Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

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 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON LITHIUM CARBONATE [1] LITHIUM CHLORIDE [2] LITHIUM HYDROXIDE [3]

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: 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
02.10.2020	France	A3M	Industry or trade association	1
Comment received				
General observations The French competent authority (ANSES) has submitted the CLH file for Lithium carbonate, chloride and hydroxide with a period to collect comments set up until October 2, 2020. The proposed classification for the three lithium salts is Repr. 1A, H360FD (e.g. may damage fertility; may damage the unborn child). Alliance of Ores, Minerals and Metals (A3M), represents the French mineral and metal industry (extraction, production, processing and recycling). The protection of human health and the environment are core values for A3M and its members. As such, a new classification of lithium salts is a key stake and prior expertise is a decisive step. This consultation is an **opportunity** for A3M to provide some general observations regarding this proposal, before the submission of the final opinion from ECHA's Risk Assessment Committee to the European Commission, which will consider the relevance of adding lithium salts. The classification of those substances is currently not harmonised at European level under the CLP regulation. A decision of the European Commission, on a classification for the tree lithium salts will have a direct impact on product labelling and could ultimately lead to a more restrictive framework for their use in Europe. As stated in the section 5 of the CLH proposal document from ANSES, these lithium salts are used by the battery value chain for three main technologies:				

• Rechargeable Li-ion batteries,
• Rechargeable nickel-based batteries,
• Primary lithium batteries.
The proposed classification may have a significant impact on the entire value chain of the battery industry which is one of the strategic axes of the policy regarding sustainable mobility in Europe .
Considering this, A3M underlines the fact that such a classification must be based on evidence from results of scientific studies developed according to GPL compliant methodologies.

Scientific foundations of the CLH proposal
A3M would like to share the following observations regarding the CLH report, detailed in the position paper of Eramet attached in annex.
The CLH proposal presents in details the following health hazards:
• Germ cell mutagenicity,
• Carcinogenicity,
• Reproductive toxicity.
We noticed in this report that the conclusions of the mutagenicity studies are mainly resulting to show no effect.

A reprotoxic effect without mutagenic or carcinogenic effect is quite possible, but in this case the toxicological mechanism is most often very specific, and it would have been interesting to further describe it in this CLH proposal.

In this CLH file, the explanation of different mechanisms are missing, therefore some questions should addressed through a more detailed approach to clarify the toxicological mechanism and justify why there are discrepancies between some results of the studies (reprotox) :
• How to better articulate studies carried out on healthy animals and studies carried out on humans with neurological diseases?
• How does the difference in the initial state impact the interpretation of the data?
Moreover, our understanding of the CLH expertise is that the reproductive toxicity studies are very heterogeneous:
• The key study of 2010 (Klimisch 1-level) and other studies of 2012 (Klimisch 2-level) show no evidence of cardiac malformations in animals after exposure to lithium compounds.
• However, these GPL compliant recent studies are compared with studies carried out more than 30 years ago without compliance with OECD standards. (Marathe and Thomas, 1986; Kelley and al., 1978; Fritz, 1988).

As a conclusion, the battery industry questions the validity of the studies that have been used by ANSES to come to the conclusion that Li salts are reprotoxic whereas results of recent studies performed under GLP show no compound related effects on developmental and reproductive toxicity .

Taking these elements into account, A3M considers it appropriate to pursue the efforts in achieving a complete data analysis, enabling a clear and evidence-based decision making regarding the classification of lithium salts.

See public attachment for the entire position with comments of Eramet on the proposal

for Harmonised Classification and Labelling for three lithium salts (lithium carbonate, lithium chloride and lithium hydroxide).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Consultation classification lithium salts- Comments of A3M.docx

Dossier Submitter's Response

Thank you for your comment.

Concerning the sentence "*A reprotoxic effect without mutagenic or carcinogenic effect is quite possible, but in this case the toxicological mechanism is most often very specific, and it would have been interesting to further describe it in this CLH proposal*", eMSCA would like to remind that the evaluation of mutagenicity/carcinogenicity or the evidence of mutagenic/carcinogenic effect is not part of the criteria for a classification as reproductive toxicant. Moreover, an absence of mutagenic or carcinogenic effect is also not a criteria to not classify a substance as reproductive toxicant. Please refer to the Guidance on the Application of the CLP Criteria. In addition, numerous substances are classified as reprotoxic without classification for mutagenic or carcinogenic effect. Finally, as clearly mentioned in the report, the reason for the non classification as mutagenic and carcinogenic is the absence of data of adequate quality, and not the absence of effect. In addition, it has to be noted that lithium chloride and hydroxide are listed in the TEDX list concerning their potential oestrogenic effect. If it was confirmed, it could, at least in part, explained the effects observed. France is currently working on the potential endocrine disruptor effects of lithium salts.

Concerning the articulation between studies carried out in healthy animals and on human with neurological diseases and how does the difference in the initial state impact the interpretation of the data. In a first place, when comparing developmental animals and human toxicology data, it has to be kept in mind that, as mentioned in Casarett & Doull's Toxicology Basic science of poisons (2013), quantitatively speaking, humans tend to be more sensitive than is the most sensitive species. Therefore, the data on human cannot be disregarded. Moreover, in the Munk-Olsen et al. (2018) study cited in the report for instance, the reference group used by the authors was composed by mothers with a mood disorder, but unexposed to lithium. The developmental effects observed seem therefore not due to the neurological disease of the mother.

eMSCA acknowledges that the quality and results of the available animal studies are heterogenous and had already point it out in the CLH report. However, it is part of the harmonised classification process to assess, present, balance and discuss all the data available to allow a informed RAC decision, as mentioned in the CLP regulation: *"Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence, see section 1.1.1. This means that all available information that bears on the determination of reproductive toxicity is considered together, such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs. Evaluation of substances chemically related to the substance under study may also be included, particularly when information on the substance is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, the presence of maternal toxicity in experimental animal studies, level of statistical significance for inter-group differences, number of endpoints affected, relevance of route of administration to humans and*

freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. A single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (see also 3.7.2.2.3).” eMSCA also acknowledges that animal studies other than the key study (2010) cited in the CLH report are of less quality, even if nonetheless of quality, and useful. However, eMSCA also reminds that the conclusion for developmental toxicity is mainly, if even exclusively, based on human data (proposal Repr 1A). Casarett & Doull’s Toxicology Basic science of poisons – 8th edition – Curtis D. Klassen – 2013
RAC’s response
Noted. RAC discussed and agreed on the classification for reproductive toxicity in a weight of evidence assessment of the experimental animal data and human data and concluded to classify the three lithium compounds (lithium carbonate, lithium chloride and lithium hydroxide) in Category 1B for adverse effects on sexual function and fertility. The classification is based on the high consistency of the findings on the male reproductive tract in the 90-day/mating study as well as in studies on male reproductive organs. For developmental toxicity RAC concluded to classify the three lithium compounds in Category 1A based mainly on evidence of a statistically significant increase in rare cardiac malformations in infants exposed to lithium during the first trimester of pregnancy noting that the population at risk, the pregnant women under lithium therapy, never will contribute to a high number of cases. Experimental animal studies supported the classification where some concerns for neurodevelopmental effects in rats and mice as well as decreased pup body weight and litter size were reported. In addition, RAC concluded on a classification for adverse effects on or via lactation 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.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	United Kingdom	European REACH Grease Thickener Consortium	Industry or trade association	2
Comment received				
The European REACH Grease Thickeners Consortium (ERGTC) fully support the comments submitted on this 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.				
Dossier Submitter’s Response				
Thank you for your comment. Please see responses to comments 7 and 23				
RAC’s response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	Belgium	RECHARGE, EPBA, EUROBAT	Industry or trade association	3
Comment received				
The battery industry is concerned about the fact that results of current guideline studies performed under GLP and showing no compound-related effects on developmental and reproductive toxicity are neglected and some much older and less robust published literature references are used for the classification instead. Consequently, the industry associations RECHARGE, EPBA and EUROBAT disagree with the classification proposal in the CLH report and are of the opinion that the lithium salts Lithium carbonate, Lithium chloride and Lithium hydroxide should not be classified for toxicity to reproduction and/or developmental toxicity. For more information, please see attached our full statement. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Joint Answer for lithium salts CLH proposal_October 2020.pdf				
Dossier Submitter's Response				
Thank you for your comment. Please see response to comment 1.				
RAC's response				
Noted. See reply to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
15.09.2020	Germany		MemberState	4
Comment received				
The anhydrated and the monohydrated form of lithium hydroxide is in the scope of the CLH dossier. Therefore, on the first page of the report this information should be added as follows: [3] Lithium hydroxide (anhydrate and monohydrate) [3] 1310-65-2, 1310-66-3 In table 3, the CAS number for the monohydrate of lithium hydroxide should be added as well with an explanation in brackets. Differences in potency/Mixtures of lithium salts Lithium has a very low atomic mass. Thus, pending on the molecular weight of the anionic part, the lithium content can be different. With regard to the lithium salts included in the CLH report the lithium content covers a range from ca. 9.4% (lithium carbonate) to 29.0 % (lithium hydroxide (anhydrous)). Concerning reproductive toxicity the lithium cation is considered as the toxicologically relevant component implying that the same amount of lithium hydroxide (anhydrous) is three-fold more toxic than lithium carbonate. This could be considered e.g. when discussing GCL/SCL. From a toxicological viewpoint, an adaption according to the lithium content would be reasonable. This should also be taken into account when a mixture is composed of different lithium salts (see also discussion on borates).				

Selection of included lithium salts
The CLH-report covers three lithium salts. Further lithium salts are already included in annex VI (table 3) of Regulation 1272/2008 or can be found on the ECHA dissemination site. For example, the following compounds could be checked for inclusion in the grouping approach, because of a comparably low toxicity of the anionic part (information on tonnage and use, which was taken from the ECHA dissemination site, demonstrates a certain relevance):
• Lithium acetate (CAS no.: 546-89-4), 10 – 100 tpa, used professional workers (widespread uses)...
• Lithium citrate tetrahydrate (CAS no.: 6080-58-6), 10 – 100 tpa, used professional work-ers (widespread uses)...
• Lithium nitrate (CAS no.: 7790-69-4), 10 – 100 tpa, used professional workers (widespread uses)...
• Lithium sulphate (CAS no.: 10377-48-7), 100 - 1 000 tpa, used by consumers, in articles, by professional workers (widespread uses)...

The inclusion of further lithium compounds would avoid „regrettable substitution".

Dossier Submitter's Response

Thank you for your comment.

Concerning the anhydrated and the monohydrated form of lithium hydroxide, it should have been precised, thank you for noting.

Indeed, the relationship between lithium content in the substance and observed response is possible. But, even if knowing the lithium cation concentration is important in a risk assessment process, in a CLP framework, the assessment focus on the hazards, and the lithium content is therefore not a major point. Concerning the discussion on SCL/GCL, for fertility endpoint, as the clasification proposal is based on a body of evidence, it seems complicated to calculate the potency of the substance. For the developmental toxicity, as the proposal is based on human data, it seems also difficult to calculate this potency.

Regarding the inclusion of other lithium compounds, this comment is relevant and we agree this is an important reflexion to have. If the lithium cation is considered responsible for the systemic toxicity of inorganic lithium compounds, then the list would be acceptable in a grouping approach.
However, unlike the three lithium compounds included in the CLP dossier, the anions in the proposed list are not naturally present in the human body. They may exhibit specific toxicity. In our opinion, it would therefore be necessary to assess the toxicity of these lithium salts before including them in the classification proposal.

