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Review article

Lithium and endocrine disruption: A concern for human health?

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ABSTRACT

Lithium is a key medication for the treatment of psychiatric disorders and is also used in various industrial applications (including battery production and recycling). Here, we review published data on the endocrine-disrupting potential of lithium, with a particular focus on the thyroid hormone system. To this end, we used PubMed and Scopus databases to search for, select and review primary research addressing human and animal health endpoints during or after lithium exposure at non-teratogenic doses. Given the key role of thyroid hormones in neurodevelopmental processes, we focused at studies of the neural effects of developmental exposure to lithium in humans and animals. Our results show that lithium meets the World Health Organization's definition of a thyroid hormone system disruptor – particularly when used at therapeutic doses. When combined with knowledge of adverse outcome pathways linking molecular initiating events targeting thyroid function and neurodevelopmental outcomes, the neurodevelopmental data reported in animal experiments prompt us to suggest that lithium influences neurodevelopment. However, we cannot rule out the involvement of additional modes of action (i.e. unrelated to the thyroid hormone system) in the described neural effects.

Given the increasing use of lithium salts in new technologies, attention must be paid to this emerging pollutant – particularly with regard to its potential effects at environmental doses on the thyroid hormone system and potential consequences on the developing nervous system.

1. Introduction

Lithium is an alkali metal naturally present in the environment, with a great geographic variation (Montelius, 2003). It is associated with mineral components or salts such as lithium carbonate, lithium chloride and lithium hydroxide (Bolan et al., 2021). Lithium sources can also originate from human activities (Bolan et al., 2021) since lithium carbonate, lithium chloride and lithium hydroxide have a variety of medical and industrial uses (Puglisi-Allegra et al., 2021; Mitchell et al., 2000; Montelius, 2003). Lithium carbonate is used as mood stabilizer to treat mania and depression, with a narrow therapeutic index since lithium toxicity occurs at doses exceeding 2 mEq/L while the therapeutic levels are in the range of 0.6 to 1.2 mEq/L (Chokhawala et al., 2024). Lithium carbonate is also used as means of controlling thermal expansion in ceramics; lithium chloride is used as a moisture absorber in air-conditioning systems and batteries, and in the production of

lightweight alloys, and lithium hydroxide is used in alkaline storage batteries, in the manufacture of lithium soaps, and as an additive in industrial batteries. Each year, the countries in the European Economic Area manufacture and/or import 10,000 to 100,000 tons of lithium carbonate and 1,000 to 10,000 tons of the two other lithium salts (ECHA, 2023a, 2023b, 2023c). Environmental exposure to lithium varies greatly between regions and depends on lithium content of food and beverages. The diet intake was estimated to be around 48.2 µg/day in France (Anses, 2011), but can be higher as in the Canary Islands where it reaches 3.6 mg/day (González-Weller et al., 2013).

The use of lithium salts is increasing, due to growing demand for novel technologies that incorporate lithium-ion batteries (e.g. electric vehicles, electronic cigarettes, mobile phones, and laptop computers) (Bibienne et al., 2020; Bolan et al., 2021). This increase of lithium use raises serious concerns for human health and the environment given its potential toxicity. Toxicokinetic studies showed that soluble lithium

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salts are readily absorbed by the gastrointestinal tract via passive diffusion (Lagerkvist and Lindell, 2002). The lithium cation (Li^+) dissociates in aqueous solutions from the corresponding physiological anion (i.e. carbonate (CO_3^{2-}), chloride (Cl^-) or hydroxide (OH^-)) (Lagerkvist and Lindell, 2002). In humans, plasma levels peaked one to four hours after a single oral dose of lithium carbonate tablets (Lagerkvist and Lindell, 2002). In rats, the plasma level increases within 15 to 30 min of a single oral dose of lithium chloride or carbonate and reached a plateau after 12 to 24 h (Hartwig, 2014). Furthermore, lithium inhalation absorption (i.e. through the lung) has been observed (Lagerkvist and Lindell, 2002). The results of studies in humans and animals have also shown that lithium ions do not bind to plasma or tissue proteins and can accumulate in various organs (Timmer and Sands, 1999). Due to its similarities with sodium and potassium cations, Li^+ can pass through sodium ion channels to reach target organs (Timmer and Sands, 1999). It has also been reported that lithium competes with magnesium ion at substrate enzyme sites, leading to the modulation of signaling pathways related to its pharmacological action in the context of neuropsychiatric disorders (Puglisi-Allegra et al., 2021). Lithium can cross the placenta (Moore, 1995) and can be excreted into breast milk (Lagerkvist and Lindell, 2002; Moore, 1995). Lithium ions are not metabolized in the body (Hartwig, 2014; Lagerkvist and Lindell, 2002) and are mainly excreted by glomerular filtration in the kidneys (Schou, 1958).

