Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Potassium bromide

EC Number: 231-830-3
CAS Number: 7758-02-3

CLH-O-0000007428-67-01/F

Adopted

14 March 2024

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON POTASSIUM BROMIDE

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: potassium bromide
EC number: 231-830-3
CAS number: 7758-02-3
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2023	Austria	The International Bromine Council BSEF	Industry or trade association	1
Comment received				
The International Bromine Council BSEF herewith provides comments on the CLH report and the proposed harmonized classification of potassium 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 KBr_2023-06-01.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH Report KBr - Supporting studies for CL.zip				
Dossier Submitter's Response				
See comment number 7.				
RAC's response				
See reply to comment number 7.				

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.

Dossier Submitter's Response

Thank you for your comments.

We understand your comment about the order of the hazard classes. However, the order in which the hazard classes are presented in the dossier is in accordance with the ECHA template for CLH Reports.

Regarding the request for more details on the read-across approach, a summary table with relevant substance specific information for each bromide salt could be added to section 9.1 under the heading "Justification for read-across from other bromide salts". Such table could include the following information:
Name; Formula; Water solubility
Potassium bromide; KBr; 687 g/L at 25°C
Sodium bromide; NaBr; 946 g/L at 25 °C
Ammonium bromide; NH_4Cl; 783-970 g/l at 25°C

Regarding your comment about ED; This dataset was scrutinized by RAC in the previous CLH proposal for ammonium bromide, with the conclusion that the effects on the thyroid based on available data were not considered sufficiently adverse to fulfil the criteria for classification in STOT RE. Thus, we do not anticipate that current data would fulfil criteria for ED, at least not for category 1. Other reasons for us to not address ED in this CLH-proposal were that the new CLP classification criteria for ED had not entered into force when this CLH dossier was prepared and we did not want to delay the submission of the CLH-proposal. Of note, there are also ongoing discussions between ECHA and some MS

(including SE) on ED assessment of biocidal active substances that are bromide releasers and it may be beneficial to await the outcome of this work as well.

We are aware that DBNPA was identified as having thyroid endocrine disruptive properties based on effects of the bromide ion, however, it is not clear to us that this organic substance is appropriate for read-across to the inorganic bromides in the current proposal.

RAC's response

Thanks for the comment. RAC re-assessed the effects on thyroid by bromide salts and concluded that STOT RE 2 for thyroid is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	3

Comment received

Three separate CLH proposals were submitted for a group of inorganic bromide salts (sodium, potassium and calcium bromide). The 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.

Dossier Submitter's Response

Thank you for your support for the read-across approach.

RAC's response

Thanks for your support and comments.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	France		MemberState	4

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.

Dossier Submitter's Response

Thank you for your comment and support for the proposed classification in Repr. 1B, H360FD and Lact. H362.

The ED10 for sexual function and fertility was based on the fertility index in the two-generation reproductive toxicity study of sodium bromide in rats (Study report 2016a):

* First cohabitation: 100, 91.3, 73.9 and 64.7% at 0, 50, 175 and 1000 mg/kg bw/day, which results in an ED10 = 59.3 mg NaBr/kg bw/day, corresponding to **68.6 mg KBr/kg bw/day**
* Second cohabitation: 100, 100, 73.7% at 0, 50 and 175 mg/kg bw/day, which results in an ED10 = 97.5 mg NaBr/kg bw/day, corresponding to **112.7 mg KBr/kg bw/day**

The ED10 for development was based on the major foetal abnormalities in the pre-natal developmental toxicity study of ammonium bromide in rats (Study report 2000b): * 2.6, 6.9, 12.2 and 40.8% at 0, 100, 300 and 1000 mg/kg bw/day, which results in an ED10 = 310 mg NH4Br/kg bw/day, corresponding to **376.6 mg KBr/kg bw/day** Thus, the estimated ED10 values are within the medium potency group (4 mg/kg bw/day < ED10 value < 400 mg/kg bw/day).
RAC's response
Thanks for your support and comments. RAC acknowledges the useful complementary information from the DS.

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	5

Comment received
The DE CA supports the classification as Repr. 1B (H360FD) and Lact. (H362) for potassium 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 include 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 acute intoxication and consequential neonatal bromism were reported to be transient. Lactation: The view of the DS is supported that, based on an overall weight of evidence approach, classification for effects on or via lactation is considered warranted. In non-guideline studies with the source substance sodium bromide it 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.
Dossier Submitter's Response
Thank you for your comments and the support for the proposed classification in Repr. 1B (H360FD) and Lact. (H362).
RAC's response
Thanks for your support and comments.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON POTASSIUM BROMIDE

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.

Dossier Submitter's Response

Thank you for your comment.

A steep dose response for general toxicity may mask adverse effects on development. Therefore it may be important to note evidence of dose-dependent changes, even if they are mild at lower doses where general toxicity is not adverse when marked effects are seen at high dose in presence of severe general toxicity.

In the post-natal developmental toxicity study of sodium bromide (study report 1995), skeletal malformations (ribs) were recorded at the highest dose (1000 mg/kg bw/day) with maternal toxicity. However, skeletal anomalies and variants (ribs, cranial centres and sternebrae) were recorded at lower doses (300 mg/kg bw/day) without maternal toxicity. These skeletal abnormalities are also considered to reflect a selective effect on embryofoetal development and not a secondary effect resulting from toxicity to the parent female. In addition, a dose-dependent increase in incidences of skeletal abnormalities and variants (kinked ribs, curved scapulae and incomplete ossification of ribs) were observed at lower dose levels (from 100 mg/kg bw/day) without associated reductions in foetal weights and without maternal toxicity in two studies of ammonium bromide in rat (Study report 2007 & study report 2000b).

A statistically significant increase in incidences of visceral malformations (reduction or absence) were seen at a dose level of 1000 mg/kg bw/day in studies of sodium bromide and ammonium bromide in rats. These defects observed in the urogenital system, uterine, spleen and thyroid at a high dose level in two studies are considered to reflect a selective effect on embryofoetal development and not a secondary effect resulting from toxicity to the parent female.

