Committee for Risk Assessment

RAC

Annex 3

Records

of the targeted consultation to take account of a new study in relation to effects on or via lactation made available by the dossier submitter for

lithium carbonate [1] lithium chloride [2] lithium hydroxide [3]

EC Number: 209-062-5 [1] 231-212-3 [2] 215-183-4 [3]
CAS Number: 554-13-2 [1] 7447-41-8 [2] 1310-65-2 [3]

CLH-O-0000007034-82-01/F

Adopted

16 September 2021

ANNEX 3 - RECORDS OF THE TARGETED CONSULTATION ON CLH PROPOSAL ON LITHIUM CARBONATE [1] LITHIUM CHLORIDE [2] LITHIUM HYDROXIDE [3] TO TAKE ACCOUNT OF A NEW STUDY IN RELATION TO EFFECTS ON OR VIA LACTATION MADE AVAILABLE BY THE DOSSIER SUBMITTER

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

The proposal for the harmonised classification and labelling (CLH) of lithium carbonate [1] lithium chloride [2] lithium hydroxide [3] (EC 209-062-5 [1] 231-212-3 [2] 215-183-4 [3]; CAS 554-13-2 [1] 7447-41-8 [2] 1310-65-2 [3]) was submitted by the France and was subject to a consultation, from 03/08/2020 to 02/10/2020. The comments received by that date are compiled in Annex 2 to the opinion.

During its July Working Group meeting the Committee for Risk Assessment (RAC) asked for comments to be provided on a new study made available by the Dossier Submitter in relation to effects on or via lactation of lithium carbonate [1] lithium chloride [2] lithium hydroxide [3]. An ad hoc consultation was launched from 08/07/2021 to 22/07/2021 and the comments received are listed below.

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: lithium carbonate [1] lithium chloride [2] lithium hydroxide [3]
EC number: 209-062-5 [1] 231-212-3 [2] 215-183-4 [3]
CAS number: 554-13-2 [1] 7447-41-8 [2] 1310-65-2 [3]
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.07.2021	Belgium	Lithium REACH consortium	Industry or trade association	1
Comment received				
The comments are provided by experts of the Lithium REACH consortium (Dr. <confidential> and Dr. <confidential>), also including input of further experts of the Eurometaux Lithium Task Force. They are also attached together with an additional reference cited as pdf in the attached file. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 1 Lithium REACH consortium 22-07-21.zip				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.07.2021	Germany		MemberState	2
Comment received				
In the study by Ahmed et al. (2021), pups exposed to lithium via breastmilk, with the dam on a human scale sub-therapeutic level (40 mg Li2CO3/d/kg bw), experienced significantly reduced (-28 %) blood thyroxine (T4) and significantly increased (+47 %) thyroid stimulating hormone (TSH) compared to control on postnatal day 18 (P18). Reduced T4 levels persist after weaning, and after lithium has been cleared from the blood. Pup blood lithium concentrations of 0.075 mmol/L at P18 were reported. A forced-swim test during breast-feeding did not reveal behavioural abnormalities. No other investigations of neurodevelopmental func-tions were conducted. Inhibition of the thyroid iodine uptake due to lithium exposure is proposed as a causal mech-anism by the authors of the study. They demonstrated that iodine supplementation of the nursing dams could reverse the adverse effects of lithium on pup thyroid function.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.07.2021	Belgium	SQM Europe N.V.	Company-Importer	3
Comment received				
SQM has hired the well known independent expert DHI for the independent assessment of the publication Ahmed et. Al. 2021 "Lithium from breast-milk inhibits thyroid iodine uptake and hormone production, which are remedied by maternal iodine supplementation". In their opinion, which we also subscribe, the reference does not provide clear evidence of adverse effect in the offspring due to transfer in the milk" as indicated in the CLP criteria, so it does not meet the criteria for a H362 classification (May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation]). See attached document Annex_DHI Assessment of Ahmed et al 2021 for Lithium Carbonate CLH Classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Annex_DHI Assessment of Ahmed et al 2021 for Lithium Carbonate CLH Classification.pdf				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
22.07.2021	Belgium	Lithium REACH consortium	Industry or trade association	4
Comment received				
Lithium REACH consortium July 22, 2021 RAC opinion formation on classification for toxicity to reproduction for Lithium carbonate, Lithium chloride and Lithium hydroxide. Comment to public consultation on the reference Ahmed et. Al. 2021 with regard to a				

