ANSES Opinion
Request No 2019-SA-0116
Related requests 2011-SA-0024; 2011-SA-0208; 2011-SA-0336; 2012-SA-0119; 2016-SA-0155 and 2017-SA-0170

The Director General

Maisons-Alfort, 16 March 2021

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the "relevance of reassessing the health risks associated with the presence of perchlorate in drinking water, in light of the work by the US EPA published on 23 May 2019"

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 16 March 2021 shall prevail.

On 25 June 2019, ANSES received a formal request from the Directorate General for Health (DGS) to undertake the following expert appraisal: Relevance of reassessing the health risks associated with the presence of perchlorate in drinking water (DW), in light of the work by the United States Environmental Protection Agency (US EPA) published on 23 May 2019.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Since 2011, ANSES has been asked on several occasions to examine the health risks associated with perchlorate in DW following the identification of situations in which resources used for DW production were contaminated. In 2011, the Agency had recommended a guideline value (GV) for perchlorate in DW of 15 µg.L^{-1} for adult consumers, derived from the toxicity reference value (TRV) of 0.7 µg.kg bw^{-1}.d^{-1} based on the inhibition of iodine uptake by the thyroid gland, and advised avoiding water contaminated by perchlorate when preparing feeding bottles for infants aged up to 6 months.

In 2012, in its opinion concerning epidemiological studies on associations between exposure to perchlorate in DW and thyroid function in specific populations, the Agency had concluded that "the results from the evaluated epidemiological studies do not enable conclusions to be drawn concerning the possible association between thyroid-stimulating hormone (TSH) levels

and perchlorate concentrations in drinking water in pregnant women and newborns [...]. The absence of information concerning the iodine status of the studied populations makes it difficult to interpret the published epidemiological data."

In its opinion of 8 April 2014 on the presence of perchlorate in infant formula and in DW, the Agency had noted the same limitations relating to the available epidemiological studies and insisted on the need to take account of the iodine status of the study population for assessing the health impact of perchlorate in humans and for interpreting the published epidemiological data.

In its most recent opinion of 26 December 2018, the Agency had concluded that recent epidemiological studies, including the one by the French Institute for Public Health Surveillance[1] (InVS) published in 2016, did not provide any additional conclusive evidence on the biological or clinical effects of perchlorate compared to those taken into account in the previous ANSES opinions (ANSES 2011, 2012, 2014). The data examined in this opinion did not call into question the conclusions of the previous ANSES opinions concerning the hazard characterisation and the TRV proposed by the Agency in 2011.

However, with regard to the assessment of exposure to perchlorate, new data made it possible to estimate the average oral exposure of the adult population to perchlorate. This estimate was based on perchlorate contamination of food (data collected by the Directorate General for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF) as part of its national surveys) and contamination of DW for the period 2014-2017 (data produced by the Regional Health Agencies (ARSs) and available in the SISE-Eaux database). On this basis, ANSES estimated that exposure via DW consumption accounted for about 25% of ingestion exposure. As this estimate was in line with the literature data and was close to the 20% default percentage defined by the WHO in 2016, the Agency felt it necessary to lower the share of exposure via water, previously set at 60%, used for calculating the GV of perchlorate in DW for adults. As a result, the proposed GV was lowered to 5 $\mu g.L^{-1}$ for the adult population.

ANSES also emphasised that the existing data on food contamination were too incomplete to characterise the distribution of the general population's exposure to perchlorate by the oral route and to assess the health risk, and recommended that perchlorate be taken into account in the third French Total Diet Study (TDS3).

In the absence of new data on the contamination of infant formula with perchlorate, the Agency also reiterated the conclusions of its 2014 expert appraisal: "daily intakes of perchlorate, calculated on the basis of perchlorate levels in infant formulas available on the French market, do not exceed the TRV of 0.7 $\mu g.kg\ bw^{-1}.d^{-1}$ for 95% of the population of children aged under 6 months consuming infant formula based on an average concentration of perchlorate of 1 $\mu g.L^{-1}$ in DW for reconstituting infant bottles" (ANSES, 2018).

Lastly, ANSES indicated in this same 2018 opinion, in Section 3.2.8 concerning the conclusions on the choice of the TRV, that "the Working Group on "Assessment of the health risks associated with chemical parameters in drinking water" and the Expert Committee (CES) on "Water" considered that in any future assessment of the health risks associated with the ingestion of perchlorate, following publication of the work under way by the US EPA, it will be

[1] Became *Santé Publique France* (SPF) on 1 May 2016

necessary to re-examine the method for determining the critical dose and establishing the TRV for perchlorate."

Background of the current request

On 23 May 2019, the US EPA published proposed toxicity reference values for perchlorate and values for its management in DW. Having adopted a different method (including toxicokinetic-toxicodynamic modelling) and selected a critical effect that differed from the biological effect considered by all the other organisations establishing TRVs (Table I), the US EPA suggested, among the three proposed values, adopting a TRV of 2.2 µg.kg $bw^{-1}.d^{-1}$, resulting in a maximum contaminant level of 56 $\mu g.L^{-1}$ perchlorate in DW.

With reference to Section 3.2.8 concerning the conclusions on the choice of the TRV in ANSES's above-mentioned opinion of 26 December 2018 and in view of the management difficulties encountered, the DGS formally asked ANSES to analyse the work of the US EPA on the assessment of the health risks associated with the presence of perchlorate in DW, in order to provide the ARSs with appropriate and proportionate guidance on the health risk (Annex 3). Depending on the conclusions of this critical analysis of the US EPA's work, it may then be necessary to reconsider ANSES's TRV of 2011, the conclusions of the health risk assessment in ANSES's opinion of 2014, and the GV established in 2018.