RAC's response

Noted. Potency considerations of a substance are not a part of the classification criteria for reproductive toxicity and lactation but could be considered for the setting of specific concentration limits (SCLs). According to the CLP Guidance (version 5.0, July 2017) "in exceptional circumstances specific concentration limits may be set by the manufacturer, importer or downstream user where he has adequate, reliable and conclusive scientific information that a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for the relevant hazard class". For lithium hydroxide no studies with sub-acute, sub-chronic exposure were included in the REACH registration or were available in the open literature. Further the CLP Guidance includes that, "the classification of substances as reproductive toxicants may be based on information such

as grouping and read across (Guidance IR&CSA, sections R.6 and R.7.2.3.1)" and this is considered relevant for lithium hydroxide. However, the CLP Guidance says that "in such cases, no direct estimate of the reproductive toxicity potency based on an ED10 value is possible". Further, since the classification of the lithium salt is based on the human data, the CLP Guidance states that "the use of human data for ED10 calculation has several drawbacks including limited data on exposure, limited data on the size of the exposed population and limited information on whether the exposure included the window of sensitivity. For all these reasons, it is difficult to determine an ED10 based on human data". Therefore, RAC considers that setting of an SCL for lithium hydroxide based on a potentially lower potency is not justified.

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2020	Belgium	Health and Environment Alliance (HEAL)	International NGO	5
Comment received				
The Health and Environment Alliance (HEAL) welcomes the opportunity to comment on France's proposal to classify three Lithium salts - lithium carbonate, lithium chloride, lithium hydroxide - as toxic to reproduction 1A and fully supports this initiative. The supporting CLH dossier is comprehensive and the methodology used to report on the scientific evidence available on different endpoints is very clear and transparent.				
Dossier Submitter's Response				
Thank you for your comment and your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	Belgium	<confidential>	Company-Importer	6
Comment received				
We are very concerned about the fact that the proposed hazard classification of Lithium carbonate, Lithium hydroxide and Lithium chloride is based on data that is contradictory and cannot support a strong enough conclusion. We believe additional studies should be conducted to obtain more robust evidence in order to support a harmonized hazard classification for these substances.				
Dossier Submitter's Response				
Thank you for your comment. eMSCA also noticed the few robust studies on the database, as for example repeated studies wich could have been helpful in the framework of this dossier. However, the harmonised classification process is based on available data, and a request for additional data is not part of this process. Considering the above, we are of the opinion that the body of evidence is robust enough to propose a classification for reproductive toxicity endpoint.				
RAC's response				
Noted. See reply to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	FUCHS Schmierstoffe GmbH	Company-Manufacturer	7

Comment received

Response to the 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. The CLH report proposes classification in category 1A for developmental effects and in category 1B for reproductive effects (male fertility). This harmonized classification and labelling of lithium carbonate, lithium chloride, and lithium hydroxide as known or presumed reproductive toxicants is inappropriate given the following evidence:
General Comments
• 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 a teratogenic outcome should be specific to the chemical at issue (Teratology Society Public Affairs Committee, 2005).
• It appears somewhat contradictory, albeit in compliance with the classification guidance, that rodent data is taken as predictive of male fertility hazard without similar evidence in humans (Classification 1B) yet, for cardiovascular teratogenicity human data is taken as supportive of a 1A classification despite no evidence of similar effects in a body of regulatory rat studies.

References
Andrews P, Blanset D, Costa PL, Green M, Green M, Jacobs A, Kadaba R, Lebron J, Mattson B, McNerney M, Minck D, Castro Oliveira L, Theunissen P, DeGeorge J. (2019) Analysis of exposure margins in developmental toxicity studies for detection of human teratogens. Regulatory Toxicology and Pharmacology. 105: 62-68.

McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR (2012) Lithium toxicity profile: a systematic review and meta-analysis. The Lancet. 379: 721-728.

Patorno E, Huybrechts KF, Bateman BT, Cohen JM, Desai RJ, Mogun H, Cohen LS, Hernandez-Diaz S (2017) Lithium Use in Pregnancy and the Risk of Cardiac Malformations. New England Journal of Medicine. 376: 2245-54.

Teratology Society Public Affairs Committee (2005) Causation in Teratology-Related Litigation. Birth Defects Research (Part A) 73:421– 423.

Yacobi S, Ornoy A (2008) Is lithium a real teratogen? What can we conclude from the prospective versus retrospective studies? A review. The Israel Journal of Psychiatry and Related Sciences. 45: 95-106.

Dossier Submitter's Response

Thank you for your comment.

- The systemic toxicity of the lithium compounds included in this CLH report is determined by the lithium ion. The read across between the different lithium salts followed the rules described in the ECHA's Read-across guidance.
- As you suggest in your comment, data assessment and classification proposal are performed in accordance with CLP guidance. Concerning fertility hazard, there is basically no human data to rely on for a classification proposal. Therefore, animals data were used. Concerning effects on development, eMSCA considers that the recent human data provide enough evidence to be classified in category 1A, Known human reproductive toxicant.

RAC's response

Noted. The read across approach between lithium carbonate, lithium chloride and lithium hydroxide based on the analogue approach were supported by RAC. Systemic toxicity is considered to be determined by the lithium cation and are not influenced by the anions. RAC notes some uncertainties related to the inclusion of lithium hydroxide in the read across due to its corrosive properties and the potential to reach high enough doses of the lithium cation to induce systemic toxicity. On the other hand, it is noted that the potency considerations of a substance are not a part of the classification criteria for reproductive toxicity and lactation but could be considered for the setting of specific concentration limits (SCL). However, RAC considered that setting of a SCL for lithium hydroxide based on a potentially lower potency is not justified.
Also see response to comment No. 1.

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Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	Belgium	Lithium REACH Consortium	Industry or trade association	8

Comment received

We are very concerned about the fact that guideline conform full study reports that were performed under GLP and rated as Klimisch 1 by both the author of the CLH report and the registrant did not get more weight and were not used as key studies as compared to publications that were in many cases limited in the information provided and did not provide equally detailed and robust information. Furthermore non-GLP Research-type studies often used extreme dose levels leading to high toxicity that is unacceptable under guideline and GLP conditions and from which no conclusion on classification can reasonably be drawn.
The basis of the Klimisch rating that the authors of the CLH report attributed to certain

studies remains unjustified and it is unclear how this judgement was performed. In many cases it is considerably different from the reliability in the REACH registration dossier and we question the criteria. For this reason we provide an annex with the basic criteria of the ratings that were applied in the REACH dossier for the respective studies and are confident that the RAC will consider the reliability, validity and relevance of the different studies carefully in a balanced weight of evidence approach. (Annex 1, "Klimisch scores of key ref REACH consortium.pdf")
We are also concerned about using reports of pharmacological side effects in patients receiving high dose Lithium carbonate treatment frequently in combination with other medications as the basis for the classification for developmental toxicity. It is difficult, if not impossible to discern effects of the underlying disease, multiple medications etc. from effects truly related to Lithium salts. This does not at all reflect the situation of healthy workers handling lithium salts.
Consequently we disagree with the classification proposal in the CLH report and are of the opinion that the lithium salts Lithium carbonate, Lithium chloride and Lithium hydroxide should not be classified for toxicity to reproduction and/or developmental toxicity.
Detailed comments are provided below and in the attached documents.
Detailed analysis of the studies was provided by experts in the field of developmental and reproductive toxicity.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020-10-02Lithium REACH consortium comments on the CLH report for Li salts Annexes.zip

Dossier Submitter's Response

Thank you for your comment.

eMSCA acknowledges the high quality of study report performed according to guidelines (Anonymous 2012). However, as already detailed in a previous response, the evaluation was performed based on the entire dataset available, and, even if the other studies available do not reach the same degree of quality, some of them are nevertheless of good quality and can not be disregarded. The results of these studies are very consistent supporting that the effects are related to lithium exposure, regarding the fact that the OECD study are more or less the only negative studies of the database.
Using a a body of evidence, as detailed in response to comment 1 and provided by the CLP regulation, the conclusion for fertility toxicity (where animal data are used) is considered robust.
Concerning your point that "*Furthermore non-GLP Research-type studies often used extreme dose levels…*" we disagree. Many studies used doses very similar to the guideline/GLP studies (maximal concentrations indicated, data on males):

- Anonymous (2012) (OECD 416): 45 mg lithium carbonate/kg for at very least 70 days in males by gavage
- Zarnescu and Zamfirescu (2006): 35 mg lithium carbonate/kg for 21 days by gavage
- Thakur et al. (2003): 44 mg lithium carbonate/kg for 90 days in diet
- Toghiani et al. (2012): 30 mg lithium carbonate/kg for 48 days by gavage

Finally, considering the wording of the OECD guideline 416 ("*the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering"* which is a principle of toxicological studies), chosen doses regarding parental toxicity described in guideline study seems to be adequate.

Thank you for the effort of rating all the studies used in the report. However, analysing the annex you provided, it is evident that some criteria are not per se Klimisch criteria. For example:

- Your first criteria is "Study performed to generally valid and/or internationally accepted test guideline". A reliability 1 study is not necessarily a guideline study. At least, not following a guideline is not a reason to downgrade the score without more in deep evaluation. For example, test procedure in accordance with generally accepted scientific standards and described in detail can reach a reliability 1. Also, this criteria overlap with others you use ;
- the question of the systemic toxicity, even of importance for reproductive toxicity studies, is not a criteria to rate in vitro studies;
- Historical controls are also not part of Klimisch criteria, at least not in addition to negative control group (criteria 8 and 13)

Finally, you do not use different criteria for in vitro and in vivo studies, which does not seem adequate to rate studies with relevance.
In the aim of transparency, for comparison, we provide in an annex a rating of each study, using the recognized software ToxRTool. You will note reading this annex that the studies rating with ToxRTool is the same than the one proposed in the CLH report for all studies except two: Toghiani et al. (2012) rate as Klimisch 2 in the CLH report and equivalent to Klimisch 1 based on ToxRTool, and Allagui et al. (2006) rate as Klimisch 2 in the CLH report and equivalent to Klimisch 3 based on ToxRTool.

Your are also "*concerned about using reports of pharmacological side effects in patients receiving high dose Lithium carbonate treatment*". In most of academic experimental studies, authors mentioned that they tried to use doses achieving serum concentrations similar to those in patients under lithium treatment. With this reasoning, experimental studies would also be performed at too high doses. Moreover, as mentioned above, as these concentrations are similar to the ones used in the guideline study report, it would mean that this guideline study would also be performed at excessive concentrations.
Concerning the fact that "*This does not at all reflect the situation of healthy workers handling lithium salts*", yes indeed but classification is based on hazard, and not on risk and therefore, all human data available have to be used to support the assessment.

Annex 1: Rating of fertility in vivo studies

RAC's response

Noted. See response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Netherlands		MemberState	9

Comment received

Read-across
A category approach is used for lithium carbonate, lithium chloride and lithium hydroxide, which is supported by us.
These inorganic lithium compounds dissociate to the lithium cation (Li+) and the corresponding anion (carbonate – CO32-, chloride – Cl-, or hydroxide – OH-) in aqueous solutions, i.e. in body fluids as well as in in vitro systems. The anions are physiological anions, which are naturally present in the body, whereas systemic toxicity is determined by the lithium ion.

Dossier Submitter's Response
Thank you for your comment and your support.
RAC's response
Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
15.09.2020	Germany		MemberState	10
Comment received				
No classification for carcinogenicity is proposed by the French CA due to the lack of data with adequate quality. We agree that the available data are not sufficient to fulfil the CLP criteria for classification of lithium carbonate, lithium chloride and/or lithium hydroxide. The proposal for no classification is supported.				
Dossier Submitter's Response				
Thank you for your comment and your support.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	France	Eramet	Company-Manufacturer	11
Comment received				
The CLH proposal reviewed in details the following health hazards: • Mutagenicity, • Carcinogenicity, • Reproductive toxicity. ANSES proposal comes to conclusion that Li salt are reprotoxic, without any evidence on other CMR effect (mutagenicity or carcinogenicity) Mutagenicity studies are conclusive to show no effect. Mutagenicity is most often linked to carcinogenicity or reprotoxicity and helpful to explain the mechanism. In some case, reprotoxic effect without mutagenic or carcinogenic effect is quite possible, but in this case the toxicological mechanism is most often specific and interesting to describe for a better understanding. In this CLH dossier, explanation mechanism are absent, however some questions should therefore be dealt with in more detail to clarify toxicological mechanism and justify why there is some important discrepancy between studies results (reprotox) : • How to better articulate studies carried out on healthy animals and studies carried out on humans with neurological diseases? • How does the difference in initial state impact the interpretation of the data? The doses used on humans are used in a medical context with the aim to obtain an effect on the disease being treated. Are the doses used and the mode of administration, acceptable and interpretable within the framework of CLP regulations? Are there any				

toxicokinetic data or even any PBPK model approach that could allow a better understanding of the toxicology of lithium and put the dose/effect relationship into perspective? This approach based on toxicokinetics is a pre-requisite, especially without any mechanistic hypotheses (toxicodynamic) highlighted in the report.
In addition, is it helpful for the understanding of the report to develop some considerations for studies whose methodology is and has been contested:

• Pastor et al. (2009). is cited to cast doubt on the absence of mutagenicity when the very high doses used lead to a proven cytotoxic effect. P. 21 : "In summary, lithium compounds have been tested for mutagenicity, chromosome aberrations, sister chromatid exchanges, DNA damage in a number of in vitro and in vivo studies. Mainly negative results were obtained, but positive results were also reported, usually at high cytotoxic doses."

