KWR

Memo

Lithium toxicity

KWR 2021.046

Date
4 May 2021

Author(s)
A. Reus, MSc. and R. Hofman-Caris, PhD
With a contribution of A. Zwartsen, PhD

Quality assurance
M.M.L. Dingemans, PhD, ERT

Client
Dr. Gerard J. Stroomberg
Dutch River Waterworks Association – Rhine

Project number
403214/001/005

Project manager
Astrid Reus, MSc.

More information
A. Reus, MSc.
T +31 30 606 9703
E astrid.reus@kwrwater.nl

Introduction

Lithium has a wide variety of uses, including in small devices such as mobile phones, batteries for electric cars, in the glass and ceramics industries (US EPA USGS, 2021) and for the treatment of mental illness (Farmacotherapeutisch kompas 2021). In response to plans to extract lithium in the Rhine basin near Karlsruhe, RIWA needs information on the potential impact on the water quality of the Rhine, including the risks of lithium in the Rhine for drinking water supplies. KWR was asked to perform a concise assessment of the toxicity of lithium, and potential risks related to lithium in drinking water. This brief report summarizes knowledge on exposure to and toxicity of lithium, possibilities for drinking water treatment and estimates a preliminary health risk guideline. The risks of other pollutants that might enter the Rhine as a result of lithium extraction are not discussed here.

Toxicity

Due to the use of lithium as a medication for (potentially) lifelong mental health problems, the health effects of chronic exposure are generally well known (Van Paemel et al. 2010). For lithium, this includes both positive health effects (intended effectiveness) and negative health effects (side effects).

Lithium (in the form of a lithium salt) can be prescribed for bipolar disorder, mood swings and depression (Barjasteh-Askari et al. 2020, Farmacotherapeutisch kompas 2021). Adverse health effects from chronic exposure manifest mainly in the kidneys (Van Paemel et al. 2010) and occur at plasma concentrations above 1.5 mmol/L (Oruch et al. 2014). McKnight et al. (2012) concluded from a systematic review and meta-analysis that lithium may be associated with an increased risk of decreased ability to concentrate urine (renal toxicity), decreased thyroid and parathyroid activity, and weight gain. The risk of congenital abnormalities is unknown/unproven for humans (McKnight et al. 2012), but there are indications for this from animal studies (Van Paemel et al. 2010). Long-term use of therapeutic doses of lithium may additionally cause side effects on the gastrointestinal system (nausea, vomiting, diarrhea), central nervous system (confusion, fatigue, seizures, coma), muscles (tremors and muscle twitching), endocrine effects (hypothyroidism; decreased production of thyroid hormone), enlargement of thyroid gland (goiter) and swelling (Oruch et al. 2014).

Since a significant relationship has been found between measured lithium concentrations in drinking water and urine, it is plausible that drinking water may be a route of exposure for the average population in some regions (Barjastesh Askari et al. 2020). Systematic review and meta-analyses show mainly positive health effects of lithium in drinking water for average concentrations up to 11.6 µg/L. In these publications lithium concentrations are associated with a decrease in suicide rates and inpatient psychiatric admissions (Barjastesh Askari et al. 2020; Eyre-Watt et al. 2021). However, some studies referenced in the publications actually reported an increase in schizophrenia and related disorders (Eyre-Watt et al. 2021). The meta-analysis did not include Dutch studies, but did include European studies (e.g. Denmark and England). It cannot be excluded that the observation of positive effects arised from the influence of other factors (Barjastesh Askari et al. 2020; Eyre-Watt et al. 2021). The positive health effect of lithium in drinking water has also been questioned by a German researcher who calculated that an individual would have to drink 1800 liters of water to ingest the therapeutic dose of a lithium salt (Bschor, 2021).

Besides chronic effects, acute (adverse) health effects of lithium have also been described (Van Paemel et al. 2010). Because low concentrations and long-term exposure generally apply to drinking water, acute effects are not described in detail in this brief report. In addition to human health effects, ecological effects of lithium in surface water have also been described (EC 2015; US EPA, 2008a). Because ecological effects are beyond the scope of the research question, they are not described here.

Health guidelines

Neither in the Netherlands nor by the WHO and US EPA have standards or guideline values been set for lithium in (drinking) water (Barjastesh Askari et al. 2020; Drinking Water Decree, 2018, RIVM, 2021). Van Paemel et al. reported in 2010 that no chronic risk limit (such as an acceptable daily intake) has been derived for lithium, nor have chronic toxicity limits such as NOAEL ("non-observed adverse effect level") values been identified by agencies to provide health-based guideline values for drinking water (Van Paemel et al. 2010). A quick-scan in databases of among others ECHA, EFSA, EMA, RIVM, TERA/ITER, US EPA and WHO did not yield (additional) information.