classification for effects during lactation.
In our opinion the publication does not provide clear evidence for any adverse effects in the offspring of rats after exposure of dams to Lithium carbonate by oral gavage during the lactation period. We have some doubts on the data provided in this reference and have identified several confounding factors and inconsistencies in the publication. We have also contacted the authors for further data and clarification and are still awaiting their response.
1. Animal number
Animal numbers in the different groups were rather small in particular with regard to maternal animals. Dams rearing offspring until PND 18: Controls: 7, Lithium carbonate exposed 7, Lithium carbonate plus iodine exposed: 4. Dams rearing offspring until PND 25: 3 controls, 3 Lithium carbonate exposed. Dams rearing offspring investigated at PND 60: 1 control, 1 lithium carbonate exposed. With such low animal numbers any effect claimed can easily be a chance effect and represent a normal variation, especially for parameters showing a high variations anyhow (please see below).

2. Diet provided to the rats.
The composition of the diet was not provided by the authors, but they mentioned the iodine content as this may play a role in the claimed effects on thyroid hormone levels. We note that the iodine content of the diet used in the study was 0.97 ppm (p.5 first paragraph) while normal rat chow used in most toxicological studies contains 2.1 ppm (e.g. SNIFF diets used by most laboratories world-wide https://www.ssniff.com/documents/01-1%20%20RM%20&%20low%20phyt.pdf). This means that the study used iodine deficient rats which could be one explanation for the observed claimed effects, that notably according to the authors disappeared after iodine supplementation of the diet.

3. Dose levels
There are contradictory statements on the dose levels which are given in an unusual way. On page 2 under methods (2.1) it is stated that the maternal animals received 1000 mg Lithium/ 12 hours/ 50 kg. This suggests 2 times dosing within 24 h resulting in a dose of 40 mg Li/kg bw/day. This would be a rather massive and toxic dose for the dams. However on page 3 under Lithium preparation and administration the dose is given as 1000 mg Lithium carbonate per 12 hours per 50 kg of bw. Assuming again 2 times per day dosing this would then correspond to 40 mg of Lithium carbonate or 7.6 mg Li/kg bw/day. We have asked the authors for clarification of the dose. In any case the maternal Lithium blood levels of 0.55 mmol/L reported are rather low related to the latter dose and still about half of the levels observed in other studies applying similar gavage doses of Lithium carbonate, which should normally result in blood levels of ca. 1 mmol/L. This casts some doubt on the accuracy of the analytical method applied here and also the blood levels of Lithium in the pups reported as 0.075 mmol/L. At all other time points no lithium was detected in the pups. It should also be noted that the Lithium blood levels in the pups were about an order of magnitude lower than reported in the dams, indicating a limited transfer of Lithium via breast milk and certainly no enrichment due to less efficient kidney in the pups.

4. Maternal toxicity was not reported by the authors. So potential influences of milk production, concentration, etc. cannot be evaluated.

5. Analytical methods for thyroid hormone measurement.
It is well known that the ELISA methods available todate give pretty variable results and this seems to be the case in this study as well. Total T4 and in particular TSH had very

wide and overlapping error bars putting into question the claimed statistical significance. The difference in control values between the P25 and P60 measurement is also striking. Therefore, the data derived from a low amount of samples and no historical control data about variations of these parameter given should be interpreted with caution (Marty et al. 2021 see attachment). Also, in the light of the low iodine content of the diet, variations in the thyroid hormone levels could be even higher than usual (see also below).