In addition, a dose-related increased incidence of displaced testis was noted at 100 and 300 mg/kg bw/day (dose levels without maternal toxicity) and 1000 mg/kg bw/day (dose level with maternal toxicity) in the pre-natal developmental toxicity study of ammonium bromide in rat.

Furthermore, in the RAC opinion for ammonium bromide (2020), for which the same data was used to assess toxicity to reproduction, it was concluded: *Specifically in Study report (2000b), mortality of 1/24 dams (i.e. < 10%) does not automatically justify discounting the developmental effects in this dose group, and a reduction in maternal body weight gain (43% of control) during the first six days could be largely attributed to marked weight loss in two of the animals. Thereafter, body weight gain was similar to control (94%). Thus, irreversible effects such as structural malformations in foetuses in this study and in Study report (1995), i.e. absence of organs (kidney, ureter, adrenal, thyroid) cannot be seen as a consequence of maternal toxicity.*

RAC's response
Thanks for the comments. RAC supports the DS explanation. It is true that developmental effects occurred at or near concentrations at which there was significant maternal toxicity in several reports. However, at least four GLP studies (Study report, 2001; Study report, 2000a; Study report, 2000b; Study report, 2007) showed clear dose-related effects on sexual function and fertility and development at concentrations with low or no maternal toxicity. These studies can be taken as key studies for the 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 potassium 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. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BSEF detailed comments on KEMI CLH report KBr_2023-06-01.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH Report KBr - Supporting studies for CL.zip				
Dossier Submitter's Response				
Thank you for your comments. The classification criteria do not consider exposure. Rather, it is the inherent toxicological properties of the substances that lead to classification.				

Regarding you comment about the reproductive effects observed in rat studies not being directly relevant to humans, we would like to point out that the human clinical studies (Sangster 1982, Sangster 1983 and van Gelderen 1993) only studied effects on the central nervous system and endocrine system (hormone levels). Effects on the reproductive organs, sexual function or fertility were not investigated in these studies or in any other human studies. Thus, there are no available studies investigating the sensitivity to reproductive toxicity in humans and hence there is no information on whether effects on fertility and/or development endpoints occur in humans at lower, similar or higher dose levels compared to rats.

Regarding your comment about the differences in sensitivity towards bromide-related hazards in rats and humans; In table 1 presented in your public attachment *BSEF detailed comments on KEMI CLH report KBr_2023-06-01.zip,* it is stated that the LOAEL for neurotoxicity in rats represents plasma levels of 21.9-34.9 mmol/L, whereas neurotoxicity in human case studies have been observed at 18-45 mmol/L. However, the plasma levels in the human case studies are probably underestimated as the blood samples were taken up to 6 days after the exposure had ceased (Finken and Robertson, 1963; Pleasure and Blackburn, 1975; Mangurten and Bann, 1974). Furthermore, in the in vivo mechanistic studies in human volunteers, neurotoxicity of low bromide doses (3.22 and 7.99 mmol/L) were assessed by changes in EEG, which is a more sensitive measure than the clinical signs of neurotoxicity that were observed in the animal studies (Sangster, 1983; van Gelderen, 1993). Thus, the plasma levels inducing changes in EEG in humans should not be directly compared to plasma levels associated with clinical signs of neurotoxicity in animal studies. In this context, we would again like to stress that regardless of the possible differences in sensitivity towards neurotoxicity, there is no information about the sensitivity towards toxicity to reproduction in humans. Thus, humans could as well have a lower dose effect level for reproductive toxicity than rat.

We would like to refer to CLP Annex I 3.7.2.3.2 and 3.7.2.5.5: "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." We consider that no clear mechanism or mode or action, nor marked toxicokinetic differences between humans and the test animals have been conclusively demonstrated.

We note that the new toxicokinetic study (Barnett 2019) was submitted during the previous public consultation on ammonium bromide and that the later analytical results (Haan and Buscher 2019; Buscher 2020) were presented during the RAC meeting. Furthermore, the importance of these new toxicokinetic studies for the classification of ammonium bromide was raised by BSEF in the preparation for 18th ATP and discussed at the 40th Meeting of Competent Authorities for REACH and CLP (CARACAL) on 29-30 June 2021. The following conclusion was reached: "RAC concluded that there was no mechanistic information available to indicate that the effects observed in animal studies on sexual function and fertility were not relevant to humans. RAC also concluded that the developmental effects observed in animal studies were relevant to humans. The observed reproductive effects were concluded not to be secondary to other toxicity. ECHA considers that the issues raised were adequately discussed by RAC and have been addressed in the recently published opinion on ammonium bromide which RAC has adopted."

In the following section, we respond to the specific comments about reproductive toxicity raised in the public attachment BSEF *detailed comments on KEMI CLH report KBr_2023-*

06-01.zip. Please note that not all comments are included here, as several comments addressed the same issues.

COMMENTS REGARDING SEXUAL FUNCTION AND FERTILITY

Two generation reproductive toxicity study of sodium bromide (Study Report 2016a)

BSEF comment:
It should be noted that the fertility index in the mid dose group, although significantly lower than concurrent controls was very close to the historical control range, as is demonstrated in the report These historical control data have been collated from 187 studies conducted
in the crl:CD(SD)rat the conducting laboratory since 2008 (https://www.criver.com/sites/default/files/resources/ReproductiveToxicologyHistoricalControlDatainRats.pdf and the CRO confirmed that the range is the same if only studies of the last two years are considered) and therefore we disagree with the comment that the validity of the statements referencing these data is low.
In total, over both cohabitation periods, all males in Groups 1, 2 and 3 mated at least one female. All control males impregnated at least one female and there was only one male in the 50 mg/kg/day group which did not achieve a pregnancy. At 175 mg/kg/day, although reduced pregnancy rates were observed at both cohabitation periods compared to concurrent controls, unusually, the affected animals differed and in total only 2 males did not impregnate a female, giving an overall male fertility index of 91.7% (within the expected range). This was likely a deficit in these males, as neither of the treated females allocated to one male became pregnant at the alternative pairing and the allocated untreated female was not mated, but the females allocated to the other male both became pregnant with alternative males.
All females in Groups 1, 2 and 3 mated during either the first or second cohabitation periods. Five females in the 175 mg/kg/day group did not get pregnant from either pairing (with treated males only), giving an overall female fertility index of 77.3% (17/22), below the concurrent control value but within the expected range. Only two of these females showed marked depletion of corpora lutea at histopathology and no corpora lutea at ovarian follicle examination. One of these females had also shown extended estrus (9 days) and a further female, showed extended periods of diestrus (which may indicate pseudopregnancy). Another female which had marked depletion of corpora lutea at
histopathology and no corpora lutea at follicle counting, was pregnant at the first pairing (but not at the second). Therefore, the conclusion of 'clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects' cannot unequivocally be drawn from these findings, owing to the potential for adverse effects on reproductive performance consequent to treatment-related effects on condition (including sedation), and to the difference in performance of individuals in both cohabitation periods.

