COMPILED COMMENTS ON CLH CONSULTATION

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

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Last data extracted on 05.10.2020

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

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.

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

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 group-

ing 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".

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.

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.

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.

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

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.				

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.				

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

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				

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.

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				

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.

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

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.

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

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.

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				

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.				

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.				

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.

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

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

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.

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]