Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

n-hexane

EC Number: 203-777-6
CAS Number: 110-54-3

CLH-O-0000007203-83-01/F

Adopted

1 December 2022

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: n-hexane
EC number: 203-777-6
CAS number: 110-54-3
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2022	France	<confidential>	Company-Downstream user	1
Comment received				
The CLH report is related to n-hexane (CAS 110-54-3; EC 203-777-6) which is registred under REACH in the 1000 - 10000 tonnes per annum. However, most of the n-hexane which reaches the consumer is not pure n-hexane but technical hexane, registred as "Hydrocarbons, C6, n-alkanes, iso-alkanes, cyclics, n-hexane rich (EC 925-292-5) in REACH and registred in the range 100 000 - 1 000 000 tonnes per annum. It will be important to apply the new classification also to EC 925-292-5. According to the recent MSDS attached, the ban of n-hexane from consumer uses which was supposed to be applied according to the Substance Evaluation Conclusion document (n-Hexane) dated May 2017, seems not to be in force yet for EC 925-292-5 in 2021. And given the known toxicity of hexane for human, it is a concerning issue. ECHA note – An attachment was submitted with the comment above. Refer to public attachment MSDS Hexane.pdf				
Dossier Submitter's Response				
For mixtures containing n-hexane the generic concentration limits will apply, triggering classification of the mixture as follows: i) STOT RE Category 1 for mixtures containing n-hexane in concentrations ≥ 10% ii) STOT RE Category 2 for mixtures containing n-hexane in concentrations ≥ 1% and <10% Accordingly, the STOT RE classification will apply for technical hexane when the generic concentration limits for n-hexane are exceeded in the mixtures.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.03.2022	Belgium	Hydrocarbon Solvents Producers Association (HSPA), a Cefic Sector Group	Industry or trade association	2

Comment received

The Hydrocarbon Solvents Producer Association (HSPA) welcomes the opportunity to comment to the proposed Harmonized Classification and Labelling for n-Hexane.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment HSPA_comments_ECHA_CLH_final_redacted.pdf
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment HSPA_comments_ECHA_CLH_final.pdf

Dossier Submitter's Response

For mixtures containing n-hexane the generic concentration limits will apply, triggering classification of the mixture as follows:

i) STOT RE Category 1 for mixtures containing n-hexane in concentrations ≥ 10%
ii) STOT RE Category 2 for mixtures containing n-hexane in concentrations ≥ 1% and <10%

According to the Guidance on the Application of the CLP Criteria, section 3.9.2.6., setting specific concentration limits above the generic concentration limits is not applicable for STOT RE, because classification for STOT RE is based on potency. Thus, substances with a low potency do not require classification for this hazard class and substances with a medium or high potency are classified in a category defined by the guidance value.

RAC's response

RAC agrees with the DS that based on the CLP criteria and guidance, it is not possible to deviate from the standard GCLs. A specific concentration limit (SCL) may only be set for substances inducing specific target organ toxicity in animal studies at a dose level or concentration clearly (more than one order of magnitude) below the guidance value for cat 1 classification (CLP Annex I, Table 3.9.2). The reasoning provided by HSPA to support higher SCL is mainly based on risk assessment considerations focusing on air levels at which polyneuropathy has been (or has not been) observed in individual epidemiological studies or on the disproportianaty of the GCL. According to the classification criteria, n-Hexane clearly fulfils criteria of STOT cat 1 and the presented data cannot provide proof that neurotoxicity of n-hexane is not relevant for mixtures with n-hexane content 1-10% in any possible exposure scenarios. RAC would also like to note that classification of mixtures containing n-hexane does not only apply to mixtures with compounds that do not exert neurotoxicity on their own (e.g. technical hexane with n-hexane concentration < 10%). As described in the CLP report and RAC opinion, there are compounds that potentiate the effects of n-hexane, e.g. by sharing the common neurotoxic metabolite 2,5-hexanedione. Overall, RAC is of the opinion that it is not possible to deviate from the standard generic concentration limits set in the CLP regulation.

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2022	France	<confidential>	Company-Downstream user	3
Comment received				
This comment supersedes the comment number 6c83c320-e22e-44d4-a5f0-03116a946c9d. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Hexane Repro and ED wo conf part.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment RE-2021-0043_v3.pdf				
Dossier Submitter's Response				
The dossier submitter appreciates the comments regarding the potential for reproductive toxicity and endocrine disruption of n-hexane. Since the hazard class of reproductive toxicity was not part of the assessment in the current CLH report, it will not be discussed this time.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
15.03.2022	Belgium	Hydrocarbon Solvents Producers Association (HSPA), a Cefic Sector Group	Industry or trade association	4
Comment received				
While we agree in principle with the proposed STOT classification and labelling harmonization for n-hexane, we also present a pragmatic approach to define the classification cut off limit that should support managing this change. As an outcome of our scientific assessment of the key studies, explained in more detail in the attached document, we argue to maintain the current classification limit of 5% by applying the STOT RE cat.2 at concentrations of > 5% but < 10%, so that consequently solvents with < 5% are not classified and resulting in the following scheme to minimalize disruptions in the REACH registrations: > 10% n-hexane – STOT RE cat.1 (H372) < 10% but > 5% - n-hexane – STOT RE cat.2 (H373) < 5% n-hexane – no classification ECHA note – An attachment was submitted with the comment above. Refer to public attachment HSPA_comments_ECHA_CLH_final_redacted.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment HSPA_comments_ECHA_CLH_final.pdf				
Dossier Submitter's Response				
For mixtures containing n-hexane the generic concentration limits will apply, triggering classification of the mixture as follows: i) STOT RE Category 1 for mixtures containing n-hexane in concentrations ≥ 10%				

ii) STOT RE Category 2 for mixtures containing n-hexane in concentrations ≥ 1% and <10% According to the Guidance on the Application of the CLP Criteria, section 3.9.2.6., setting specific concentration limits above the generic concentration limits is not applicable for STOT-RE because classification for STOT-RE is based on potency. Thus, substances with a low potency do not require classification for this hazard class and substances with a medium or high potency are classified in a category defined by the guidance value.
RAC's response
Noted, please see to the reply to comment number 2.

