



**Committee for Risk Assessment**  
**RAC**

Annex 2  
**Response to comments document (RCOM)**  
to the Opinion proposing harmonised classification and  
labelling at EU level of

**ethylbenzene**

**EC number: 202-849-4**

**CAS number: 100-41-4**

ECHA/RAC/CLH-O-0000001542-81-03/A2

**Adopted**  
**5 June 2012**

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ETHYLBENZENE

**COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION**

*[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]*

**Substance name:** ethylbenzene  
**CAS number:** 100-41-4  
**EC number:** 202-849-4

**General comments**

Date	Country/ Person/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
24/02/2011	UK / MSCA	<p>Page 28- justification that action is required on a community-wide basis-The guidance on preparation of CLH dossiers under section 6.2 (substances where a harmonised C&amp;L has been agreed by the Technical Committee on Classification and Labelling and hand-over dossier) states that 'a justification for action at the community level should be provided for classification proposals in hazard classes and/or categories other than CMR and RS, unless the substance is an active substance in PPP or BP for which no justification is needed'. Therefore, we consider that being identified as a priority substance in the existing chemicals program alone is not sufficient for action at the community level.</p> <p>Page 4 – proposed labelling. In addition to proposed classifications, the report should include proposals for labelling under both the DSD and CLP systems. In addition to the S-phrases already listed in table 3.2 of Annex VI (S2-16-24/25-29), we consider that the safety phrase S62 'If swallowed do not induce vomiting: seek medical advice immediately and show this container or label' should be added.</p>	<p>DE: Thank you.</p> <p><u>Justification for CWA</u></p> <p>In our view, the observed toxicity following repeated administration of ethylbenzene (ototoxicity) could potentially be considered severe enough to fulfil the criteria of Article 57 f of the REACH Regulation. If the proposed C &amp; L is adopted, the need might thus be identified to propose ethylbenzene as a candidate substance for Annex XIV.</p> <p>In accordance with ECHA's 'Guidance for the preparation of an Annex XV dossier on the</p>	<p>We agree to the proposal of DE</p>

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			<p>identification of substances of very high concern' ('[...]Nonetheless, it is recommended to propose and achieve an entry for a harmonised classification in Annex I to Directive 67/548/EEC before a CMR substance is proposed to be identified for inclusion in the candidate list for authorisation. [...]), we have therefore thought it appropriate to first seek agreement on CLH. This dossier can then be referenced by an SVHC proposal at a later stage.</p> <p>The text of the justification was amended accordingly.</p> <p>DE: We agree to the proposal of UK and will amend the CLH-Report accordingly!</p>	
02/03/2011	Belgium / Oliver Sloan / Styrene Producers Association, CEFIC / Industry of trade association	The Styrene Producers Association at Cefic appreciates the opportunity to comment on the proposed changes to the harmonised Classification and Labelling of ethylbenzene. Generally we agree with the Classification and Labelling changes proposed by Germany. Specifically, we support the proposed Classification and Labelling based on Directive 67/548/EEC (DSD) criteria of 'Xn; R65 Harmful: May cause lung damage if swallowed' and the proposed classification based on GHS (CLP) criteria of 'Asp.Tox.1 - H304 May be fatal if swallowed and enters airways' and 'STOT Rep.2 - H373 May cause damage to organs through prolonged or repeated exposure'.	DE. Thank you. Data on irritation were re-evaluated in the process of generating this CLH proposal and, as a result of this re-evaluation, the respective endpoints were removed from the classification proposal (cf. below and also the CLH	We agree DE

Date	Country/ Person/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		<p>However, based on our review of the available data, we believe the available toxicology data warrant classification and Labelling of:</p> <ul style="list-style-type: none"> <li>- Irritation: 'R36/37/38 - Irritating to eyes, respiratory system and skin' (DSD) and 'Skin Irritant Category 2 - H315 Causes skin irritation', 'Eye Irritant Category 2 - H319 Causes serious eye irritation', and 'STOT-SE Cat 3 - H335 May cause respiratory irritation' (CLP) and,</li> <li>- Repeated dose toxicity (inhalation) of 'R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation' (DSD).</li> </ul> <p>Our argumentation for these additional classifications is provided below for your consideration.</p>	report p. 5, 'Proposed notes (if any)'.	
02/03/2011	Sweden/ Ing-Marie Olsson/ MSCA	The proposals for harmonized classification and labelling should refer to the criteria of Dir. 67/548/EEC and of Reg. (EC) No 1272/2008. Please replace reference to the GHS criteria on page 4 with the latter.	De: Thank you. We have changed the text accordingly.	ok