DS reply: In the OECD GD 43 it is stated that *"Comparison of concurrent study control data with the data from treated animals should always take precedence over comparison with historical control data".* In this case the fertility index in the parental generation was decreased to 73-74% (in both first and second cohabitation, $p \leq 0.01$) at 175 mg/kg bw/day compared to control. This is still outside the range of the available HCD (75-100%). Furthermore, in the first cohabitation where all doses were included, the decreased fertility index seem dose-

dependent, although only the change in the intermediate and high dose groups were significant compared to the control.

In your comment you make a point that there is an inconsistency in fertility index between affected individuals in the two cohabitations of the P generation. Although there were 2 out of 22 males and 5 out of 22 females that were reported to have decreased reproductive capacity in both cohabitations, there were additionally 11/22 affected males and 5/22 affected females in either one of the cohabitations (excluding those animals that were not paired in the second cohabitation or animals that were euthanized before second cohabitation). It is well known that rats have a very high reproductive capacity, and for that reason the observed effects on fertility still demonstrate that the fertility is disturbed but not completely diminished. We therefore consider that it is not contradictory that different individuals are affected in the two cohabitations of the P generation.

The study did not however reveal this disturbance in the successive generation F1. Why there was no effect on fertility index at the same dose level in F1 generation, where only 1 out 15 females did not get pregnant (fertility index 93.3% for both males and females), we do not have a clear answer. Nevertheless, we consider that the effects on fertility in P generation cannot be disregarded.

Regarding the individual female with marked depletion of corpora lutea at histopathology and no corpora lutea at follicle counting being pregnant in the first cohabitation but not the second, we would like to point to the fact that, obviously, counting of follicles can only be performed at termination, i.e. after second cohabitation. And indeed, this female did not get pregnant in second cohabitation.

The following points regarding reduction in number of corpora lutea can be noted from the Study report (extracts from the original study report):
- At 500 mg/kg/day, 5/8 terminal kill females evaluated had no corpora lutea present, and there were 5 further females terminated early which also had no corpora lutea. As 3/20 females treated at 500 mg/kg/day in the recent 90 day study [Study report 2016b] had no corpora lutea present, and as a reduction in the number of corpora lutea per female was observed at the high dose level of 19200 ppm/kg diet (in excess of 1000 mg/kg body weight/day) in a published study (van Logten et al 1974), this finding may be related to administration of sodium bromide
- As the 175 mg/kg/day dose group females in the F1-Generation appeared to have fewer atretic follicles and follicular types were not as well represented, the possibility of an effect of sodium bromide treatment cannot be discounted
- With regard to Group 3 F1-generation female rats, while corpora lutea were present in all animals evaluated, a qualitative notation was made in the data that for this group in general, corpora lutea were largely regressed. Since depletion of corpora lutea is commonly associated with this test article, an effect of administration of sodium bromide should not be ruled out
- Therefore, under the conditions of the protocol, although administration of sodium bromide did not appear to affect the development of primordial follicles, there appeared to be an effect of this test article upon the development of corpora lutea in both P and F1-generation female rats.

BSEF comment:
Determination of the number of corpora lutea was variable and depends on the oestrous stage at termination. Ovarian follicle counts seem to be a more reliable endpoint. We recommend to not draw conclusions on any possible substance-related effect from these

variable counts of corpora lutea, as variation in numbers is expected within a normal cycle (Yoshida 2009).
The additional reference to effects reported in the van Logten et al, 1974 publication is equally uncertain, and was reported only at severely toxic dose levels that should not be used for the evaluation of adverse reproductive effects.

DS reply: We agree that histopathological evaluation of ovaries is complicated and not straight forward for several reasons. We also note in OECD GD 43 that "multiple litters produced by a single dam will compromise corpora lutea count; in dams after multiple pregnancies, corpora lutea counts are not likely to be reliable, since corpora lutea remnants from previous pregnancies may be included in the count." Consequently, due to the design of this two-generation reproductive toxicity study with two cohabitations, the number of corpora lutea may have been an overestimation, and therefore the toxicity of the female gonads may have been underestimated.

BSEF comment:
It should be noted that all findings in the 175 mg/kg/day dose group that were flagged as statistically significant compared to the concurrent control group where well within the historical control range and therefore these changes are not toxicologically relevant. As in many laboratories, the variation observed in control males for these parameters is relatively high and we do not think it is justified to conclude a clearly substance-related effect from these findings. As acknowledged in the CLH report, the findings did also not correlate with the pregnancy outcome of the pairing.

DS reply: In the OECD GD 43 it is stated that "Comparison of concurrent study control data with the data from treated animals should always take precedence over comparison with historical control data. Furthermore, we note that the study period of the HCD for sperm parameters (1998-2013) is much wider than what is recommended in OECD GD 43; *If historical control data are used, the most appropriate of these are from studies conducted in the same laboratory, within a reasonable amount of time prior to the study being interpreted (e.g., ± 2 years) in order to avoid genetic drift in the laboratory animal population, and under the same study conditions (e.g., identical species, strain, source, age, vehicle, route and duration of administration, technical personnel, etc.)*. Thus, we consider the HCD of less relevance for comparison.

We consider that statistically significant changes compared to control in sperm parameters still gives an indication that the male reproductive organ may be a target organ for the test substance and histopathology of gonads may be among the most sensitive parameters to detect adverse effects on male fertility. Furthermore, changes in sperm parameters may provide important information because in humans even a slight reduction in sperm quality/count may be critical for fertility.