The US EPA (2008b) describes a reference dose (RfD) of 0.002 mg/kg-bw/day, which is based on the lower limit of therapeutic lithium concentration of 0.6 mmol/L in serum. This 0.6 mmol/L corresponds to a LOEAL of 2.1 mg/kg-bw/day and an uncertainty factor of 1000 was used by the US EPA to determine the RfD, (10 for intraspecies variation, 10 for extrapolation from LOAEL to NOAEL and 10 for database insufficiencies). Based on the RfD of 0.002 mg/kg-bw/day, the US EPA has proposed a non-statutory Health Based Screening Level (HBSL) of 10 µg/L (US EPA USGS, 2018). This derivation assumes an adult body weight of 80 kg, a 20% allocation to drinking water, drinking water consumption of 2.5 L per day, and rounding (Lindsey et al. 2021, US EPA USGS, 2018).

When a similar approach is based on the lowest therapeutic dose as reported by the Dutch Pharmacotherapeutic Compass (2021), an uncertainty factor of 1000, an adult body weight of 70 kg, a 20% allocation to drinking water and a drinking water consumption of 2 L/day, an indicative health-based drinking water guideline value can be derived as follows (Baken et al. 2018, EC 2018):

(0.0011 mg/kg day [1] * 70 kg * 0.2 [2]) / 2 L/day = 0.0075 mg/L = 7.5 µg/L.

By drinking 2 liters of water per day at this concentration, a daily intake is reached after about 5,000 days (~14 years) (75 mg [1] / (0.0075 mg/L x 2 L) = 5,000).

In 2014, the background concentrations of lithium in fresh and salt surface water in the Netherlands were 3.5 µg/L and 120 µg/L, respectively (RIVM, 2021). In 2019, the average background values of lithium in the Rhine were 10.4 µg/L (annual average of four sample locations) with site-specific maxima up to 16 µg/L (RIWA, 2020). Concentrations of lithium in Dutch drinking water are not publicly available, and retrieving these data was beyond the scope of this brief report.

---

[1] The lowest therapeutic dose is in the Netherlands 400 mg lithium carbonate per day for elderly people, this corresponds to 75 mg lithium per day. With a body weight of 70 kg (in line with the Water Framework Directive, EC 2018) and a uncertainty factor of 1000 (10 for intraspecies variation (10 for extrapolation of LOAEL to NOAEL and 10 for database insufficiencies, in line with the US EPA, US EPA 2008b), the acceptable daily intake was estimated to be 0.0011 mg/kg-bw/day. The lowest therapeutic dose for adults (non-elderly) is 600 mg/kg-bw per day (Farmacotherapeutisch Kompas 2021).

[2] The Water Framework Directive (WFD, EC 2018) assumes a standard allocation of 20% to drinking water. If the proportion of lithium exposure via food or the environment is relatively high, the allocation assigned to drinking water may reduced to less than 20%. Relative exposures have not been investigated further for this brief report.

As a result of the planned lithium extraction it is to be expected that concentrations in the Rhine will increase and will be (structurally) above 7.5 µg/L. Based on the (limited) toxicological information, there seems to be reason for concern for adverse human health effects. However, the indicative drinking water guideline value derived here is very conservative, because the acceptable daily intake (on which the drinking water guideline value is based) was determined with an uncertainty factor of 1000.

Other known, widely used databases (ECHA, EFSA, EMA, RIVM, TERA/ITER WHO) lack a health-based guidance value for lithium (at this moment). The accuracy of the indicative drinking water guidance value derived here needs to be further investigated. Availability of a realistic, reliable NOAEL provides a better basis for deriving an indicative drinking water guideline value for lithium.

Lithium in drinking water treatment

Lithium (CAS number 7439-93-2) usually occurs in (surface) water in the form of a positively charged ion (Li^+) which is smaller than sodium. In conventional drinking water treatment (i.e. coagulation/flocculation/sedimentation) this is not removed. Activated carbon can adsorb lithium ions, but only after chemical pretreatment (Jeong, Rhee et al. 2015, Kamran, Heo et al. 2019, Güneysu 2020) applied to extract lithium (not to remove lithium from water). The standard activated carbon applied in a drinking water treatment plant is probably not suitable for lithium removal.