6. Statistical analysis
We do not think that the statistical methods applied are correct for this data set: ANOVA is normally used to compare multiple (more than 2) groups. It seems that the authors compare all the data in one analysis, meaning comparison of P18 Control, P18 Li, P25 Control and P25 Li.
However, they should have compared only the control and the Li group from the same time point: one analysis for P18 control vs P18 Li and a second analysis on P25 control vs P25 Li. Therefore, they should have used a t-test (student) (for parametric data) or Mann-Whitney test (for non-parametric data as this is probably the case).
The type of analysis can influence the results. Without the raw data, it is difficult to confirm what the results would be with a Mann-Whitney test. We have asked the authors to provide the raw data, but did not get a reply yet.
7. Postulated effects on thyroid hormone levels:
a. We note that no information is given on the time of the day the blood samples were taken, which may already cause the variation observed
b. Free T3 and T4 were not different from controls and free T3 is the active thyroid hormone. Thus, adverse effects cannot be deduced and were also not reported by the authors although they claim adversity in the discussion. It should also be noted that if the postulated mode of action by the authors was correct, the level of free T3 and T4 should be more affected than the total T4, which was not the case at all.

8. Analytical determination of iodine in the thyroid tissue
In figure 3 the error bars for the iodine measurements are extremely high and overlap. From this no scientifically sound conclusion can be drawn. Also the Lithium determination seems highly uncertain given the large error bars here as well.

9. Analysis of Lithium in mothers milk
The presence of lithium in the milk has only been determined qualitatively in the publication. No quantification was made. This confirms that lithium can distribute to mother's milk, but it is questionable if the quantities are sufficient to lead to adverse effects.
10. Claim of the authors that the pups showed symptoms of hypothyreoidism.
The only indication the authors give is a claimed increased body weight of the Lithium treated pups. However, if one compares the numbers the body weights are all in the range of the controls although the pups with the highest weight were chosen from each litter as described on page 3 under animals. Initial weights of the animals were not given. Furthermore, the authors also found a slight and reversible indication of kidney function impairment at PND 28 as indicated by the BUN analysis. This normally results in an increased water uptake as noted in several studies with Lithium, which could also explain potential slightly higher body weights. The thyroid hormone level changes are far from clearly treatment related and can for sure not be used as an indication of an adverse effect or being indicative for a hypothyreoidism. Important to note, the behavioral tests performed did not show any difference between treated and control groups.

Overall conclusion:

This publication does not support a clear adverse effect of Lithium of pups receiving it via lactation. It confirms that Lithium ions to some extend can pass into the milk of lactating rats, but dose levels and levels in the milk remain unclear. At least the blood levels reported in pups indicate a rather limited transfer and a fast excretion in pups. As adverse effects have not been demonstrated, this publication does not support a classification for effects via lactation.

Additional Reference:
Marty et al. 2021, Sue Marty, Manon Beekhuijzen, Alex Charlton, Nina Hallmark, Bethany R.
Hannas, Sylvia Jacobi, Stephanie Melching-Kollmuss, Ursula G. Sauer, Larry, P. Sheets, Volker Strauss, Daniel Urbisch, Philip A. Botham & Bennard van Ravenzwaay. Towards a science-based testing strategy to identify maternal thyroid hormone imbalance and neurodevelopmental effects in the progeny – part II: how can key events of relevant adverse outcome pathways be addressed in toxicological assessments?, Critical Reviews in Toxicology, 51:4, 328-358,

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 1Lithium REACH consortium 22-07-21.zip

RAC's response

Thank you for comments to the publication by Ahmed et al. (2021). In this study it was shown that Llithium was transmitted through breast milk and was measured in the pups plasma (0.075 mmol/L). At PND 18 the pups showed increased body weight (42.5 vs 40.31 g in control pups, $p < 0.05$), increased TSH (1.38 vs 0.94 mlU/min in control pups $p < 0.05$) reduced blood thyroxine (T4) (67.2 vs 93.41 nmol/L in control pups, $p < 0.05$), and elevated blood urea nitrogen (BUN) levels (6.71 vs 5.25 nmol/L in control pups, $p < 0.05$), indicating impairment of thyroid and kidneys, while mothers had low therapeutic blood lithium levels (in the human lower therapeutic ranges). The swim time measured at PND 18 was slower in lithium exposed pups, however, not reaching statistical significance (447 vs 492 sec. in controls). A transient increase in BUN was observed, suggesting reduced kidney function which resolved shortly after weaning and lithium clearance. In the thyroid, exposed pups had higher TSH and reduced blood T4, and these changes were indicated to be related to hypothyroidism and persisted after weaning, and after lithium was cleared from the blood. Thyroid iodine uptake was similarly reduced during breast-feeding and shortly after. Based on the effects reported in the infants in the Ahmed et al., 2021 study, as well as effects reported in infants exposed to lithium only during lactation in other studies assessed in the draft opinion on lithium salts, RAC concluded based on a weight of evidence assessment on a classification for lactation.