We agree that there was no correlation to the functional reproductive performance, but would like to emphasize that mechanistic evidence is not needed to explain deficit functional performance for classification for adverse effects on sexual function and fertility.

Three-generation reproductive toxicity study of sodium bromide (Van Leeuwen et al.,1983)

BSEF comment:
This publication contains so little detail on experimental method that it is considered unreliable data. In particular, there is obvious confusion in terminology where pairing of

animals is reported as 'mating'. In the absence of data on actual mating at each pairing and on the systemic toxicity observed, no conclusions on fertility impairment can be drawn from this study. Any further assumptions as to what sex might have been affected are speculative since the practices of using 4 month old, proven males at the study start, of breeding at least 3 times in the first generation and of combining litter data from different pairings are all confounding factors. In addition, although the age and reproductive status of animals used in the crossover study are not reported, it would appear that this was a fourth mating for the treated animals and thus, since reproductive senescence in mature rats can begin as early as 6 months of age (Seller 2007) any effect on fertility cannot reasonably be deduced. It is of note that levels of bromide reported in maternal plasma after 7 months of treatment in this publication range from 0.5 mmol/L at 75 ppm to 7.8 mmol/L at 1200ppm (the NOAEL for reproductive effects) and compare to human reference values from background levels up to the therapeutic range eliciting 'possible coma' (25 – 37.5 mmol/L). It is evident, therefore that any reproductive effects occur at exposure levels which are not relevant for human exposures. However, at the 4800ppm LOAEL, maternal plasma levels were 27.6 mmol/L ie in excess of human exposure levels referenced as 'severely toxic' (>12.5 mmol/L), and within the range eliciting 'possible coma'(25 – 37.5 mmol/L). It is evident, therefore that any reproductive effects occur at exposure levels which are not relevant for human exposures.

DS reply: We do agree that this study has limitations and that it is not robust enough to draw a firm conclusion from findings on reproductive toxicity by its own. Hence, we have, as you rightly have pointed to, only concluded that there were indications of effects on fertility in this study and added this information to the total weight of evidence evaluation.

Regarding your comment about neurotoxic effects at plasma levels showing reproductive toxicity, please see our previous answer.

***BSEF comment**:*
In addition to the weaknesses quoted above, BSEF would like to point out the following shortcomings in this publication:
BSEF contends that the published studies are not of the quality expected for safety evaluation and have been superseded by new GLP compliant studies, which should form the basis of the assessment. The most important points are:
- The publications would warrant a Klimisch score of 3 at best and as such should not be the basis of classification
- The van Leeuwen paper is a review article and too brief to provide detail on the study design for the multigeneration study or robust data for analysis
- The studies do not comply with any OECD guidance on study design: the multigeneration study appears to be based on concurrent US FDA guidance (3 generation/2 litters per generation)
- The number of animals in the multigeneration study is unclear and seems to vary in each
generation: data from different generations have been combined in some cases, yet the exposure profile differs (the parental generation were not exposed in utero)
- It is unclear whether mating was monitored directly or presumed from pregnancy status, and if littering was observed directly – and hence whether the absence of any pregnancies in the high dose group and reduced pregnancy rate at 4800 ppm was due to mating performance (possibly secondary to severe clinical response to treatment), infertility postmating or total litter loss pre- or early post-partum
- It cannot be confirmed whether the studies were GLP compliant but from the date and the
performing laboratory it is considered unlikely

- No diet analysis was conducted to verify the achieved concentrations and consistency of formulations
- Fixed target dosages of 0, 75, 300, 1200, 4800 and 19200 mg Sodium Bromide per kilogramme of diet (ie ppm) reported as corresponding to (3.75), 15, 60, 240 and 960 mg/kg bw/day but likely to have exceeded these levels at critical stages eg late gestation and lactation where food intake increases. Dietary administration also brings pups into direct contact with test material in the diet from birth, as well as early exposure as soon as pups begin to consume solid food. Given the steep dose-response curve, this has likely affected the outcome of the study and interpretation of results (the new studies have been conducted by gavage to prevent this drift from target dose).
- The high dose level in the multigeneration study elicited clinical signs and body weight changes at the higher dosages which exceed levels of toxicity currently considered acceptable. As clinical signs define the response to treatment for Bromides (rather than the conventional markers of toxicity ie body weight gain and food intake) and since Bromide has known sedative effect, it is considered that the more subtle effects at lower dosages are unlikely to have been fully characterised: By their nature, signs such as ataxia, prostration, lethargy, abnormal gait require diligent and frequent observation to assess in nocturnal animals.
Although the CLH report only speaks about 'indications of impaired fertility' BSEF contends that the weaknesses of the study preclude any conclusions on fertility, even as 'indications'.
Therefore, in the context of regulatory decision making, when GLP studies compliant with current guidance are available, these data are inadequate and too unreliable for consideration.

DS reply:
As written in the report, we do not consider that any reliable/definitive conclusions can be drawn from this study but it may give indication on adverse effects on sexual function and fertility. We note that in the REACH registration a Klimisch score of 2 is suggested.

90-day oral repeated dose toxicity study of sodium bromide in rats, including recovery assessments (Study report 2016b)

BSEF comment:
Retained spermatids at the luminal surface or in basal Sertoli cell cytoplasm is a subtle change which can occur in isolation or can be associated with abnormalities in sperm parameters (number, motality, and/or morphology) or with other degenerative changes seen in the seminiferous tubule epithelium. These changes can affect fertility and can be associated with testosterone deficiency but there was no evidence of this in any other parameters measured on this study. Retained spermatids are not unknown in untreated animals, so the observation is recorded when an increase over the control incidence is identified. It should also be noted that these findings were not apparent in recovery animals.

DS reply: From the study report (2016b) it is noted that the study author states: "Although a few retained spermatids can be seen normally, this finding occurred in an obvious increase over controls in 2/10 in the 175 and in 9/9 500 mg/kg terminal euthanasia animals. This change can occur in isolation (e.g., boric acid, 2, 5-hexanedione) or can be one of many other degenerative changes (e.g., ethylmethanesulphonate) seen in the seminiferous tubule epithelium." The incidence of retained spermatids in control was 0/10.
We would like to make clear that hormone levels of testosterone has not been determined in this study, thus it is not possible to make a conclusion on the correlation of retained spermatids with testosterone levels.

