiers did not classify for this hazard class. The dossier submitter reviewed the toxicity data of chlorobenzene and found that the existing harmonised classification on chlorobenzene should be revised for 'skin irritation'.

The minimum classification as Acute Tox. 4* for the inhalation route was also reviewed.

Although there are indications that chlorobenzene may have irritative effects on the eye and the respiratory tract, no endpoints other than acute inhalation toxicity and skin irrition were addressed by the dossier submitter's proposal.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The dossier submitter (DS) provided an overview of the toxicokinetic data and summarised the results from available acute inhalation studies.

For acute inhalation toxicity in rats, the dossier submitter concluded that the lowest LC_{50} values for chlorobenzene are 15,5 mg/l (Bonnet *et al*, 1982) and 16,1 mg/l (De Jongh, 1998). According to the CLP Regulation, chlorobenzene should be classified as Acute Tox Cat. 4 because the LC_{50} is within the range $10,0 < \text{ATE} \leqslant 20,0$ (vapours, mg/l). Therefore the minimum classification Acute Tox. Cat. 4*, is considered no longer necessary.

Comments received during public consultation

Five member states supported the proposed classifications as specified in the dossier. One member state stated that the CLH report would had benefitted from more details on the method and observed effects and indicated that in one study the reported LC_{50} of 16,1 mg/l was based on a PB-PK model using LC_{50} values retrieved from literature (De Jongh, 1998).

Assessment and comparison with the classification criteria

RAC in general agreed with the dossier submitter's conclusion on the classification on acute inhalation toxicity.

The CLH report summarised results from three acute inhalation studies that were identified by the dossier submitter as key studies. Two of these studies were assessed by the DS as being compliant with OECD TG 403. In fact, none of the studies was in full agreement with the guideline test design. Information on the purity of the test substance was lacking in all studies. Exposure durations were shorter or longer than the 4 h standard exposure time and all LC_{50} values were extrapolated to a 4h LC_{50} value. The test groups in one study included 3 (instead of 5) animals/sex. In the end, the calculated LC_{50} values of all studies were in the same size range (15.5 mg/l, 16.1 mg/l, 29.7 mg/l).

The small differences in LC_{50} values between the two guideline-compliant studies provide evidence that these values may be relied on for the purpose of classification. However, the information on the LC_{50} from the Klimisch (1988) study is very scarce. The only information on

observed effects that is given in this publication is that an LT_{50} value (the time of exposure after which 50% of the animals died) was 1.8 hours at a nominal concentration of 66 mg/l chlorobenzene (corresponding to an extrapolated 4h value of 29.7 mg/l). As no information is given on whether other vapour concentrations were tested and how many animals died after 1.8 h, it can not be excluded that the LC_{50} value could actually be lower.

The lowest LC_{50} value of 15.5 mg/l (from Bonnet *et al*., 1982) is used for the categorisation. This LC_{50} value is within the range of 10.0 < ATE ≤ 20.0 (vapours, mg/ml), corresponding to Acute Tox. 4.
The published LC_{50} value for mice is also consistent with the Acute Tox. 4 category criteria.

RAC agreed with the proposal to remove the reference indicating minimum classification for Acute Tox. 4 for the inhalation route. According to the CLP regulation, chlorobenzene should be classified as Acute Tox. 4, H332 (Harmful if inhaled).

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

The dossier submitter gave an overview on the experimental studies on skin irritation. Two studies were identified as key studies (Suberg, 1983a; BASF AG, 1960), but only the Suberg study was compliant with OECD TG 404. Limitations were also reported for the BASF study (no GLP, use of internal scoring system, only two animals). A third study (Irish, 1962) was identified as not suitable for assessment (Klimish score of 4).

The dossier submitter concluded that the decision on classification of chlorobenzene as skin irritant was based on the test performed by Suberg (1983a). The test was performed according to OECD TG 404. The shaved skin of three rabbits were tested with 0.5 ml of pure chlorobenzene in a 4 h-exposure followed by a post-exposure period of 14 days. Mean scores over 24, 48, and 72 hours for each animal, obtained in the above mentioned test, were 2.7 of max 4 for erythema and 1 of max 4 for oedema and the results meets the criteria for classification of the substance as skin irritant in the CLP Regulation.

The CLH report also documented skin irritation properties of chlororbenzene in 5 volunteers (Oettel, 1936). Dermal exposure for 1 h resulted in burning pain, hyperaemia, whealing, and erythema formation at the application site. At 12 hours post-exposure, minimal local vesiculation was seen. After 5 hours exposure this vesiculation was slightly increased.

Comments received during public consultation

Four member states supported the proposed classifications as specified in the dossier. One member state did not comment on skin irritation.

Assessment and comparison with the classification criteria

Based on the results from the study of Suberg (1983a), mean scores over 24, 48, and 72 hours from all 3 animals were 2.7 for erythema, and 2 out of 3 animals had erythema scores of 3 at 24, 48, and 72 hours. All skin findings were reversible within 6 days after the end of treatment. According to CLP classification criteria, a substance fulfills the criteria for classification for skin irritation in category 2 (H315, Causes skin irritation) if mean values of ≥2.3 - ≤4 for erythema/eschar or for oedema are observed in at least 2 of 3 tested animals from gradings at 24, 48 and 72 h after patch removal.

RAC agreed with the dossier submitter's assessment that classification of chlorobenzene as Skin Irrit. 2 according to the CLP Regulation is warranted.

REFERENCES (additional to CLH report):

Chemicals Evaluation and Research Institute (CERI), Japan (2007). Available at http://www.cerij.or.jp/ceri_en/hazard_assessment_report/pdf/en_108_90_7.pdf.

GDCh BUA (1990). German Chemical Society-Advisory Committee on Existing Chemicals of Environmental Relevance. Chlorobenzene. BUA Report No. 54, S. Hirzel Verlag, Stuttgart.

Ogata M, Taguchi T, Hirota N, Shimada Y, Nakae S (1991). Quantitation of urinary chlorobenzene metabolites by HPLC: concentrations of 4-chlorocatechol and chlorophenols in urine and of chlorobenzene in biological specimens of subjects exposed to chlorobenzene. *Int Arch Occup Environ Health* 63:121-128.

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 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).