In view of the environmental and health concerns described above, France submitted a harmonised classification and labelling dossier for lithium with regard to the European Union's classification, labelling and packaging (CLP) regulations (ECHA, 2020). The Committee for Risk Assessment then adopted a harmonized classification in which lithium salts were designated as known reprotoxicants (ECHA, 2021). Here, we report the work subsequently performed by the French Agency for Food, Environmental and Occupational Health & Safety (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, ANSES) to assess the lithium salts' potential endocrine-disrupting (ED) properties and their impact on human health. According to the World Health Organization (WHO), an endocrine disruptor (ED) is defined as a substance that (i) exhibits endocrine activity, (ii) has an adverse effect on an intact organism or its offspring or future generations, and (iii) displays a biologically plausible link between the endocrine activity and the adverse effect. This definition is now included into the European Union's CLP regulation (ECHA, 2018), for which classification of a substance as an endocrine disruptor for human health is to make on the basis of an assessment of the total weight of evidence using expert judgment. The endpoints for lithium exposure investigated by the ANSES included neurodevelopment and reproductive, renal and thyroid functions. Here, we only review the adverse effects of lithium on thyroid function and neurodevelopment because there is a large body of evidence to show that thyroid hormone system disruption can lead to neurodevelopmental impairments (Korevaar et al., 2016; Levie et al., 2019; Pop et al., 1999). We selected and analyzed publications containing epidemiological data (in humans) and experimental data (in animals) on these endpoints and that met specific quality criteria.

2. Methods

The assessment of lithium salts' potential ED properties and impact on human health was performed following the weight-of-evidence analysis methodology previously reported by the Anses (2017, 2021).

The literature search was performed using PubMed and Scopus databases up until November 2021 (for the Regulatory Management Option Analysis on lithium salts, Anses, under preparation) and then December 2022 (for the present review), according to the PECO (Population, Exposure, Comparator, and Outcome) statement described in Table 1.

A flow diagram summarizes the methodology used (Fig. 1) as previously described (Beausoleil et al., 2022). In addition, a supplemental excel file details the search keywords per endpoint, the retrieved articles

Table 1
PECO (Population, Exposure, Comparator, and Outcome) Statement.

Element	Type of evidence
Population	Human: any population without previously reported thyroid dysfunction Animal: nonhuman vertebrate laboratory animal models
Exposure	Any lithium salt alone, including administration during pregnancy
Comparators	A comparison population exposed to lower levels (or no exposure) of lithium salt; experimental studies should include an untreated or vehicle control
Outcomes	Thyroid cancer and other thyroid dysfunctions, adverse neurological effects (e.g., neurodevelopmental and behavioral effects)

after removal of duplicates, and the inclusion and exclusion criteria per article. Two additional references (Jacobson et al., 1992; Schou et al., 1976) were not found by the used search terms, but were retrieved during the process of article analysis.

The exclusion criteria presented in Fig. 1 and detailed in Supplemental Excel File comprised lithium doses above 12 mEq/kg/d, adult subjects or adult exposure (for neurodevelopment endpoint), lithium chloride used for aversive tests, in vitro analysis, and non-rodent models for the experimental studies. Indeed, studies of the high doses of lithium (>12 mEq/kg/d) known to induce teratogenic effects or kidney failure (well-known adverse events associated with long-term treatment with lithium salts) were excluded from the present analysis.

For the thyroid and neurodevelopmental effects, the screening of data by title/abstract was performed by two screeners for each reference. When there was uncertainty about the relevance of the study, the full text was analyzed.

For the thyroid effects, the search terms did not target a specific period of exposure; the majority of retrieved and analysed studies concerning adulthood as explained in the "Results" section. Our evaluation of the neural effects of lithium focused on critical development periods. These included prenatal and postnatal periods, known to be important in the organization of the nervous system and highly sensitive to thyroid disruption.

Concerning the experimental animal studies, as the risk assessment focused on human health, we selected and analysed only studies performed in rodents (rats and mice).

3. Results

Fig. 1 indicates the different steps of data screening related to *in vivo* analyses. A total of 609 and 3198 articles for thyroid and neurodevelopment endpoints, respectively, were retrieved. Among these articles, 192 studies on thyroid and 26 articles on neurodevelopment were retained on the basis of title/abstract assessment. At full text level, 37 articles including 8 human studies and 29 experimental data were retained for the thyroid endpoint. Seventeen studies were selected for neurodevelopment including 11 on humans (2 additional studies were retrieved during the analysis process as explained above) and 6 on rodents.

3.1. Effects of lithium on thyroid function

3.1.1. Data from studies of humans

Many researchers have investigated the effect of lithium on thyroid function in general and in lithium-treated patients (typically exposed to between 600 and 1200 mg/d) in particular (Table S1). In the study by Ozpoyraz et al. (2002), the prevalence of clinical hypothyroidism was 12 % in lithium-treated patients ($n = 49$), whereas no clinical or sub-clinical hypothyroidism was observed in the control group ($n = 46$). In contrast, Kusalic and Engelsmann (1999) observed a higher prevalence of hypothyroidism among patients: 39.6 %. In a longitudinal study, Lombardi et al. (1993) found that the mean thyroid-stimulating