BSEF comment:
In accordance with the authors of the study, BSEF do not consider the effects on the sperm parameters in the 175 mg/kg dose group as treatment related, as the number was well within the historical control range and the control values were at the low end of the historical control or below (for detached heads, see table at p. 61 of the CLH report). Thus although there was statistical significance when compared to concurrent controls these findings are not considered biologically significant.

DS reply: In the study report, the study author states: "At 175 mg/kg/day, the number of sperm with detached/no head was higher than the concurrent control but considered unlikely to have been an effect of treatment as it was closer to the expected (historical control mean) value than was the unusually low control value".
The dossier submitter notes that the historical control data spans years 1996-2012 which is considered to be a much too long time period and too far off from when the current study was performed than what is recommended in OECD GD 43 and therefore (as stated in the CLH-report), less relevant for comparison. The submitted HCD (from 1996-2012) for detached head was mean: 6.0 and range: 1.0-19.4. The incidences of detached heads in the current study from 2016 were: 0.8, 1.0, 5.0* and 20.6** in 0, 50, 175 and 500 mg/kg bw/day dose groups respectively.
Also, in the two-generation reproductive toxicity study (2016a), the incidences of detached head were increased: 4.4, 6.0, 7.3*, 23.7** at 0, 50, 175 and 350 mg/kg bw/day respectively, pointing to a consistent picture and an effect difficult to disregard.

BSEF comment:
We do not consider the isolated finding of no corpora lutea in the ovaries of 3 females of the high dose group as indicative of a substance related effect for the following reasons: there were no other effects on female reproductive organs and there were technical issues with sectioning of the ovaries. This finding can, at most, be regarded as inconclusive.

DS reply: See our earlier answer in this document.

Non-guideline study: 90-day oral repeated dose toxicity study (Van Logten et al., 1974)

BSEF comment:
The conclusion deviates from the principle that studies at excessively high doses should not be used in the assessment when other studies are available. We have further analysed the study and would like to draw your attention to the fact that, as this was a dietary study, dose levels had a wide range: Calculation of the Sodium Bromide intakes based on the food intake and body weight data available indicate that these data show that exposures for females ranged from 4-15, 17-60, 70-240, 278-960 and 1113- 3840 mg/kg bw/day for the 75, 300, 1200, 4800 and 19200 ppm dose groups, respectively, with the highest exposure at the start of the study. For males, the corresponding intakes ranged from 4-14, 15-55, 60-220, 247-878, 1190-3360 mg/kg bw/day for the low to high doses. The high dose level was therefore well in excess of the limit dose of 1000 mg/kg/day defined OECD guidance. Decreased prostate weight was observed in males at 4800 and 19200 ppm but there was no significant change in relative testes or ovarian weight, which is pertinent for the assessment of reproductive effects since testis weight is the primary indicator of testicular damage. The description of the other observations is ill-defined, vague and only reported at excessive dose levels. BSEF considers, therefore, that this study should not be included in the assessment.

DS reply: As stated in the CLH-report, we agree that the histopathological findings relevant for reproductive toxicity are observed at very high dose levels and are thus only considered as supporting evidence for classification.

Dose-range finding study for reproductive toxicity of ammonium bromide in rat (Study report, 2001)

BSEF comment:
This study is considered not suitable for classification purposes for the following reasons: Although GLP compliant, this is a dose-range finding study, falls short of an OECD Guideline 421 compliant screening study (which ECHA indeed define as 'not meant to provide complete information on all aspects of reproduction and development') and the small group size precludes any definitive assessment of reproductive capacity.

DS reply: We agree that a OECD TG 421 study does not provide complete information on all aspects of reproduction and development, and that the dose-range finding study has a small group size precluding statistical analysis of findings etc. However, this does not preclude to use observed adverse findings from such studies as (supporting) evidence for classification. In particular when they are in line with findings from other studies, which is the case for this dose-range finding study for reproductive toxicity of ammonium bromide in rat.

As a general note, we consider non-guideline studies to be relevant to review and present for transparency in the hazard assessment. Furthermore, findings in these studies point to similar effects and thus give a consistent picture of potential adverse effects of bromide that is relevant to consider in a total weight of evidence assessment.

BSEF comment:
We disagree that the general toxicity was not significant. Reductions in body weight were reported in males at 6400 ppm and 3200 ppm, but throughout the toxicology programme it is clear that clinical signs are the most sensitive marker of toxicity, and the CLH report acknowledges this in the proposed classification for sedative effects. In this study, even though clinical signs were only recorded at the minimum of once daily, signs in males included the typical rolling gait, piloerection and hunched posture and females showed signs of hyperactivity. Both sexes also showed staining and unkempt appearance – attributed to their 'generally ill condition'. Collectively, these signs are clear evidence of clinical condition so perturbed as to interfere with mating and reproductive performance, including litter loss due to poor maternal care.

DS reply: In the dose-range finding study for reproductive toxicity of ammonium bromide in rat (Study report, 2001) body weights in males at 6400 ppm were 94% of control during premating (weeks 1 and 2) and body weight gains were 66% of control (29 g versus 44 g in control) during this time period. Other than that there were no differences in body weights compared to control that would indicate marked general toxicity during premating that would interfere with mating and reproductive performance. There were also no significant effects on body weight or body weight gains in females during premating. With regards to the clinical condition of the animals and interference with mating and reproductive performance it could be noted that at 6400 ppm 4/10 females were observed with hyperactive behaviour and 10/10 females with rolling gait (weeks 2-11). Nevertheless, 7/10 females had signs of mating. In contrast, only one became pregnant. At 3200 ppm there were 9/10 males with rolling gait, but only two males did not sire. At the same dose, 6/10 females were observed with rolling gait and only one was not pregnant. It is therefore clear that mating did occur, as evidenced by

"vaginal plug" or sperm, and consequently we do not consider that the inability to conceive is secondary to the observed clinical signs.
We do agree with the comment that litter loss due to poor maternal care is probably caused by perturbed clinical conditions of the dams.