As regards the number of animals, the Ahmed et al. (2021) study included 11 pups/litter, 7 litters/group resulting in 84 pups/dose group. RAC considered the number of pups/dose group as sufficent for an assessement at PND 18.

The dose levels of lithium used in the study is not considered by RAC to be a massive toxic dose. 40 mg lithium carbonate/day corresponds to 7.6 mg Li/kg bw/d. In comparison, the Anonymous (2010b) study (or Van Deun et al., 2021) developmental toxicity study with doses of 0, 10, 30 and 90 mg lithium carbonate/kg bw/d showed limited maternal toxicity in the high dose group. No maternal toxicity was reported at 30 mg/kg bw/d. In the study by Ahmed et al. (2021) no marked maternal toxicity is

anticipated at a dose of 7.6 mg Li/kg bw/d, leading to maternal lithium levels of 0.55 mmol/L which is half of levels reported in other developmental toxicity studies (1 mmol/L) and is in the lower therapeutic range for humans.

Overall, RAC considered that based on the presence of lithium in human breast milk and infant serum, and the potential for a slower excretion of lithium in infants due to the immature excretory system, together with the reported effects in rats on kidney and thyroid functions in offspring exposed to lithium only during lactation there is a concern for the health of children breast-fed to mothers on lithium therapy. This is considered to be in accordance with the CLP criteria: "However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child shall be classified and labelled to indicate this property hazardous to breastfed babies".
RAC therefore concluded that a classification for effects on or via lactation with Lact.; H362 "May cause harm to breast-fed children" for the three lithium compounds is warranted.

Date	Country	Organisation	Type of Organisation	Comment number
21.07.2021	Germany		MemberState	5

Comment received

Comments on a new study made available by the DS in relation to effects on or via lactation of lithium carbonate [1] lithium chloride [2] lithium hydroxide [3]:

It was shown by Ahmed et al. (2021) that lithium is present in breast milk of dams exposed from P04 until weaning (P21) and was also found in pup blood, demonstrating lithium uptake by breastfed pups. This is consistent with the finding of lithium transfer into human breast milk (Viguera, Newport et al. 2007).

Significantly reduced (-28 %) T4 and significantly increased (+47 %) TSH on P18 reveal ef-fects of lithium exposure on HPT axis function.
Significant reductions of T4 were seen at P18 and P25. The value was still elevated at P60, albeit at a non-significant level. P25 is shortly after weaning (P21). The mean value for P18 (with the maximum increase) is mainly allocated to the uptake via breast milk as pups starting progressively from P14 earliest to feed solid food. As dams were treated with 1 ml solu-tions given by gavage, an impact of lithium uptake via food during the late period of lactation can be ruled out. That means effects in pups can exclusively be attributed to breast milk.

Lithium levels were significantly increased at P18, no difference was seen at P25 underlining that the increase is caused by breast feeding and no difference compared to control values were seen at P25 after weaning. Thus, elevated lithium values could solely be allocated to the lactation.

Importantly, as a causative mechanism responsible for the observed effects on thyroid hormone concentrations Ahmed et al. (2021) proposed the inhibition of the thyroid iodine uptake, a human relevant mechanism. In pups of dams treated with lithium and iodide no reduction of T4 occurred in pup at P18.

Uptake of iodide (I-) into the thyroid gland via the sodium-iodide symporter (NIS) is the first step in the biosynthesis of thyroid hormones. According to AOP 54

(https://aopwiki.org/aops/54), inhibition of NIS leads to thyroid hormone imbalance and learning and memory impairment as adverse outcome.

Neonatal hypothyroidism in human population is a known neurodevelopmental concern.

In addition, elevated blood urea nitrogen at P18 indicates lithium-depended effects on the kidney, where the excretion of urophanic substances with urine is disturbed. Kidney has been identified as a target organ in several studies. As the effect was not seen at P25, this effect can be allocated to lactation.

However, limitations of the paper by Ahmed et al (2021) have to be taken into account:

- No guideline followed;
- Only one dose tested;
- Poor study characterisation;
- No information on maternal toxicity;
- Brain histology of pups or their behaviour and learning not examined.