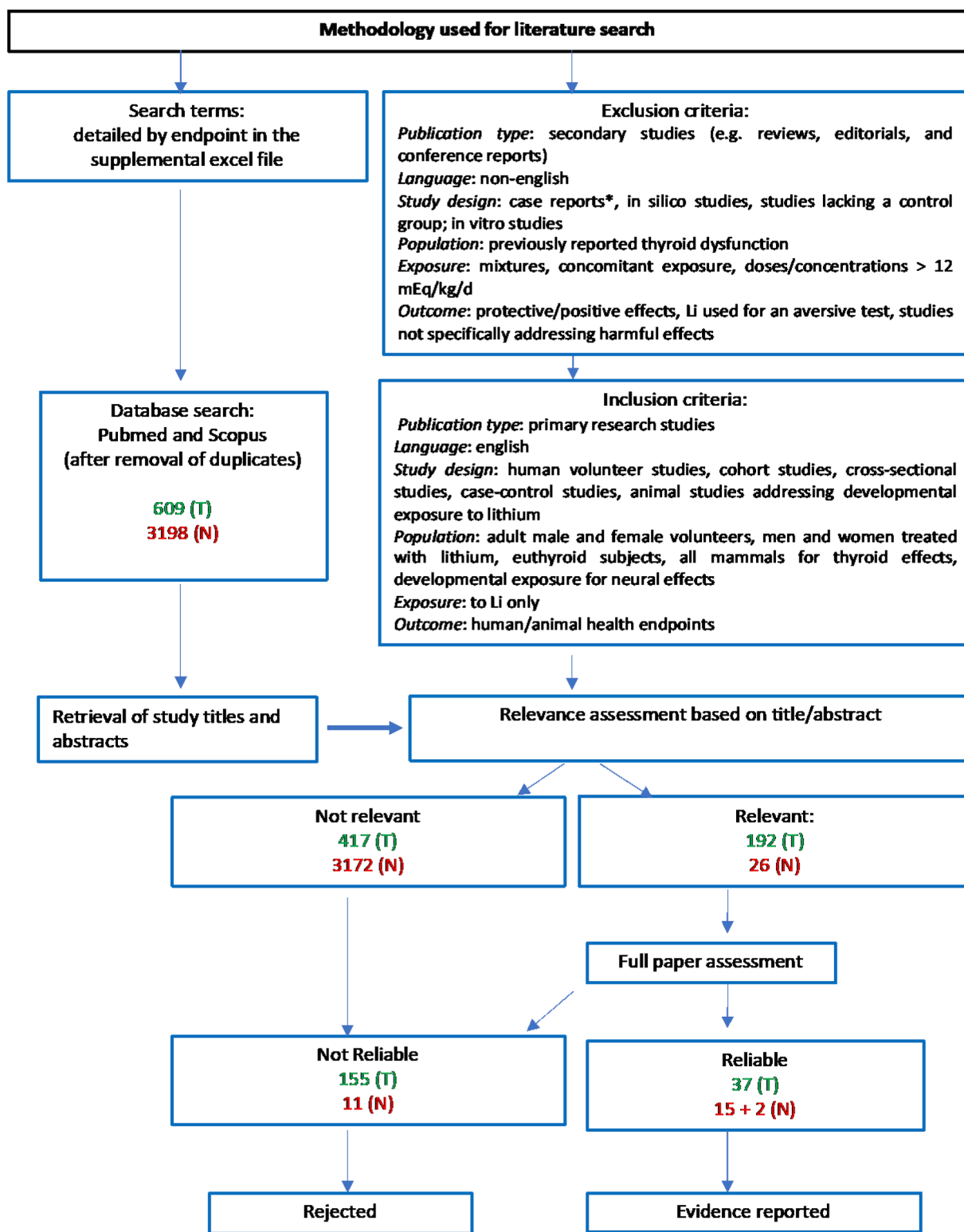


Fig. 1. Methodology used for literature search. The search terms per endpoint and the inclusion/exclusion criteria of articles are detailed in the Supplemental excel File. *Except for breastfeeding. The number of articles for thyroid (T) and neurodevelopment (N) endpoints at each step of analysis are indicated.

hormone (TSH) level increased significantly ($p < 0.05$) 10 days after the initiation of lithium therapy and remained significantly higher than the pretreatment level for at least one year. The same biological profile was reported by Perrild et al. (1984) in a small cohort of young healthy subjects ($n = 16$) who received lithium carbonate for four weeks.

The elevated prevalence of hypothyroidism in lithium-treated

individuals was confirmed by Johnston and Eagles (1999) in a retrospective study of 718 patients. Compared with the overall prevalence of hypothyroidism in the same geographical area, the relative risk (RR) of developing clinical hypothyroidism was significantly higher in lithium-treated people and especially so in younger adults (RR [95 % confidence interval (CI)] = 11.3 [5.6–22.7] for women aged 20–39, 5.65 [3.7–8.7]

for women aged 49–59, 1.98 [1.24–3.13] for women aged 60–79, 9.5 [4.38–20.7] for men aged 40–59, and 4.25 [1.69–10.6] for men aged 60–79). Interestingly, Lambert et al. (2016)'s study of a cohort of 24,574 adult patients with at least two diagnoses of bipolar illness in their medical history found that clinical hypothyroidism occurred more frequently in lithium-treated individuals (10.7 %, vs 7.5 % in those not treated with lithium). The estimated four-year cumulative incidence of hypothyroidism in lithium-treated patients ranged from 1.06-fold (relative to quetiapine-treated patients) to 1.39 (relative to oxcarbazepine-treated patients) ($p < 0.001$ for both). Lastly, Shine et al. (2015)'s retrospective study investigated the prevalence of hypothyroidism in a cohort of 4,678 lithium-treated patients and 689,228 controls. After adjustment for age, sex, and evidence of diabetes, the presence of lithium was significantly associated with hypothyroidism (hazard ratio [95 %CI] = 2.31 [2.05–2.60]; $p < 0.0001$) but not with hyperthyroidism (1.21 [0.96–1.55]; $p = 0.1010$).