In view of this, ANSES was also asked to re-examine the assessment of the health risks associated with the ingestion of perchlorate, in light of the US EPA's work. The ultimate objective of this current expert appraisal was therefore to determine whether ANSES's current TRV should be maintained and to develop a new TRV if necessary. With regard to the scope of the expert appraisal, ANSES points out that the economic impact analysis carried out by the US EPA was outside the scope of the formal request and was therefore not assessed by ANSES.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

The expert appraisal falls within the sphere of competence of the CES on "Water" and the CES on "Health Reference Values" (VSR), whose members are listed in Annex 1. ANSES entrusted the expert appraisal to the *ad hoc* WG on "Perchlorate".

The work conducted for this opinion was presented to the CES on "Water" on 10 November 2020, 12 January and 2 February 2021 and to the CES VSR on 23 October 2020 and 8 January 2021. The work was validated by the CES VSR on 5 February 2021.

This work was also presented to the WG on "Assessment of the health risks associated with chemical parameters in drinking water" on 27 November 2020 and to the WG on "Endocrine Disruptors" on 18 January 2021. The work was therefore conducted by committees and groups of experts with complementary skills.

Mr Tim Korevaar, author of the publication used by the US EPA in its approach (Korevaar *et al*. 2016), responded by email to questions from the WG on "Perchlorate".

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are published on the ANSES website (https://dpi.sante.gouv.fr/).

The expert appraisal was based on the US EPA reports, previous ANSES opinions, and scientific articles published since the last ANSES work. The first step in the work of the WG on "Perchlorate" was to assess the Biologically Based Dose Response (BBDR) model developed by the US EPA. In parallel, analyses were conducted of the studies selected by the US EPA, the key study (Korevaar *et al.,* 2016) adopted, and the critical effect adopted by the US EPA. Lastly, ANSES points out that in view of the time available for responding to the formal request, the WG on "Perchlorate" was unable to check operation of the scripts of the BBDR model and therefore concentrated on the analysis of the results presented by the US EPA.

3. ANALYSIS AND CONCLUSIONS OF THE WG ON "PERCHLORATE" AND THE CES VSR

3.1. Introduction

3.1.1. Physiology of thyroid function

3.1.1.1. Physiological basis

Thyroid hormones (THs) comprise two main hormones: thyroxine (T4), which is produced entirely by the thyroid gland within the follicles, and triiodothyronine (T3), 20% of which is produced by thyroid secretion and the rest by tissue deiodination of T4 (see below). Thyroid follicles consist of an epithelium synthesising and secreting THs, the thyrocytes, and a central cavity filled with a storage protein for the iodine precursors of THs, thyroglobulin, which forms the colloid substance. The latter therefore contains significant reserves of iodine (Figure 1 in Annex 4).

In the bloodstream, THs are mostly bound to specific high-affinity transporters (thyroxine-binding globulin or TBG; transthyretin or TTR) or non-specific transporters such as albumin. The free forms of T4 (free thyroxine or fT4) and T3 (free triiodothyronine or fT3) are active.

Production and secretion of THs is subject to hypothalamic-pituitary control. The hypothalamic neurohormone TRH (thyrotropin-releasing hormone) stimulates the secretion of pituitary TSH, which in turn stimulates the synthesis, secretion and cell dynamic activities of the thyroid gland. In order to maintain the balance of the thyroid axis, THs exert negative feedback at the hypothalamic-pituitary level (Figure 2 in Annex 4).

THs and their metabolites are the only endogenous molecules containing iodine, a trace element that is essential for the production of TH and whose main source is food. Iodine is

transferred to the thyroid follicles in large quantities through an active transporter: the sodium-iodide symporter (NIS) expressed on the basolateral membrane of thyrocytes (Figure 1 in Annex 4).

TH metabolism ensures the recycling of iodine which, stored in the thyroid follicles, persists for several months in the body.

There are two main pathways for TH metabolism:

- tissue deiodination, thanks to deiodinases type 1 (D1), 2 (D2) and 3 (D3). Peripheral deiodinases allow the recycling of circulating iodine for its re-uptake by the thyroid gland;
- hepatic metabolism in which THs undergo glucurono- and sulphoconjugation (Visser, 1996). The glucuronides in THs are rapidly excreted in the bile and some undergo an enterohepatic cycle. Nevertheless, about 20% of the daily T4 production is eliminated in the faeces (Peeters and Visser, 2017).

THs have a pleiotropic effect on many functions such as growth, metabolism and development. They are necessary for cell proliferation and differentiation, particularly in the central nervous system (CNS) during development.

3.1.1.2. Maternal-foetal thyroid function

In humans, THs in the first trimester of pregnancy come exclusively from the mother. The foetal thyroid only starts to become functional from the second trimester of pregnancy (Figure 3 in Annex 4). However, the foetus expresses the nuclear receptors for THs (thyroid hormone receptor α or TRα and TRβ) from the ninth week (Bernal *et al.*, 1984), suggesting that THs are important even before the foetus is able to synthesise them.

There is an estimated increase of around 50% in maternal T4 requirements and synthesis to meet pregnancy-specific needs (Glinoer, 1997), mainly due to the following physiological changes:

- the oestrogen-dependent increase in circulating TBG concentrations from the beginning of pregnancy, which results in a progressive increase in circulating concentrations of total T4 and then T3 (Ain *et al*., 1987);
- the increase in glomerular filtration rate, which increases iodine clearance;
- the transfer of T4 from the mother to the foetus via specific transporters expressed in the placenta (organic anion transporting polypeptides 1C1 or OATP1C1, monocarboxylate transporter 8, or MCT8 and MCT10), modulated by D3 which inactivates T4 into rT3 (reverse T3).

Maternal human chorionic gonadotropin (hCG), secreted by the placenta, is a weak TSH agonist, which contributes to the stimulation of T4 and T3 hormone synthesis by the maternal thyroid and to a transient decrease in circulating TSH levels. Although changes in free TH levels, particularly in early pregnancy, differ depending on the assay method used (Andersen *et al*., 2020), it appears that there is a moderate and temporary increase in fT4 during the first trimester of pregnancy, which then declines (Medici *et al*., 2016).