BSEF comment:
We would also like to draw your attention to the fact that the target dosages of Ammonium Bromide for the study were 120, 240 and 480 mg/kg bw /day but actual dosages generally exceeded the target, especially in pregnant and lactating females.

DS reply: We note the actual achieved dosages of ammonium bromide as pointed out in your comment. In this study, findings of decreased fertility index was used in the total weight of evidence for assessment of adverse effects on sexual function and fertility. Thus, information from lactating females are not taken into consideration.
Since classification in reproductive toxicity is based on the strength of evidence and is not potency based there are no guidance values for classification and therefore this information does not influence the outcome of the classification. Moreover, doses are still below the "limit dose" as recommended in OECD TG 421.

BSEF comment
At 3200 ppm, fertility index was lower than control values as 2 males did not sire a pregnancy but, as nonmated males were replaced with proven males, only one female was not pregnant. The Study Director considered the difference from control too small to indicate an effect of treatment.

DS reply: We still think that 2/10 animals not siring a litter points to an effect in treated males since at the next higher dose level only 1/10 males sired a litter.

BSEF comment:
It is of note that the fertility index was calculated as the percentage of pairings that resulted in pregnancy, which emphasises the difference whereas conventionally this is divided into mating index (percentage of pairings that result in matings) and fertility index (percentage
of matings that result in pregnancy).

DS reply: When assessing the individual data on the number of females with clear indication of mating it can be seen that only one female out of seven with clear indication of mating became pregnant at 6400 ppm, thus female fertility index (calculated as percentage of matings that result in pregnancy) is 14%.

BSEF comment:
The variation in dosage over the treatment period, which did not follow the same pattern in each sex/dose group, is considered to affect the interpretation of results, given the known steep dose response curve. We therefore consider that no firm conclusions on treatment related reproductive effects can be drawn from this inadequate dose-range finding study.

DS reply: Since the classification for reproductive toxicity is not dependent on actual used doses we do not consider that this variation in doses preclude the inclusion of the findings of decreased fertility index in the total weight of assessment for classification.

Summary of effects on the reproductive system
BSEF comment:

There was no adverse effect on female gonads in the 90-day study with Ammonium Bromide (Barton 2000). In the 90 day with sodium bromide (Hoberman 2016b), 3 females in the 500 mg/kg/day group showed depletion of corpora lutea (one of which was based only on an incomplete set of partial sections) but no effect on the oestrous cycles. In the 2 generation study (Hoberman 2016b 5/15 females at 500 mg/k/day had no corpora lutea, but at 175 mg/kg/day there was only 1/24 females with no corpora lutea at terminal kill. There were, however, 3 in various groups on the study were reported to have corpora lutea, even though they were not mated or pregnant. We suggest therefore that the assessment of corpora lutea may have been less than rigorous and therefore the interpretation of the
findings is not clear. This should not be taken as evidence for impairment of female fertility leading to a classification.

DS reply: You indicate in your comment that there is a discrepancy between the 90-day repeated dose toxicity study in rat of ammonium bromide compared with 90-day repeated dose toxicity study of sodium bromide in rat and the two-generation reproductive toxicity study of sodium bromide in rat. If there are contradictory findings between a repeated dose toxicity study and a reproductive toxicity study the findings from the reproductive toxicity studies are considered as more relevant than the repeated dose toxicity study. The findings on ovaries are consistently seen in the two guideline studies on sodium bromide from 2016. It is to be noted also that in these two studies the test substance is administered via oral gavage, whereas in the 90-day repeated dose toxicity study of ammonium bromide the test substance is administered orally via the diet.

Comparison with the CLP criteria

BSEF comment:
We do not agree with the first statement since there are no guideline compliant studies on fertility with ammonium bromide, only with sodium bromide. The GLP and OECD guideline compliant 90 day study with Ammonium Bromide (Barton 2000) showed no adverse pathology of reproductive organs, even at a high dose of 500/750 mg/kg/day where significant toxicity was observed.

DS reply: We agree that the strongest evidence is obtained from the studies of sodium bromide. However, the robustness of assessing effects on reproductive organs is higher in generational studies were the entire course of spermatogenesis and folliculogenesis is covered, compared to repeated dose toxicity or reproductive screening studies.

BSEF comment:
These effects were only clearly observed at the highest, toxic dose levels, so not relevant for classification, and the effects at the mid dose level were much less marked, often within the historical control levels and not considered biologically relevant (please also see abovem comments on each study evaluation in the CLH report. CLH Guidance (2017) in section 3.7.2.2.1.1 specifically indicates that adverse effects on fertility seen only at dose levels causing 'marked systemic toxicity (eg lethality, dramatic reduction in body weight, coma) are not relevant for classification purposes'.

DS reply: A steep dose response for general toxicity may mask adverse effects on fertility and sexual function. Therefore it may be important to note evidence of dose-dependent changes, even if they are mild at lower doses where general toxicity is not adverse when marked effects are seen at high dose in presence of severe general toxicity.

BSEF comment:
Furthermore, the new studies on kinetic data and differences in sensitivity of humans and rodents to the neurotoxic effects of bromide were not adequately considered as outlined in the attached commenting paper and the first comments provided in this section. These should be relevant to consider a downgrading of the classification in accordance with the CLP regulation: "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.

DS reply: See our previous comment above

COMMENTS REGARDING ADVERSE EFFECTS ON DEVELOPMENT

Pre-natal developmental toxicity study of sodium bromide in rat (Study report, 1995)

BSEF comment:
The fetal abnormalities seen at 1000 mg/kg/day in this study were very similar to those observed in the ammonium bromide study at the same dosage, and the minor, reversible effects on ossification at the lower dose levels were also very similar. It is very likely that the absence of any effects on fetal bodyweight in this study are related to the fact that dosing stopped on Day 15 of gestation (as was the practice in the concurrent OECD guideline), and the majority of fetal growth occurs in the later stages of gestation. We therefore consider that this study does not raise the level of concern, and therefore does not support classification.

