Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

carvone

EC number: 202-759-5 (d/l mixture of stereoisomers)

218-827-2 (d-carvone)

229-352-5 (l-carvone)

CAS number: 99-49-0 (d/l mixture of stereoisomers)

2244-16-8 (d-carvone)

6485-40-1 (l-carvone)

CLH-O-0000003038-78-03/A2

Adopted

4 June 2013

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

Substance name:

Carvone; 5-isopropenyl-2-methylcyclohex- 2-en-1-one; d/l mixture	202-759-5	99-49-0
d-carvone	218-827-2	2244-16-8
l-carvone	229-352-5	6485-40-1

Dossier submitter: Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
05/12/2012	Sweden		MemberState	1

Comment received

Page 6, 1.2. Harmonised classification and labeling proposal:
We agree that Carvone is classified as a Skin irrit. Cat 2 and Skin Sens. Cat 1B according to the CLP Regulation and as Skin irrit. R38 and Skin Sens. R43 according to the DSD.
NB. Overall the CLH proposal is good but it could be further elaborated and refined.

Page 6, Table1: Substance identity:
The Chemical and IUPAC names, Molecular weight and Molecular formula need to be mentioned.

Page 14: Structural formula:
The chemical structure on the image shows only one isomer (d-carvone). The l-isomer needs to be corrected and of course a better image could be replaced.

Dossier Submitter's Response

Thank you for the support of the proposal.

Page 6, table 1: The Chemical and IUPAC names, Molecular weight and Molecular formula do not need to be included in table 1 of part A (according to the format). They are included in table 5 on page 14 (Part B).

Page 14: Structural formula: The image, as present in our word document, does show both isomers with clear differences. However, the pdf version as published on the web is less clear and does not show the differences between the two isomers. Therefore, no changes need to be made.

RAC's response

Concerning substance identity and structural formula RAC accepts the corresponding dossier submitter's response.

RAC decided not to classify the carvone isomers as skin irritants: RAC stresses that there was no severity information for the only relevant dermal reaction (desquamation). It is not known whether there would have been persistence of the skin desquamation up to the usual observation period of 14 days. Thus, overall, there is no sufficient information on the severity and persistence of skin desquamation in order to justify classification. Furthermore, scores for erythema/oedema were not sufficiently high for classification in all three species tested.

RAC decided to classify the carvone isomers for skin sensitisation. The decision is based on the positive results of a guinea pig maximisation (GPMT) and a Freund's complete adjuvant test (FCAT). Because there was a high sensitisation rate in the FCAT at the intradermal induction concentration of 5% and no further experimental testing at lower intradermal induction concentrations the classification proposal is for Skin Sens. 1 without subcategorisation.

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	Ireland	REACH24H Consulting Group	Company-Manufacturer	2

Comment received

We identify L-Carvone skin irritation as no classified.

Dossier Submitter's Response

See comment skin hazard.

RAC's response

The RAC proposed not to classify the carvone isomers for skin irritation. See RAC's response to comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	Germany		MemberState	3

Comment received

The German CA supports to establish a harmonised classification and labelling for carvone, which is an active ingredient in plant protection products.

Nevertheless, it's not clear whether the proposal for classification and labeling covers all isomers and all mixtures of isomers or only the substance defined as active substance for plant protection with a minimum purity of 930 g/kg d-carvone in the technical product with a d/l ratio of at least 100:1. In the report some details indicate that all isomers and all mixtures of isomers are covered (e.g. three CAS Numbers on the cover page) and some indicate that only the substance reviewed in the Commission Review Report is covered (e.g. paragraph 3).

Dossier Submitter's Response

The proposal for classification and labelling covers all isomers and all mixtures of isomers, as indicated by the 3 CAS numbers on the cover page. Paragraph 3 (Justification that action is needed on a community level) could have been clearer in this respect.

RAC's response

The RAC accepts the corresponding dossier submitter's response.