The only source of iodine for the foetus and breastfed infant is maternal. Iodine requirements vary according to age and physiological circumstances. They are around 100 $\mu g.d^{-1}$ in children

and 150 µg.d^{-1} in adolescents and adults. These requirements increase in pregnant or breastfeeding women (250 µg.d^{-1}) due to an increase in iodine clearance and the specific needs of the foetus or infant (WHO, 2007). The NIS is expressed in the placenta and mammary gland, and is essential for supplying iodine to the foetus and/or infant. Furthermore, NIS expression in the foetus is an important element of thyroid ontogeny. In the human foetus, the ontogeny of the thyroid gland begins with the formation of precolloidal substance. "Mature" colloidal substance begins to form at around 10 weeks of pregnancy shortly before the start of TH synthesis. Thyroid follicle growth becomes significant at around 12 weeks. Expression of the *slc5a5* gene (encoding NIS) in the foetal thyroid increases significantly and is concomitant with the start of colloid formation. Expression of the *slc5a5* gene in the foetus towards the end of the first trimester of pregnancy is therefore a limiting factor in the development of foetal thyroid function (Szinnai *et al.*, 2007). Disruption of expression of this gene or of the functionality of NIS by exposure to goitrogens, from the start and throughout pregnancy, is associated with adverse effects on brain development. This is all the more critical since the foetal thyroid is particularly sensitive to transient changes in iodine intake because it stores little iodine.

As mentioned earlier, THs play an essential part in development of the CNS, as evidenced by cases of congenital hypothyroidism due to deficient maternal TH levels during pregnancy (Morreale de Escobar *et al.*, 2004a; Zoeller and Rovet, 2004). Indeed, changes in TH synthesis and bioavailability during pregnancy have a negative effect on neurodevelopment from embryo to child (Giannocco *et al.*, 2020), including consequences for behaviour and cognition (Zoeller and Rovet, 2004). From the ninth week of pregnancy, maternal T4 regulates neuronal proliferation processes and the initiation of neuronal migration in the cerebral cortex, hippocampus and medial eminence of the foetus (Williams, 2008; Morreale de Escobar *et al.*, 2004b). From week 14 onwards, the foetus progressively contributes to the supply of THs while neurogenesis, neuronal migration, axonal growth, dendritic arborisation, synaptogenesis, glial cell differentiation and myelination become established (Howdeshell, 2002). From week 28 onwards, both mother and foetus contribute equally to the TH levels available to the foetus and thus to the ongoing maturation of the CNS. However, despite the increase in circulating foetal TH concentrations, the thyroid is not fully mature before birth and insufficient maternal blood TH concentrations can still cause potentially harmful effects. After birth, the child depends exclusively on TH synthesis by its own thyroid, while the process of myelination and the migration of granular cells in the dentate gyrus of the hippocampus and the cerebellum, pyramidal cells in the cortex and Purkinje cells in the cerebellum continues.

Conditions that affect T4 availability can affect both mother and foetus (Springer *et al*., 2017), including in a context of moderate disruption of thyroid homeostasis.

- Clinical hypothyroidism (CH) is defined as below normal fT4 levels[2] accompanied by TSH levels above 10 mIU/L (Garber *et al.*, 2012). Its incidence varies from 0.3 to 0.5% in pregnant women (Budenhofer *et al*., 2013).

[2] Usual values in humans: It should be noted that the values of this parameter depend on the technique used for its measurement. As an indication, the most frequently observed values are: 10 – 23 pmol/L, or 8 – 18 ngl/L (http://www.cnci.univ-paris5.fr/pharmacie/Constantes_biologiques_adultes_2009.pdf).

- Subclinical hypothyroidism (SCH) is defined as elevated TSH (>4.5 mIU/L) accompanied by normal fT4 concentrations. Its prevalence varies according to population, region, age and sex. Studies of large populations in various countries have reported a prevalence of 3-17% in the adult population, with higher frequencies in women and the elderly (Kim *et al*., 2014). The prevalence of SCH is high in pregnant women, between 2 and 4% (Biondi *et al*., 2012). When iodine intake is high, the frequency of SCH is below 0.2%, while in countries with normal or slightly deficient iodine intakes the incidences are 2-5% (Kim *et al*., 2014).
- Isolated hypothyroxinaemia is defined as a normal serum TSH concentration associated with a decreased fT4 concentration. Its incidence, significance and consequences are assessed in different ways.

3.1.2. Effects of perchlorate on thyroid function

The target organ in humans and animals for perchlorate (ClO_4^-) is the thyroid, where it competitively inhibits iodine uptake through the NIS, which ensures the entry of iodide together with sodium (two Na^+ ions for one I^- ion) and the accumulation of iodide in thyrocytes. *In vitro* data indicate that perchlorate is a potent NIS inhibitor (Schlosser, 2016). This effect has also been observed *in vivo* in humans and in other species (Concilio *et al*., 2020). The median inhibitory concentration (IC_{50}) in humans was found to be 1.56 µM (Concilio *et al.*, 2020).

Unlike thiocyanates, perchlorate does not disrupt the subsequent steps of hormone biosynthesis after entering the thyroid cell. It may interfere competitively with iodide for uptake through pendrin, an ion transport protein (Attanasio *et al.*, 2011) that ensures the transfer of iodine from the follicular cell to the colloidal substance, without its impact on possible modifications of thyroid physiology being clearly established.

The uptake of iodides by the thyroid through NIS is the initial limiting step in TH synthesis (Section 3.1.1 and Figure 1 in Annex 4). In the event of a change in iodine intake (excess or deficiency of exogenous iodine, including via food), several compensatory phenomena occurring in the thyroid, hypothalamus and pituitary gland maintain normal functioning of the thyroid. These mechanisms are overwhelmed in the event of a prolonged decrease in iodine supply to the thyrocytes (Lisco *et al*., 2020). Chronic iodine deficiency states contribute to goitrogenesis and increased plasma TSH concentrations before T4 and then T3 concentrations are lowered, indicating hypothyroidism.

