Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Benzoic Acid

EC Number: 200-618-2

CAS Number: 65-85-0

ECHA/RAC/CLH-O-0000001687-65-02/F

Adopted

25 November 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 (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:

Substance Name: **Benzoic Acid**

EC Number: 200-618-2

CAS Number: 65-85-0

The proposal was submitted by **Germany**
and received by RAC on **2 December 2010.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification

	CLP	**DSD**
Current entry in Annex VI to CLP Regulation	-	-
Proposal by dossier submitter for consideration by RAC	Skin Irrit. 2 (H315) Eye Dam. 1 (H318) STOT RE 2 (lungs) (H373)	Xi; R37/38-41
Resulting harmonised classification (future entry in Annex VI to CLP Regulation) based on the proposal by the dossier submitter	Skin Irrit. 2 (H315) Eye Dam. 1 (H318) STOT RE 2 (lungs) (H373)	Xi; R37/38-41

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/web/guest/harmonised-classification-and-labelling-previous-consultations*** on **30 August 2011**. Parties concerned and Member-State Competent Authorities (MS-CA) were invited to submit comments and contributions by **14 October 2011.**

ADOPTION

Rapporteur, appointed by RAC: **Benjamin Pina**
Co-rapporteurs, appointed by RAC: **Katalin Gruiz**

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 **25 November, 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 the RAC was adopted by **consensus.**

OPINION OF RAC

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

Classification and labelling in accordance with the criteria of 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)		
-	Benzoic Acid	200-618-2	65-85-0	Skin. Irrit. 2 Eye Dam. 1 STOT RE 1	H315 H318 H372 (lungs; inhalation)	GHS05 GHS08 Dgr	H315 H318 H372	-	-	-

Classification and labelling in accordance with the criteria of the DSD, 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
-	Benzoic Acid	200-618-2	65-85-0	Xi; R38-41 T; R48/23	T R: 38-41-48/23 S: (1/2-)26-39-45-63	-	-

SCIENTIFIC GROUNDS FOR THE OPINION

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

HUMAN HEALTH HAZARD ASSESSMENT

Irritation

Summary of the Dossier Submitter's proposal

Benzoic acid is a moderate skin irritant in animals (rabbit, Guinea pig and rat), but there is a solid evidence of erythema and oedema in human volunteers. It is a strong eye irritant in rabbits, with reported irreversible consequences, but it produces no convincing respiratory irritation in animals or humans.

Comments received during public consultation

- Four Member states agreed with the proposal for classification of benzoic acid as Skin Irrit. 2 (H315) and Eye Dam. 1 (H318) according to CLP, (DSD, Xi; R38 and R41).
- One Industry representative considered Skin Irrit. 2 (H315) not to be justified because:

  1) Benzoic acid does not show skin irritating properties in any available animal studies according to EC or OECD guidelines, and the classification proposal is only based on human data; and

  2) The skin irritating effects of benzoic acid only affect a low portion (below 1%) of the human population. According to the comment received, this is due to special susceptibility in these persons.
- Two Member states and one Industry representative noted the irritant effects on the respiratory tract and suggested a discussion on STOT SE and/or STOT RE (respiratory tract).

Additional key elements

Several toxicity reports, including US EPA, OECD, and EC DAR reports as well as industry manuals (including the cosmetic database "Skin Deep") categorise benzoic acid and/or benzoates as being irritating to skin. Using various criteria and mostly based on human data (see the table below), these classifications range from "Possible" to "Skin Irritant Cat III (caution)".