### **Carcinogenicity, Mutagenicity, Toxicity to reproduction, Respiratory sensitisation**

Date	Country / Person / Organisation /MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		<b>No comments received</b>		

### **Other hazards and endpoints**

Date	Country/ Person/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
18/02/2011	France/ MSCA	<p>The proposed classification of ethylbenzene for human health is supported in agreement with the classification proposed in the CLH report.</p> <p>However, it would be more relevant if the ototoxicity after repeated exposure was specifically identified in the classification "STOT Rep 2; H373 May cause damage to hearing organs through prolonged or</p>	DE: Thank you. We have changed the text of the CLH report accordingly.	We accept the position of DE, dermal exposure is not supported by valid data

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		repeated exposure" because hearing organs are the main target organ of ethylbenzene. Inhalation is the only exposure which causes such severe effects on the hearing and the outer hair cells but no valid data are available by dermal route and the route of exposure cannot be specified although it should be discussed in the CLH report.		
24/02/2011	UK / MSCA	<p>Page 25- Repeated Dose Toxicity- We agree that the data supports classification of ethylbenzene as STOT-RE 2 (H373). Please include an explanation as to why R48/20 has not also been proposed.</p> <p>Page 26- Aspiration Hazard - we agree that the data supports classification of ethylbenzene as Xn; R65 and Asp Tox 1 (H304) according to DSD and CLP, respectively.</p>	<p>DE: <u>Irritation</u></p> <p>The difference in the proposal is explained by different guidance values in the old and new regulation (cf. CLH report p. 5, 'Proposed notes (if any)').</p>	Reply accepted by RAC
02/03/2011	Belgium / Oliver Sloan / Styrene Producers Association, CEFIC / Industry of trade association	<p>Irritation: page 5 notes that Classification and Labeling as 'R36/37/38 irritating to the eyes, respiratory tract and skin' is not warranted; however, in animal experiments irritation of the skin and eyes has been observed in rabbits (Yant et al., 1930; Carpenter et al., 1946; Wolf et al., 1956; Smyth et al., 1962). There were no indications for corrosive effects or burns on these tissues. Clear respiratory tract irritation after inhalation of high concentrations was described in humans and in mice (Yant et al., 1930; De Ceaurriz et al., 1981; Nielsen and Alarie, 1982). At a lower concentration of about 100 ppm there was an indication for subjective sensory irritation in sensitive humans (self-reported Multiple Chemical Sensitivity) (Van Thriel et al., 2002) and in repeated animal experiments signs indicative of irritation were observed at concentrations of 400 ppm and above (Cragg et al., 1989). Therefore Classification and Labelling of 'R36/37/38 Irritating to eyes, respiratory system and skin' (DSD) and 'Skin Irritant Category 2 - H315 Causes skin irritation', 'Eye Irritant Category 2 - H319 Causes serious eye irritation', and 'STOT-SE Cat 3 - H335 May cause respiratory irritation' (CLP) appears warranted.</p> <p>References: Carpenter, C. P.; Smyth, H. F. (1946). Chemical burns of the rabbit cornea. Am. J. Ophthalmol. 29:1363-1372.</p>	<p>DE: As noted above, in the view of the German CA, a review of the available data (including - with the exception of the van Thriel paper - all references listed here by Industry) resulted in the withdrawal of our original CLH proposal with respect to irritation.</p> <p>The publication by van Thriel et al. reports sensory irritation which is not a sufficient basis for harmonised C &amp; L with respect to irritation/corrosion.</p> <p><u>R48/22</u> The position of the German CA is founded on</p>	