This sequence, which is well documented in adults, can be assessed in a relevant and reliable way by measuring circulating THs. In an equilibrium state, in the absence of hypothalamic-pituitary abnormalities and methodological artefacts, a normal TSH concentration in a pregnant woman means that her own TH needs are adequately met.

Assessing foetal hormonal needs, however, is more indirect and imperfect. Due to placental transfers of TH and iodides (to an embryo dependent on maternal hormones alone) inherent in pregnancy, it is possible that the effects of an iodine inhibitor, even if regarded as negligible in adults, may not be compensated. This may be compounded if there is even a slight iodine deficiency during pregnancy. In this context, assessing the effects of perchlorate on regulation of maternal thyroid function solely on the basis of TH and/or TSH measurements may not be appropriate (Glinoer, 1997).

As mentioned in a previous opinion by the Agency (ANSES, 2014), sodium perchlorate can be used under temporary authorisations for use (ATU) for therapeutic purposes to treat ore prevent recurrence of cases of hyperthyroidism due to type 1 thyrotoxicosis induced by amiodarone (a Vaughan-Williams class III antiarrhythmic drug), as well as for diagnostic purposes to identify iodine organification disorders (perchlorate discharge test). The usual dosage in adults varies from 400 to 1000 mg.d^{-1} (ANSM, 2020; Bartalena *et al.*, 1996).

3.1.3. Available toxicity reference values (TRVs) for chronic oral exposure to perchlorate

In 2011, ANSES proposed a chronic oral TRV for perchlorate of **0.7 µg.kg bw^{-1}.d^{-1}** (ANSES, 2011). It drew on the study by Greer *et al.* (2002) carried out in healthy volunteers (21 women and 16 men) exposed to perchlorate in drinking water at doses of 7 – 20 – 100 and 500 µg.kg bw^{-1}.d^{-1} for 14 days and in whom a reduction in uptake of thyroidal radioiodine (^{123}I) was measured.

A statistically significant decrease (16.4%) in iodine uptake was observed from 20 µg.kg bw^{-1}.d^{-1}. However, no significant changes in serum TH concentrations were found, even at the highest doses.

The dose of 7 µg.kg bw^{-1}.d^{-1} was therefore identified as the no observed effect level (NOEL). The TRV was established by applying an inter-individual uncertainty factor (UF_H) of 10, to take into account the existence of more sensitive individuals (ANSES 2011, 2012, 2018).

The NOEL of 7 µg.kg bw^{-1}.d^{-1} was chosen for deriving the TRV for the following reasons:

- iodine uptake by the thyroid is one the first steps in synthesis of THs;
- clinical situations of congenital hypothyroidism have demonstrated the impact of TH deficiency in the embryo, foetus or infant on neurocognitive development. In addition, recent data show an association between moderate maternal TH changes during pregnancy and neurodevelopmental disorders, particularly in the first trimester when only maternal TH is present (Fetene *et al.,* 2018; Moog *et al.*, 2017; Thompson *et al.,* 2018). These results suggest that the embryo, foetus and newborn are *a priori* the most sensitive populations at the neurodevelopmental level to the effects of even transient or moderate TH depletion.

The choice of critical effect, key study and critical dose used to calculate the TRV and the uncertainty factor of 10 for inter-individual variability (UF_H) adopted in ANSES's 2011 opinion have also been proposed by other agencies, including the National Research Council (NRC) (2005), the US EPA (2005), the Agency for Toxic Substances and Disease Registry (ATSDR) (2009) and the National Institute for Industrial Environment and Risks (INERIS) (2011).

Like the other agencies, ANSES did not feel it necessary to apply an uncertainty factor linked to the short duration of the key study (UF_S) in view of the nature of the critical effect considered (precursor biological effect) and the non-accumulation of perchlorate in the body.

Until the work published by the US EPA in 2019, the TRVs developed by the various agencies were all based on the study by Greer *et al.* (2002) (Table I). The main difference between the TRVs adopted by ANSES (2011), US EPA (2005), ATSDR (2009), OEHHA (2015) and EFSA (2014), and those selected by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (2011) and the WHO (2016) was the magnitude of the critical effect considered. The first organisations (US EPA, ATSDR, INERIS and ANSES) used the highest dose of

perchlorate associated with no significant effect on iodine uptake by the thyroid (NOEL), whereas JECFA and the WHO used the dose leading to 50% inhibition of this uptake (Benchmark Dose 50% or $BMD_{50}L_{95}$). EFSA (2014) considered that prolonged inhibition of 50% of iodine uptake by the thyroid could increase the risk of toxic multinodular goitre and selected a Benchmark Response (BMR) of 5% (default BMR value used for continuous variables). Health Canada recently adopted a BMR of 20% based on intra-individual variability in the radioactive iodide uptake (RAIU) test, in order to develop a preliminary value in DW.