DS reply: In this study, findings of structural visceral malformations and skeletal abnormalities are consistent with findings in the PNDT studies of ammonium bromide in rat. None of these findings were seen in control animals or in lower dose groups. Litter incidences were:
- Absent kidney 13.6% (3/22)
- Absent ureter 18.2% (4/22)
- Absent uterine horn 9% (2/22)
- Distorted/minimally distorted/ossification irregularities ribs 18.2% (4/22)

These effects were seen in presence of maternal toxicity manifested as clinical neurotoxicity including signs of unsteady gait (nearly all animals at each day of treatment), feet falling through cage grid floor during ambulation, poorly coordinated movements and reduced bodytone. These clinical signs were not seen in control or the lower dose groups. Maternal bodyweights were reduced in the 300 and 1000 mg/kg dose groups by 15% and 16% compared with controls, but there were no effects on fetal weights in these groups.

As stated in the CLH-report, the observed major malformations that are consistent with findings in a later PNDT study of ammonium bromide in rat, cannot be considered as

being secondary to maternal toxicity and should be taken into account for the total weight of evidence assessment for classification.

Postnatal Growth and Brain Development study (no guideline) of ammonium bromide (Disse et al., 1996)

BSEF comment:
BSEF consider that the limitations of the study are such that it warrants only a Klimisch 3 score and therefore should not be considered even 'indicative' of developmental neurotoxicity.

DS reply: Indeed there are limitations of this study, and therefore we have stated in the CLH-report that findings are indicative but not conclusive. It could be noted that in the REACH registration this study is rated with a Klimisch score of 3 and indicated as a supporting study.

Pre-natal developmental toxicity study (no guideline) of sodium bromide in rats (Harned et al., 1944)

BSEF comment:
'Reduced learning' was determined by assessment of speed and errors in a 5-unit U maze in rats from Days 61 to 85 of age. Pups from dams in the high dose group showed more errors and were slower than those in other groups at the start of monitoring on Day 61 but were equivalent by Day 85, suggesting that growth impairment may have been the underlying cause, and differing sex ratios between each group will also have been a confounding factor. Maternal response to treatment was not reported but the pup survival rates indicate lack of maternal care which may also have contributed. BSEF consider that this very old, nonstandard, non GLP study, with such limited reporting warrants a Klimisch 3 (unreliable) score and should be excluded from any assessment of developmental neurotoxicity.

DS reply: We agree that the study has limitations that prevent any firm conclusion on developmental neurotoxicity and thus our overall conclusion on developmental toxicity in the CLH-report is as you point out "not conclusive". Again, it could be noted in the REACH registration that this study is stated as being a supportive study for neurotoxicity, and is even given a Klimisch score of 2.

Pre-natal developmental toxicity study of ammonium bromide in rat (Study report, 2000b)

BSEF comment:
We refer to CLH guidance (Annex I: 3.7.2.4.3) which indicates 'when a substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification
when seen in association with maternal toxicity'.
We consider that the toxicity observed at the high (limit) dose level are so severe that this dose level should be omitted from CLP assessment, as indicated in CLP Guidance, Annex 1 Section 3.7.2.5.8. We disagree with the conclusion that the major and minor malformations are a direct effect of the substance and not secondary to the effects of maternal toxicity. The maternal toxicity was excessive at the top dose level of 1000

mg/kg/day (with severe neurological signs and one death) and such disruption of maternal homeostasis could well have been the cause of the major malformations observed. The minor skeletal effects with reduced ossification are a common consequence of maternal toxicity (Chahoud 2005, Carney 2007, Kimmel 2014, Chahoud 2015, De Sesso 2018) and are reversible, as is demonstrated in the subsequent study discussed below.

DS reply: The maternal toxicity at 1000 mg/kg bw/day was reported as adverse clinical observations and marked reduction of body weight gain (-18%) over the dosing period. The mortality was 1 out 24 dams in this dose group, i.e. <10% and should thus not automatically be discounted for further evaluation (CLP Annex I, 3.7.2.4.4.). Moreover, in CLP Annex I, 3.7.2.4.2. it is stated that "*Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by- case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.".*

From the individual data it is clear that all animals at 1000 mg/kg bw/day display clinical signs (including neurotoxicity) as also indicated in the CLH-report. There was a reduction in body weight gain (43% of control) during the first six days of treatment (Days 6-12 of gestation), and there was a notable weight loss for two of the animals of this dosage group during this period. However, at GD 18 the body weight in high dose group was similar (94%) to control body weight. Moreover, looking at individual data of the dams there is no clear correlation between severity of maternal toxicity and litter incidence of fetal abnormalities and variants. The overall litter incidence of major abnormalities was 20/22 compared to 5/22 in control. In the 100 and 300 mg/kg bw/day dose groups, there were no adverse clinical signs reported and body weights and body weight gains were similar to control. In these two dose groups the litter incidences of major foetal abnormalities were 11/22. Curved scapula and kinked ribs were seen in all dose groups, including control but it could be noted that bilateral curved scapula was seen only in substance treated groups (litter incidence 1/22, 1/22 and 6/22 in 100, 300 and 1000 mg/kg bw/day). The litter incidence of incomplete ossification of ribs was dose-related increased from 100 mg/kg bw/day and was 0 in control.

See below a table with incidences of foetuses (litters) with major foetal abnormalities [only showing abnormalities with the highest litter incidence]:

	0	100	300	1000
Total numbers examined	191 (22)	247 (22)	188 (22)	208 (22)
Number with major abnormality	5 (5)	17 (11)	23 (11)	85 (20)
Curved scapula	1 (1) (Litter based: 4.5%)	2 (2) (Litter based: 9%)	2 (2) (Litter based: 9%)	18 (8) (Litter based: 36%)
Kinked ribs	3 (3) (Litter based: 14%)	11 (7) (Litter based: 32%)	17 (9) (Litter based: 41%)	52 (18) (Litter based: 82%)
Incomplete ossification of ribs	0	5 (3) (Litter based: 14%)	17 (8) (Litter based: 36%)	34 (14) (Litter based: 64%)
Left kidney absent/small/displaced, with/without absent left adrenal and absent left ureter	0	0	0	26 (7) (Litter based: 32%)
Spleen flattened and/or reduced in size	0	1 (1) (Litter based: 4.5%)	0	19 (7) (Litter based: 32%)
Narrow left uterine horn with flattened ovarian end, and displaced from ovary	0	0	0	14 (5) (Litter based: 23%)

As stated on the CLH-report, we do not consider the observed major and minor fetal abnormalities in this study as being unspecific and secondary to maternal toxicity. Moreover, in presence of some maternal toxicity there were irreversible effects such as structural malformations in foetuses in this study, i.e. absence of organs (kidney, ureter, adrenal, thyroid) that cannot be disregarded as being secondary to maternal toxicity.