• Zaidan, (2014) is cited P.28, while results of this study were questioned, as the influence of confounders was not appropriately checked. And, this study could have been subject to selection/inclusion bias because it has been conducted in a specialized nephrology department and the limited number of cases.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on ANSES CLP proposal about Lithium compounds.pdf

Dossier Submitter's Response

Thank you for your comment.
Please see response to comment n°1.
Concerning human data, please see response to comment 8.

There is no toxicokinetic data found other than the one described in the CLH report.

- Concerning your point on the study from Pastor (2009), the quoting in your comment refers to the entire germ cell mutagenicity endpoint. In this study, the increased cytotoxicity in comparison with control group is statistically significant for concentrations of 5 mM and higher for lithium carbonate, and 10 mM and higher for lithium chloride. However, induction of micronuclei is statistically significant at concentrations of 2.2 mM and higher for lithium carbonate, and 5 mM and higher for lithium chloride. Therefore, we confirm our conclusions, i.e. "*However, an aneugenic potential of lithium salts could not be excluded considering positive results obtained in in vitro micronucleus test associated with an increase of kinetochore positive micronuclei*"
- Concerning the study from Zaidan et al. (2014), even if we highlighted limitations of the study in the report, it seems relevant for us to mentioned it, in a sake of body of evidence approach and because it is a basis ot the PRAC (Pharmacovigilance Risk Assessment Committee) recommendations for product information (*Renal tumours: Cases of microcysts, oncocytomas and collecting duct renal carcinoma have been reported in patients with severe renal impairment who received lithium for more than 10 years (see Section 4.8)*.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	France	A3M	Industry or trade association	12

Comment received

The CLH proposal reviewed in details the following health hazards:
• Mutagenicity,
• Carcinogenicity,
• Reproductive toxicity.

ANSES proposal comes to conclusion that Li salt are reprotoxic, without any evidence on other CMR effect (mutagenicity or carcinogenicity)
Mutagenicity studies are conclusive to show no effect. Mutagenicity is most often linked to carcinogenicity or reprotoxicity and helpful to explain the mechanism. In some case, reprotoxic effect without mutagenic or carcinogenic effect is quite possible, but in this case the toxicological mechanism is most often specific and interesting to describe for a better understanding. In this CLH dossier, explanation mechanism are absent, however some questions should therefore be dealt with in more detail to clarify toxicological mechanism and justify why there is some important discrepancy between studies results (reprotox) :

• How to better articulate studies carried out on healthy animals and studies carried out on humans with neurological diseases?
• How does the difference in initial state impact the interpretation of the data?
The doses used on humans are used in a medical context with the aim to obtain an effect on the disease being treated. Are the doses used and the mode of administration, acceptable and interpretable within the framework of CLP regulations? Are there any toxicokinetic data or even any PBPK model approach that could allow a better understanding of the toxicology of lithium and put the dose/effect relationship into perspective? This approach based on toxicokinetics is a pre-requisite, especially without any mechanistic hypotheses (toxicodynamic) highlighted in the report.

In addition, is it helpful for the understanding of the report to develop some considerations for studies whose methodology is and has been contested:
• Pastor et al. (2009). is cited to cast doubt on the absence of mutagenicity when the very high doses used lead to a proven cytotoxic effect. P. 21 : "In summary, lithium compounds have been tested for mutagenicity, chromosome aberrations, sister chromatid exchanges, DNA damage in a number of in vitro and in vivo studies. Mainly negative results were obtained, but positive results were also reported, usually at high cytotoxic doses."

• Zaidan, (2014) is cited P.28, while results of this study were questioned, as the influence of confounders was not appropriately checked. And, this study could have been subject to selection/inclusion bias because it has been conducted in a specialized nephrology department and the limited number of cases.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Consultation classification lithium salts- Comments of A3M.docx

Dossier Submitter's Response

Same comment as n°11. Please refer to response to comment number 11

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.09.2020	Germany		MemberState	13
Comment received				
The French CA proposes no classification for germ cell mutagenicity due to the lack of data with adequate quality. We agree that the database is not sufficient to conclude on mutagenic/genotoxic potential of lithium carbonate, lithium chloride and/or lithium hydroxide. The proposal for no classification is supported.				
Dossier Submitter's Response				
Thank you for your comment and your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	Belgium	RECHARGE, EPBA, EUROBAT	Industry or trade association	14
Comment received				
Reference to page 24 - Mutagenicity studies are conclusive to show no effect. Therefore, it appears important in the CLP proposal report to improve explanation on the possible mechanisms involved in the supposed reprotoxicity. A reprotoxic effect without mutagenic or carcinogenic effect is quite possible, but in this case the toxicological mechanism is most often specific and interesting to describe for a better understanding. The following questions should therefore be dealt with in more detail in the report: How to better articulate studies carried out on healthy animals and studies carried out on humans with neurological diseases? How does the difference in initial state impact the interpretation of the data? ECHA note – An attachment was submitted with the comment above. Refer to public attachment Joint Answer for lithium salts CLH proposal_October 2020.pdf				
Dossier Submitter's Response				
Thank you for your comment. Please see response to comment n°1.				
RAC's response				
Noted. See response to comment No. 1.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
30.09.2020	Sweden		MemberState	15
Comment received				
The Swedish CA agrees with the proposed classification of lithium chloride, lithium carbonate and lithium hydroxide as Repr. 1A, H360FD.				

Adverse effects on the development of the offspring
The epidemiological data enclosed within the CLH-report seem to be contradictory and of various quality. Additional epidemiological studies that could be used to strengthen the WoE proposed by the DS are available in the open literature, including a recent prospective population-based mother-child cohort study by Harari et al (2015). This study investigated the effects of environmental exposure of lithium on pregnant women residing in Argentina. Lithium exposure through drinking water was associated with impaired foetal size that seemed to be initiated in early gestation. Lithium in maternal blood (median 25; range 1.9–145 μg/L) and urine (1645; 105–4600 μg/L) was inversely associated (apparently linearly) with all foetal measures (body, head and femur) in the second trimester, and with birth length (β − 0.53 cm per 25 μg/L increase in blood lithium, 95% CI − 1.0; − 0.052). An increase of 100 μg/L in blood was associated with 2 cm shorter newborns.

Adverse effects on or via lactation
We do agree that the animal studies enclosed in the CLH-report do not show clear effects on the pups via lactation.

However, we note that lithium is contraindicated during breastfeeding in several international treatment guidelines: by UK's National Institute for Health and Clinical Excellence (NICE) clinical guideline for antenatal and postnatal mental health, by the American Psychiatric Association Steering Committee practice guideline for the treatment of patients with bipolar disorder , by the Royal Australian and new Zealand College of Psychiatrists clinical practice guidelines for mood disorders , and by the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders guidelines for the management of patients with bipolar disorders . Furthermore, the American Academy of Pediatrics Committee on Drugs has classified lithium as contraindicated during breastfeeding, since it has been associated with significant effects on some breastfed infants and, if necessary, should therefore be administered to nursing mothers with caution. Also, on the leaflets of some lithium-based medicines it is stated that the treatment is contraindicated during breastfeeding .

A potential mechanism of toxicity could be explained by the immature excretory systems of infants that increase the possibility of adverse reactions, since lithium is eliminated via renal excretion. These reactions have been reported in nursing infants and include cardiac arrhythmia, goiter, electrolyte imbalance, hypothyroidism, tremor, muscle weakness, gastrointestinal problems and nephrotoxicity (Chaudron and Jefferson, 2000). Further concern rises from the results of experimental studies showing lithium-induced severe renal structural changes in the developing rat kidney (Christensen et al. 1982). An additional reason for not being compatible with breastfeeding is the potential of lithium to accumulate in the developing bone of the infant, thus causing a decrease in bone calcium (Chaudron and Jefferson, 2000).

Moreover, we note some studies from the open literature indicating that Li affects the secretion of prolactin. Galactorrhea was reported in a 21-year old female who was treated with lithium carbonate as sole therapy for 50 days; lactation ceased when the treatment was discontinued (Ohishi and Higashimura, 1983). Conversely, a study investigating the correlation between lithium carbonate treatment and prolactin secretion in men showed stat. sign. decreased serum prolactin levels (9.72 ng/mL vs. 16.55 ng/mL in healthy controls) in long-term treated patients (> 6 months; n=20) (Basturk et al. 2001).

References

Harari, F., Langeén, M., Casimiro, E., Bottai, M., Palm, B., Nordqvist, H., & Vahter, M. (2015). Environmental exposure to lithium during pregnancy and fetal size: a longitudinal study in the Argentinean Andes. Environment international, 77, 48-54.

Chaudron, L. H., & Jefferson, J. W. (2000). Mood stabilizers during breastfeeding: a review. Journal of Clinical Psychiatry, 61(2), 79-90.

Christensen, S., Ottosen, P. D., & Olsen, S. (1982). Severe functional and structural changes caused by lithium in the developing rat kidney. Acta Pathologica Microbiologica Scandinavica Series A: Pathology, 90(1-6), 257-267.

Ohishi, K., & Higashimura, T. (1983). A case of manic state in which lactation occurred after Li2CO3 administration. Psychiatry and Clinical Neurosciences, 37(1), 33-36.

Baştürk, M., Karaaslan, F., Eşel, E., Sofuoğlu, S., Tutuş, A., & Yabanoğlu, İ. (2001). Effects of short and long-term lithium treatment on serum prolactin levels in patients with bipolar affective disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 25(2), 315-322.

Dossier Submitter's Response

Thank you for your support and for the supplementary data.
Regarding the lactation point you raise, we agree that the additional data you provide suggest effect by lactation. The need for a classification would deserved to be discussed during the RAC session.

RAC's response

Noted. See response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	France	A3M	Industry or trade association	16

Comment received

About reproductive toxicity (adverse effects on development):

ANSES wrote p.57 of the CLP report :"Data on animals are inconclusive, due to the heterogeneity of results and the overall quality of the dataset. …"

The dataset collected in the report is the cause of this heterogeneity. The key study of 2010 (Klimmich 1-level) and an others studies of 2012 (Klimmich 2-level) show no evidence of cardiac malformations in animals after exposure to lithium compounds. However, they are compared with studies carried out more than 30 years ago without compliance with OECD standards. (Marathe and Thomas, 1986; Kelley and al., 1978; Fritz, 1988)

It therefore, seems more conclusive to write, as mentioned a few lines below in P.57, that there is no cardiac malformation observed in the animal.: « Moreover, the observations on some studies are not in line with the findings from human studies (no increase of cardiac malformation seen in animals studies), …"

Moreover, the second part of this sentence should be more fully developed, the differences in results between human and animal is very quickly addressed, and the important difference between the two cases studied is not mentioned. Indeed, the animals studied are healthy, they do not suffer from neurological disorders that require medical treatment. "…which can be explained by a difference in mechanism of action between rodents and human. However, human data, and particularly the homogeneity of recent robust human studies are considered sufficient by themselves to give evidence of developmental effect of lithium.

Finally, there is no homogeneity in the conclusions of the three studies cited in the report. The report cites : « In recent publications, a more precise pattern of the effects of lithium on development seems to emerge: authors from reviews (Yacobi et al., 2008), meta-analysis (McKnight et al., 2012) or
cohort study (Patorno et al., 2017) lead to very similar conclusions, i.e.,"

While the last study concluded that there was an association between maternal exposure to lithium and cardiac malformation, the other two studies did not find an association and concluded that there was uncertainty about the causal link.