Date	Country	Organisation	Type of Organisation	Comment number
07/12/2012	France		MemberState	4

Comment received
We agree with the proposed classification Xi, R38, R43 (DSD criteria) and/or skin irritation cat. 2, H315 and skin sensitisation Cat.1B, H317 (CLP Regulation). We agree with the absence of classification for the environmental hazards.
Dossier Submitter's Response
Thank you for the support
RAC's response
The RAC proposed not to classify the carvone isomers for skin irritation. The proposal for skin sensitisation is Skin Sens. 1 without subcategorisation. See RAC's response to Comment number 1.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	Germany		MemberState	5
Comment received				
We support the proposal to classify carvone as skin irritant, cat 2 (H315). Carvone shows only a slightly positive reaction in an OECD 404 study. However, one effect (desquamation) was found to persist over the whole observation period. Hence, it fulfils the criteria set in Reg. (EC) No 1272/2008 and requires classification.				
Dossier Submitter's Response				
Thank you for the support				
RAC's response				
The RAC proposed not to classify the carvone isomers for skin irritation. See RAC's response to Comment number 1.				

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	Ireland	REACH24H Consulting Group	Company-Manufacturer	6
Comment received				
Dear Sir/ Madam, As the Lead Registrant of L-Carvone (CAS# 6485-40-1) under EU REACH, We (REACH24H Consulting Group as technical support) have different comment for skin irritation classification of L-Carvone, comparing with CLH report proposal for Harmonised Classification and Labelling. In CLH report, Carvone (a D/L ratio of at least 100:1) is classified as with Xi and R38 according to the DSD and as category 2 irritant (H315) according to the CLP Regulation. However, our self-classification of skin irritation for L-Carvone is not classified based on a GLP study report from Symrise. In the light of CLH report, the basis of classification adopts a skin irritation study which was performed in according with OECD guideline 404. But other key points are still short on information, such as GLP or not, specified isomer ratio, mammalian sex and study date etc. Author considered Carvone as mildly irritant to rabbit skin as a result of desquamation during the end of the observation period. We can make sure this study is not conducted recently, because desquamation is not be used as the assessment criteria now. Hence, the study report in CLH report may be not quite satisfied for skin irritation classification. In Symrise study report, an acute dermal toxicity showed that LD50 of L-Carvone (purity is 99.4%) was found to be higher than 2000 mg/kg body weight in rats, according to OECD guideline 402 and GLP compliance. The individual dermal reactions were observed in detail at the dose level of 2000 mg/kg body weight in 5 female rats. The observation index contains erythema, oedema and other symptom, conforming to the updated evaluation indexes. As a result, there were no sign of dermal				

irritation noted during the study. The reliability is assessed as Rel 1 (reliable without restriction) (Symrise, 1999). According to the Column 2 of REACH regulation Annex Ⅷ, if an acute toxicity study by the dermal route does not indicate skin irritation up to the limit dose level (2000 mg/kg body weight), in vivo skin irritation does not need to be conducted. Therefore, skin irritation is considered as not classified.

To sum up, we identify L-Carvone skin irritation as no classified.

Dossier Submitter's Response

The skin irritation study described in the CLP report is from 1995, was performed in accordance to GLP and used 1 male and 2 female rabbits. The only missing information is the isomer ratio. However, the reliability of the study is assessed as 1. Although the word 'desquamation' is not used in the CLP criteria, one of the criteria is inflammation persisting to the end of the study in at least 2 animals, taking into account (ao) scaling. Desquamation was observed in all 3 animals at the end of the study period, which was 7 days, instead of 14 days. No data are available for 14 days.