Pre-natal developmental toxicity study of ammonium bromide in rat (Study report, 2007)

BSEF Comment:
The second study used 0, 50, 300, 600 and 800 mg/kg/day, ie only a slightly lower top doseon Days 6-19 of gestation. The study design was adapted to include extra animals to allow some litters from the control and 300 mg/kg dose group to litter and raised to weaning to study any persistence of fetal effects. Severe maternal toxicity was observed at the two top dose levels and one animal at 600 mg/kg/day was euthanised on Day 11 due to the severity of the effects. Increased incidences of kinked ribs, curved scapulae and other indicators of retarded ossification were observed at the top three dose levels compared with the controls.
In the 300 mg/kg/day group which was allowed to litter and raise pups to weaning, the incidence of abnormalities of the ribs, scapulae and pelvis was the same as in the controls.
We suggest that this study supports our comment above that the irreversible abnormalities observed in the previous 2000b study were related to the severe toxicity at 1000 mg/kg/day, and they were not present in this study. Furthermore, it provides evidence for the minor and reversible nature of the rib, scapulae and other ossification effects observed at the lower dose levels.

DS reply: As stated in our comments above on the PNDT study (2000b), it cannot be unequivocally demonstrated that the observed malformations manifested as absence of organs (kidney, ureter, adrenal), which are considered as irreversible effects, are secondary and unspecific effects to maternal toxicity/disturbed maternal homeostasis. The dose-response curve of bromide appears to be steep and since the dose of 1000

mg/kg bw/day was not tested in the current study, the absence of findings of major structural visceral malformations does not contradict the earlier PNDT study. On the other hand, increased incidences of curved scapula and kinked ribs, seen from 100/300 mg/kg bw/day in the earlier PNDT study (Study report, 2000b) are also seen from 300 mg/kg bw/day in this study.

It is noted that the reversibility assessment of the ribs and scapulae was only done in the 300 mg/kg bw/day dose group compared to control and not in the two higher dose groups.

Human studies of bromide

BSEF comment:
There are no robust clinical data on effects of bromide in human infants. No report of single case studies can determine causality for developmental growth retardation, not least because of uncertain exposure scenarios of both bromide products and any coexposures, or other confounding factors such as smoking, alcohol consumption, diet or maternal age, nutritional status and health status. The authors of several papers clearly state that any association between maternal exposure to bromide and the outcome for the infant is circumstantial or may be coincidental.

DS reply: We agree that there are no robust human studies on developmental toxicity of bromide and that there are no proven causality for developmental growth retardation. For this reason, the information included in the CLH-report from human case studies are not used in the total weight of evidence and comparison with criteria, but briefly summarised for completeness. In any event, there are no indications that this information contradicts the available animal data.

RAC's response
RAC agrees with the very detailed DS reply.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2023	France		MemberState	8
Comment received				
FR agrees with the classification STOT SE 3, H336				
Dossier Submitter's Response				
Thank you for your comment and the support for the proposed classification in STOT SE 3.				
RAC's response				
Thank you for your comment and support.				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	9
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.				

Dossier Submitter's Response
Thank you for your comment and the support for the proposed classification in STOT SE 3.
RAC's response
Thank you for your comment and support.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
01.06.2023	Austria	The International Bromine Council BSEF	Industry or trade association	10

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 KBr_2023-06-01.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment CLH Report KBr - Supporting studies for CL.zip
Dossier Submitter's Response
Thank you for your comment. The cut off limits for STOT RE are not applicable to human data. In the response to comments document (RCOM, 2020) for ammonium bromide, RAC addressed this issue: "RAC notes that animal data are showing neurotoxic effects at or around the CLP guidance value 100 mg/kg bw/day which is the borderline between STOT RE 2 and no classification after a 90-day exposure. Existing human case studies indicating bromism are considered to justify classification as STOT RE 1 with the nervous system as target organ. Positive human data, regardless of the dose, predominates over animal data."
RAC's response
Thanks for the comment. RAC agrees with DS reply; bromism is a well-known adverse condition that affects the nervous system and that is definitely described in humans (hence, STOT RE 1).

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 Potassium bromide is not considered as STOT RE Thyroid? (This comment joins the one on endocrine disruptor hazard).				
Dossier Submitter’s Response				
Thank you for your comment and the support for the proposed classification in STOT RE 1, H372 (nervous system). The effect on the thyroid based on the dataset presented in the dossier has previously been evaluated in the process of the harmonized classification of ammonium bromide. At that time, the dossier submitter of the ammonium bromide CLH proposal proposed a classification in STOT RE 2 for effects on the thyroid. However, it was concluded by RAC that the severity on the thyroid was not sufficient to include it as a target organ (for full evaluation, see RAC opinion for ammonium bromide, 2020). Thus, we consider this dataset to already be sufficiently scrutinized by RAC for thyroid effects.				
RAC’s response				
Thanks for the comment. See our reply to comment 2.				

Date	Country	Organisation	Type of Organisation	Comment number
23.05.2023	Germany		MemberState	12
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 not considered severe enough for it to be included as target organ.				
Dossier Submitter’s Response				
Thank you for your comment and the support for the proposed classification in STOT RE 1, H372 (nervous system).				
RAC’s response				
Thank you for your comment and support. Relative to thyroid effects, please refer to our reply to comment 2.				

PUBLIC ATTACHMENTS
1. BSEF detailed comments on KEMI CLH report KBr_2023-06-01.zip [Please refer to comment No. 1, 7, 10]

CONFIDENTIAL ATTACHMENTS
1. CLH Report KBr - Supporting studies for CL.zip [Please refer to comment No. 1, 7, 10]