Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of
2-Ethoxyethanol

ECHA/RAC/CLH-O-0000001587-67-01/F

Adopted

9 March 2011

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT COMMUNITY 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: ***2-Ethoxyethanol (stabilised)***

EC Number: ***203-804-1***

CAS Number: ***110-80-5;***

The proposal was submitted by ***Germany*** and received by RAC on ***20 August 2010***

	Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI of CLP Regulation (EC) No 1272/2008	Flam. Liq. 3 – H226 Repr. 1B – H360FD Acute Tox. 4 * – H332 Acute Tox. 4 * – H312 Acute Tox. 4 * – H302	R10 Repr. Cat.2; R60-61 Xn; R20/21/22 Note E
Proposal by dossier submitter for consideration by RAC	Removal of Acute Tox. 4 * – H312, no changes to remaining human health classifications	Removal of Xn; R21, no changes to remaining human health classifications
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by dossier submitter	Flam. Liq. 3 – H226 Repr. 1B – H360FD Acute Tox. 4 – H332 Acute Tox. 4 – H302	R10 Repr. Cat.2; R60-61 Xn; R20/22 Note E

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 ***20 August 2010*** Parties concerned and MSCAs were invited to submit comments and contributions by ***4 October 2010***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Marja Pronk***
Co-rapporteur, appointed by RAC: ***Marian Rucki***

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

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***9 March 2011,*** 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 RAC Opinion was adopted by consensus.

OPINION OF RAC

The RAC adopted the opinion that ***2-Ethoxyethanol (stabilised)*** should be classified and labelled as follows[1]:

Classification & Labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard state-ment Code(s)	Pictogram, Signal Word Code(s)	Hazard state ment Code(s)	Suppl. Hazard statement Code(s)		
603-012-00-X	2-ethoxyethanol; Ethylene glycol monoethyl ether	203-804-1	110-80-5	Flam. Liq. 3 Repr. 1B Acute Tox. 3 Acute Tox. 4	H226 H360FD H331 H302	GSH02 GSH08 GSH06 Dgr	H226 H360FD H331 H302			

Classification & Labelling in accordance with Directive 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
603-012-00-X	2-ethoxyethanol; ethylene glycol monoethyl ether	203-804-1	110-80-5	R10 Repr. Cat. 2; R60-61 Xn; R20/22	T R: 60- 61- 10- 20/22 S: 53-45		E

[1] Note that not all hazard classes have been evaluated

SCIENTIFIC GROUNDS FOR THE OPINION

Substance for which a harmonised C&L has been agreed at TC C&L

For 2-ethoxyethanol, TC C&L in September 2007 agreed to a harmonised C&L in accordance with a proposal by Germany to delete R21 from the Annex I entry under Directive 67/548/EEC while keeping the remaining human health classifications unchanged. An identical classification proposal has been submitted by Germany in the present CLH dossier.

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion. The Opinion relates to the classification proposal by Germany to delete the existing harmonised classification for acute dermal toxicity and to keep unchanged the existing harmonised classification for reproductive toxicity and for acute oral and acute inhalation toxicity.

Acute toxicity

The following information on the acute toxicity of 2-ethoxyethanol is taken from the relevant chapter in the background document.

Summary and discussion by dossier submitter

Human data are only available for acute oral toxicity of mixtures of toxic substances containing 2-ethoxyethanol. In animals the acute toxicity of the substance is low as considered on the basis of oral LD_{50} values for rats of 2300-4700 mg/kg body weight. Oral LD_{50} values in guinea pigs and in rabbits were reported to be 1400 mg/kg and 1275 mg/kg, respectively. The lowest inhalation LC_{50} value was reported for female rats (7.36 mg/l/8 hours, corresponding to 10.4 mg/l/4hours), and dermal LD_{50} values of 3720 -4576 mg/kg bw were reported for male respectively female rabbits.

Conclusion under Regulation (EC) No 1272/2008:

Criteria for **acute toxicity by oral route** - Category 4: 300 mg/kg body weight < ATE ≤ 2000 mg/kg body weight	
Species	LD_{50}
Guinea pig	1400 mg/kg body weight
Rabbit	1275 mg/kg body weight
Criteria for **acute toxicity by inhalation route** - Category 4: 10.0 mg/l < ATE ≤ 20,0 mg/l (based on 4 hour testing exposures)	
Species	LC_{50}
Female Rat	7.36 mg/l/8 hours, corresponding to 10.4 mg/l/4hours
Criteria for **acute toxicity by dermal route** - Category 4: 1000 mg/kg body weight < ATE ≤ 2000 mg/kg body weight	
Species	LD_{50}
Male Rabbit	3720 mg/kg body weight
Female Rabbit	4576 mg/kg body weight

Conclusion under Directive 67/548/EEC:

Based on an oral LD_{50} value of 1400 mg/kg obtained for guinea pigs and a LD_{50} of 1275 mg/kg reported for rabbits existing classification as 'Harmful if swallowed' and labelling with R22 is warranted.
The existing classification as "Xn - Harmful by inhalation" and labelling with R20 is confirmed.
For acute dermal toxicity no classification is required. The current classification with R21 should be deleted.

RAC Opinion

The evaluation by RAC relates to the classification proposal of the dossier submitter to delete the existing harmonised classification for acute dermal toxicity and to keep unchanged the existing harmonised classification for acute oral and acute inhalation toxicity. This classification proposal is in line with the agreed TC C&L recommendation, and was not questioned during public consultation.