Conclusion of the article from Yacobi et al., 2008 : "…Reviewing the data accumulated until today
regarding lithium exposure and cardiovascular anomalies, including Ebstein's anomaly, it is to be
concluded that the risk is much lower than previously thought". And the authors also assumed that the rate of cardiac anomalies from lithium registry seems to be due to the fact that some cases were reported in several publications.

Conclusion of the article from McKnight et al., 2012 :"… The risk of congenital malformations is uncertain; the balance of risks should be considered before lithium is withdrawn during pregnancy. Because of the consistent finding of a high prevalence of hyperparathyroidism, calcium concentrations should be checked before and during treatment."

In fine, ANSES wrote p.58 of the report : "the evidence that lithium is teratogenic is quite weak, and the findings showed that the risk has been previously over-estimated".

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Consultation classification lithium salts- Comments of A3M.docx

Dossier Submitter's Response

Thank you for your comment.

For the first part of your comment concerning the animal dataset, please refer to responses to comment n°1.

Concerning our conclusions p57 (in fact 59) of the report, when we wrote that the observations in animal studies are not in line with human studies, we meant qualitatively

since both animal and human studies report developmental toxicity. Animal studies do not demonstate precisely cardiac malformations but show for example neurodevelopmental toxicity (Abu-Taweel, 2012; Teixeira et al., 1995) (a causal relationship which can be maybe more difficult to highlight in human) or decreased mean pup weight or litter weight, reduced litter size, reduced implantations, increase in number of resorptions… Regarding these observation, animals studies can be considered as suggestive of developmental toxicity.
Having said that, the classification proposal is in any case not based on this data.

Concerning the 3 human recent studies mentioned (Yacobi et al., 2008; McKnight et al., 2012 and Patorno et al., 2017), and your quoting of the report, we would like to reproduce here the whole sentence "*In recent publications, a more precise pattern of the effects of lithium on development seems to emerge: authors from reviews (Yacobi et al., 2008), meta-analysis (McKnight et al., 2012) or cohort study (Patorno et al., 2017) lead to very similar conclusions, i.e.,* ***the evidence between lithium exposure during pregnancy and cardiac malformation is quite weak, but there is an association, with a magnitude lower than previously reported***" Which in our understanding change the meaning as it is clearly said that there is an association.

Concerning the study from Yacoby and Ornoy (2008), which is a review of data from decades, and which is not focused (only) on hazard (i.e. classification) effect but on medical management (risk and benefit-risk ratio), they also add on their conclusion that "*the real impact of lithium is under-represented since many women who become pregnant while being treated with lithium may prefer to abort the malformed fetuses. Indeed, Jacobson et al. (50) reported a higher rate (though not statistically significant) of therapeutic abortions in the lithium exposed group (10%) compared to 6% in the control. This was also corroborated in our findings: 8.6% in the lithium group vs. 2.9% in the controls (51).*" This is a point of great importance to take into account in the assessment of the data to our point of view, as if these abortions had not occurred, the conclusions could have been substantially different: if no abortions had occurred, the incidence of pups with malformations could have been higher. In this situation, the hazard is then underestimated. This difficulty is also confirmed in Casarett & Doull's Toxicology Basic science of poisons (2013), authors explaining "*Another challenge to epidemiologists is the high percentage of human pregnancy wastage, perhaps as much as 31% in the peri-implantation period (Wilcox et al., 1988) and an additional 15% that are clinically recognized. Therefore, pregnancy failure related to a particular exposure may go undetected in the general population. Furthermore with the availability of prenatal diagnostic procedures, some pregnancies with malformed embryos (particularly NTD's) are electively aborted.*"
Moreover, in a recent epidemiological study, Poels et al. (2020, see reference) confirm the higher risk of miscarriage in women with bipolar disorder exposed to lithium during pregnancy. The objective of this retrospective cohort study was specifically to investigate the risk of miscarriage. Authors analyzed the data of all the pregnancies of the women in the study with a diagnosis of bipolar I disorder for which detailed data on lithium exposure and pregnancy outcomes were available (n = 443). Miscarriages occurred in 20.8% of the lithium-exposed pregnancies (16/77), compared with 10.9% of the unexposed pregnancies (40/366), (OR = 2.14; 95% CI: 1.13–4.06, p = 0.018). After adjusting for the age at conception and the clustering of pregnancies per woman, the odds ratio of miscarriage after lithium use during pregnancy was 2.94 (95% CI: 1.39–6.22, p < 0.005). Based on this study, a causal relationship between the psychiatric

disease and the increase of miscarriage can be excluded, as the control group consists in women suffering from bipolar disorder but not exposed to lithium.

We could also remind the results of the recent study from Munk-Olsen et al. (2018) showing an association between lithium and major malformations (OR = 1.71, 95% CI : 1.07-2.72). There is also an association between exposure and cardiac malformation even if not significant (OR = 1.54, 95% CI : 0.64-3.70). Authors explained that this lack of significance for cardiac malformation could be due to lacks of power when studying very rare events. This good quality study adjusted the results for marital and education status, antiepileptic use during pregnancy (other than valproate as pregnancies exposed to this drug were excluded a priori), and treatment with other psychotropic drugs as individual covariates, including antidepressants, antipsychotics, benzodiazepines and hypnotics, and psychostimulants. The association was observed for an exposure during the first trimester of pregnancy, and the authors also concluded that the absolute risk is smaller than previously observed (meaning that there is indeed a risk), which is very consistent with the conclusions of the robust study of Patorno et al. (2017). To note that authors also reported as potential limitation the risk of abortion, as they "*chose to only include pregnancies ending with live-born children due to lack of information on stillbirths at some study sites. If lithium use during pregnancy increases the risk of stillbirths or miscarriage, conditioning on live-born children could have led to underestimation of adverse effects*".
Considering human data described in the CLH report, authors often conclude that the risk/association is lower than previously thought. This statement means that there is indeed an association between lithium exposure and developmental toxicity. Considering the fact that the classification under CLP regulation is hazard based (and not risk based), this evidence of association is sufficient to make a proposal.

All things considered, from our point of view these data deeply highlight the developmental toxicity of lithium.

Casarett & Doull's Toxicology Basic science of poisons – 8th edition – Curtis D. Klassen – 2013
Poels, E.M.P.; Kamperman, A.M.; Vreeker, A.; Gilden, J.; Boks, M.P.; Kahn, R.S.; Ophoff, R.A.; Bergink, V. Lithium Use during Pregnancy and the Risk of Miscarriage. J. Clin. Med. 2020, 9, 1819.

RAC's response

Noted. See response to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	United Kingdom	European REACH Grease Thickener Consortium	Industry or trade association	17

Comment received

The ERGTC identifies concerns relating to the interpretation of data that lead to the proposed overall classification of 1A for reproduction and/or developmental toxicity 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.

Dossier Submitter's Response

Please see answer to comments 7 and 23.

RAC's response
Noted. See response to comment No. 11.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	Belgium	RECHARGE, EPBA, EUROBAT	Industry or trade association	18
Comment received				
Reference to page 61 - The two-generation study in Wistar rats with Lithium carbonate was the only study conducted under GLP and fully covering the systemic toxicity, reproductive function and fetal outcome. The other publications that investigated the reproductive toxicity in rats and mice had many deficiencies. They were not conducted under GLP and were mostly incomplete. Some studies investigated the animals under conditions of overdosing. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Joint Answer for lithium salts CLH proposal_October 2020.pdf				
Dossier Submitter's Response				
Thank you for your comment. Please see response to comment n°1.				
RAC's response				
Noted. See reply to comment No. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
15.09.2020	Germany		MemberState	19
Comment received				
The German CA does not agree with the French MSCA proposal to add classification on sexual function and fertility in category 1B and on development in category 1A resulting in classification to Repr. 1A (H360FD) for the following reasons: Sexual function and fertility No adverse effects on sexual function and fertility up to doses inducing some systemic toxicity were observed in the OECD TG 416 study (according to GLP). Fertility effects are indicated in various other non-guideline studies. However, the quality of evidence is less convincing due to deficiencies in the studies, e.g. substance purity information missing, no information on systemic effects/absence of systemic effects. It should be checked whether Thakur et al. (2003) and Zarnescu and Zamfirescu (2006) deserve a Klimisch 1 classification as given in the CLH-report. As the DS states, human data for lithium effects on male fertility are not sufficient to serve as basis for a classification. Thus, the criteria for a classification in category 1B with regard to sexual function and fertility are not fulfilled. Classification with category 2 appears to be more appropriate. Development Existing epidemiological studies are of varying quality and rather contradictory. Confounding factors and limited statistical power lead to quite weak evidence. No developmental effects were observed in the OECD TG 414 study (GLP compliant). The				

reliability of the available non-guideline studies is questionable, because information on the absence of (other) systemic effects in dams and substance purity data is often missing.
Medicinal product leaflets state that an increase in the overall rate of malformations was observed in children exposed in utero to lithium, indicating a clinical/medical database exists. Medical data were not available for the proposal for harmonised classification and labelling.
The current paucity of high quality data and substantiated evidence limits the conclusiveness. Therefore, the criteria for a classification in category 1A with regard to development are not fulfilled. Classification with category 2 appears to be more appropriate.

Dossier Submitter's Response

Thank you for your comment.

Sexual function and fertility
Concerning the Klimisch cotation, please refer to the annex provided where we score studies with the ToxRTool software. As mentioned earlier, you will note reading this annex that the studies cotation with the software is the same than the one proposed in the CLH report for all studies except two: Toghiani et al. (2012) rate as Klimisch 2 in the CLH report and equivalent to Klimisch 1 based on ToxRTool, and Allagui et al. (2006) rate as Klimisch 2 in the CLH report and equivalent to Klimisch 3 based on ToxRTool. Also the lack of information concerning the substance purity is not a critical criteria for the assessment of a study. We nevertheless acknowledge the lack of information on systemic toxicity for many of these studies. However as they were performed with comparable doses, comparable duration of exposure et same strain of rats as in the OECD 416 guideline study we considered that the systemic/general toxicity could be negligible since no overtoxicity was observed in this last study.
The classification proposal is therefore based on a body of evidence.
eMSCA acknowledges that the guideline study – of better quality than the published academic studies - does not show any effect. As we were not able to explain these discrepancies between the "negative" results from the guideline study and the "positive" results from published academic studies, we used a body of evidence approach based on aggregated results.

The proposed classification as Repr. 1B for fertility is based on consistent effects on reproduction observed in several adequate studies. Even if we cannot explain the lack of any effect in the guideline study, it cannot dismiss the consistent evidence provided by the published academic studies.

Development
Concerning the developmental toxicity endpoint, please see responses to comments 1 and 16.
Regarding medical product leaflets, as mentioned in the report, French Agency for the Safety of Health Products was contacted and gave us access to the archives of regulatory affairs (marketing authorisation provided by laboratories). Unfortunatly, no useful data in the framework of a classification dossier could be retrieved (probably due to the fact that lithium based drugs are on the market since more than 50 years).

Adequate robust data is available from human data. Studies on animals are rather unconsistent and associated with methodological deficiencies. Human data, if adequate, should be prefer as a basis for classification. In this context, a classification as Repr. 1A for development is fulfilled.

Annex 1: Rating of fertility in vivo studies

RAC's response

Noted. See reply to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	United States	<confidential>	Company-Importer	20

Comment received

We do not agree with broad classification of these substances as reproductive category 1A (page 61, CLH report) based on the weight of evidence from available human and animal data.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Recommendation_Lithium repro classification_01Oct2020.pdf

Dossier Submitter's Response

Thank you for your comment and for the annex provided.

P6 of your document, you claimed that there are eleven guideline animal studies performed on inorganic and organic lithium compounds. Not to mention the fact that references of these studies were not given, in the tables describing the results, you quoted some of these studies as Klimisch 3, which, by definition, indicate that they do not follow guidelines.
Some studies, as the one from Canolty et al. (1989) is only an abstract and cannot reasonably be used for classification purpose. In addition, these data were published later by the authors (brahim and Canolty, 1990), a study which is described in the CLH report.