Table I – Chronic oral TRVs for perchlorate published by North American, European and international health risk assessment agencies

Organisation	**NRC US EPA**	**ATSDR**	**INERIS**	**ANSES**	**JECFA**	**EFSA**	**OEHHA**	**WHO**	**Health Canada**
Year	2005	2009	2011	2011	2011	2014	2015	2016	2020
TRV	RfD	*Minimal risk level* (MRL)	Ref-erence value	TRV	Provisional maximum tolerable daily intake (PMTDI)	*Tolerable Daily Intake (TDI)*	*Acceptable Daily Dose* (ADD)	PMTDI	Tolerable Daily Intake (TDI)
TRV value ($\mu g.kg\ bw^{-1}.d^{-1}$)	0.7				10	0.3	0.37	11	1.09
Critical effect	Inhibition of radiolabelled iodine uptake by the thyroid								
Species	Humans (healthy volunteers)								
Route of exposure	Oral (drinking water)								
Duration of exposure	14 days								
Point of departure ($mg.kg\ bw^{-1}.d^{-1}$)	NOEL = 0.007				$BMD_{50}L_{95}$ = 0.11	BMD_5L_{95} = 0.0012	BMD_5L_{95} = 0.0037	Ditto JECFA (2011)	$BMD_{20}L_{95}$ = 0.0109
Adjustments	/							/	/
Uncertainty factors	10 UF_H = 10				10 UF_H = 10	4 UF_H = 4*	10 UF_H = 10	10 UF_H = 10	10 UF_H = 10
Key study	Greer *et al.,* 2002								

*: Based on physiologically-based pharmacokinetic (PBPK) modelling, which shows a maximum fourfold difference in iodine uptake inhibition regardless of the population considered, EFSA applied a UF of 4 to this BMD_5L_{95} to take account of the toxicokinetic component of intra-species variability. No UF was applied to account for the toxicodynamic component of intra-species variability as EFSA considered that a 5% inhibition of iodine uptake would not result in an adverse effect, regardless of the population (ANSES, 2018).

3.1.4. TRV proposed by the US EPA in May 2019 based on a neurodevelopmental effect

In accordance with the recommendations of its Science Advisory Board (SAB), the US EPA has generated extensive work over the past decade based on perchlorate's mode of action (Figure 4 in Annex 4) and its effects on the most sensitive populations, in order to gain a better understanding of the potential health effects and associated health risks of environmental exposure to perchlorate.

In particular, with the help of a group of external experts, the US EPA developed a "BBDR" model to predict the effect of perchlorate on the thyroid. In order to consider the most

vulnerable population, the US EPA adopted the following assumptions: pregnant women in the first trimester of pregnancy with a low serum fT4 concentration (< 10th percentile), a low daily iodine intake (75 µg.d^{-1}) and weak TSH feedback.

In May 2019, the US EPA proposed new TRV values based on a two-step approach combining the results of the BBDR model in pregnant women in the first trimester with quantitative data from an epidemiological study on the impact of a decrease in maternal fT4 in the first trimester of pregnancy on the neurodevelopment of the child as measured by a decrease in the intelligence quotient (IQ) (Figure I).

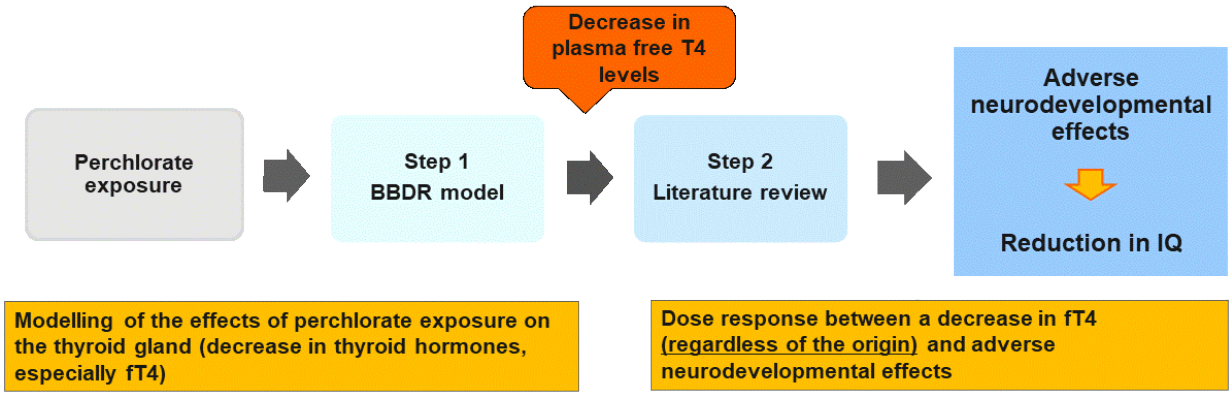


Figure I – US EPA's proposed approach

Therefore, after matching the results of the BBDR model with the dose-response function estimated from an independent analysis of the data from the study by Korevaar *et al*. (2016), the US EPA identified critical doses of 3.1, 6.7 and 10.8 µg.kg bw^{-1}.d^{-1} perchlorate corresponding to a 1-, 2- and 3-point decrease in IQ, respectively. As the IQ is standardised to an average of 100, a 1-point decrease is equivalent to a 1% decrease compared to the standard average IQ.

The US EPA therefore proposed a reference dose (RfD) of 2.2 µg.kg bw^{-1}.d^{-1} for chronic exposure to perchlorate by ingestion, corresponding to a 2-point (or 2%) decrease in IQ and including a UF_H of 3. Alternative TRVs of 1 and 3.6 µg.kg bw^{-1}.d^{-1} corresponding to a 1- and 3-point decrease in IQ, respectively, were also submitted for comment.

Table II – Chronic oral TRV values for perchlorate proposed by the US EPA (2019)

Critical effect *Key study*	**Corresponding reduction in fT4 pmol.L^{-1}**	**Critical dose (µg.kg bw^{-1}.d^{-1})**	**UF**	**TRV (µg.kg bw^{-1}.d^{-1})**
Decreased IQ				
1%	0.21	3.1		RfD = 1
2%	**0.41**	**6.7**	**3**	**RfD = 2.2**
3%	0.61	10.8		RfD = 3.6
Korevaar *et al*. (2016) Mother-child cohort		*BBDR model*	UF_H = 3	

The experts note that the TRV value proposed by the US EPA corresponding to the consideration of a 1% decrease in IQ (i.e. 1 µg.kg $bw^{-1}.d^{-1}$) is close to the value selected by ANSES in 2011 based on data from Greer *et al*. (2002).