Broberg et al. (2011) evaluated the effects of chronic exposure to lithium through environmental sources in the Andes of Northern Argentina, where lithium concentration can exceed 1 mg/L (Concha et al., 2010), resulting in a total daily lithium intake of 2–3 mg from only drinking water. They reported that the urine lithium concentration was inversely associated with free thyroxine (FT_4) levels (after adjustment for elevated levels of elements in drinking water in the same region, age, parity, and body mass index) and positively associated with TSH levels; these findings suggested strongly that lithium induced hypothyroidism.

Despite some limitations in these epidemiological studies (including small sample sizes, the lack of a control group, and different definitions of clinical hypothyroidism with regard to TSH alone or both TSH and T_4), they showed consistently that lithium therapy or environmental exposure to lithium in adults induced thyroid disturbance in general and hypothyroidism in particular.

3.1.2. Data from studies of animals

3.1.2.1. Thyroid effects. The 29 analyzed *in vivo* studies in rodents addressed the effects of oral exposure to lithium salts on various markers of the thyroid function (Table S2). Biosynthesis of thyroid hormones (the only endogenous iodinated molecules) is strictly dependent on iodine active uptake by thyrocytes through the Na^+/I^- symporter (NIS) and on iodide oxidation, followed by the incorporation of reactive iodide into tyrosine residues of the thyroglobulin storage protein (iodine organification) by thyroid peroxidase (TPO) (Fig. 2).

In the 26 studies analyzing the effects on the thyroid function in adult animals, lithium treatment was always associated with changes in circulating levels of thyroid hormones and, to a lesser extent, TSH (Table S2). Most of these studies reported low T_4 levels (Aydin et al., 1996; Bagchi et al., 1982; Burrow et al., 1971; El-Mahalaway et al., 2019; Eravci et al., 2000; Jaffer et al., 1993; Kumar et al., 2019; Li et al., 2017; Ljunggren et al., 1971; Maiti et al., 2010; Männistö et al., 1973; Morley et al., 1981; Petrov et al., 1985; Pradhan et al., 2012; Toplan et al., 2013). Only three studies reported no effect on T_4 (Bolaris et al., 1995; Frankenfeld et al., 2002) or TSH levels (Caberloto et al., 2013). In accordance, lithium treatments led to increased size of thyroid follicles and colloid abundance (Aydin et al., 1996; Bagchi et al., 1982; Glumova et al., 1979; Singh et al., 2015). A change in iodine uptake was the most frequently described effect of lithium *in vivo* (Berens et al., 1970; Glumova et al., 1979; Hullin et al., 1970; Lazarus and Muston, 1978; Li et al., 2017; Männistö et al., 1971, 1973; Singh et al., 1994; Takasugi et al., 1989). In some instances, this change was associated with lower circulating concentrations of total triiodothyronine (T_3) and/or T_4 and/or elevated TSH levels (Kumar et al., 2019; Li et al., 2017; Takasugi et al., 1989). An elevated thyroid iodine half-life was also consistently reported (Kumar et al., 2019; Li et al., 2017; Petrov et al., 1985). The results of a study of the effect of lithium on the thyroid/serum iodine ratio in hypophysectomized, TSH-treated rats suggested that the effect

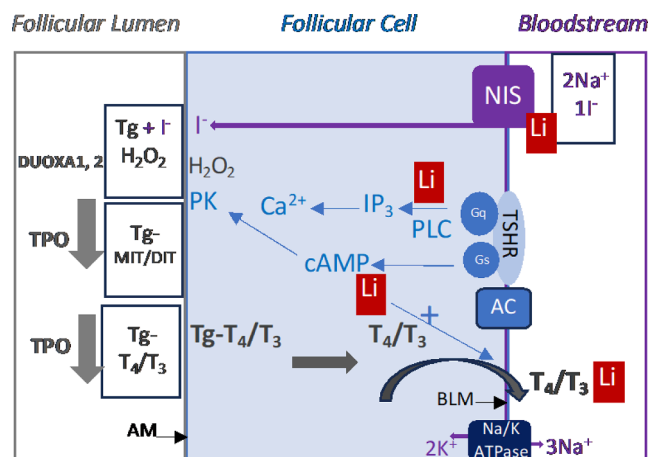


Fig. 2. Mechanisms underlying the effects of lithium (Li) on the thyroid function. Adapted from Czarnywojtek et al. (2020). AC: adenylate cyclase; AM: apical membrane; BLM: basolateral membrane; cAMP: cyclic adenosine monophosphate; DIT: diiodotyrosine; DUOXA1,2: dual oxidases 1 and 2; Gq: G protein from family q, activates phospholipase C; Gs: G protein from family s (stimulating), activates adenylate cyclase; H_2O_2 : Oxygen peroxide; I^- : iodide; IP_3 : Inositol triphosphate; MIT: mono-iodotyrosine; Na^+ : sodium ion; NIS: sodium-iodide symporter; PK: Protein Kinase; PLC: Phospholipase C; T_3 : triiodothyronine; T_4 : thyroxine; Tg: thyroglobulin; TPO: thyroid peroxidase; TSHR: thyroid-stimulating hormone receptor; Li: Lithium; Ca^{2+} : calcium ions. Tg-MIT/DIT: MIT and DIT on thyroglobulin; Tg- T_4/T_3 : T_4 or T_3 on thyroglobulin.

on iodine uptake was at least partly independent of TSH regulation (Berens et al., 1970).