Concerning studies with organic compounds containing lithium reported in your document (table 2), these substances are structurally too different from the inorganic lithium compounds. It is therefore difficult to use them for a read-across.

We disagree with your statement that significant liver and kidney toxicity is observed in dams in the OECD 416 study (Anonymous 2012). We paste below the summary of the ECHA disseminated website:
"Microscopically, higher incidence of increased cytoplasmic rarefaction was observed in the liver at 45 mg/kg bw/day dose group in males. In females, higher incidences of focal basophilic hepatocytes and hepatocellular hypertrophy were observed at 45 mg/kg bw/day. Hepatocellular hypertrophy was of minimal severity and not observed in the lower dose groups. The basophilic hepatocytes involved approximately 10 to 15 hepatocytes with focal distribution. The relation of this lesion to test item administration is not clear as only low incidences were observed with minimal severity and focal distribution.
In kidneys, higher incidences with minimal severity of dilated tubules were observed in 45 mg/kg dose groups of both males and females (11/25 and 3/25, respectively). In addition, a slightly more severe (mild) dilatation was observed also in males and females (10/25 and 13/25, respectively) Increased incidences were also observed at 15 mg/kg bw/day in males (P: 11/25, F1:6/25) and females (P: 3/25, F1:8/25)."

In our opinion, the observations in liver could even be considered as adaptive effects. Indeed, the magnitude of the liver weight increase (+ 13% relative to BW, only in males), is by itself, very borderline to be considered relevant as an adverse outcome (see Karbe et al., 2001: "*While an increase of liver weight by induced hypertrophy and hyperplasia, at least up to 20% in the absence of other liver pathology, is often regarded as non-adverse effect in rodent*"). Moreover, if we based on the successive steps proposed by Hall et al. (2012) to assess if a liver weight increase is adverse or not, in the absence of histological evidence of structural degenerative or necrotic change and the absence of biochemical data, these liver changes may very well be considered as adaptative.
For kidney, it is specified that the changes are of minimal or mild severity.
At least, these effects cannot be reasonably considered as marked systemic toxicity.
According to the guidance on application of CLP criteria:
"*Fertility effects: Adverse effects on fertility and reproductive performance seen only at dose levels causing marked systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma) are not relevant for classification purposes. There is no established relationship between fertility effects and less marked systemic toxicity. Therefore it should be assumed that effects on fertility seen at dose levels causing less marked systemic toxicity are not a secondary consequence of this toxicity. However, mating behaviour can be influenced by parental effects not directly related to reproduction (e.g. sedation, paralysis), and such effects on mating behaviour may not warrant classification*".
Therefore, at the dose levels tested in the OECD 416 study, it seems reasonable to consider that there is no marked systemic toxicity precluding a classification as reproductive toxicant. It has also to be noted that the doses tested in the OECD 416 study are consistent with those tested in the published academic studies, even if there is no data on systemic toxicity.

Also P14 of your document, you described study from Thakur et al. (2003). Regardless the apparent mistake on the doses (not 500, 800 and 1000 mg/kg/day, but **0, 500, 800, 1100 mg/kg diet for 90 days**, and not 20, 32 and 44 mg Li/kg bw/day, but **0, 20, 32, 44 mg lithium carbonate/kg bw/day**), you mentioned the absence of systemic toxicity data as a limitation of the study.
We acknowledge this point, but we would like to insist on the need to consider all adequate studies available for reaching a body of evidence assessment of fertility endpoint. This study, as others cited in the report and showing effects on fertility, used similar doses, with similar exposure time, and similar strain (if not same parameters) as the OECD 416 study where a lack or a very slight dam toxicity was observed. We therefore consider in our assessment that the concentrations tested by Thakur et al. should not lead to overtoxicity in rats.

In the conclusion, you indicate that : "*It is our opinion that classification of lithium based on limited data from pregnant women treated with lithium carbonate should not apply broadly to all lithium-containing compounds regardless of use but selectively according to product chemistry*". It is exactly what we have done in this classification proposal, restricting it to 3 lithium compounds, contrarily to your document where you used the results of different and numerous lithium organic compounds to demonstrate the lack of developmental toxicity. Moreover, the use of a chemical has not to be taken in consideration in a classification purpose.

Karbe, E., Williams, G.M., Lewis, R.W., Kimber, I., Foster, P.M.D. Distinguishing between adverse and non-adverse effects. Journal of Toxicologic Pathology. Volume 14, Issue 4, 2001, Pages 321-325
Hall, A.P., Elcombe, C.R., Foster, J.R., Harada, T., Kaufmann, W., Knippel, A., Küttler, K., Malarkey, D.E., Maronpot, R.R., Nishikawa, A., Nolte, T., Schulte, A., Strauss, V., York, M.J. Liver hypertrophy: A review of adaptive (adverse and non-adverse) changes-conclusions from the 3rd international ESTP expert workshop. Toxicologic Pathology Volume 40, Issue 7, October 2012, Pages 971-994

RAC's response

Noted. See reply to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2020	Belgium	Health and Environment Alliance (HEAL)	International NGO	21

Comment received

As regards reproductive toxicity:
- The description of the methodology is particularly clear and we welcome the transparent reporting about the strength of the various studies investigated.
- Sexual functions and fertility: We concur with the MSCA conclusion that despite the overall negative findings in the two-generation study, the findings of two other important and strong studies (the 90-day/mating study and the studies on male reproduction) clearly demonstrate effects on fertility. Therefore we fully support the proposal for a classification of the three lithium salts in category 1B for reproductive toxicity.
- Development: We agree that human data can be considered strong supportive evidence of the developmental effects of the substance and that the warning about increased malformation rates among children exposed in utero to lithium via lithium-based drugs add to such evidence. We are in favour of the proposal for classification of lithium in category 1A for development.

Based on the above, we support the proposed classification: Repr. 1A, H 360FD; May damage fertility, May damage the unborn child.

Dossier Submitter's Response

Thank you for your comment and your support.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	Belgium	<confidential>	Company-Importer	22

Comment received

Adverse effects on sexual function and fertility
SQM supports the arguments of Lithium REACH Consortium raised against the use of studies in rodents other than the guidance- and GLP-compliant two-generation study with lithium carbonate as the basis of the proposed classification for lithium compounds as adverse effects on sexual function and fertility.
Studies considered as key studies (Zarnescu and Zamfirescu, 2006 and Thakur et al.,

2003) or supportive studies (Allagui et al., 2006; Toghiani et al., 2012) do not provide enough evidence to disregard systemic toxic effects of lithium carbonate or cannot disregard that effects on reproductive organs are not a secondary non-specific consequence of other toxic effects. In addition, both the registration dossier and the CLH report are coincident that the study Anonymous, 2012 is a robust study compliant with OECD guideline and GLP that at highest dose level produced an adequate degree of systemic toxicity (LOAL 45 mg/kg bw/day. Consequently, this two-generation study should be considered as the pivotal study for the classification and labelling of lithium compounds for effects on fertility, and Lithium carbonate, Lithium hydroxide and Lithium chloride should not be classified as Reproductive toxicant for fertility.

Adverse effects on development:
According to the CLH report, studies in animals do not provide clear evidence of developmental toxicity due to gestational lithium exposure, consequently Lithium carbonate, Lithium hydroxide and Lithium chloride should not be classified as Reproductive toxicant for development Category 1B.
In human, the CLH report states altogether, available epidemiological studies are contradictory, and most of them do not fulfil todays requirements (insufficient number of patients, deficiencies in exposure estimate). If there is some evidence in humans on adverse effects on development, that is still not clear, it is not sufficiently convincing to place the substance in Category 1A.
As argument for classification, the CLH report states "Considering also drug labels recommended discontinuation of treatment until the 9th week of amenorrhea, evidence is considered sufficient to recommend a classification in category 1A." We disagree with this statement, since labeling can be used as Precautionary Principle in case of Suspected human reproductive toxicant, but it cannot be considered as clear evidence or criteria for classification in category 1A under CLP. Consequently, Lithium carbonate, Lithium hydroxide and Lithium chloride should not be classified as Reproductive toxicant for development Category 1.

Dossier Submitter's Response

Adverse effects on sexual function and fertility
Please see responses to comments 8, 19, and 20.
Moreover, concerning the use of studies other than those performed according to the guidelines, eMSCA would like to quote the ECHA guidance on the application of CLP criteria: "*Appropriate classification will always depend on an integrated assessment of all available data and their interrelationship using a weight of evidence approach. Individual datasets should be analysed case by case using expert judgment*."

Adverse effects on development:
Please see response to comment 16.
Concerning drug labels, please refer to response to comment 19. Moreover, we would like to make clearer the reference to drug labels. It is obviously not used as a classification criteria by itself. However, it seemed important to mention this element in the report which, to our understanding, reinforces the proposal.

RAC's response

Noted. See reply to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Germany	FUCHS Schmierstoffe GmbH	Company-Manufacturer	23

Comment received

Comments on Category 1A for Developmental Effects
Human data detailed in the CLH report centred on two review documents (Yacobi and Ornoy, 2008; McKnight et al., 2012) which showed only weak associations of lithium treatment with a small risk of cardiovascular defects in the foetus. Cardiovascular malformation was identified as a potential hazard in a large cohort study conducted between 2000 and 2010 (Patorno et al., 2017) in which pharmaceutical lithium exposure during the first trimester of pregnancy was confirmed in 663 women who formed the basis of the assessment. However, although still of reasonable concern, in a manuscript addressing lithium carbonate and lithium chloride by Andrews et al., 2019, written by representatives from the US-FDA, Health Canada, Brazil-ANVISA, Netherlands-CBG-MEB and a number of global pharmaceutical companies, lithium was not added to the "known" human teratogen list because the human data was inconsistent and effects were lacking in the animal model.
A significant body of animal studies, predominantly in the rat, but also in pigs and mice, examining the potential for developmental effects revealed no consistent increased incidence of foetal malformations or anomalies at doses of lithium, in the form of lithium carbonate, ranging from approximately 2 – 90 mg Li/kg bw/day. In many studies, dose levels of approximately ≥15 mg Li/kg bw/day were associated with various forms of severe maternal toxicity. Hence, experimental animal studies do not support the plausibility of a causal relationship.
Comments on Category 1B for Reproductive Effects (male fertility)
There is weak scientific justification for which all lithium substances are proposed to be reproductive toxicants in animals. The regulatory GLP Two-Generation Reproduction Toxicity Study should be considered as the "key study" with a Klimisch 1 score for the basis of interpretation; this study showed no evidence of reproductive toxicity. Instead, the proposal is heavily based on a non-GLP study by Thakur et al., 2003, assigned a Klimisch 1 score. We strongly disagree and believe this study should be given a Klimisch 3 score because all remaining male fertility studies of this quality were assigned Klimisch 3. The referenced study should not be considered a "key study" for the following reasons:
• There are no results for systemic toxicity (i.e., clinical observations, body weight, food consumption and reproductive laparotomy parameters) for the rats. This makes interpretation of the data speculative. Lithium is a very light element (Mr = 6.9), and is only present in biological systems as the cation Li+, which implies that apparently small doses represent a relatively large electrolyte concentration: 0.3 g Li+ is equivalent to 1.0 g Na+. From the data given, it can easily be deducted that quite severe paternal toxicity was present in the mid and high dose; and therefore, the effects observed were not specific to lithium carbonate at all, but were due to general toxicity.
• There is questionable significance of the organ weights. The authors showed statistical significance of absolute organ weights, which can be highly variable; however, % relative to body weight was not significant. For example, although body weights were not reported, from the absolute testis weights, which were reduced by 19% and 37% compared to control in the mid and high dose group, the relative testis weight was not statistically significantly altered. Hence, the changes in organ weights were due to

significantly reduced body weights in the mid and high dose group.
• Lack of knowledge of the physiological differences that contribute to interspecies variation between man and animals can prevent the effective application of animal data to the assessment of human reproductive hazard/risk. The measurement of rat sperm parameters can be an insensitive indicator of reproductive function because of high sample-to-sample variability, high number of sperm in rodents, and should be used in a weight of evidence. For instance, fecundity index % = pregnant females/mated females (positive presence of sperm in vagina) x 100 should be the major adverse indicator but it was not calculated, nor was laparotomy data included to calculate whether male fertility index included pregnancies with total litter resorptions. Male fertility index (%) = (no. of males that became sire (i.e. produce a litter)/no. of males placed with females [cohabitation]) × 100.