For assessment of dermal acute toxicity one rabbit study with a reported LD_{50} of 3720-4576 mg/kg bw is available. This LD_{50} is above the threshold value of 2000 mg/kg bw for both R21 (DSD) and Acute Tox. 4 – H312 (CLP). Consequently, RAC agrees that 2-ethoxyethanol should not be classified for acute dermal toxicity, and is in support of deleting R21/Acute Tox. 4 – H312 from the existing Annex VI entry.

Following oral administration, the acute toxicity of 2-ethoxyethanol in rats (reported LD_{50} values ranging from 2300-4700 mg/kg bw) and mice (one reported LD_{50} value of 4300 mg/kg bw) seems to be somewhat lower than the acute toxicity in guinea pigs (reported LD_{50} values of 1400 and 2500 mg/kg bw) and rabbits (one reported LD_{50} value of 1275 mg/kg bw). Based on the 1400 mg/kg bw LD_{50} in guinea pigs and the 1275 mg/kg bw LD_{50} in rabbits, the existing classification of 2-ethoxyethanol with R22/Acute Tox. 4 – H302 seems appropriate to RAC, as these LD_{50} values are within the threshold values of 200-2000 mg/kg bw for R22 (DSD) and 300-2000 mg/kg bw for Acute Tox. 4 – H302 (CLP).

When rats were exposed to vapours of 2-ethoxyethanol, one study reported no mortalities following exposure to 20.9 mg/l for 3 hours, whereas all animals died following exposure to that same concentration for 7 hours. Another study reported an LC_{50} of 7.36 mg/l for an 8-

hour exposure (corresponding to 10.4 mg/l/4h). In mice, an LC_{50} of 6.4-6.7 mg/l/7h was reported for 2-ethoxyethanol vapour (corresponding to 8.5-8.9 mg/l/4h). The reported LC_{50} values for rats and mice fit the existing classification of 2-ethoxyethanol with R20, as these values are within the threshold values of 2-20 mg/l/4h for R20 (DSD). The corresponding classification according to the CLP criteria is a borderline case between Acute Tox. 4 – H332 (threshold values 10-20 mg/l/4h) and Acute Tox. 3 – H331 (threshold values 2-10 mg/l/4h). Based on the lowest reported LC_{50}, which is the one in mice, RAC considers Acute Tox. 3 – H331 more appropriate than the current (translated) classification as Acute Tox. 4* – H332, and therefore recommends to change the Annex VI entry accordingly.

Reproductive toxicity

The following information on the reproductive toxicity of 2-ethoxyethanol is taken from the relevant chapter in the background document.

Summary and discussion by dossier submitter

Human data from several epidemiological studies may indicate an association between exposure to 2-ethoxyethanol and impairment of reproduction in male and female humans. From the occupational studies, mainly focusing on spermatotoxic effects, work-related exposures give evidence for a negative influence on sperm count and sperm morphology. The observations from epidemiological studies in males appear plausible since testes toxicity was demonstrated in numerous studies in laboratory animals.

Experimental data from studies with mice demonstrated that 2-ethoxyethanol adversely affects male reproductive organs (testes atrophy) as well as sperm parameters and sperm morphology. 2-Ethoxyethanol was further shown to adversely affect reproductive capability and capacity in both sexes for at least one generation.

It is however evident from various other studies using different species and applying different routes of exposure, that 2-ethoxyethanol specifically affects male reproductive organs (testes atrophy) and is spermatotoxic at clearly lower dose/concentration ranges depending on which parameters had been determined.

In addition studies with rabbits, rats and mice using the inhalation, oral and dermal route of exposure consistently demonstrated that 2-ethoxyethanol adversely affects embryonic and fetal development in terms of embryo-/fetomortality, fetal growth retardation and visceral/skeletal malformations and variations in a dose-related manner. Significantly increased incidences of these developmental effects were induced already at dose levels without obvious maternally toxic effects, respectively borderline effects. Comparable effects could also be revealed by use of the dermal route of exposure. The teratogenic effects such as increase in skeletal and cardiovascular malformations were seen predominantly in rats and rabbits, whereas exencephaly and cleft palate were only seen in the mouse.

Conclusion: Based on the evaluation of the available animal data classification and labelling as Reprotox. Cat. 2, R 60/R 61 is confirmed.

RAC Opinion

The evaluation by RAC relates to the classification proposal of the dossier submitter to keep unchanged the existing harmonised classification for fertility impairment and developmental

toxicity. This classification proposal is in line with the agreed TC C&L recommendation, and was not questioned during public consultation. Based on a comparison of the available reproductive toxicity data with the DSD and CLP classification criteria, RAC agrees that these data fit the existing classification of 2-ethoxyethanol as Repr. Cat. 2; R60-61 (DSD)/Repr. 1B – H360FD (CLP). Although the human data seem to indicate a possible effect on reproduction for (ethylene) glycol ethers, a higher classification is not considered appropriate by RAC because the data do not present sufficient evidence for a direct association with 2-ethoxyethanol.

ANNEXES:

Annex 1 Background Document (BD)[1]

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

[1] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by the dossier submitter. The original CLH report may need to be changed as a result of the comments and contributions received during the public consultation(s) and the comments by and discussions in the Committees.