Furthermore, the effect of lithium on iodine uptake appears to be at least partly dependent upon the duration of exposure. Indeed, elevated iodine uptake was rarely reported and concerned short-term exposure only (Hullin et al., 1970; Kumar et al., 2019). In contrast, long-term exposure was most frequently associated with low iodine uptake (Table S2). These observations suggest the presence of a compensatory mechanism that protects the thyroid gland from the excess tissue iodine triggered by an initial increase in iodine uptake.

Using Raman spectrometry, Law et al. (2017) studied the effect of two weeks of exposure to lithium on iodine uptake and thyroid hormone synthesis in mice. The researchers concluded that lithium induced a loss of iodine organification, which suggests that lithium has an effect on NIS and/or TPO activity (Fig. 2). An effect on NIS is consistent with the data showing low iodine uptake. This type of mechanism is encountered in the acute Wolff-Chaikoff effect (Wolff and Chaikoff, 1948), an autoregulatory phenomenon whereby a large amount of ingested iodine acutely inhibits iodine organification within the follicular cells – irrespective of the serum TSH level.

Overall, the effects of lithium on the adult thyroid function are quite consistently reported. Although the nature of the effects varied from one study to another, none of these studies found that lithium never had an effect on any thyroid-related variables presented above and in Table S2 (T_3 , T_4 and TSH levels, thyroid iodine uptake and/or concentrations, thyroid histology...). The most frequently reported mechanisms were related to iodine trafficking.

Two studies examined the effects of gestational and/or lactational treatment of dams on the thyroid function of their offspring (Ahmed et al., 2021; Mohammed et al., 2020). They reported reduced thyroid hormone levels (total and free T_4 and T_3) and elevated TSH levels in dams and their neonates. In addition, Ahmed et al. (2021) showed that the iodine uptake by thyroid follicles was inhibited, leading to reduced tyrosine iodination in lithium-exposed offspring, but iodine supplementation improved the thyroid function.

3.1.2.2. Analyses of the molecular initiating events and the link with adverse effects. *In vitro* and *ex vivo* studies have shown that lithium can inhibit TSH signalling via inositol triphosphate production in FRTL-5 cells (Santisteban et al., 1987) and cyclic adenosine monophosphate (cAMP)-dependent pathways (Dumont, 1971; Urabe et al., 1991). These two signalling pathways mediate the TSH-induced control of thyrocyte function, including most of the steps in thyroid hormone synthesis, storage and release. The cAMP-dependent pathway is a particularly important target of lithium. Lithium has been shown to not only decrease TSH-induced cAMP production in perfused mouse thyroids (Mori et al., 1989) but also act downstream of this second messenger in porcine thyroid cells in culture (Tsuchiya et al., 1990). These findings suggest that the inhibitory effect of lithium on iodine uptake may result from its direct action on follicular cell responsiveness to TSH, leading to reduced NIS expression. Consistently, lithium has been found to reduce iodine uptake in several *in vivo* studies (Table S2). The effect of lithium appears to be exerted (at least in part) from the inhibition of G protein/adenylate cyclase/protein kinase A signalling pathways (Fig. 2). Experimental data on these systems clearly show that the molecular initiating event (MIE) can specifically impair TSH-mediated events; some of these events (iodine uptake, for example) have functional significance with regard to thyroid hormone production. Along with its adverse effect on iodine trafficking, lithium might also disrupt thyroid homeostasis by modulating deiodinase activities – particularly in the rat central nervous system (Eravci et al., 2000). Lithium had a tissue-specific effect on deiodinase activity in thyroid-responsive tissues (Eravci et al., 2000). Acute treatment (intraperitoneal injection) with a non-toxic dose (0.44 mEq) of lithium was associated with greater deiodinase (D)-II activity in the rat cortex, amygdala, hypothalamus and cerebellum (Eravci et al., 2000) but did not affect D-II activity in the pituitary. Consistently, T₄ levels were low in the four structures (indicating elevated D-II activity) and T₃ levels were elevated in all the structures other than the hypothalamus (Eravci et al., 2000). Sub-chronic treatment with lithium was associated with low D-II activity and an elevated T₄ level, whereas higher doses were associated with elevated D-II activity and a low T₄ level. Levels of T₃ and TSH were not affected (Eravci et al., 2000). Interestingly, gestational and lactational exposure to lithium increased DII and DIII gene expression levels in the cerebrum of rat offspring (Mohammed et al., 2021).

In conclusion of Section 3.1. on the thyroid effects induced by lithium, the analyzed human and animal studies were mainly focused on adult exposure to lithium. Only two rat studies examined the potential effects of lithium exposure during vulnerable developmental stages (e.g. the foetal and postnatal (PN) periods (Ahmed et al., 2021; Mohammed et al., 2020)). However, it is well known that maternal thyroid hormones have key roles during the early and even late stages of prenatal neural development in rodents and humans (de Escobar et al., 2004). In this context, the data presented in this section should be taken into consideration with regard to the potential neurodevelopmental consequences of disruption of the maternal thyroid hormone system.

3.2. Effects of lithium on neurodevelopment

We focused on the potential neural effects of lithium exposure during critical developmental periods, during which thyroid hormones regulate key cellular processes (such as neurotransmitter synthesis and cell differentiation, migration, maturation, and synaptogenesis) in the developing brain (Bernal, 2005).