In addition, there is a small number of animal studies, predominantly in the rat, in which effects on sperm production and viability together with testicular function, pathology and steroidogenic activity have been investigated. In these studies doses of lithium, mainly in the form of lithium carbonate, have ranged from approximately 2 – 8 mg Li/kg bw/day. Only three small studies have been reported in humans where there has been an attempt at assessing potential effects on male fertility and none of these can be considered conclusive. Some reports on men who were treated with lithium found reduced sperm quality and sperm movement, while others have not. One of these reports found no evidence that fertility is reduced. Therefore, it is considered that the human health data is inconsistent for lithium effects on male fertility and does not support rodent data from Klimisch 3 quality studies.

Dossier Submitter's Response

Thank you for your comment.

Comments on Category 1A for Developmental Effects
Unfortunately, even if it seems of great interest, without the reference, we were unable to find the manuscript addressing lithium carbonate and lithium chloride by Andrews et al., 2019 you mentioned in your comment. We therefore cannot comment on this point. Concerning the point raised on animal studies, please refer to responses of previous comments.

Comments on Category 1B for Reproductive Effects (male fertility)
Concerning the study of Thakur et al. (2003), as already mentioned earlier, we provided in an annex a complete ToxRTool excel file to justify the Klimisch score of 1 assigned.

- As detailed in response to comment 8, we consider very unlikely a marked systemic toxicity, as the doses used and the duration of exposure are highly similar to the OECD 416 study.
- Concerning the point on testis weight change: Not to mentioned the other effects of lithium on testosterone, sperm number, sperm production, the Guidance Document On Mammalian Reproductive Toxicity Testing And Assessment of OECD clearly highlight the importance of absolute weight in male reproductive organ assessment ("*Both absolute and relative weights of the male reproductive organs should be considered as a decrease in absolute weight may occur and may not necessarily be related to a reduction in body weight gain. However, care should be taken in interpreting data where a substantial bodyweight effect is evident. Since there is low inter-animal variability in testis weight, a significant change in absolute testis weight (increase or decrease) can indicate an adverse effect*").

- The effect of lithium on sperm parameters is very consistent between studies. Also, effect on level of several hormones (testosterone, LH, FSH), histological observations, and dose dependent decrease of male fertility index were observed. These elements can be considered as body of evidence.

We agree that data on human are sparse and not sufficient to propose a classification as Repr. 1A. However, due to there inadequate quality, they cannot be used to dismiss evidence from animal studies.

Annex 1: Rating of fertility in vivo studies
OECD Environment, Health and Safety Publications. Series on Testing and Assessment No. 43. Guidance Document On Mammalian Reproductive Toxicity Testing And Assessment. Paris, 2008.

RAC's response

Noted. See reply to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	France	Eramet	Company-Manufacturer	24

Comment received

About reproductive toxicity (adverse effects on development):

ANSES wrote p.57 of the CLP report :"Data on animals are inconclusive, due to the heterogeneity of results and the overall quality of the dataset. …"

The dataset collected in the report is the cause of this heterogeneity. The key study of 2010 (Klimmich 1-level) and an others studies of 2012 (Klimmich 2-level) show no evidence of cardiac malformations in animals after exposure to lithium compounds. However, they are compared with studies carried out more than 30 years ago without compliance with OECD standards. (Marathe and Thomas, 1986; Kelley and al., 1978; Fritz, 1988)

It therefore, seems more conclusive to write, as mentioned a few lines below in P.57, that there is no cardiac malformation observed in the animal.: « Moreover, the observations on some studies are not in line with the findings from human studies (no increase of cardiac malformation seen in animals studies), …"

Moreover, the second part of this sentence should be more fully developed, the differences in results between human and animal is very quickly addressed, and the important difference between the two cases studied is not mentioned. Indeed, the animals studied are healthy, they do not suffer from neurological disorders that require medical treatment. "…which can be explained by a difference in mechanism of action between rodents and human. However, human data, and particularly the homogeneity of recent robust human studies are considered sufficient by themselves to give evidence of developmental effect of lithium.

Finally, there is no homogeneity in the conclusions of the three studies cited in the report. The report cites : « In recent publications, a more precise pattern of the effects of lithium on development seems to emerge: authors from reviews (Yacobi et al., 2008), meta-analysis (McKnight et al., 2012) or
cohort study (Patorno et al., 2017) lead to very similar conclusions, i.e.,"

While the last study concluded that there was an association between maternal exposure to lithium and cardiac malformation, the other two studies did not find an association and concluded that there was uncertainty about the causal link.

Conclusion of the article from Yacobi et al., 2008 : "…Reviewing the data accumulated until today
regarding lithium exposure and cardiovascular anomalies, including Ebstein's anomaly, it is to be
concluded that the risk is much lower than previously thought". And the authors also assumed that the rate of cardiac anomalies from lithium registry seems to be due to the fact that some cases were reported in several publications.

Conclusion of the article from McKnight et al., 2012 :"… The risk of congenital malformations is uncertain; the balance of risks should be considered before lithium is withdrawn during pregnancy. Because of the consistent finding of a high prevalence of hyperparathyroidism, calcium concentrations should be checked before and during treatment."

In fine, ANSES wrote p.58 of the report : "the evidence that lithium is teratogenic is quite weak, and the findings showed that the risk has been previously over-estimated".

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on ANSES CLP proposal about Lithium compounds.pdf

Dossier Submitter's Response
Thank you for your comment. Please see response to comment 16
RAC's response
Noted. See reply to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
02.10.2020	Belgium	Lithium REACH Consortium	Industry or trade association	25

Comment received

Reproductive toxicity
Chapter 10.10.1 Adverse effects on sexual function and fertility and 10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility.
Summary of the comments and discussion on the reproductive toxicity evaluation. For detailed comments on the publications quoted in the CLH proposal, see attached Annex 2, "comments on Chapter 10-10-1.pdf". This document also contains the respective additional references.
The two-generation study in Wistar rats with Lithium carbonate was the only study conducted under GLP and fully covering the systemic toxicity, reproductive function and fetal outcome. It was preceded by a 28-day dose range finding study to optimize the dose selection that could be tolerated in the two-generation study for at least 70 days dosing. Paternal and maternal toxicity were demonstrated by increase of food intake in males and

females, net weight gain, increased water intake (up to 40%) in males compared to control and morphological changes in main target organs liver and kidneys. Lithium carbonate was tolerated during the full study and did not lead to excessive toxicity nor mortality during this study. It is known that the therapeutic window of Lithium is small, and that at higher doses the animals quickly come in bad condition (deteriorate) with decreased food and water consumption and decreased body weights, after which they may die. This was observed in the dose range finding study and also in other studies in literature.
The other studies (publications) that investigated the reproductive toxicity in rats and mice had many deficiencies. They were not conducted under GLP and were mostly incomplete, in particular with regard to systemic toxic effects/and or nutritional status. Some studies investigated the animals under conditions of overdosing. In laboratory rodents, conditions of overdosing are characterized by an apparently stable condition where they eat and drink enough to maintain their reduced weight and they behave like normal rats. After 2 to 4 weeks, they can abruptly become ill, show further weight loss and die (Trautner et al., 1958). The animals may also develop a diabetes insipidus status, further resulting in many secondary findings (Allagui et al., 2006). At these excessive conditions the rodent model cannot be used to predict reproductive toxicity in humans. Most of the publications do not report the typical parameters that are needed to follow-up the animal's condition and that are mandatory to be reported in guideline-compliant studies, i.e. clinical observations, weekly body weights and food consumption and most importantly water consumption data are missing. Some of them provide histological analysis, but only for the gonadal organs, whereas target organs such as liver and kidney are not investigated to assess the level of toxicity.
It is known that in rats food restriction can be associated with testicular degeneration and atrophy of epididymis, seminal vesicles and prostate and changes in testosterone levels (Greaves, 2008); the same applies for a decreased cyclicity in females.
- Laboratory animals developed testicular atrophy spontaneously, with incidences of 2.5% in oral studies and 9.4% in inhalation studies in Sprague-Dawley rats; the higher incidence in inhalation studies was ascribed to the stress associated with the restraint of the animals (Lee et al., 1993). Dietary restriction (25% of ad libitum-fed controls) of Sprague-Dawley rats for 2 weeks was associated with mild testicular degeneration (Levin et al., 1993). This underlines the care needed in the assessment of testicular changes in rodents, as food restriction or reduced food intake and reduced body weights can confound the results during toxicological studies.
- Dietary alterations have also been shown to produce prostatic changes in rats; both 4 and 18 months old Long-Evans rats fed a protein-free diet for 20 days developed relatively little change in testicular weight but the weights of the prostate gland and seminal vesicles showed significant reduction in association with reduced testosterone levels (Esashi et al., 1982). Other studies have shown similar reductions in the weights of prostate glands and seminal vesicles of rats following food restriction (Duffy et al., 2001; Howland, 1975).
- Food restriction (10% reduction) was studied versus a control group in male pubertal 23-day-old rats (12/group) up to 45, 49, 52, 56, or 59 days of age. Despite a 10% body weight differential, pubertal onset was not significantly delayed and testes weights were conserved at this young age. Absolute prostate, ventral prostate, seminal vesicles, epididymides, and liver weights were decreased by food restriction. Relative weights for the prostate, ventral prostate, and seminal vesicles were similar to controls, but relative epididymides and liver weights exhibited changes. The confounding effects of body weight on some endpoints are described by Marty et al., 2003.
- Dietary deficiency and decrease in essential amino acids is known to induce cessation of

the rat estrous cycle (Narita et al., 2011). Ovulatory cyclicity was monitored by daily cytological evaluations of vaginal smears after continuous feeding of the deficient diet (in threonine, lysine, tryptophan, methionine or valine), a persistent diestrus or anovulatory state was induced most quickly by the valine-deficient diet and most slowly by the lysine-deficient diet. These disturbances of the estrous cycle by amino acid deficiency were quickly reversed by the consumption of a normal diet. The continuous anovulatory state in this study is not attributable to a decrease in caloric intake but to an imbalance in the dietary amino acid composition. With a shortage of well-balanced amino acid sources, reproduction becomes risky for both the mother and the fetus.

In the CLH report, numerous studies were used that only focused on the effect of lithium (carbonate or chloride) on male or female reproductive tracts, but that did not study the systemic (maternal/paternal) toxicity. In these studies, animals were either overdosed with clear signs of systemic toxicity (mortality, kidney toxicity) or they were dosed at lower levels without investigating the signs of systemic toxicity (body weight, food consumption, water consumption, haematology and clinical chemistry, urinalysis, gross pathology, organ weights, histopathology of target organs). The studies do not allow an interpretation as to whether the reproductive findings were related to the given substance, or rather secondary to the food intake reduction, body weight loss, massive changes in water intake or kidney toxicity. Often fixed concentrations of lithium were given in the diet but due to the higher intake during the first weeks, animals were overdosed. The conditions of these studies were mostly not under control. All studies have been separately investigated and commented in detail in the table attached as Annex 2, "comments on Chapter 10-10-1.pdf".