Date	Country/ Person/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		<p>Cragg, S. T. ; Clarke E.A. ; Daly, I.W.; Miller, R.R.; Terrill, J.B.; Ouellette, R.E. (1989). Subchronic inhalation toxicity of ethylbenzene in mice, rats and rabbits. <i>Fundam. Appl. Toxicol.</i> 13:399-408.</p> <p>De Ceaurriz, J. C.; Micillino, J. ; Bonnet, P. ; Guenier, J. (1981). Sensory irritation caused by various industrial airborne chemicals. <i>Toxicol. Lett.</i> 9:137-144.</p>	<p>the guidance values provided by the DSD.</p> <p>Given the gradual transition from DSD to CLP, perhaps the regulatory need is not very strong, as the C&amp;L according to CLP contains STOT RE 2.</p>	
		<p>Nielsen, G. D.; Alarie, Y. (1982). Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: Prediction of safe industrial exposure levels and correlation with their thermodynamic properties. <i>Tox. Appl. Pharm.</i> 65:459-477.</p> <p>Smyth, H. F., Jr.; Carpenter, C. P.; Weil, C. S.; Pozzani, U. C.; Striegel, J. A. (1962). Range finding toxicity data: List VI. <i>Am. Ind. Hyg. Assoc. J.</i> 23:95-107.</p> <p>van Thriel, C.; Haumann, K.; Kiesswetter, E.; Blaszkawicz, M.; Seeber, A. (2002). Time courses of sensory irritations due to 2-butanone and ethylbenzene exposure: Influences of self-reported multiple chemical sensitivity (sMCS). <i>Int. J. Hyg. Environ. Health.</i> 204:367-369.</p> <p>Wolf, M. A.; Rowe, V.K.; McCollister, D.D.; Hollingworth, R.L.; Oyen, F. (1956). Toxicological studies of certain alkylated benzenes. <i>AMA Arch. Ind. Health.</i> 14:387-398.</p> <p>Yant, W. P.; Schrenk, H.H.; Waite, C.P.; Patty, F.A. (1930). Acute response of guinea pigs to vapours of some new commercial organic compounds II Ethylbenzene. <i>Publ. Health Res.</i> 45:1241-1250.</p> <p>Repeated Dose Toxicity (Inhalation): page 5 notes that the proposal</p>		See above mentioned

Date	Country/ Person/ Organisation/ MSCA	Comment	Dossier submitter's response to comment	RAC's response to comment
		<p>for 'R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation' is not warranted as, according to Directive 67/548/EEC, the R48/20 is foreseen for a guidance value of &lt; 0.25 mg/L air/6 h/d, although 'STOT Rep.2 – H373 May cause damage to organs through prolonged or repeated exposure' is proposed due to the guidance value range of 0.2 &lt; C &lt; 1.0 mg/L/6 h/d according to Regulation (EC) No. 1272/2008 (Annex I, Table 3.9.2). We agree with the proposed 'STOT Rep 2 – H373 May cause damage to organs through prolonged or repeated exposure' Classification and Labelling based on minimal damage of auditory function and of sensory cells of the cochlea in rats at 200 ppm (0.88 mg/l) after 13 weeks of exposure with an extrapolated NOEC of 114 ppm (0.5 mg/l) (Gagnaire et al., 2007). However, although according to Directive 67/548/EEC the classification limit for R48/20 (0.25 mg/l) is not formally attained, irreversible damage of auditory function and of sensory cells of the cochlea is a serious health concern. Regarding potency, ethylbenzene produces experimental ototoxicity comparable to styrene and less than that of toluene, both of which are or proposed to be assigned 'R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation'. In conclusion, this Classification and Labelling for ethylbenzene also appears to be warranted.</p> <p>References: Gagnaire, F.; Langlais, C.; Grossmann, S; Wild, P. (2007). Ototoxicity in rats exposed to ethylbenzene and to two technical xylene vapours for 13 weeks. Arch. Toxicol. 81:127-143.</p>		
02/03/2011	Sweden / Ing-Marie Olsson / MSCA	<p>Aspiration: SE supports classification of ethylbenzene (Cas No 100-41-4) for aspiration toxicity as specified in the proposal. SE agrees with the rationale for classification.</p> <p>STOT: SE supports classification of ethylbenzene (Cas No 100-41-4) for Specific Target Organ Toxicity – repeated exposure, in Category 2 as specified in the proposal. SE agrees with the rationale for classification.</p>	DE: Thank you.	Accepted too