Source	Observations
ECCO Peer Review Meetings/DAR (2003)	Benzoic acid is known to cause non-immune immediate contact reactions (NIICRs) in man, as demonstrated in the study of Young et al. (1987). Due to the high incidence of skin reactions observed in this study, PSD considered that classification as a skin irritant for the active substance and preparation may be appropriate.
SIDS Initial Assessment Report, OECD	Benzoic acid and benzyl alcohol are slightly irritating to the skin, while sodium benzoate was not skin irritating. No data are available for potassium benzoate but it is also expected not to be skin irritating.
EPA report 2005 Data Package 0315790	Skin Irritant Cat III (caution)
Skin Deep® Cosmetics Database	One or more human occupational studies show possible skin irritation (Lahti, 1995)
Hazardous substances data sheet, NJ Dept Health and Senior services	Benzoic acid can irritate the skin causing a rash, redness and burning feeling on contact.
LAHTI et al., 1995. Contact Dermatitis 33, 177-182	IMMEDIATE IRRITANT REACTIONS TO BENZOIC-ACID ARE ENHANCED IN WASHED SKIN AREAS// Benzoic acid caused immediate skin reactions (erythema and/or oedema) in all test subjects. Washing increased the strength of reactions.
Concise International Chemical Assessment Document 26, UNEP (2005)	"Although there is a wide range of results from mostly non-standardized tests using various scoring systems, it can be concluded that benzoic acid is slightly irritating to the skin and irritating to the eyes."
Nair, 2001, Final Report on the Safety Assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. International Journal of Toxicology 2001 20: 23. DOI: 10.1080/10915810152630729	"Clinical data indicated that these ingredients can produce non-immunologic contact urticaria and non-immunologic immediate contact reactions, characterized by the appearance of wheals, erythema, and pruritis. In one study, 5% benzyl alcohol elicited a reaction, and in another study, 2 % benzoic acid did likewise."
Basketter and Wilhelm, 1996 Studies on non-immune immediate contact reactions in an unselected population. Contact Dermatitis, 1996, 35, 237-240	Erythema: 500 mM benzoic acid: 30% "perceptible"; 25% "Distinct", 1% "Well developed".

RAC assessment and comparison with the classification criteria

Under CLP, benzoic acid should be classifdied as Skin Irrit. 2, H315 (DSD, Xi; R38) since human data shows that it is capable of inducing non-immunological contact urticaria, which is regarded as an irritation reaction according to e.g. Lahti and Basketter (2006). The reaction does not require previous sensitization. Its incidence, which could be quite high (>80%) even in healthy test subjects (Larmi *et al.*1989), as well as severity, depends on **applied dose** (Basketter and Wilhelm, 1996), **vehicle** (Lahti *et al.,* 1993) and **exposed skin site** (Larmi *et al.,* 1989; Zhai *et al.,*2011).

Animal data from the Guinea pig ear swelling test support the observations in humans. Benzoic acid, as well as certain other chemicals such as sorbic acid and cinnamic acid, produces no skin response in the rat or mouse, but the Guinea pig's ear reacts by swelling *(*Lahti and Maibach*,* 1985). This test is considered as a predictive assay for evaluating the ability of substances to produce non-immunological contact urticaria.

The study by Young and Houwing (1987) may not be relevant for the present evaluation since: 1) The tested outcome is sensitization, not irritancy, and 2) Benzoic acid is not tested as a separate substance.

The authors tested 'balsam of Peru', and not benzoic acid alone. Benzoic acid is present in 'balsam of Peru', but it also contains a variety of other substances such as cinnamic, benzoic and benzyl acid alcohols and aldehydes, and resinous substances, many of which are known as potent irritants and contact allergens.

(See also T.R.U.E. TEST web page:
http://www.truetest.com/PatientPDF/Patient_Balsam%20of%20Peru.pdf)

Benzoic acid induces skin irritation in a significant fraction of exposed human volunteers (close to 100% in some tests). Various different international regulatory bodies and chemical assessment programmes have classified benzoic acid and/or benzoates as skin irritants with grades ranging from "possible" to "moderate". EPA classified benzoic acid as "Skin Irritant Cat III (caution)". Based on the effects on humans (erythema and oedema), RAC considers that a Skin Irritation Category 2 classification is adequate.

Based on the effect in rabbits (irreversible eye damage in more than 1/3 of exposed animals), a classification as Eye Damage Category 1 is adequate.

The data on respiratory tract irritation are evaluated in the discussion on STOT SE / STOT RE. The labelling R37 (Respiratory Irritation) is considered not justified.