Further in the CLH report, other studies were used where rodents were exposed via subcutaneous and intraperitoneal route. (Chapter 10.10.2, p. 35 to 39). They were considered by ANSES with 'less relevance', but still the information was used in the overall assessment. It must be noted that these studies were performed under even more extreme conditions which are not relevant for humans. The studies also did not provide the parameters to assess systemic toxicity, and the impact of the injection procedure is questionable, as it will bypass the liver and may have an immediate local effect on gonads. In other studies, ovariectomy was applied, or hormones were supplied, which are drastic experimental conditions that may further influence the animals' condition and the results. Detailed comments are provided to these studies in Annex 2 "comments on Chapter 10-10-1.pdf".
In conclusion, the studies used from literature were often incomplete to assess the confounding effect of maternal/paternal systemic toxicity and its influence on the reproductive system. The reported effects on the reproductive system are most likely not directly due to Lithium carbonate (or chloride) but rather secondary to excessive toxicity or extreme study conditions. The results need to be interpreted with care, and they cannot be used as 'clear' evidence.
The guideline conform 2-generation study should instead be used as the pivotal study for classification. No classification for fertility should be concluded based on this high quality key study.
Page 31, Table 20: Anonymous 2012
The last sentence states that no detailed sperm parameters were given in the two generation study. This is incorrect as the sperm parameters were reported in the study report that was shared with ANSES by the REACH Lithium consortium. We have summarized the findings in the detailed comments document provided Annex 2, "comments on Chapter 10-10-1.pdf".

Chapter 10.10.3 Comparison with CLP criteria, Conclusions
Based on the arguments above we do not agree with the conclusions of the report to disregard the guideline conforming pivotal 2-generation study in rats. The claimed consistency of published information is biased by the selection of the studies for evaluation (e.g. results in literature studies with limitations but supporting the results of the guideline compliant study were considered Klimisch 3 and not taken into account whereas studies with other results but similar or even more limitations were evaluated as relevant and robust (Klimisch 1 or 2) see also annex 1) and neglected possible secondary effects due to systemic toxicity as outlined above and in our detailed comments. We therefore propose to not classify the three Lithium compounds for sexual function and fertility effects based on the absence of such effects in the pivotal 2-generation study.

Chapter 10.10.4 Adverse effects on development
Summary of the comments and discussion on the reproductive toxicity evaluation. For detailed comments on the publications quoted in the CLH proposal, see attached Annex 3 "comments on Chapter 10-10-4.pdf". This document also contains the respective additional references.
Comments on the animal studies summarized in Table 22, p. 42 to 47 Summary table of animal studies on adverse effects on development:
The prenatal development toxicity study in Wistar rats with Lithium carbonate (anonymous, 2010) was the only study conducted under GLP and fully covering the dose response (including toxic doses) and toxicokinetics (demonstrating the proportional increases in serum levels from 0.5-1.0 mEq Lithium/L). It was preceded by a dose range finding study in pregnant rats at doses up to 200 mg/kg bw (the latter dose showing mortality) to optimize the dose selection that could be tolerated in the main prenatal developmental toxicity study. In the main study, maternal toxicity was demonstrated at the highest tested dose of 90 mg/kg bw/day by pilo-erection in four dams and visually increased drinking water intake, statistically significant decreased net weight gain and decreased food consumption periodically during gestation. In conclusion, the developmental NOEL was above 90 mg/kg bw/day and the maternal NOEL was 30 mg/kg bw/day. It is known that the therapeutic window of Lithium is small, and that at higher doses the animals quickly deteriorate with decreased food and water consumption and decreased body weights, after which they may die. In the dose range finding study for the developmental toxicity in Crl:CD(SD) rats dosed by oral gavage (Hansen, 2010), the highest dose of 200 mg/kg bw/day was clearly of excessive toxicity, as demonstrated by mortality and other severe toxicity signs.
Most of the other studies (publications) quoted in Table 22 that investigated the developmental toxicity in rats and mice had many deficiencies. They were not conducted under GLP and were mostly incomplete regarding investigation and reporting of maternal toxicity parameters; others investigated the animals under conditions of overdosing. In laboratory rodents, conditions of overdosing are characterized by an apparently stable condition where they eat and drink enough to maintain their reduced weight and they behave like normal rats. After 2 to 4 weeks, they can abruptly become ill, show further weight loss and die (Trautner et al., 1958). Under these excessive conditions the rodent model cannot be used to predict developmental toxicity in humans. Many or most of the publications do not report the typical parameters that are needed to follow-up the animal conditions and are mandatory to be reported in guideline-compliant studies, i.e. clinical observations, weekly body weights and food consumption and most importantly water consumption data are missing.
Pregnant animals demonstrate a substantial increase in body weight and food/water consumption during the gestation and subsequent lactation period. Either dosing in the

diet, via oral gavage and via the drinking water will result in proportional increased doses of the test substance. The dose schedule therefore needs to be carefully selected and adapted during the various phases of gestation and lactation. Follow-up of the dams is also very important to avoid overdosing. In absence of this maternal monitoring, pups may be more vulnerable to the influence of the maternal toxicity.

Under these extreme conditions of dosing, following effects may also appear:
- Incomplete ossification or reduced ossification is one of the most common findings in developmental toxicity studies. Both minor delays in ossification and wavy ribs seem to be readily repairable via postnatal skeletal remodeling, are not mechanistically linked to malformation, and often are seen in the presence of maternal toxicity. Fetal ossification is highly dependent on maternal nutritional status and utero-placental blood flow. Bones formed via endochondral ossification include the skull, the vertebral column, pectoral and pelvic regions and long bones of the extremities. In both animals and humans, skeletal development continues postnatally and includes the formation of secondary ossification centers in many bones until closure of the suture lines between skull bones on reaching adulthood. The timing and sequence of skeletal ossification is slightly different in humans, as compared with animals. One of the difficulties in extrapolating animal data on skeletal ossification to humans is that animal studies almost always evaluate skeletal maturation in term fetuses, whereas human skeletal development is usually assessed postnatally (Carney & Kimmel, 2007).
- Mice are particularly very sensitive to stress. Mice are notorious for spontaneously developing cleft palate, and the question of the biological significance of increased incidences in mice was raised (Chernoff et al., 1990). Thus the tendency of mice to exhibit cleft palate for a variety of reasons unrelated to treatment can potentially compromise the utility of the mouse (Barrow, 2013: p 279). The findings of cleft palate in mice (Szabo 1979, Loevy and Catchpole 1973) reported in the CHL report on p. 46, 53 and 57 must be interpreted taking into account this information. The CLH report considers this fact in the comments to the respective study, but in the overall assessment the effect is considered relevant at high systemic doses. This seems to be a contradiction.

In the CLH report, numerous studies were used that only focused on the foetal effect of lithium (carbonate or chloride) but that did not study the systemic (maternal) toxicity. In these studies, animals were either overdosed with clear signs of systemic toxicity (mortality, kidney toxicity) or they were dosed at lower levels without investigating the signs of systemic toxicity (body weight, food consumption, water consumption, haematology and clinical chemistry, urinalysis, gross pathology, organ weights, histopathology of target organs). The studies were insufficient to make a correct interpretation whether the developmental findings were either related to the given substance, or rather to the food intake reduction, body weight loss, massive changes in water intake, or kidney toxicity. In particular, there was one study in rats where dilatation of renal pelvis with obsolete or missing papillae was observed in the fetuses at maternal dose of 100 mg Li carbonate/kg bw/day, however this was clearly maternally toxic and also lethal in fetuses (half of the pups died). The fetal renal findings were not observed at 60 mg Li carbonate/kg bw/day, therefore this effect was clearly threshold related and only seen at high maternally toxic doses as a direct toxic target organ effect.

The CLH report disregarded some other studies that confirmed the GLP prenatal developmental toxicity study. They were considered by ANSES with 'less relevance'.
The study of Ibrahim and Canolty, 1990 (p. 43 CLH report) used only one dose level and was conducted to an older standard and reported with limited details, but the dose level

of 1000 ppm in the diet calculated as > 76 mg Li carbonate/kg bw/day was clearly maternally toxic and led to unspecific effects on body weight and organ weights in the offspring that are expected at the high maternal dose levels and most likely secondary to maternal toxicity including limited maternal care during lactation.
The study of Gralla and McIlhenny (1972) also has some deficiencies, but is generally well reported and confirmed that no malformations were observed up to toxic dose levels of 150, 50 and 50 mg/kg bw/day, respectively rats, monkeys, rabbits.
In addition, the also available guideline-compliant 2-generation study in rats (Klimisch 1 according to both the authors of the report and the registrant) did not indicate any developmental toxic effects at maternal toxic doses.
In conclusion, the studies used from literature were often incomplete to assess the confounding effect of maternal systemic toxicity and its influence on the foetal development. The effects observed in the foetuses are most likely secondary to excessive toxicity or extreme study conditions. The CLH report states for some studies that they cannot be used as 'clear' evidence, however other studies are used in the CLH report as 'sufficient information', such as kidney effects in the offspring at excessive maternal toxic doses, an effect regarded as 'substance-related', and investigations in mice pointing to neurotoxic effects and induction of cleft palate of gestational lithium exposure. These effects are both observed under extreme conditions or in a model which is not appropriate.
Detailed comments to the studies mentioned in the report including Chapter 10.10.5 p. 52 to 54 are provided in the attached Annex 3 "comments on Chapter 10-10-4.pdf".

Conclusion on animal data
The pivotal key studies performed according to OECD guidelines and GLP, a prenatal developmental study (OECD 414) and the 2-generation study in rats (OECD 416) did not show any indications of developmental toxicity that would lead to a classification. The literature studies quoted by the CLH report in support of a classification are all confounded by massive maternal toxicity or conditions, like excessively changed food and water intake and the effects reported are most likely secondary to maternal toxicity or those conditions as outlined in detail in Annex 3. Therefore these publications should not be used as a basis for classification in the presence of valid and well reported guideline studies not showing an effect.

Human data:
Detailed comments are provided in the attached Annex 3 "comments on Chapter 10-10-4.pdf".
The availability of human data in the CLH report are originating from the pharmaceutical therapeutic use of mainly Lithium carbonate in the treatment of bipolar disorders at relatively high dose levels. In the years 1960 and 1970 some case reports on a rare cardiac malformation Ebstein's anomaly and other related defects were reported in the medical literature in patients with bipolar disorders receiving Lithium treatment. Many countries set up so called Lithium Baby registers to follow up on these reports.
This means that these patients were and are surveyed closely and medical decisions consider a possible side effect in a precautionary approach. It also means that such defects are likely to be better detected in such patients than under normal circumstances creating a kind of reporting bias. It should be mentioned, that this malformation is rare, but was also observed in cases where Lithium exposure can clearly be excluded.
The collected data were used in several publications to further study a possible association. Interestingly, more recent studies (meta-analysis) based on large levels of data find in many cases weaker or no associations and some also find similar incidences

in patients with bipolar disorders that did not receive lithium treatment during pregnancy. As frequently those studies have only limited possibilities to control for other confounding factors especially if the underlying data are rather old.
Despite the surveillance of pregnant women and their children since the seventy years when the first cases were reported, there is still doubt about the causal relationship between lithium exposure and the effects observed. This becomes also clear from the CLH report, as it is is concluded that the human data, and particularly the homogeneity of recent robust human studies are considered sufficient by themselves to give evidence of a developmental effect of lithium, but it is unclear what evidence this statement is based on, or what the developmental effect is.
This indicates in our opinion that sufficient evidence, in particular for classification and labelling purposes as category 1A developmental toxic is not provided by these data.
It remains to be discussed if any effects observed under the conditions on associations of disease without/or with treatment relationship should be used as a basis for classification for industrial uses of substances in completely different circumstance in particular with the lack of findings in guideline compliant animal studies. These possible effects are taken care of in the pharmaceutical regulations and considerations where there may or may not be a link with the treatment.
For Lithium hydroxide it should also be considered that its intrinsic corrosive property prevents a systemic uptake of doses that would come close to a therapeutic dose range from the pharmaceutical applications of Lithium carbonate.

10.10.6 Comparison with CLP criteria
We cannot follow the rational in the CLH report outlining the contradictory human data and yet concluding they should be sufficient for classification into category 1A. As outlined above the robust animal data, which in our opinion should be used for the classification decision do not point to a classifiable hazard for developmental toxicity.
Based on the available high quality animal data and a very particular, yet contradictory epidemiology and human data base from therapeutical use, we are of the opinion that Lithium carbonate, lithium chloride and lithium hydroxide should not be classified for developmental toxicity under CLH.