## **ANNEX2.2. ASSESSMENT OF THE INFORMATION RECEIVED DURING THE PUBLIC CONSULTATION AND RAC DISCUSSIONS**

Regular RAC Stakeholder observers and invited experts agreed with the Classification and Labelling changes proposed by Germany. They support the proposed Classification and Labelling based on Directive 67/548/EEC (DSD) criteria of 'Xn; R65 Harmful: May cause lung damage if swallowed' and the proposed classification based on GHS (CLP) criteria of 'Asp.Tox.1 – H304 May be fatal if swallowed and enters airways' and 'STOT RE 2 – H373 May cause damage to organs through prolonged or repeated exposure'. Based on their review of the available data, they believe the available toxicology data warrant classification and labelling of:

- Irritation: 'R36/37/38 - Irritating to eyes, respiratory system and skin' (DSD) and 'Skin Irritant Category 2 – H315 Causes skin irritation', 'Eye Irritant Category 2 – H319 Causes serious eye irritation', and 'STOT-SE Cat 3 – H335 May cause respiratory irritation' (CLP) and,
- Repeated dose toxicity (inhalation) of 'R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation' (DSD).

In detail the following data was presented for classification Irritation R36/37/38. In animal experiments irritation of the skin and eyes has been observed in rabbits (Yant et al., 1930; Carpenter et al., 1946; Wolf et al., 1956; Smyth et al., 1962). There were no indications for corrosive effects or burns on these tissues. Clear respiratory tract irritation after inhalation of high concentrations was described in humans and in mice (Yant et al., 1930; De Ceaurriz et al., 1981; Nielsen and Alarie, 1982). At a lower concentration of about 100 ppm there was an indication for subjective sensory irritation in sensitive humans (self-reported Multiple Chemical Sensitivity) (Van Thriel et al., 2002) and in repeated animal experiments signs indicative of irritation were observed at concentrations of 400 ppm and above (Cragg et al., 1989).

The submitter replied by a statement explaining that ethylbenzene was a priority substance in the Existing Chemicals program (EEC) 793/93. In the transitional Annex XV Dossier on ethylbenzene it is noted that the discussion on the risk assessment report was not concluded at the Technical Committee for New and Existing Substances (TC NES). The current classification for ethylbenzene with regard to human health is: Xn, R 20. In the draft Risk Assessment Report (November 2008) on ethylbenzene it was noted that the substance should be classified and labelled additionally with:

R36/37/38 - Irritating to eyes, respiratory tract and to skin

R48/20 - Harmful: Danger of serious damage to health by prolonged exposure through inhalation

R65 - Harmful: May cause lung damage if swallowed

After re-evaluation of the toxicity of ethylbenzene, classification and labelling as 'R 36/37/38 Irritating to eyes, respiratory tract and to skin' is no longer supported. In detail the submitter finds, that the publication by van Thriel et al. reports sensory irritation which is not a sufficient basis for harmonised classification and labelling with respect to irritation/corrosion.

Furthermore, the proposal for 'R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation' was discussed in the sight of the classification of toluene regarding the ototoxicity and the quite different LOAEC. According to Directive 67/548/EEC the R48/20 is foreseen for a guidance value of  $\leq 0.25$  mg/l air/6 h/d. Given the gradual transition from DSD to CLP, the submitter means that perhaps the regulatory need is not very strong, as the classification and labelling according to CLP contains STOT RE 2.

A further argumentation of the stakeholders targeted to irreversible damage of auditory function and of sensory cells of the cochlea as a serious health concern. In comparison to styrene and less than that of toluene, which are or proposed to be assigned 'R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation' ethylbenzene has a more serious toxic endpoint. However, styrene or toluene have additional serious neurotoxic and haematotoxic properties, other than ethylbenzene.

Other comments regard the exposure route by inhalation, data on dermal exposure are lacking. However ethylbenzene was attributed by SCOEL with a skin notation regarding that the dermal route may contribute to a critical exposure in occupational settings.