Of the membrane processes, only reverse osmosis (RO) could be somewhat effective, but according to Fedorova (2020) the process does not work well, probably because lithium ions are smaller than sodium ions. The only technique mentioned in the literature as effective for drinking water treatment is ion exchange, where lithium ions are replaced by sodium ions. However, lithium concentrations were low compared to sodium concentrations in the water (0.41 mg/L versus 184 mg/L, in subpermafrost groundwater in Yuketia) (Fedorova and Kryzhanovsky 2018, Fedorova 2020).

It may be possible to remove lithium from water using a technique such as electrodialysis (Jarma, Çermikli et al. 2021), but this has not yet been tested on a small scale for drinking water treatment only (lab or pilot setup). The same is true for biological removal by bacteria (Bacillus sp. HX11, Bacillus sp. HA120a, Kocuria sp. SA129b and Brevibacterium sp. SX139) (Martínez, Rajal et al. 2021).

It can be assumed that in common drinking water treatment plants, lithium is poorly or not removed.

Conclusion

As a result of the planned lithium extraction, concentrations in the Rhine are likely to increase and to reach (structurally) the indicative drinking water guideline value derived here. The (limited) toxicological information and on the assumption that lithium is poorly or not at all removed in the usual drinking water treatment raises a concern for adverse human health effects due to exposure to lithium via drinking water.

References

Baken KA, Sjerps RMA, Schriks M, van Wezel AP. (2018). Toxicological risk assessment and prioritization of drinking water relevant contaminants of emerging concern. Environ Int. 118:293-303. Toxicological risk assessment and prioritization of drinking water relevant contaminants of emerging concern - ScienceDirect

Barjasteh-Askari F, Davoudi M, Amini H, Ghorbani M, Yaseri M, Yunesian M, Mahvi AH, Lester D. (2020) Relationship between suicide mortality and lithium in drinking water: A systematic review and meta-analysis. J Affect Disord. 264:234-241. Relationship between suicide mortality and lithium in drinking water: A systematic review and meta-analysis - ScienceDirect

Bschor, T. (2021). Faszinierend, weil ungeklärtes Wirkungsmechanismus. InFo Neurologie + Pysychiatrie 23(2).

Drinkwaterbesluit (Dutch drinking water regulation), 2018. wetten.nl - Regeling - Drinkwaterbesluit - BWBR0030111 (overheid.nl) Accessed on March 19, 2021.

EC 2015. Science for environment policy. Lithium accumulates in plasma and brains of fish after short-term exposure. Lithium accumulates in plasma and brains of fish after short-term exposure (europa.eu). Accessed on March 19, 2021.

EC. 2018. Technical guidance for deriving environmental qualilty standards. Guidance Document No. 27. Updated version 2018. Document endorsed by EU Water Directors at their meeting in Sofia on 11-12 June 2018. https://rvs.rivm.nl/sites/default/files/2019-04/Guidance%20No%2027%20-%20Deriving%20Environmental%20Quality%20Standards%20-%20version%202018.pdf. Accessed on April 13, 2021.

Eyre-Watt B, Mahendran E, Suetani S, Firth J, Kisely S, Siskind D. (2021) The association between lithium in drinking water and neuropsychiatric outcomes: A systematic review and meta-analysis from across 2678 regions containing 113 million people. Aust N Z J Psychiatry. 55(2):139-152. The association between lithium in drinking water and neuropsychiatric outcomes: A systematic review and meta-analysis from across 2678 regions containing 113 million people - Brenton Eyre-Watt, Eesharnan Mahendran, Shuichi Suetani, Joseph Firth, Steve Kisely, Dan Siskind, 2021 (sagepub.com)

Farmacothearapeutisch kompas 2021, Lithium. lithium (farmacotherapeutischkompas.nl) Accessed on April 8, 2021.

Fedorova, S. and A. Kryzhanovsky (2018). The using of ion exchange method of Urban Territories' sub-surface waters purification in Sakha (Yakutia). MATEC Web of Conferences. The using of ion exchange method of Urban Territories' sub-surface waters purification in Sakha (Yakutia) (matec-conferences.org)

Fedorova, S. V. (2020). Use of Subpermafrost Groundwater Resources for Drinking Water Supply in Yakutia. IOP Conference Series: Earth and Environmental Science. Use of Subpermafrost Groundwater Resources for Drinking Water Supply in Yakutia - IOPscience

Güneysu, S. (2020). Lithium sorption from aqueous solution with cationic resins.Desalination and Water Treatment 177: 102-108.