Date	Country	Organisation	Type of Organisation	Comment number
18.03.2022	Sweden		MemberState	5
Comment received				
The dossier submitter (Federal Institute for Occupational Safety and Health, BAuA) proposes to modify the harmonised classification for n-hexane from STOT RE 2* (H373) to STOT RE 1 (H372, nervous system) and delete the specific concentration limit of ≥5%. The SE CA supports this modification. Background: The current harmonized classification of n-hexane (STOT RE 2*; H373) arises from the translation of the classification according to Dangerous Substances Directive (DSD) to CLP. During a substance evaluation of n-hexane, the eMSCA concluded that sufficient information on the neurotoxicity of n-hexane in humans is available to justify classification as STOT RE 1. Human occupational cohort studies (retrospective, n=4), case control studies (retro- and prospective, n=3) and surveillance/case-studies (n=9) show consistent neurological effects among the studies, including polyneuropathy, decreased motor nerve conduction velocities, increased distal latencies, sleepiness, dizziness, weakness in the limbs, paresthesia, hypoesthesia, dysesthesia of limbs. Some of these neurological effects are also observed in experimental animal studies in rat and mouse (including 5 non-guideline studies and 1 study equivalent to OECD TG 413). Sub-chronic and chronic exposure to n-hexane from dose levels of 500 ppmV (1.76 mg/L, whole body inhalation) show neurobehaviour effects (i.e., hindlimb paralysis, unsteady gait, foot drop, muscular atrophy, reduced motor nerve conduction velocity, prolonged distal latencies, decreased locomotor activity) in relation to neurohistopathological changes (i.e., multifocal axonal swellings, adaxonal myelin infolding, paranodal myelin retraction, excessive number of neurofilaments, vesicles, multivesicular bodies, mitochondria, myelin figures, and dense bodies in the paranodal axoplasm and no neurotubules). The lowest effective dose in the animal studies (1.76 mg/L/6h/day) is about one magnitude higher than the guidance value (C ≤ 0.2 mg/L/6h/day) for classification in category 1, and thus do not fulfil the criteria. However, the available human data is considered sufficient for classification in category 1, in accordance with CLP Annex I, 3.9.2.10.2.				
Dossier Submitter's Response				
The dossier submitter appreciates the comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.01.2022	France	<confidential>	Company-Downstream user	6
Comment received				
The classification of n-hexane as STOT RE 1, H372 (nervous system) is consistent with the toxicological database available. According to the bibliographic report attached, n-hexane should also be classified as Repr. 1A, H360 (May damage fertility on human) and EDC Human - suspected (Endocrine Disruptor compound for human). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Hexane Repro and ED wo conf part.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment RE-2021-0043_v3.pdf				
Dossier Submitter's Response				
The dossier submitter appreciates the comments regarding the potential for reproductive toxicity and endocrine disruption of n-hexane. Because the hazard class of reproductive toxicity was not part of the assessment in the current CLH report, it will not be discussed this time.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2022	Italy		Individual	7
Comment received				
Please find attached a peer reviewed paper from Cheng et al (2012) "Exposure to 2,5-hexanedione can induce neural malformations in chick embryos". 2,5-Hexanedione has been known for decades as being the first metabolite of hexane (either ingested or inhaled) for human and the reason for its toxic effect. Hexane is today proposed to remain classified as Repr. 2, H361f*** (suspected of damaging the fertility) however the attached paper shows that 2,5-hexanedione has a teratogenic effect on chick embryos. It is proven that at least part of hexane ingested or inhaled by the human body is turned into 2,5-hexanedione. Given the severity of the effect induced by 2,5-Hexanedione in chick embryos, it seems to me that hexane should be classified as Repr. 1B, H360 with a warning related to teratogenic effect. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cheng et al. - 2012 - Exposure to 2,5-hexanedione can induce neural malf.pdf				
Dossier Submitter's Response				
The dossier submitter appreciates the comments regarding the potential for reproductive toxicity and endocrine disruption of n-hexane. Since the hazard class of reproductive toxicity was not part of the assessment in the current CLH report, it will not be discussed this time.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2022	France		MemberState	8
Comment received				
FR agrees with the reasoning based on human data rather than animal data, and then supports the proposal to classify n-hexane as STOT-RE 1 based on neurotoxicity.				
Dossier Submitter's Response				
The dossier submitter appreciates the comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.02.2022	Czech Republic	<confidential>	Company-Importer	9
Comment received				
We do not have any toxicological and ecotoxicological studies to improve the following proposed future entry in Annex VI of CLP Regulation by the dossier submitter.				
Dossier Submitter's Response				
The dossier submitter appreciates the comment.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. MSDS Hexane.pdf [Please refer to comment No. 1]
2. Cheng et al. - 2012 - Exposure to 2,5-hexanedione can induce neural malf.pdf [Please refer to comment No. 7]
3. HSPA_comments_ECHA_CLH_final_redacted.pdf [Please refer to comment No. 2, 4]
4. Hexane Repro and ED wo conf part.pdf [Please refer to comment No. 3, 6]

CONFIDENTIAL ATTACHMENTS
1. HSPA_comments_ECHA_CLH_final.pdf [Please refer to comment No. 2, 4]
2. RE-2021-0043_v3.pdf [Please refer to comment No. 3, 6]