Moreover, effects of 40 mg Li2CO3/d/kg bw on pup neurodevelopment were not specifically examined.

Ahmed et al (2021) indicates a clear evidence of lithium transfer in breast milk and in pups' blood. Correspondingly, elevated blood levels were associated with effects on thyroid hor-mone levels and the blood urea nitrogen. Thus, data support the classification of lithium car-bonate, lithium chloride and lithium hydroxide for effects on or via lactation in a weight of evidence approach.

According to CLP Regulation, classification for effects on or via lactation can be assigned based on the

"(a) human evidence indicating a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals which provide clear evidence of ad-verse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk."

Comparing the overall evidence from the study of Ahmed et al. (2021) with the given crite-ria, the criteria c) is clearly fulfilled, and it is likely that criteria b) is fulfilled. No evidence of criteria a) is given, however, the excretion with human milk has been demonstrated.

References:

Viguera, A. C., D. J. Newport, J. Ritchie, Z. Stowe, T. Whitfield, J. Mogielnicki, R. J. Baldessa-rini, A. Zurick and L. S. Cohen (2007). "Lithium in breast milk and nursing infants: clinical implications." Am J Psychiatry 164(2): 342-345.

RAC's response

Thank you for the support for a classification for effects on or via lactation. See further response to comment No. 4.

Date	Country	Organisation	Type of Organisation	Comment number
22.07.2021	Belgium	SQM Europe N.V.	Company-Importer	6
Comment received				
Independent experts from DHI have evaluated the reference "Ahmed et al. (2021). Lithium from breast-milk inhibits thyroid iodine uptake and hormone production, which are remedied by maternal iodine supplementation. Bipolar Disorders. DOI: 10.1111/bdi.13047" on behalf of SQM to determine if this reference provides sufficient evidence to classify as reproductive Toxicity for effects on or via lactation according to CLP criteria. See full assessment in the attached document Annex_DHI Assessment of Ahmed et al 2021 for Lithium Carbonate CLH Classification. The DHI interpretation in relation to classification is: The study by Ahmed et al. (2021) documents that lithium is distributed into breast milk and result in lithium exposure of the pups, however, at a considerably lower level compared to the mother animals that were exposed to rather high levels corresponding to levels used in medical treatment. The lactational exposure resulted in transient and reversible changes in hormonal levels of T4 and TSH and BUN (a biomarker for impaired kidney functioning). Also, the effects can be considered dependent of the concurrent iodine intake/ status of the animals. Although the study has documented the distribution of lithium to breast milk this was not shown in the study by Ahmed et al. (2021) to occur at a level where "the substance is present in potentially toxic levels in breast milk" as indicated in the CLP criteria. The study by Ahmed et al. (2021) showed that lactational exposure can result in mild and transient effects in the pups, but the exposure did not "provide clear evidence of adverse effect in the offspring due to transfer in the milk" as indicated in the CLP criteria. Therefore, the study in some way supports the lack of human evidence for adverse effects in babies/ infants nursed by mothers in lithium therapy. In conclusion, the rather low distribution to breast milk and the mild effects associated to this as shown in the Ahmed et al. (2021) study do not provide sufficient evidence to meet the criteria for a H362 classification (May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation]). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Annex_DHI Assessment of Ahmed et al 2021 for Lithium Carbonate CLH Classification.pdf				
RAC's response				
See response to comment No. 4.				

Date	Country	Organisation	Type of Organisation	Comment number
22.07.2021	United Kingdom	European REACH Grease Thickeners Consortium (ERGTC)	Industry or trade association	7
Comment received				
The European REACH Grease Thickeners Consortium (ERGTC) fully support the comments submitted on this targeted consultation by FUCHS, the lead registrant of lithium 12-hydroxystearate, a downstream user of lithium hydroxide, and would refer to the detailed comments provided by FUCHS. The ERGTC identifies concerns relating to the				

interpretation of data that lead to the proposed overall classification of the lithium salts Lithium carbonate, Lithium chloride and Lithium hydroxide and considers that the evidence is not sufficient to result in such a classification.
RAC's response
See response to comment No 4.