Conclusion:
RAC agrees with the proposal from the dossier submitter to classify benzoic acid as Skin Irrit. 2 (H315) and Eye Dam. 1 (H318) according to CLP (DSD, Xi; R38 and R41). RAC considers the proposed DSD labelling with R37 as not justified.

Specific target organ toxicity - repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

In the Classification table, the dossier submitter proposes STOT RE 2 (lungs) – H373 under CLP, but without a corresponding classification according to DSD. However, in the text it is concluded that "No classification and labelling regarding repeated dose toxicity or chronic toxicity is necessary".

Comments received during public consultation

- One Member State proposed classification as STOT SE 3 or STOT RE 1 based on respiratory tract effects.
- Another Member State asked for a clarification on STOT classification (or on the lack thereof), with a special remark on respiratory tract effects.
- One Industry representative noted that "In the REACH Registration dossier the lead registrant proposed classification as a respiratory irritant as follows: STOT SE 3 (Hazard statement: H335: May cause respiratory irritation). Affected organs: Lungs. Route of exposure: Inhalation. We note the comments on this being due to the physicochemical nature of the substance; however, our experience with manufacturing and handling this substance in a powder form leads us to consider this applicable and warranted." The dossier submitter asked RAC for a clarification on this point in the Response to comments document.

RAC assessment and comparison with the classification criteria

With oral and dermal administration, no effects were observed in any animal species (except cats) at doses <500 mg/kg bw. As cats seem to be particularly sensitive for reasons not applicable to humans, no classification is required for repeated dose toxicity or chronic toxicity for these exposure routes.

The results of the 28-day inhalation study in rats support STOT RE for effects on lungs, and not respiratory irritation, since histopathological findings of interstitial inflammation, fibrosis and decrease in the weight of lungs and trachea are more severe effects than those related to irritation only. In addition, possible clinical signs of irritation in the study (reddish discharge around the nares) began after repeated exposure; on the 4th day at the middle and high dose, and on the 13th day at the low dose, while respiratory irritation is included in STOT SE Category 3 (i.e. after single exposure).

RAC considers that there is evidence for pulmonary toxicity after repeated exposure to benzoic acid dust via inhalation, and this observation was included in the accordance check report. The dossier submitter considers this effect not relevant, as it does not apply to dissolved preparation (as used in biocides). However, RAC considers (a point of view supported by at least one comment received during Public consultation) that workers may be exposed also to solid benzoic acid and/or benzoates. The CLP Regulation (Art. 5.1) states that the information used for classification shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used. Benzoic acid is manufactured as a crystalline (powder form solid) product, and the solution is a kind of mixture. Based on this, the hazards of the powder form should be taken into consideration and classification should be extended to that form. All the professional actors involved in the consultation found the proposal justified; the inhaled powder should be considered the agent responsible for the respiratory tract and lung symptoms.

In this regard, the study by Rop *et al*. (1981) is considered relevant. Lung fibrosis is considered as a severe and irreversible effect, relevant for humans. The guidance value for STOT RE Category 1 for inhalation of dust is C ≤0.02 mg/litre/6h/day for 90 day-studies. This can be extrapolated by applying Haber's rule to C < 0.06 mg/litre/6h/day for 28 day studies. These values are similar to Directive 67/548/EEC guidance values for T; R48 (0.025 and 0.075 mg/litre/6h/day for 90- and 28-day studies, respectively). The reported LOAEL of < 0.025 mg/litre/6h/day (28 days, 5 days per week) for pulmonary effects (interstitial inflammation and lung fibrosis) in rats is close to the 90-day guidance values and clearly below the extrapolated 28-day guidance values.

Conclusion:
The RAC proposes classification with STOT RE 1 (H372; lungs, inhalation) under CLP (DSD, T; R48/23, "Toxic: danger of serious damage to health by prolonged exposure through inhalation").

It is recommended to use the precautionary statement P260 (Do not breathe dust) for the label.

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 (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 the dossier submitter; the evaluation performed by RAC is contained in RAC boxes.