3.2. Analysis of the US EPA's proposed TRV (2019)

The work of the WG on "Perchlorate" was divided into three major steps. The first step was the analysis of the BBDR model (Section 3.2.1) and the second step was the analysis of the US Agency's bibliographical research to identify studies that have assessed incremental changes in fT4 in relation to neurodevelopmental alterations (Section 3.2.2). Following these two steps and their conclusions, the WG on "Perchlorate" conducted a literature update to identify data on associations between exposure to perchlorate and adverse effects or changes in thyroid parameters, published since the ANSES opinion of 26 December 2018 (Section 3.3).

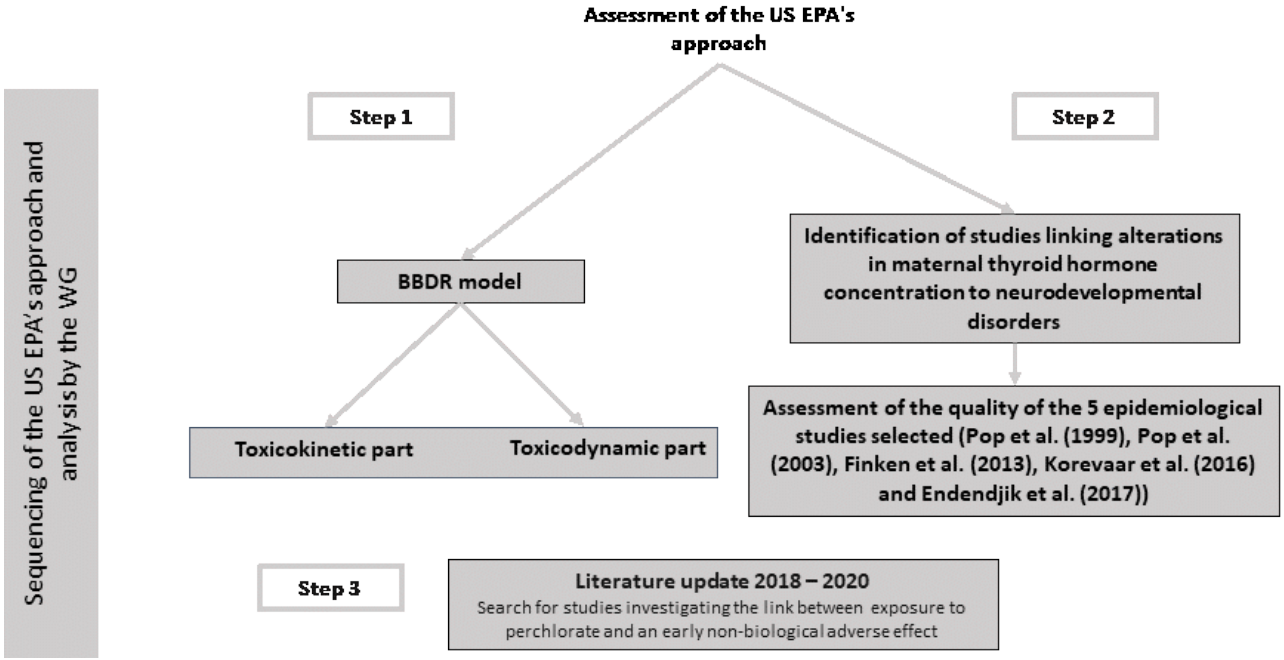


Figure II – Steps in the analysis of the US EPA's approach

3.2.1. Step 1: Biologically-based dose-response (BBDR) model

The objective of the BBDR model (US EPA, 2019) is to estimate the impact of perchlorate on the thyroid gland, in particular on serum TH concentrations, in women of childbearing age and in pregnant women up to the 16th week of pregnancy. It consists of two parts:

- a toxicokinetic part, for modelling the processes of absorption, distribution, metabolism and excretion (ADME) of perchlorate and iodide. This toxicokinetic model, associated with an exposure scenario, is used to predict the concentration of perchlorate and iodide in the thyroid gland;
- a toxicodynamic part that models the combined effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent TH production.

The BBDR model was reviewed by the experts of the WG on "Perchlorate" according to a roadmap reiterating the WHO's principles for assessing this type of model (IPCS, 2010), reported in Annex 5.

However, as mentioned above, in view of the limited time available, the WG on "Perchlorate" was unable to check operation of the scripts of the BBDR model and therefore concentrated on the analysis of the results presented by the US EPA.

