**Committee for Risk Assessment**

**RAC**

# 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/F

**Adopted**

**5 June 2012**

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# 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 the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

**Substance name:** **Ethylbenzene**

**EC Number:** **202-849-4**

**CAS Number:** **100-41-4**

The proposal was submitted by **Germany**
and received by RAC on **17 January 2011**

**The proposed harmonised classification:**

| | **CLP Regulation (EC) No 1272/2008** | **Directive 67/548/EEC** |
|---|---|---|
| **Current entry in Annex VI of CLP Regulation (EC) No 1272/2008** | Flam. Liq. 2 - H225<br>Acute Tox. 4* – H 332 | F; R11<br>Xn; R20 |
| **Proposal by dossier submitter for consideration by RAC** | Asp.Tox.1 – H304<br>STOT RE 2 (hearing organs) – H373 | Xn; R65 |
| **Resulting harmonised classification (future entry in Annex VI of CLP Regulation)** | Flam. Liq. 2 - H225<br>Acute Tox. 4* – H 332<br>Asp.Tox.1 – H304<br>STOT RE 2 (hearing organs) – H373 | F, R11<br>Xn; R20-65 |

## PROCESS FOR ADOPTION OF THE OPINION

**Germany** 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on **17 January 2011**. Parties concerned and MSCAs were invited to submit comments and contributions by **3 March 2011**.

## ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Erich Pospischil**

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

The opinion of RAC on the proposed harmonised classification and labelling has been reached on **5 June 2012**, in accordance with Article 37(4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

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

## OPINION OF RAC

The RAC adopted the opinion that **ethylbenzene** should be classified and labelled as follows:

**Classification and labelling in accordance with the CLP Regulation (EC) 1272/2008**

| 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 statement Code(s) | Suppl. Hazard statement Code(s) | | |
| 601-023-00-4 | Ethylbenzene | 202-849-4 | 100-41-4 | Flam. Liq. 2<br>Acute Tox. 4*<br>Asp.Tox. 1<br>STOT RE 2 | H225<br>H332<br>H304<br>H373 (hearing organs) | GHS02<br>GHS07<br>GHS08<br>Dgr. | H225<br>H332<br>H304<br>H373 | | | |

**Classification and labelling in accordance with Directive 67/548/EEC**

| Index No | International Chemical Identification | EC No | CAS No | Classification | Labelling | Concentration Limits | Notes |
|---|---|---|---|---|---|---|---|
| 601-023-00-4 | Ethylbenzene | 202-849-4 | 100-41-4 | F; R11<br>Xn; R20-R48/20-65 | F; Xn<br>R: 11-20-48/20-65<br>S: (2-)16-24/25-29-62 | - | |

## SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by Germany.

The opinion relates only to those endpoints for which a classification is proposed. It does not reflect on hazards deriving from carcinogenicity, mutagenicity or reprotoxicity and does not re-evaluate existing harmonised hazard endpoints.

## HEALTH HAZARDS

### Repeated dose toxicity

Vyskocil et al. (2008) reviewed a number of studies on ototoxicity following inhalation or oral exposure. Six studies on rats of two different strains and one study on guinea pig were identified (Cappaert et al, 1999, 2000, 2001, 2002; Gagnaire et al., 2007, Gagnaire and Langlais, 2005) regarding the ototoxicity potency of ethylbenzene. Five studies were performed in the same laboratory. An ototoxic effect was observed in 5 inhalation and 1 oral studies (Gagnaire and Langlais, 2005.). Susceptibility to ethylbenzene is species dependent. Ethylbenzene causes a permanent damage to auditory system of the rat. The auditory system of the guinea-pig is not injured by ethylbenzene (Cappaert 2002).

Significant and persistent adverse auditory effects have been shown in animals after acute- and intermediate-duration inhalation exposures to ethylbenzene and after short-term oral exposures. Outer hair cells (OHCs) in the organ of Corti (located in the cochlea) are a sensitive target of toxicity of ethylbenzene. Significant losses of OHCs in the organ of Corti were observed in male rats after acute-duration inhalation exposure to ≥400 ppm and mid-term inhalation exposure to ≥200 ppm ethylbenzene. These losses in OHC were observed 8–11 weeks after the last exposures. Inhalation of ≥400 ppm ethylbenzene for 5 days or 4 weeks also resulted in a significant deterioration of auditory thresholds. The magnitude of the shifts in auditory thresholds observed after the first 4 weeks of exposure did not change during a 13-week exposure period or after an 8-week post-exposure recovery period.

The more recent study by Gagnaire et al. (2007) can demonstrate in an inhalation study (male rats,; 200, 400, 600, 800 ppm/6h/d, 6 d/w13 weeks) a 30 % OHC losses in the mid-frequency region in 4 of the 8 animals at 200 ppm by light and electron microscopy. At 400 ppm there were considerable OHC losses and at 600 ppm and 800 ppm nearly complete losses in the three rows of the OHC were found. The auditory brainstem response were affected at 400 – 800 ppm, but not effect was reported at 200 ppm. The increased thresholds at all frequencies were observed after the first 4 weeks of exposure and did not recover after an 8-week post-exposure period. Inner hair cells were affected by ethylbenzene only at ≥600 ppm in a mid-term study.