Jarma, Y. A., E. Çermikli, D. İpekçi, E. Altıok and N. Kabay (2021). Comparison of two electrodialysis stacks having different ion exchange and bipolar membranes for simultaneous separation of boron and lithium from aqueous solution. Desalination 500. Comparison of two electrodialysis stacks having different ion exchange and bipolar membranes for simultaneous separation of boron and lithium from aqueous solution - ScienceDirect

Jeong, J. M., K. Y. Rhee and S. J. Park (2015). Effect of chemical treatments on lithium recovery process of activated carbons. Journal of Industrial and Engineering Chemistry 27: 329-333. Effect of chemical treatments on lithium recovery process of activated carbons - ScienceDirect

Kamran, U., Y. J. Heo, J. W. Lee and S. J. Park (2019). Chemically modified activated carbon decorated with MnO2 nanocomposites for improving lithium adsorption and recovery from aqueous media. Journal of Alloys and Compounds 794: 425-434. Chemically modified activated carbon decorated with MnO2 nanocomposites for improving lithium adsorption and recovery from aqueous media - ScienceDirect

Lindsey BD, Belitz K, Cravotta CA 3rd, Toccalino PL, Dubrovsky NM (2021). Lithium in groundwater used for drinking-water supply in the United States. Sci Total Environ. 767:144691. Lithium in groundwater used for drinking-water supply in the United States - ScienceDirect

Martínez, F. L., V. B. Rajal and V. Irazusta (2021). Removal of lithium from aqueous solutions using halotolerant bacteria from El Salar del Hombre Muerto. Journal of Environmental Chemical Engineering 9(2). Removal of lithium from aqueous solutions using halotolerant bacteria from El Salar del Hombre Muerto - ScienceDirect

McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. (2012) Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 379(9817):721-8. Lithium toxicity profile: a systematic review and meta-analysis - ScienceDirect

Oruch R, Elderbi MA, Khattab HA, Pryme IF, Lund A. (2014) Lithium: a review of pharmacology, clinical uses, and toxicity. Eur J Pharmacol. 740:464-73. Lithium: A review of pharmacology, clinical uses, and toxicity - ScienceDirect

RIVM, Rijksdienst voor Volksgezondheid en Milieu (Dutch National Institute for Public Health and the Environment), 2021. Zoeksysteem | Risico's van stoffen (rivm.nl) Accessed on March 19, 2021.

RIWA, Vereniging van Rivierwaterbedrijven (Association of River Waterworks) 2020, Annual report 2019 – Rhine. Jaarrapport 2019 - De Rijn - Riwa (riwa-rijn.org) Accessed on March 19, 2021.

US EPA, United States Environmental Protection Agency, 2008a. Rule 57 Aquatic values datasheet Lithium mi_al_395_06162008.pdf (epa.gov). Accessed on March 19, 2021

US EPA, 2008b. Provisional Peer Reviewed Toxicity Values for Lithium. Provisional Peer Reviewed Toxicity Values for Lithium (CASRN 7439-93-2) (epa.gov). Accessed on March 22, 2021.

US EPA USGS, US EPA United States Geological Survey 2018, Lithium. HBSL Home (usgs.gov). Accessed on March 19, 2021.

US EPA USGS, US EPA United States Geological Survey 2021, Lithium Statistics and Information. Lithium Statistics and Information (usgs.gov). Accessed on April 14, 2021.

Van Paemel, M. Dierick, N. Janssens, G, Fievez, V., De Smet S. (2010). TECHNICAL REPORT submitted to EFSA Selected trace and ultratrace elements: Biological role, content in feed and requirements in animal nutrition – Elements for risk assessment. Selected trace and ultratrace elements: Biological role, content in feed and requirements in animal nutrition – Elements for risk assessment (wiley.com) p.623-631. Accessed on March 19, 2021.

Year of publishing
2021

More information
Astrid Reus, MSc.
T +31 30 606 9703
E Astrid.Reus@kwrwater.nl

Keyword(s)
Lithium

Groningenhaven 7
Postbus 1072
3430 BB Nieuwegein
The Netherlands

T +31 (0)30 60 69 511
F +31 (0)30 60 61 165
E info@kwrwater.nl
I www.kwrwater.nl

KWR 2021.046 | 4 May 2021 ©KWR