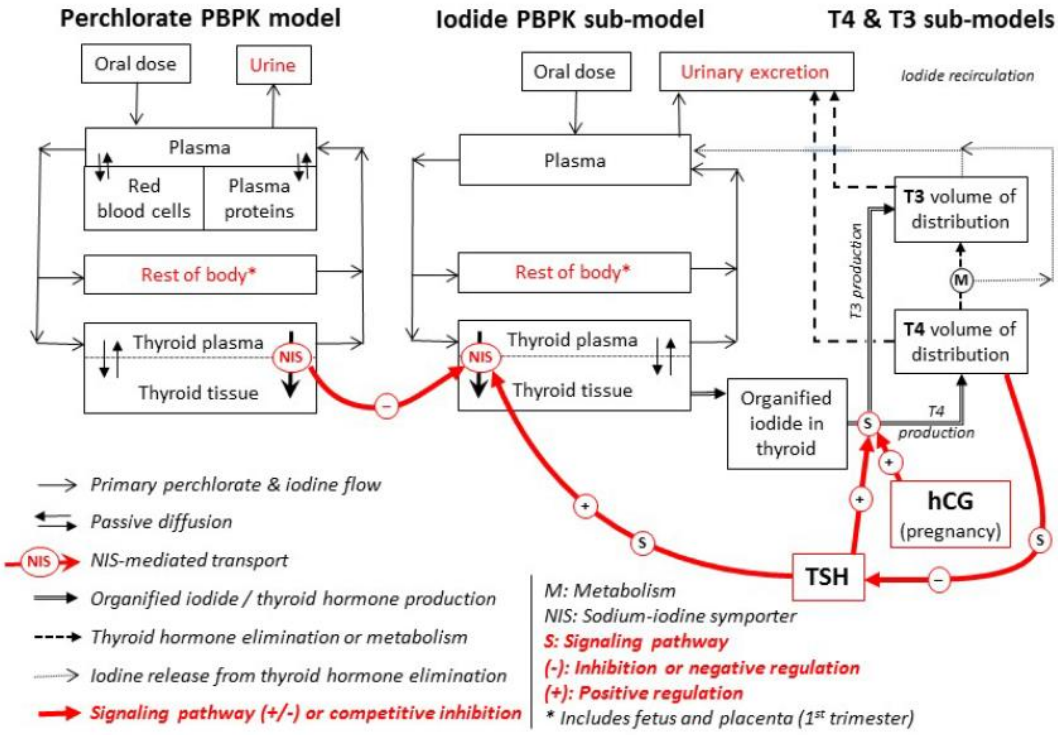


Figure III – Structure of the BBDR model – early pregnancy (US EPA 2019a)

3.2.1.1. Toxicokinetic part: perchlorate and iodide

Different versions of toxicokinetic models for perchlorate and iodide have been developed and revised since 2005 (Merrill *et al.*, 2005; Clewell *et al.*, 2007; Lumen *et al*., 2013). These models are based on similar assumptions for ADME processes with varying levels of detail and focus on different periods (adulthood, pregnancy, breastfeeding, breastfed infant). The US EPA built on this previous work to develop the BBDR model shown in Figure III above. This model, adopted by the US EPA in 2019, was adapted from the model of Lumen *et al*. published in 2013 and specific to the third trimester of pregnancy (for the perchlorate part), and from the model by Fisher *et al.* published in 2016 and specific to breastfeeding (for the iodide and TH part). Both models are themselves adaptations of the one by Clewell *et al*. (2007), which was reviewed by the US EPA in 2009.

- **Structure and ADME processes**

The 2019 version of the BBDR model is limited to the first trimester of pregnancy. This model has a simplified structure with only three compartments: plasma, thyroid and "rest of body"

(ROB), which includes the foetus and placenta. The US EPA chose not to describe the foetus and placenta as a separate compartment because of their negligible weights in the first trimester of pregnancy. The US EPA also pointed out that there are few quantitative data on the physiology of the placenta and the foetus and their biochemical interactions with perchlorate and iodide in early pregnancy with which to make predictions with reasonable confidence. Changes in certain physiological parameters of the toxicokinetic model during the first trimester of pregnancy – such as body weight, cardiac blood flow, or plasma volume – were taken into account.

The assumptions on toxicokinetic and metabolic processes (ADME) made by the US EPA were:

- absorption: 100% oral for perchlorate and iodide;
- distribution: the perchlorate model incorporates the binding and distribution of perchlorate to plasma proteins and red blood cells. This sub-compartmentalisation of the plasma compartment is justified in order to correctly reproduce the short-term kinetics and be able to assess the model against existing experimental data. As this sub-compartmentalisation has no impact on chronic exposure, the US EPA decided not to take it into account for the iodide model. The distribution of perchlorate and iodide in the ROB compartment is described as being dependent on plasma perfusion. The active transport of iodide and perchlorate by the NIS in the thyroid was described by dividing each "thyroid" compartment into blood and tissue sub-compartments. Perchlorate and iodide compete at the plasma level in the thyroid for uptake through the NIS, which is described by a Michaelis-Menten equation;
- elimination: perchlorate and iodide are excreted via urine without any prior metabolism.

■ Model calibration

The parameter values used in the toxicokinetic model were retained from previous toxicokinetic models, except for four parameters specific to perchlorate and iodide. These four parameters were: i) urinary ion clearance, ii) urinary iodide clearance, iii) the affinity constant (K_m) in the Michaelis-Menten equation governing perchlorate transport by the NIS, and iv) the maximum velocity (V_{max}) of iodide uptake by the thyroid gland. These four parameters were calibrated with toxicokinetic data from the study by Greer *et al.* (2002).

As shown in Annex 5, the new values for the four parameters result in perchlorate having a greater predicted effect on iodide uptake by the thyroid compared to previous models. It should be noted that the non-pregnant model rather than the pregnant model was used to calibrate these parameters.

■ Model validation

For serum concentration, two studies were available for assessing the perchlorate model (Merrill *et al.* 2005; Greer *et al*., 2002), bearing in mind that the study by Greer *et al.* (2002) was used to calibrate the four modified model parameters. In both studies, the exposed individuals were men and non-pregnant women. The model predictions compared to the available observed datasets were within an error range of a factor of 2, therefore allowing its acceptance in accordance with the IPCS guidance document (WHO, 2010).

Urinary excretion was assessed in three early publications (Durand, 1938; Eichler, 1929; Kamm and Drescher, 1973) in which men were exposed. The prediction of cumulative excretion was correct outside the first 12 hours, which has a negligible effect in a chronic exposure scenario.

- **Uncertainties related to the toxicokinetic part of the model**

Data were obtained on a limited number of individuals (mainly urinary excretion data) and on adult men and non-pregnant women. The model could therefore not be assessed for the population of interest, i.e. pregnant women in their first trimester.

No justification was given by the US EPA on the need to re-estimate certain parameters instead of using the same parameter values as in the previously developed PBPK models. There are significant differences (between a factor of 2 and a factor of 5.5) between the values chosen by the US EPA and those defined in the model of Lumen *et al*. (2013).

The new values for the four parameters result in a much greater predicted effect of perchlorate on iodine uptake by the thyroid compared to previous models (see Annex 5 of this opinion "Analysis of the US EPA's BBDR model according to the roadmap drawn up by ANSES during the European Human Biomonitoring Initiative (HBM4EU) project – November 2020"), which appears to be more protective.