3.2.1. Data from studies of humans

Ten epidemiological studies addressed the possible influence of lithium on neurological development in children exposed to the substance *in utero*. Four studies found that maternal consumption of lithium led to lithium exposure via breastfeeding (Flaherty et al., 1997; Gehrman et al., 2021; Marin Gabriel et al., 2018; Viguera et al., 2007). No neurological effects were reported in the children, other than one case of

voluntary maternal intoxication that resulted in lethargic suck-shallow coordination (before delivery, the mother had a lithium level of 2.6 mEq/L, and the infant's initial lithium level at birth was 2.1 mEq/L, remaining at 1.4 mEq/L at the third day of life). The infant required enteral feeding, and the problem resolved after seven days (Flaherty et al., 1997). However, the extremely small sample sizes in the four studies (1 to 10 individuals) make it impossible to draw firm conclusions about the safety of lithium exposure through breastfeeding.

Six studies investigated the relationship between prenatal exposure to lithium and neurological development. Auerbach et al. (1992) compared 12 children born to manic-depressive women treated with psychotropic drugs (including lithium, in one case) during pregnancy with 17 children born to women with no history of psychiatric illness. No neurological differences were observed at delivery or on the third and 14th days after birth. Santucci et al. (2017) investigated 197 mother-infant dyads: 81 of the women had a bipolar disorder at the time of pregnancy (either not treated (n = 27) or treated with a psychotropic drug (n = 54, including 7 cases of lithium) and the other 116 did not have bipolar disorder and had not been exposed to psychotropics. By rating the Bayley Scales of Infant Development, Santucci et al. (2017) found no differences in the Psychomotor Development Index, the Mental Development Index or the Behavioral Rating Scale at 12, 26 and 52 weeks of age. However, the researchers reported a specific effect of prenatal psychotropic exposure on the quality of motor function at 52 weeks. Forsberg et al. (2018) evaluated full-scale performance and the verbal intelligence quotient (IQ) in 39 children aged between 4 and 5 years and did not observe any differences between those exposed *in utero* to lithium for a maternal mood disorder (MMD) (n = 20), those exposed to MMDs during pregnancy only (n = 8), and those not exposed to MMDs or lithium during pregnancy (n = 11). Van der Lugt et al. (2012) used various scales (including the Bayley and Wechsler scales) to evaluate the IQ in 15 children aged variously between 3 and 15 years and having been exposed to lithium *in utero* but not during breastfeeding. Growth, behaviour and general development variables were within the normal ranges, except in one child with signs of a minor neurological dysfunction and a lower IQ. Based on the retrospective Lithium Baby Register, Schou et al. (1976) reported the absence of mental or neurological abnormalities in 60 children exposed *in utero*, relative to their 57 non-exposed siblings. Jacobson et al. (1992) prospectively collected the pregnancy outcomes of women who had contacted a public teratogen information service and reported the absence of neurological adverse events in the 22 children exposed to lithium during pregnancy. However, these results must be interpreted with caution as the assessment was carried out directly by the mothers, who were contacted by postal or phone questionnaire, without physical examination.

Ando S. et al. (2017) investigated the association between daily environmental exposure to lithium in tap water during adolescence and mental health problems in a cohort of 3040 Japanese teenagers. The lithium concentration in tap water (mean ± standard deviation value: 0.48 ± 0.52 g/L) was inversely associated with self-reported depressive symptoms (p = 0.02) and interpersonal violence (p = 0.02) but not with suicidal ideation (p = 0.82) as evaluated with the 12-item General Health Questionnaire.

In conclusion, and with the exception of documented cases of poisoning in which neurological effects of lithium are well documented (Baird-Gunning et al., 2017), one cannot conclude from the epidemiological data that lithium exposure *in utero* has neurological consequences. However, the published studies had small sample sizes and included women who were taking medications (known to have neurological side effects) other than lithium to treat their psychiatric disorders. This design constitutes a major source of bias because it was impossible to examine the neurological effect of lithium in isolation. Lastly, the results of the study addressing environmental exposure to lithium suggest that the substance can impact the nervous system in young populations but do not provide insights into the mode of action.

3.2.2. Data from studies of animals

We reviewed six studies in which rodents were exposed to lithium *in utero* and after birth (Abu-Taweel, 2012; Mohammed et al., 2020, 2021; Rastogi and Singhal, 1977a; Rastogi and Singhal, 1977b; Youngs et al., 2006) (Table S3). It is noteworthy that in rodents, the time window for sensitivity of the brain to thyroid hormones extends from the foetal period to PN weeks 3–4 (Anderson et al., 2003). In particular, a peak of thyroid hormone release (corresponding to maturation of the pituitary-thyroid axis) occurs after birth (Walker et al., 1980).

3.2.2.1. Neurodevelopmental effects. In the study by Abu-Taweel (2012), Swiss-Webster female mice were exposed to lithium chloride in drinking water (0.35 or 0.7 mEq/kg of lithium) from gestational day 1 to PN day (PND) 15. At both dose levels, the offsprings' righting reflex, cliff avoidance, and the rotating reflex were impaired from PND1 to PND22. Eye opening and hair appearance were also delayed. These effects were associated with a dose-dependent relative reduction in body weight suggestive of lithium-induced growth retardation. At PND22, locomotor activity (as assessed in the open-field test) and mobility were impaired.