References
Allagui MS, Hfaiedh N, Vincent C, et al. Changes in growth rate and thyroid- and sex-hormones blood levels in rats under sub-chronic lithium treatment. Human & Experimental Toxicology. 2006;25(5):243-250. doi:10.1191/0960327106ht620oa
Carney EW & Kimmel CA. Interpretation of Skeletal Variations for Human Risk Assessment: Delayed Ossification and Wavy Ribs. Birth Defects Research (Part B) 80:473–496 (2007).
Duffy PH, Seng JELewis SM, Mayhugh MA, Aidoo A, Hattan DG, Casciano DA and Feuers RJ. The effects of different levels of dietary restriction on aging and survival in the Sprague-Dawley rat: Implications for chronic studies. Aging Clin. Exp. Res. 13: 263-272, 2001.
Esashi T, Suzue R and Laethem JH. Influence of dietary protien depletion and repletion on sex organ weight of male rats in relation to age. Journal of Nutritional Science and Vitaminology 28, 163-172, 1982.
Gralla EJ & McIlhenny HM. Studies in Pregnant Rats, Rabbits and Monkeys with Lithium Carbonate. TOXICOLOGY AND APPLIED PHARMACOLOGY 21, 428-433 (1972).
Greaves P. Histopathology of preclinical toxicity studies. Chapter 11. Male genital tract./ Chapter 12. Female genital tract. Third edition, Elsevier 2008.
Ibrahim HS & Canolty NL. Effects of dietary lithium on pregnant and lactating rats and

their progeny. [1990] NUTRITION RESEARCH, Vol. 10, pp. 315-324,1990.
Lee KP, Frame SR, Sykes GP et al. Testicular degeration and spermatid retention in houng male rats. Toxicologic Pathology 21, 292-302 (1993).
Levin S, Semler D and Rubin Z. Effects of two weeks fo feed restriction on some common toxicological parameters in Sprague-Dawyley rats. Toxicologic Pathology 21, 1-14 (1993).
Marty MS, Johnson KA, and Carney EW. Effect of Feed Restriction on Hershberger and Pubertal Male Assay Endpoints. Birth Defects Research (Part B) 68:363–374 (2003).
Narita K, Nagao K, Bannai M, Ichimaru T, Nakano S, et al. (2011) Dietary Deficiency of Essential Amino Acids Rapidly Induces Cessation of the Rat Estrous Cycle. PLoS ONE 6(11): e28136. doi:10.1371/journal.pone.0028136
Trautner EM, Pennycuik PR, Morris RJH, Gershon S, Shankly KH. The effects of prolonged sub-toxic lithium ingestion on pregnancy in rats. Australian Journal of Experimental Biology and Medical Science 1958 Vol.36 pp.305-321.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2020-10-02Lithium REACH consortium comments on the CLH report for Li salts Annexes.zip

Dossier Submitter's Response

Reproductive toxicity

Regarding the two-generation study, we do not agree to consider the increase food intake and net weight gain as toxic effect of lithium. However, we are glad to see that we agree on the fact that lithium was well tolerated during the entire study, and not lead to excessive toxicity. Therefore, the toxicity in the 2-generation study is considered negligible in a fertility toxicology assessment framework, as we explained in a previous response.

Concerning the doses used in the other publications, you mentioned conditions of overdosing. As already detailed in previous responses (see in particular response to comment 8), doses used for numerous of publications are very similar to the one used in the OECD compliant study (416). Therefore, even if systemic or general toxicity was not reported, no significant toxicity is expected based on the results from the 2 generation study. Moreover, you mentioned that "*Either dosing in the diet, via oral gavage and via the drinking water will result in proportional increased doses of the test substance*". We have to admit that, even if via drinking water or diet dose have to be carefully monitored, via gavage, we do not see how it could result in increased doses of the substance. Our conclusions are therefore based on a body of evidence of the entire dataset, where many studies show consistent reproductive toxicity at doses inducing negligible general toxicity.

Concerning the Allagui et al. (2006) study, we acknowledge the overdosing situation and we have in fact revised our judgment on the Klimisch score from Klimisch 2 to Klimisch 3 (please refer to the annex with our cotation of study using the ToxRTool software).

We don't call into question the fact that a food restriction can have an impact on fertility parameters/organs, a condition which is not demonstrated in the studies presented in the report.

Concerning the claim that the conditions of studies presented in the report were mostly not under control due to exposure via the diet, we would like to cite for instance the study

of Zarnescu and Zamfirescu, 2006, were animals were exposed by gavage, as the OECD studies, at a concentration of 35 mg/kg BW, i.e. less that the OECD studies (same strain, shorter duration of exposure). We could also cited studies from Toghyani (2012, 2013).

Concerning studies performed with other routes of exposure, we obviously agree that they do not provided the same level of information that studies by oral route. However, some of them are informative on mechanistic aspects for instance and deserve to be included in the CLH report (particularly studies on avariectomised rats or with hormones supply).

We would like to recognize a mistake in the table 20 p33 of the report where we stated that no sperm parameters were given in the two-generation study. In fact, study report was only obtained after the submission of the dossier to ECHA for accordance check. When we resubmitted it for public consultation, we forgot to delete this sentence. Sperm count was only performed at the hightest dose on 10 animals. This being said, considering the wording of the OECD guideline ("*If treatment-related effects are observed or when there is evidence from other studies of possible effects on spermatogenesis, sperm evaluation should be conducted in all males in each dose group*") we are of the opinion that a sperm count for every dose group should have been performed regarding the results of previous published litterature.
Finally, we would like to reaffirm that the guideline two-generation study was not disregarded as you mentioned, but took into account and balanced with other data in a body of evidence approach.

Adverse effects on development
Concerning the animal studies quality, please refer to the ToxRTool files provided in addition to our responses. Particularly concerning the study of Gralla and McIlhenny, 1972, we disagree with the fact that "*is generally well reported*", as this study provided very few details.
Concerning the used of animal studies, we would like to reiterate that the basis for developmental classification is human data as the proposal is 1A. Robust human data is available and must be taken into account in priority for classification against experimental data which, as you noted, are associated with methodological deficiencies and unconsistency.
Concerninng the relevance of human data, and particularly the follow-up of pregnancies of women under lithium, please see responses to comments 1 and 16. We also note that you do not try to explain in your comment the rather robust results of the recent study from Patorno et al. (2017), were a dose response is highlighted and confounders were taken into account.

Annex 1: Rating of fertility in vivo studies

RAC's response

Noted. See reply to comment No. 1.

Date	Country	Organisation	Type of Organisation	Comment number
01.10.2020	Netherlands		MemberState	26

Comment received

Sexual function and fertility
The NL-CA agrees with the proposed Repr. 1B (H360F) classification for adverse effect on

sexual function and fertility. The data of the only GLP- and guideline-compliant (OECD 416) rat study available with lithium carbonate showed slight but significant reductions in maternal net weight and food intake. However, no effects on reproductive function, weight and histopathology of reproductive organs or sperm parameter were observed up to the highest dose tested (45 mg/kg bw/day). Other key studies, although not conducted according to OECD guidelines or GLP-compliant, found effects on the male reproductive tract. One 90-day study (with only males exposed prior to mating) reported a dose dependent reduced male fertility index at 32 and 44 mg lithium carbonate/kg bw/day in addition to dose-dependent effects on various sperm parameters (noticing that dose levels are similar to those applied in the OECD 416 study with only minimal parental toxicity and no reproductive toxicity at all) (Thakur 2003). In line with this, rats treated with 35 mg lithium carbonate/kg bw/day demonstrated abnormal or degenerated spermatids and structural abnormalities (Zarnescu 2006). Other experimental studies included in the dossier report consistent effects on sperm number/production, sperm function, and/or male reproductive organ structure, but also on testosterone levels. Human data is limited, however the observations on sperm parameters, morphological changes of the reproductive organs and effects on male fertility index observed in rats can be regarded as relevant for the human situation. All things considered, and despite the negative findings in the OECD 416 study, we support the Dossier Submitters conclusion that lithium carbonate, lithium chloride and lithium hydroxide fulfill the requirements for classification as Repr. 1B (H360F).

Developmental toxicity
The NL-CA agrees with the proposed Repr. 1A (H360D) classification for adverse effect on development. The data of the OECD 414 rat study showed slight maternal toxicity (pilo-erection, reduced net body weight and food intake) at the highest dose (90 mg lithium carbonate/kg bw/day). However, no fetal developmental effects were observed. Other rat developmental toxicity studies, not conducted according to OECD guidelines or GLP-compliant, indicate that lithium may induce developmental toxicity, including malformations. However, these studies are of limited quality and data on maternal toxicity is often not (fully) reported, which impedes the interpretation of these studies. We agree with the Dossier submitter that the animal data are inconclusive with respect to outcome and limited with respect to design (for example maternal toxicity not investigated in all studies), thereby hampering a proper interpretation of the results and, thus overall, the animal data do not present clear evidence for an adverse effects on development.
Regarding the human data, there is some considerable discrepancy between the findings but also differences in the quality of the studies. Two review studies found weak evidence for developmental lithium toxicity and both concluded that the risk was lower than previously thought (Yacobi and Ornoy 2008; McKnight 2012). A more recent cohort study identified a dose-dependent correlation between lithium exposure early in pregnancy and cardiac malformation in the child (Patorno 2017). A recent meta-analysis of 6 cohorts associated lithium exposure during the first trimester with an increased risk of major malformations but not of cardiac malformations (Munk-Olsen 2018). The shortcomings in study design of other studies are noted.
In conclusion, experimental data on developmental toxicity of lithium is inconclusive. However, recent human data provide sufficient evidence to suspect developmental effects upon lithium exposure. We support the Dossier Submitters conclusion that lithium carbonate, lithium chloride and lithium hydroxide fulfill the requirements for classification as Repr. 1A (H360D).

Effects on/via lactation Experimental studies on toxicological effects of lithium carbonate exclusively upon exposure via lactation are limited and of insufficient quality. Based on the presented data in the CLH-dossier of the lithium salts and taking into account the criteria for classification for lactation, i.e.: (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 adverse 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, lithium does not meet the first criterion, i.e. there is no human evidence available indicating a hazard to babies. For the second criterion, two studies show a significant decrease in pup weight upon lithium exposure via lactation (Teixeira 1995; Ibrahim and Canolty 1990). The latter study also described a decrease in absolute heart and spleen weight. Unfortunately, the quality of this study can be questioned. With respect to the third criterion, there is no doubt that lithium can be detected in breast milk and can be transferred to infants via breast milk. In order to fulfill this criterion, lithium should be present in breastmilk in "potentially toxic levels". It is stated in the CLH Dossier that the infants serum level are approximately one fourth of the maternal serum levels upon exposure via breast milk. One case study reports toxic effects in a breast fed child but these symptoms could be traced back to extremely high (16 mM) maternal lithium concentrations (HCN, 2000). The Dossier Submitter is requested to reflect on this issue.
Dossier Submitter's Response
Thank you for your comment and your support. Regarding the lactation point you raise, we agree with you that this is an interesting point, but, considering the wording of the guidance (*"the mere presence of the substance in the milk alone, without a strong justification for a concern to offspring, would normally not support classification for effects on or via lactation"; "classification for effects on or via lactation can be assigned on the basis of toxicokinetic data or a well substantiated estimate of the exposure through the milk alone provided that it is supported by an argument clearly justifying that the level present in the breast milk would be likely to harm developing offspring"*), we still think that the data available are not sufficient to support a classification. However, we agree it is an open point and we would be pleased to discuss it during the RAC session and hope that RAC members will add aditionnal arguments in one way or another.
RAC's response
Noted. See reply to comment No. 1.

PUBLIC ATTACHMENTS
1. Comments on ANSES CLP proposal about Lithium compounds.pdf [Please refer to comment No. 11, 24]
2. 2020-10-02Lithium REACH consortium comments on the CLH report for Li salts Annexes.zip [Please refer to comment No. 8, 25]
3. Consultation classification lithium salts- Comments of A3M.docx [Please refer to comment No. 1, 12, 16]

4. Joint Answer for lithium salts CLH proposal_October 2020.pdf [Please refer to comment No. 3, 14, 18]

CONFIDENTIAL ATTACHMENTS
1. Recommendation_Lithium repro classification_01Oct2020.pdf [Please refer to comment No. 20]