COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 05.06.2023

Substance name: Calcium bromide
CAS number: 7789-41-5
EC number: 232-164-6
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	1
Comment received				
Three separate CLH proposals were submitted for a group of inorganic bromide salts (sodium, potassium and calcium bromide). Read-across between these substances was performed in the dossiers. Another read-across substance, ammonium bromide (EC no. 235-183-8), was added to Table 3, Annex VI of the CLP regulation in February 2022 with a harmonised classification as Repr. 1B (FD), Lact., Eye Irrit. 2, STOT SE 3 and STOT RE 1. The read-across is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	France		MemberState	2
Comment received				
The way the file is structured does not necessarily help with understanding. We think it would be more relevant to describe the systemic effects first, then the effects on "the sexual function and fertility" or "development". We would appreciate if more details could be added in the read across approach. Indeed, in the TK summary, some table with more details could be added (with chemical structure, solubility values…). We note that detailed data are included in the annex I, but in our view, a table summarizing the effects of the different substances would have provided a cross-sectional view of the dossier. Endocrine disruption properties: Regarding effect on thyroid, there are indications that bromides could have endocrine disrupting properties. In the CLH report, it is clear that bromides have adverse effect on the thyroid (STOT RE justification on thyroid). For information, in 2019, the active substance 2,2-Dibromo-2-cyanoacetamide (DBNPA) has				

been assessed for its endocrine properties and DBNPA fulfils the criterion (d) of Article 5(1) for human health. The endocrine disrupting effects of DBNPA are attributed to the bromide ion (Opinion of the Biocidal Products Committee on the application for approval of the active substance 2,2-Dibromo-2-cyanoacetamide (DBNPA) for product type 4). The documents are available on : https://echa.europa.eu/fr/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1224/PT04

The COMMISSION IMPLEMENTING DECISION (EU) 2023/459 was released on the 2nd of March 2023, not approving 2,2-Dibromo-2-cyanoacetamide (DBNPA) as an existing active substance for use in biocidal products of product-type 4 in accordance with Regulation (EU) No 528/2012 of the European Parliament and of the Council.
Moreover, it seems interesting to compare these effects with those observed for fluoride and chloride. FR is currently evaluating fluoride, for its endocrine disrupting properties on thyroid.
Halogenated compounds seem to have the same effects on the thyroid.

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2023	Austria	The International Bromine Council BSEF	Industry or trade association	3

Comment received

The International Bromine Council BSEF herewith provides comments on the CLH report and the proposed harmonized classification of calcium bromide as prepared by the Swedish Chemicals Agency. These comments are accompanied by a new toxicokinetic study to provide further supporting evidence for the classification proposed by BSEF on the endpoint reproductive toxicity.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment BSEF detailed comments on KEMI CLH report CaBr2_2023-06-01.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH Report CaBr2 - Supporting studies for CL.zip

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	4

Comment received

The DE CA supports the classification as Repr. 1B (H360FD) and Lact. (H362) for calcium bromide based on read-across to sodium and ammonium bromate.

Fertility:
In accordance with the DS, the criteria for classification in Repr. 1B for adverse effects on sexual function and fertility are considered fulfilled based on the clear evidence of dose related effects on impaired fertility noted in the male and female rats in studies with the source substance sodium bromide. These effects are not considered a secondary consequence of general systemic toxicity. Moreover, there was evidence from studies with the source substance sodium bromide in rats of effects on male reproductive organs and on female gonads in the absence of severe systemic toxicity.

Development:
In accordance with the DS, the criteria for classification in Repr. 1B for adverse effects on

the development of offspring are considered to be fulfilled: There is clear evidence of adverse dose-related effects on the development of offspring recorded in animal studies with the source substance sodium bromide. These included visceral and skeletal malformations and some evidence of increased pup mortality and retarded growth in treated rats. It is furthermore supported that a classification as Repr. 1A is not warranted based on the available human studies, because observed effects of neonatal bromism were reported to be transient.

Lactation:
The view of the DS is supported that, based on an overall weight of evidence assessment, classification for effects on or via lactation is considered warranted. In non-guideline studies with the source substance sodium bromide it is was shown that bromide can be transferred via mothers` milk to their pups. Milk production was decreased and the elementary composition of the milk was changed resulting in malnutrition and lowered viability of pups. Thus, there is evidence from animal studies and also weak indication from a human case report that bromide may cause harm due to its effects on and via lactation.

