

## Comments on Proposal for Harmonised Classification and Labelling for three lithium salts (lithium carbonate, lithium chloride and lithium hydroxide).

The French competent authority has submitted the CLH dossier for Lithium carbonate, chloride and hydroxide with a commenting period until 2 October 2020. The proposed classification for the three lithium salts is **Repr. 1A, H360FD** (May damage fertility; May damage the unborn child).

### Comments on a toxicological point of view:

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.

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 (Paterno *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”.