In another study, Sprague Dawley rats received intraperitoneal injections of 1.6 mEq/kg lithium carbonate from PND25 to PND31 (Rastogi and Singhal, 1977a). To induce hyperthyroidism, the animals had also been treated with a subcutaneous dose of 10 µg/100 g T₃ from PND1 to PND30. The resulting data showed that T₃ treatment was associated with greater locomotor activity, while cotreatment with lithium carbonate during the last six days was associated with lower (control) levels of activity (Table S3). In a comparable study, the same authors cotreated control or T₃-treated rats with 1.6 mEq/kg lithium during the last 10 days of vehicle or T₃ treatment (Rastogi et al., 1977b). The data showed similar elevated locomotor activity in hyperthyroid animals, while this activity was lowered to the control level in animals co-treated with lithium. It thus appears that prenatal and/or postnatal exposure to lithium is associated with lower activity in both basal and T₃-induced hyperthyroid conditions.

Youngs et al. (2006) evaluated the effects of oral exposure to 1.08 mEq/kg lithium carbonate from PND20 to PND41 on the level of anxiety in Sprague Dawley rats. In both the open-field and elevated plus maze tests two or six weeks after end of the exposure, lithium-treated rats explored anxiogenic areas less than control rats. In contrast, no effects on the conditioned fear response and spatial memory were observed. Thus, lithium treatment selectively induced long-term effects on basal anxiety-related behaviour. These changes were associated with changes in transcription levels of genes coding for synapse and cytoskeleton components in the amygdala – a key brain area involved in modulation of the level of anxiety (Ressler, 2010).

3.2.2.2. The mode(s) of action underlying neurodevelopmental effects. The behavioural impairments observed in rodents exposed to lithium during their development were associated with changes in several neurotransmitter pathways. Low acetylcholine esterase activity was measured in PN brain homogenates from lithium-treated male mice (Abu-Taweel, 2012). Levels of monoamines (serotonin, norepinephrine, and dopamine) were also measured in the cerebrum of Wistar rats exposed orally to 1.18 mEq/kg lithium chloride from gestational day 1 to lactational day 28 (Mohammed et al., 2020). Altered monoamine and dopamine levels were observed at all studied PN stages (Table S3). In another study by the same authors and under similar experimental conditions, lithium treatment altered the histology of the cerebral cortex and the oxidant/antioxidant ratio and affected the expression level of deiodinases II and III (Mohammed et al., 2021). In the studies by Rastogi and Singhal (1977a, 1977b), the increased locomotor activity induced by T₃ treatment in rat pups was associated with high dopamine levels in several brain areas. Interestingly, concomitant treatment with lithium carbonate during the last 6 or 10 days of PN T₃ administration reduced the rats' dopamine levels to control value (Table S3). In euthyroid

control rats, lithium co-treatment during the last 6 days of T₃ treatment was also associated with low PN dopamine levels in the striatum – one of the key brain areas modulating locomotor activity (Rastogi and Singhal, 1977). These findings indicate that lithium exposure may dampen basal and T₃-induced increases in dopamine levels and can thus counteract the neural effects of thyroid hormones.

4. Discussion

Our review confirmed that pharmacological doses of lithium induce hypothyroidism in adult humans and rodents. Interestingly, we found that (i) the studies of lithium exposure during pregnancy in humans did not document maternal thyroid function, and (ii) developmental exposure to lithium in animals can induce behavioural effects. Given the role of maternal thyroid hormones in the regulation of several neural processes and the known association between thyroid hormone levels during early pregnancy and the offspring's IQ (Korevaar et al., 2016), we consider that lithium exposure during pregnancy can impact maternal thyroid hormone levels, which may then impair neurodevelopment. Whether environmental levels of lithium could trigger these effects is discussed below.

Lithium's disruption of the human thyroid system is evidenced by the epidemiological data on hypothyroidism. Furthermore, and despite limitations in the oldest studies, a consistent body of data from animal studies highlights the effects of lithium on thyroid function. The effects induced by lithium were possibly related to disruption of NIS and/or TPO activities. One of the suggested MIEs corresponds to the inhibition of cAMP production in thyrocytes. This mechanism can occur in other cell types, since lithium is known to inhibit G protein signal transduction pathways and thus intracellular messenger production. Although lithium might inhibit cAMP production elsewhere in the organism, this MIE primarily targets the thyroid. Lithium can specifically interfere with TSH-mediated events (including iodine uptake), which reduce thyroid hormone production. It is important to note that changes in circulating thyroid hormone levels and/or thyroid gland histology are considered to be harmful effects.

A majority of experimental studies investigating the thyroid effects of lithium were conducted in adult animals. However, two studies addressing the effect of gestational and/or lactational exposure to lithium indicated a hypothyroid state of dams and their offspring (Ahmed et al., 2021; Mohammed et al., 2020). It is well known that maternally sourced thyroid hormones are required during the first trimester of gestation in humans and during the first two weeks of pregnancy in rodents, when the foetal thyroid gland is inactive (Prezioso et al., 2018). Thereafter, both maternal and foetal thyroid hormones are necessary for normal cerebral development. Given the crucial role of maternal thyroid hormones in neurodevelopmental processes and the thyroid effects induced by lithium in adult humans and rodents, there is a high level of evidence for a relationship between thyroid disruption and neurodevelopmental impairments.

