MEMO

To:	SQM Europe N.V., Antwerpen, Belgium
Att.:	[redacted]
DHI ref.:	[redacted], Chief Toxicologist, DHI (Author) [redacted], Principal Toxicologist, ERT (QA)
Project:	Assessment of CLH classification of lithium carbonate in relation to reproductive and developmental toxicity
Date:	22. July 2021
Subject:	Adverse effects on or via lactation in the project report dated 25-06-2021.

- Ahmed et al. (2021). Lithium from breast-milk inhibits thyroid iodine uptake and hormone production, which are remedied by maternal iodine supplementation. Bipolar Disorders. DOI: 10.1111/bdi.13047

Study design

In this study 26 female rats after the delivery of pups were gavaged during the lactation period from perinatal day 4 to 21 (P4-P21) with either: 0 (N=11), 40 mg lithium carbonate/kg bw/day (N=11), or 40 mg lithium carbonate /kg bw/day + drinking water containing 0.05% iodine (N=4).
The litter size was after delivery fixed to 12 pups in all groups.

Li-levels were measured at P18 in the female rats and in subgroups of the pups P18 and P25. Furthermore, the examination of the pups covered:

- bodyweight on P18, P25,
- BUN levels in blood (kidney toxicity) on P18, P25,
- T4 level in blood on P18, P25; P60,
- free T4 level in blood on P18
- free T3 level in blood on P18
- TSH level in blood on P18
- Forced swimming test on P18
- LIBS and XRF measurement of chemical content in thyroids on P18 and P25

Results

The following findings associated to the lactational lithium exposure of the pups were reported:

No lithium (below limit of detection of 0.007 µmol/L) was found in control pups, whereas 0.075 ± 0.03 mmol Li /L was measured in lithium exposed pups at P18 (~15% of the maternal levels). However, no lithium was found in the blood of any pups at later time points.

Lithium exposed pups appeared to weigh more than controls at P25 (74.95 ± 6.2 vs. 72.31 ± 4.6 g) and P60 (333 ± 68 vs. 310 ± 91 g), but the differences were not significant.

BUN measurements in lithium pups at P18 were significantly higher than that of controls (6.71 ± 0.27 vs. 5.25 ± 0.49 nmol/L, $p < 0.05$). This indicates reduced kidney function during lithium exposure from breast-feeding. After weaning, this difference disappeared.

Total T4 was significantly reduced ($p < 0.05$) in lithium pups, compared with controls, at P18 (67.2 ± 5.21 vs. 93.41 ± 10.60 nmol/L, $p < 0.05$) and P25 (40.06 ± 5.79 vs. 52.61 ± 3.03 nmol/L, $p < 0.05$). Total T4 was numerically lower in lithium pups at P60 (47.63 ± 11.0 vs. 54.2 ± 14.59 nmol/L), albeit not significantly.

TSH was significantly increased in Lithium pups, likely as a compensatory mechanism to the Li-induced reduction in thyroid hormone output.

XRF analysis of the thyroids indicated that lithium exposure significantly reduces thyroid iodine. Inhibition of iodine uptake was therefore, considered a key step in the mechanism behind lithium inhibition of thyroid hormone production.

Iodine supplementation to the dam while on lithium increased pup total T4 significantly compared with lithium only pups (85.6 ± 8.32 vs. 67.2 ± 5.21 nmol/L, $p < 0.05$). Importantly, total T4 in lithium + iodine pups were not far from those in controls (85.6 ± 8.32 vs. 93.41 ± 10.60 nmol/L). Similarly, iodine supplementation to the dam while on lithium also balanced TSH (1.38 ± 0.63 vs. 1.15 ± 0.55 µIU/ml) when compared with controls, whereas there was significant difference ($p < 0.05$) between lithium (0.94 ± 0.58 µIU/ml) and control groups (1.38 ± 0.63 µIU/ml).

No behavioural abnormalities were observed in the lithium exposed pups.

Overall, the authors found that increased body weight, reduced total T4 and increased TSH of lithium pups suggests that Lithium exposure, even indirectly through breast milk, can inhibit thyroid hormone output, leading to symptoms similar to those of hypothyroidism. The inhibition persists a period after weaning and after lithium has cleared from the blood.

DHI interpretation in relation to classification

The study by Ahmed et al. (2021) documents that lithium is distributed into breast milk and result in lithium exposure of the pups, however, at a considerably lower level compared to the mother animals that were exposed to rather high levels corresponding to levels used in medical treatment.

The lactational exposure resulted in transient and reversible changes in hormonal levels of T4 and TSH and BUN (a biomarker for impaired kidney functioning). Also, the effects can be considered dependent of the concurrent iodine intake/ status of the animals.

Although the study has documented the distribution of lithium to breast milk this was not shown in the study by Ahmed et al. (2021) to occur at a level where "*the substance is present in potentially toxic levels in breast milk"* as indicated in the CLP criteria.

The study by Ahmed et al. (2021) showed that lactational exposure can result in mild and transient effects in the pups, but the exposure did not "*provide clear evidence of adverse effect in the offspring due to transfer in the milk"* as indicated in the CLP criteria.

Therefore, the study in some way supports the lack of human evidence for adverse effects in babies/ infants nursed by mothers in lithium therapy.

In conclusion, the rather low distribution to breast milk and the mild effects associated to this as shown in the Ahmed et al. (2021) study do not provide sufficient evidence to meet the criteria for a H362

classification (May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation]).