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	France		MemberState	5
Comment received				
FR agrees with the classification Repr. 1B, H360FD. Could you please specify which endpoint value was taken into account when estimating the ED10 and what is the justification? FR agrees with the classification Lact., H362.				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	United Kingdom	Health and Safety Executive	National Authority	6
Comment received				
Reproductive toxicity – adverse effects on development We note that, in the pre-natal developmental toxicity studies with ammonium bromide and one pre-natal developmental toxicity study with sodium bromide (Study report, 1995; Study report, 2000b; Study report, 2007), malformations were reported at doses that also caused maternal toxicity. We would welcome a discussion about the maternal toxicity and its impact on the relevance of the malformations for the proposed Category 1B classification.				

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2023	Austria	The International Bromine Council BSEF	Industry or trade association	7
Comment received				
The International Bromine Council BSEF is of the opinion that the reproductive effects observed in rat studies, which form the basis of the proposed Repr. 1B; H360 FD, classification for calcium bromide, are not directly relevant to humans. These effects appear in rats at plasma levels which, in humans, cause severe neurotoxicity. Based on new				

information confirming the differences in the sensitivity towards bromide-related hazards in rats and humans and which raises doubt about the relevance and transferability of the findings made in rodents to humans, a classification as Repr. 2; H361 f, and a non-classification for developmental toxicity is considered more appropriate, in accordance with chapter 3.7.2.1.1 of the CLP Regulation (EC 1272/2008: "Category 1B Presumed human reproductive toxicant The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate." In addition, Chapter 3.7.2.3. of annex I Weight of evidence is relevant for this data and should be applied accordingly, 3.7.2.3.2: "Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may provide relevant information which reduces or increases concerns about the hazard to human health. If it is conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified." This paragraph clearly applies to the bromide salts in our opinion.

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OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	8
Comment received				
The proposed classification as STOT SE 3 is supported based on transient CNS effects in humans and supporting evidence of transient narcotic effects in animal studies.				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	France		MemberState	9
Comment received				
FR agrees with the classification STOT SE 3, H336				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	10
Comment received				
The proposed classification as STOT RE 1 with the nervous system as target organ is supported based on the available human data on bromism (case reports) with supporting animal data. The effects on the thyroid are considered not severe enough for it to be included as target organ.				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	France		MemberState	11
Comment received				
FR agrees with the classification STOT RE 1, H372 (nervous system). Regarding STOT RE for thyroid effects, we agree on the fact that : ”In this case of sodium bromide and bromide salts, histopathological changes (i.e. follicular hypertrophy and/or hyperplasia) in the thyroid, and changes in the circulating levels of thyroid hormones have been reported. Thus, human relevance of thyroid disruption of ammonium bromide cannot be ruled out.” Therefore, could you please provide a robust justification explaining why the Calcium bromide is not considered as STOT RE Thyroid? (This comment joins the one on endocrine disruptor hazard).				

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2023	Austria	The International Bromine Council BSEF	Industry or trade association	12
Comment received				
The International Bromine Council (BSEF) agrees that the toxicity of the bromide ion is characterized by neurotoxicity and that humans have been shown to be more sensitive to bromide-induced neurotoxicity than rats. A revisit of the available human data demonstrates that following conversion of blood levels to a dose in mg/kg bw/day, the dose levels which cause neurotoxicity in humans are largely observed at doses which do not qualify for a classification into category 1 for STOT RE. Bromide-related neurotoxicity may start at blood levels of 6 – 12 mmol/L corresponding to about 32 – 64 mg/kg bw/day based on a body weight of 60 kg and assuming a blood volume of 4 L. The cut off limit of STOT RE 1 is 10 mg/kg bw/day for a 90-day exposure period equivalent to 2.5 mg/kg bw/day in humans following correction for allometric scaling. In the available human case studies, e.g. the observations made in pregnant women, the exposure duration was longer than 13 weeks. In the study of Sangster (Sangster et al., 1983), mild effects on neurophysiological function were observed at 4 mg/kg bw/day after 3 months. This dose is above the cut-off limit of 2.5 mg/kg bw/day adjusted for allometric scaling. Based on the weight of the evidence from human studies, a classification with STOT RE 2; H373 (nervous system) is, therefore, more appropriate. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BSEF detailed comments on KEMI CLH report CaBr2_2023-06-01.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH Report CaBr2 - Supporting studies for CL.zip				

PUBLIC ATTACHMENTS
1. BSEF detailed comments on KEMI CLH report CaBr2_2023-06-01.zip [Please refer to comment No. 3, 7, 12]

CONFIDENTIAL ATTACHMENTS
1. CLH Report CaBr2 - Supporting studies for CL.zip [Please refer to comment No. 3, 7, 12]