This relationship is also underpinned by the existence of two adverse outcome pathways (AOPs) 54 and 42 (Crofton et al., 2019; Rolaki et al., 2019). AOPs use the available knowledge to link molecular and cellular events to adverse outcomes through plausible modes of action (Browne et al., 2020, 2017). In particular, AOPs 54 and 42 link changes in iodine trafficking through the modulation of NIS and/or TPO activities, respectively, to neurodevelopmental issues such as impairment in hippocampal and cognitive functions. It is possible that by reducing NIS and/or TPO activities, lithium exposure results in lower circulating levels of thyroid hormones and, ultimately, the disruption of cognitive processes. In addition, the availability of thyroid hormones can be impacted in the brain as shown by the changes in the expression levels of deiodinases in the cerebrum of postnatal offspring exposed through their dams (Mohammed et al., 2021).

Although the cognitive effects of lithium exposure need to be better characterized, the results of animal studies show that lithium exposure

impairs locomotor activity (Abu-Taweel, 2012; Rastogi and Singhal, 1977). Motor activity and skills are known to be regulated by thyroid hormones (Báñez-López et al., 2019). It remains to be established whether the effects of lithium on locomotor activity and the underlying brain catecholaminergic pathways are direct (i.e. by acting on neural cells) or indirect (via thyroid hormone system disruption). Lithium's broad effects include the inhibition of excitatory neurotransmitters (dopamine and glutamate) and the stimulation of inhibitory ones (gamma-aminobutyric acid (GABA)). One of the lithium's mechanisms of action in the treatment of bipolar disorders is related to the inhibition of dopamine neurotransmission (Malhi et al., 2013). Therefore, the reduction of striatal dopamine levels under both basal and T₃-induced conditions (Mohammed et al., 2020; Rastogi and Singhal, 1977a, 1977b) is of interest and might explain (at least in part) the observed low level of locomotor activity observed after lithium treatment. Along with dopaminergic neurons, thyroid hormones are also involved in the development of cholinergic, and glutamatergic and GABAergic neurons (for a review, see Martin and Mayerl, 2023). By altering thyroid hormone levels, lithium might also interfere with these neurotransmission pathways. Overall, a thyroid-mediated neurodevelopmental effect of lithium is plausible but cannot be dissociated from a direct, non-endocrine action on cerebral neurotransmitter pathways. It is possible that lithium targets simultaneously both pathways.

Most studies of the effects of lithium on human focused on therapeutic doses, which were ranged between 0.6 to 0.9 mEq/L (equivalent to 4.16 to 6.24 mg/L). Recent studies have found that lithium concentrations in drinking water are sometimes high – up to 1.5 to 1.7 mg/L in some cases (Lindsey et al., 2021; Neves et al., 2020; Seidel et al., 2019). The contribution of drinking water in lithium intake represents around 35 % for adults since lithium can be also supplied by diet (Anses, 2011). Given the rapid absorption of lithium, the cation's ability to cross physiological barriers (as evidenced in toxicokinetic studies) and the increasing use of lithium in new technologies, assessment of the effects of exposure to these environmental doses is of great importance. In this context, a small body of data from human studies suggests that environmental doses of lithium can induce thyroid and neural effects. Broberg et al. (2011) described thyroid effects of chronic exposure to environmental lithium, including lithium in drinking water. In a more recent ecological study including 52,706 Danish children, Liew et al. (2023) found that the environmental exposure to lithium through tap water during pregnancy was associated with a significantly elevated risk of autism spectrum disorder (odds ratio [95 %CI]: 1.46 [1.35–1.59]). Although this study was of good quality, the estimation of lithium internal dose was based only on home address information. In addition, exposure level through other sources (e.g. diet) was not measured.

5. Conclusions

The weight-of-evidence analysis of data from studies on humans and animals shows unambiguously that lithium exposure induces thyroid dysfunction (with similarities to hypothyroidism) and histopathological changes in the thyroid gland. Lithium therefore meets the WHO's definition of an endocrine disruptor. The reported differences in thyroid hormone levels might have neurodevelopmental consequences, as supported by AOPs linking changes in thyroid hormone levels to neurodevelopmental effects. Studies in animals have shown that developmental exposure to lithium induces behavioural effects. However, it is not yet known whether the underlying mode(s) of action involve thyroid pathways and/or other endocrine or non-endocrine pathways.

It is clear that therapeutic doses of lithium disrupt the thyroid system (Czarnywojtek et al., 2020). However, there are few published data on thyroid disruption at environmental concentrations of lithium. Given the increasing use of lithium in several industrial applications (including the production and recycling of batteries), environmental levels of lithium will probably rise (Bibienne et al., 2020; Bolan et al., 2021).

Particular attention must be paid to this emerging pollutant and its potential effects on human health and the environment.

CRedit authorship contribution statement

Nicolas Chevalier: Writing – review & editing, Formal analysis. **Pauline Guillou:** Writing – original draft, Formal analysis. **Catherine Vigié:** Writing – review & editing, Formal analysis. **Jean-Baptiste Fini:** Writing – review & editing, Formal analysis. **Laurent M. Sachs:** Writing – review & editing, Formal analysis. **Cécile Michel-Caillet:** Writing – review & editing, Formal analysis. **Sakina Mhaouty-Kodja:** Writing – review & editing, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108861>.

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