Date	Country	Organisation	Type of Organisation	Comment number
22.07.2021	Germany	FUCHS Schmierstoffe GmbH	Company-Downstream user	8

Comment received

Response to the RAC discussion on the publication Ahmed et al. 2021 - consultation on the proposal for harmonized classification of lithium carbonate, lithium chloride and lithium hydroxide for reproductive toxicity

A document submitted by ANSES (on behalf of the French MSCA) was published in June 2020 containing a proposal for harmonised classification (CLH) for reproductive toxicity category 1A for lithium carbonate (EC#209-062-5; CAS#554-13-2), lithium chloride (EC#231-212-3; CAS#7447-41-8) and lithium hydroxide (EC#215-183-4; CAS#1310-65-2). The European REACH Grease Thickeners Consortium (ERGTC) in collaboration with FUCHS, the lead registrant of lithium 12-hydroxystearate, a downstream user of lithium hydroxide, is hereby submitting input on the consultation in relation to the publication by Ahmed et al. 2021.

This harmonized classification and labelling of lithium carbonate (EC#209-062-5; CAS#554-13-2), lithium chloride (EC#231-212-3; CAS#7447-41-8) and lithium hydroxide (EC#215-183-4; CAS#1310-65-2) as known or presumed reproductive toxicants on the basis of lithium carbonate exposure via lactation route in rats is inappropriate as there are no clear adverse effects demonstrated and this opinion is supported by the following evidence:

General Comments

• Read-across: For effective read-across, ECHA has required there to be points of reference in the data set of target and source substances in order to support the predicted similarities in response. There are insufficient points of reference in the toxicity data between lithium carbonate and lithium chloride for both developmental data and reproductive data to support a read-across for these endpoints. Data for these endpoints have not been generated at all for lithium hydroxide due to the corrosive nature of the substance. Therefore, the principles for determination of a causal relationship between a chemical and an adverse outcome should be specific to the chemical at issue (Teratology Society Public Affairs Committee, 2005).

• Human exposure: It is contradictory, albeit in compliance with the classification guidance, that rodent data is taken as predictive of reproductive hazard without similar evidence in infants. There is an abundance of human data available on lithium exposure during pregnancy and lactation even though it inaccurately states in the publication that, "Only few and limited human studies have examined the effects of lithium during the breast-feeding period" and only references 3 studies. Hence, in this case, the animal data is not essential.

o "Lithium is excreted into breast milk (Fries 1970; Kirksey and Groziak 1984; Moretti et al. 2003; Shou and Amdisen 1983Sykes et al., 1976; Tunnessen and Hertz 1972). Milk levels are approximately 40-50% of the maternal serum concentration (Kirksey and Groziak 1984; Moretti et al. 2003; Tunnessen and Hertz 1972). Infant serum and milk levels are approximately equal. In a 2003 study, milk lithium levels were determined in 11 lactacting women (daily dose 600-1500 mg) who were taking the drug for the

management of bipolar disorder (Moretti et al., 2003). No adverse effects were observed in the infants. The estimated infant dose from milk ranged from 0-30% of the mother's weight-adjusted dose. These data suggested that monitoring lithium levels in milk and/or the infant's blood combined with close observation of nursing infant for adverse effects, was the approach chosen by clinicians." - Drugs in Pregnancy and Lacation, 9th ed on lithium carbonate

- WHO/UNICEF/ICCIDD: The consensus reached in 2007 was that pregnant women should not be recommended to take iodine-containing supplements if the population in general had been iodine sufficient for at least 2 years. This is in conflict with the recommendation of the authors to supplement their diet with iodine.
- Infant formula: The decision to breastfeed is highly personal and is often influenced by many factors, such as taking lithium carbonate for bipolar disorder. Under certain situations, breastfeeding might not be possible, unsuitable or inadequate, which warrants an interruption or cessation in breastfeeding. Globally, only 38% of infants are exclusively breastfed. For healthy newborns whose mothers are unable to provide sufficient breast milk, the current option of choice is infant formula (Martin et al., 2016).
- Regulatory perspectives: Experts in the field including those from US-EPA, Netherlands-RIVM, RIAS and UK- RSA stated in a publication by Beekhuijzen et al. 2018, that there is an imperative need for clarification and guidance regarding the collection, assessment, and interpretation of thyroid hormone data for regulatory toxicology and risk assessment, let alone classification and labeling.