Guinea pigs exposed to ethylbenzene at 2,500 ppm for 5 days did not show auditory deficits or losses in outer hair cells, whereas significant deficits and hair cell loss were observed in rats exposed to ethylbenzene at 550 ppm (Cappaert et al., 2002). An almost complete loss of OHC was reported in male rats 10 days after an acute-duration oral exposure to ethylbenzene. The mechanisms of the species differences between rats and guinea pigs are not understood. After simultaneous exposure to noise and ethylbenzene (Cappaert, et al. 2001), physiological measurements (distortion product otoacustic emission DPOAE and electrocochleography EC) did detect a synergistic interaction between noise and ethylbenzene exposure.

In conclusion, ethylbenzene damages hair cells in the cochleae of rats. The effect is dose-related. Higher ethylbenzene concentrations lead to greater death of hair cells. The mid-frequency hearing loss is most often reported. Morphologic examination determined a corresponding loss of OHC in the middle frequency region of the rat cochlea. After 8 weeks after end of exposure no recovery of the auditory brain stem response was seen. No chronic studies were identified. There is no ethylbenzene induced hearing loss for subacute exposure of rats up to about 300 ppm (Cappaert 2001) or for subchronic expo-

sure of rats to 200 ppm (Gagnaire 2007). Concentrations greater than 300 ppm show threshold shifts directly related to ethylbenzene concentration (Cappaert 2000, Gagnaire 2007).

Hair cell loss is a more sensitive endpoint than auditory threshold. The OHC losses were observed at 200 ppm (corresponds to 0.9 mg/l) (Gagnaire 2007). This LOAEC does not meet the DSD criteria for Xn, R 48 (≤ 0.25 ml/l for a 90-day study), which is lower than the CLP criteria (when there are results of studies of more than one duration available then those from the study of the longest duration should normally be used).

In the classification criteria (Annex I of CLP Regulation (EC) No. 1272/2008) category 2 for specific target organ toxicity after repeated exposure is, among others, foreseen when significant toxic effects are observed in a 90 day repeated dose study after inhalation exposure to vapour concentrations ranging from 0.2 to 1.0 mg/l air (guidance value). The LOAEC for irreversible cell death of outer hair cells of the cochleae was 0.9 mg/l air (200 ppm).

No relevant human data is available concerning repeated dose toxicity or ototoxicity of ethylbenzene.

With respect to repeated dose toxicity RAC supports the proposal from the dossier submitter to classify ethylbenzene as:

STOT RE 2; H373 - Warning: May cause damage to hearing organs through prolonged or repeated exposure

The comments received during public consultation and contributions of the RAC members lead to an intense discussion regarding classification and labelling based on Directive 67/548/EEC (DSD), for repeated dose toxicity (inhalation) of 'R48/20 Harmful: Danger of serious damage to health by prolonged exposure through inhalation' (DSD). Ethylbenzene leads to irreversible damage in outer hair cells of the hearing organ with major functional changes in hearing assessed by appropriate methods (electrophysiology). In the criteria for classification and labelling it is stated that serious damage to health is to be considered to include death, clear functional disturbance or morphological changes which are toxicologically significant. It is particularly important when these changes are irreversible. Evidence indicating that R48 should be applied when major functional changes in the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods (e.g. electrophysiology) occurred.

Regarding to the ototoxicity of toluene, impaired hearing function has been caused by exposure concentration levels of 1000-1400 ppm (3800-5320 mg/m$^3$) for 2-8 weeks in rats. In one study an exposure level of 700 ppm (2660 mg/m$^3$) was determined as a no-effect concentration for auditory toxicity. Further, transient auditory system impairment has been revealed at a much lower toluene concentration when using distortion product otoacoustic emission to evaluate auditory function (McWilliams, 2000). Toluene was classified as Xn: R 48/20. Remarkably, the LOAEC of ethylbenzene was 200 ppm, which was quite lower than the LOAEC of toluene. This gives rise to concern for a possible harmful effect of hearing loss. Hence, it cannot be excluded that functional damage (hearing loss) can occur during normal handling and use in occupational settings concerning substances with a high saturated vapour concentration. RAC therefore proposes classification as:

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

Although percutaneous resorption is demonstrated for ethylbenzene, no valid studies with repeated dermal applications are available.

## Aspiration hazard

Ethylbenzene has a very low kinematic viscosity of 0.63 mm$^2$/s as determined at 40 °C following the standard method ASTM D445 (Knothe and Steidley, 2005). This method which - according to [http://www.astm.org/Standards/D445.htm] (as of 2010-10-11) -

corresponds to method ISO 3104 directly assesses kinematic viscosity of liquids in the range of 0.2-300000 $mm^2/s$.

The aspiration hazard of ethylbenzene is supported by experimental data (Gerarde and Linden, 1963).

As the kinematic viscosity of 0.63 mm²/sec at 40°C is below the guidance value of 20.5 mm²/sec under CLP and $7*10^{-6}$ m²/s (=7 mm²/s) under DSD the proposed classification 'Asp.Tox.; H304 – Danger: May be fatal if swallowed and enters airways' is justified.

It is therefore proposed by RAC to classify/label ethylbenzene with respect to aspiration toxicity as follows:

- according to Annex I of CLP Regulation (EC) No. 1272/2008 as:

  Asp.Tox. 1; H304 – May be fatal if swallowed and enters airways

- according to the criteria of Directive 67/548/EEC as:

  Xn; R65 - Harmful: May cause lung damage if swallowed

## Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

## ANNEXES

Annex 1 Background Document (BD)[1]

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

[1] The Background Document (BD) gives detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by a dossier submitter.