The Symrise study (from 1999) is well conducted, according to OECD 402 (which is for acute toxicity and not for skin irritation) and GLP. In all rats (5 males and 5 females, Draize scores were 0 at all timepoints (day 1-14, daily observations). The skin irritation part of the study resembles OECD 404, except for the species, higher number of animals and longer exposure period. However, no information is available on the amount of L-carvone per cm^2 as used in the acute dermal study in rats. As described in footnote d to Figure R.7.2-2 of Chapter R.7A of the Guidance on information requirements and chemical safety assessment, the dose per cm^2 is normally approximately 20 mg/cm^2 in an acute dermal limit test in the rat. This is four fold below the required dose of 80 mg/cm^2 in a rabbit skin irritation test. Further, it is stated that the rat skin is less sensitive compared to the rabbit skin. The conclusion is drawn in this footnote that the results of dermal toxicity testing in rats will not be adequate for classification with respect to skin irritation. The CLP guidance refers to Figure R.7.2-2 with regard to other tests in animals (chapter 3.2.2.3.2.2).

In conclusion, we have a study using carvone with an unknown isomeric ratio showing skin effects warranting classification in a study designed to determine the skin irritating potential of substances but also a negative result with L-carvone in a study using the same route of exposure but at a lower dose per cm^2 and using a less sensitive species. Seen the likely lower sensitivity of the acute dermal study in rat, we prefer to use the results of the skin irritation study warranting classification. Therefore, we remain with our proposal to classify carvone and both isomers as skin irritants category 2.

RAC's response

The RAC proposed not to classify the carvone isomers for skin irritation. See RAC's response to Comment number 1. For more details see the Carvone Opinion Document.

OTHER HAZARDS AND ENDPOINTS – Skin Senzitation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
05/12/2012	Sweden		MemberState	7

Comment received

Page 23, 4.6.1.1 and 4.6.1.2.

Carvone has been studied and there are data on its skin allergenic effects in humans. One can find more references in the open literature as the substance is used widely in various consumer products. The cited references and the studies documented seem to be limited to few. There are other studies on the two isomers of carvone on structure activity relationships, animal studies and diagnostic human patch test studies as well showing the skin sensitizing effects of carvone in the literature. The following literature would strengthen the CLH proposal if included and discussed to clarify the status of the substance in skin sensitization.

Karlberg A-T, Bergström MA, Börje A, Luthman K and Nilsson JLG (2008) Allergic Contact Dermatitis-Formulation, Structural Requirements, and Reactivity of Skin Sensitizers. Chem. Res. Toxicol. 21:53-69.

Divikovic M, et al. (2005) Hapten–protein binding: from theory to practical application in the in vitro prediction of skin sensitization. Cont. Derm. 53: 189-200.

Nilsson A-M, et al, (2001) Mechanism of the antigen formation of carvone and related μ, β-unsaturated ketones. Cont. Derm. 44: 347-356.

Page 24, 4.6.1.5.

Yes, Carvone deserves classification with Xi and R43 according to the DSD and as a Skin Sens. 1B according to the CLP Regulation, respectively.

Dossier Submitter's Response

Thank you for the additional references. Indeed, especially the 3rd reference (Nilsson) shows that both isomers of carvone are sensitising in guinea pigs and humans. We agree that this information should be included in the CLH dossier since it strengthens the proposal for classification for skin sensitisation.

RAC's response

The additional reference (Nilsson) is taken into account. The proposal for skin sensitisation is Skin Sens. 1 without subcategorisation. See RAC's response to Comment number 1.

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	Germany		MemberState	8

Comment received

We support to classify carvone as skin sensitizer, cat 1B We support the proposal to classify carvone as skin sensitizer, cat 1B (H317). Carvone shows positive reaction in >30% of animals in a GPMT after challenge with carvone (concentration >1%). Hence, it fulfils the criteria set in Reg. (EC) No 1272/2008 and respective guidance documents.

Dossier Submitter's Response

Thank you for the support

RAC's response

The proposal for skin sensitisation is Skin Sens. 1 without subcategorisation. See RAC's response to Comment number 1. See the Carvone Opinion Document as well.

ATTACHMENTS RECEIVED:

Study Details (File name: 1999016.pdf), submitted on 06/12/2012 by REACH24H Consulting Group