Specific comments regarding Ahmed et al. 2021
The following bullet points are made in critique of the paper:
1. The "breast feeding model" used in this study was a standard post-partum rat entering the lactation period. "Breast feeding" in rats, more commonly known as "weaning", involves a host of chemical changes e.g. reduced adrenal secretions which are not always representative of the process in humans.
2. The number of animals distributed in the various groups in this study is initially difficult to follow but, whilst the number of pups comprising each group is large, the actual maternal source is small and, therefore, not considered significantly diverse as required by many guidance documents for reproductive toxicity studies. For example, only 4 dams comprised the lithium+iodine group and only 11 dams in each of the lithium and control groups. This does not compare favourably with regulatory study designs for developmental toxicity which requires evaluation of a minimum of 16 pregnant females in each group.
3. Whilst information is very nicely presented in colourful schematic form, there is a lack of detail on the actual data generated in this study. For example, whilst it is stated that blood measurements were carried out on N=240, the group distribution of this N is not given. Only circulating thyroid hormone levels were measured which showed a small (but statistically significant) reduction in T4 in the lithium only group without similar changes in T3….is this really indicative of a direct effect on the thyroid? It would have been useful to know if this scenario was also represented in the dam. Unsurprisingly, TSH was slightly (but statistically significantly) raised in the lithium group only. This is a typical rodent response to low circulating T4 levels in an attempt to maintain normal T4 levels. So, this is not convincing data to demonstrate a direct effect on thyroid hormone production but may also be linked to metabolic clearance of thyroxine in the pups?
4. In rats, if one was to measure just one parameter as an indicator of renal dysfunction then serum creatinine would have been a far better marker for this endpoint than BUN.
5. Very limited pathological follow up in the thyroid and no pathological investigations in other relevant tissues such as kidney and liver.

References
1. Andersen, SL and Laurberg P. (2016) Iodine Supplementation in Pregnancy and the Dilemma of Ambiguous Recommendations. Eur Thyroid J. 5(1): 35–43.
2. Beekhuijzen, M., Schneider, S., Barraclough, N., Hallmark, N., Hoberman, A., Lordie, S., Moxon, M., Perks, D., Piersma, AH., and Makris, SL.(2018) The urgency for optimization and harmonization of thyroid hormone analyses and their interpretation in developmental and reproductive toxicology studies. Reproductive Toxicology. 80:126-13.
3. Friedman, JM (2017) Editorial In Bed with The Devil: Recognizing Human Teratogenic Exposures.
BDR. 109 (18): 1407-1413.
4. Fries H.(1970) Lithium in pregnancy. Lancet.;1(7658):1233.
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7. Sykes, PA., Quarrie, J., and Alexander, FW. (1976) Lithium carbonate and breast-feeding. Br Med J. 2(6047):1299.
8. Tunnessen, WW. and Hertz, GC. (1972) Toxic effects of lithium in newborn infants: a commentary. J Pediatr. 81(4):804-7.
9. Shou M., Amdisen, A., and Steenstrup, OR. (1973) Lithium and pregnancy. II. Hazards to women given lithium during pregnancy and delivery. Br med J. 2:137-138.
10. Shou M., and Amdisen, A., (1973) Lithium and pregnancy. III. Lithium ingestion by children breast-fed by women on lithium treatment. Br Med J. 2:138.
11. Martin, CR, Ling, PR 2 and Blackburn GL. (2016) Review of Infant Feeding: Key Features of Breast Milk and Infant Formula. Nutrients 8(5), 279.

RAC's response

Thank you for the references to studies showing that lithium is excreted into breast milk. The levels included in the studies are considered to be in the same range as the studies already included in the CLH report by the DS.

This ad hoc consultation was on the study by Ahmed et al. (2021), so reponses included are related to this study. See further response to comment No. 4.

PUBLIC ATTACHMENTS
1. Annex_DHI Assessment of Ahmed et al 2021 for Lithium Carbonate CLH Classification.pdf [Please refer to comment No. 3, 6]

CONFIDENTIAL ATTACHMENTS
1. Lithium REACH consortium 22-07-21.zip [Please refer to comment No. 1, 4]