In addition, although there are uncertainties inherent in considering a common placenta-foetus compartment different from the rest of the body, there are also uncertainties arising from simplification of the compartments. The WG on "Perchlorate" points out, however, that it is difficult to judge the consequences of all these uncertainties, since it is impossible to know whether they compound and/or compensate for each other.

Conclusion on the toxicokinetic part of the model

In general, the toxicokinetic part of the BBDR model for perchlorate has been rigorously assessed by the US EPA. This assessment shows that the kinetic model of perchlorate effectively reproduces the different data available in the literature, i.e. the changes in plasma concentration and cumulative urinary excretion in adults. This part of the model fulfils the IPCS (WHO, 2010) requirements for use in health risk assessment.

However, the WG on "Perchlorate" notes that some choices lack justification, or are based on datasets obtained from a small number of individuals, not representative of the population of interest.

3.2.1.2. Toxicodynamic part

The toxicodynamic part of the model aims to predict the effects of perchlorate exposure on the thyroid gland, in particular serum TH concentrations, during pregnancy. The current version of the BBDR model is a revised version of the model originally developed by the US EPA.

As mentioned above, following a public consultation by the US EPA, the following information and changes were added:

- extension of the model to early pregnancy;

- inclusion of a low iodine intake considered as input data (75 µg.d^{-1});
- incorporation of feedback control of TH production via TSH using a coefficient called "pTSH", to take account of pregnant women with weak feedback (pTSH value 0.398) versus normal feedback (pTSH value 1);
- incorporation of feedback control of hCG, which has a mimetic effect on TSH receptors in early pregnancy;
- calibration of the model and its ability to predict lower and upper percentiles of the North American population, as well as the median;
- uncertainty analyses were performed for the added parameters.

Based on iodine intake, TH synthesis, distribution and elimination were modelled to estimate plasma levels of total T4, fT4, total T3, fT3 and TSH. For example, a decrease in fT4 leads to a physiological increase in TSH. This in turn results in increased NIS expression and production constants for T4 and T3.

This part of the US EPA's work was extensively analysed and critiqued by Clewell's team in 2019 (Clewell *et al.,* 2019), in order to determine whether the model and approach developed by the US EPA would be suitable for regulatory purposes to establish an RfD and ultimately a maximum contaminant level goal (MCLG) for DW in the US. The WG on "Perchlorate" notes the quality of the work by Clewell *et al*. and shares a number of their conclusions, which are cited in this opinion.

■ Model calibration

When calibrating the model, the US EPA changed a number of physiological parameters. One of the critical parameters is the strength of the TSH feedback. The US EPA chose to take a TSH response of 0.398 from the median/97.5th percentile ratio of the TSH value in the US National Health and Nutrition Examination Survey (NHANES), corresponding to weak TSH feedback, whereas a value of 1 corresponds to a normal feedback.

The "worst case" scenario of low iodine intake, weak TSH feedback and the 10th percentile for the population of interest (hypothyroxinaemic women) was chosen by the US EPA to protect populations regarded as sensitive.

However, as highlighted by Clewell *et al*. (2019), this scenario is inconsistent with the fundamental biological relationship between TSH and THs (production and release of T3 and T4). As noted by these authors, matched samples for TSH, T3 and T4 would be needed to understand the biological feedback within the same individual. However, the NHANES study, a large cohort designed to assess the health and nutritional status of adults and children in the United States, does not include matched data for TSH and THs (total T3, total T4 and fT4). It is therefore difficult to understand biological feedback in an individual, let alone an entire population.

The WG also notes, as raised by Clewell *et al*. (2019), that the relationship between the change during pregnancy in parameters controlling changes in iodide uptake (VCHNG) and parameters controlling hCG hormone levels (HCGreg) contradicts what is biologically expected, namely a proportional relationship between the two parameters.

As shown in Figure A-46 of US EPA Volume II (Figure 1 in Annex 6), 14 studies (Cotzias *et al.*, 2008; Elhaj *et al.*, 2016; Khalid *et al.*, 2014; Li *et al*., 2014; Männistö *et al*., 2011; Medici *et al*., 2012; Moleti *et al*., 2011; Moncayo *et al*., 2015; Moon *et al*. 2015; Panesar *et al*., 2001;

Soldin *et al*., 2004; Stricker *et al*., 2007; Yan *et al.,* 2011; Zhang et *al*., 2016) were selected by the US EPA to calibrate the relationship between plasma TSH and fT4 concentrations. Although the relationship curves in the publication by Hadlow *et al*. (2013) corresponding to these different studies tend to show the same association, there is high variability between plasma TSH and fT4 concentrations in the available studies, which does not allow for robust model calibration.

- **Model validation**

The US EPA validated this part of the BBDR model by comparing its predictions with the results of a single cross-sectional study (Steinmaus *et al.,* 2016), involving 1880 pregnant Californian women potentially exposed to perchlorate through drinking water (median: 1 µg.L^{-1}, maximum concentration: 8 µg.L^{-1}).

Using a regression model, Steinmaus *et al.* (2016) found an association between increased maternal urinary perchlorate concentrations and decreased total T4 and fT4 concentrations measured between weeks 15 and 20 of pregnancy, as well as an increase in TSH concentration. The association between urinary perchlorate and total T4 was greater with co-exposure to thiocyanate and nitrate (inhibitors of NIS like perchlorate), and in cases of pre-existing thyroid autoimmunity. On the other hand, according to these authors, the iodine status of the pregnant women had no effect.

The study by Steinmaus *et al.* (2016) has a number of limitations, including a 10-week interval between the taking of perchlorate urine samples and fT4 blood samples. However, according to these authors, statistically significant decreases in total T4 and fT4 concentrations were observed with increasing concentrations of perchlorate.

The US EPA used the results of the study by Steinmaus *et al*. (2016) to estimate the external dose from exposure to perchlorate, based on urine data collected from pregnant women in this study. Urinary perchlorate concentrations were converted to external exposure doses using the following equation:

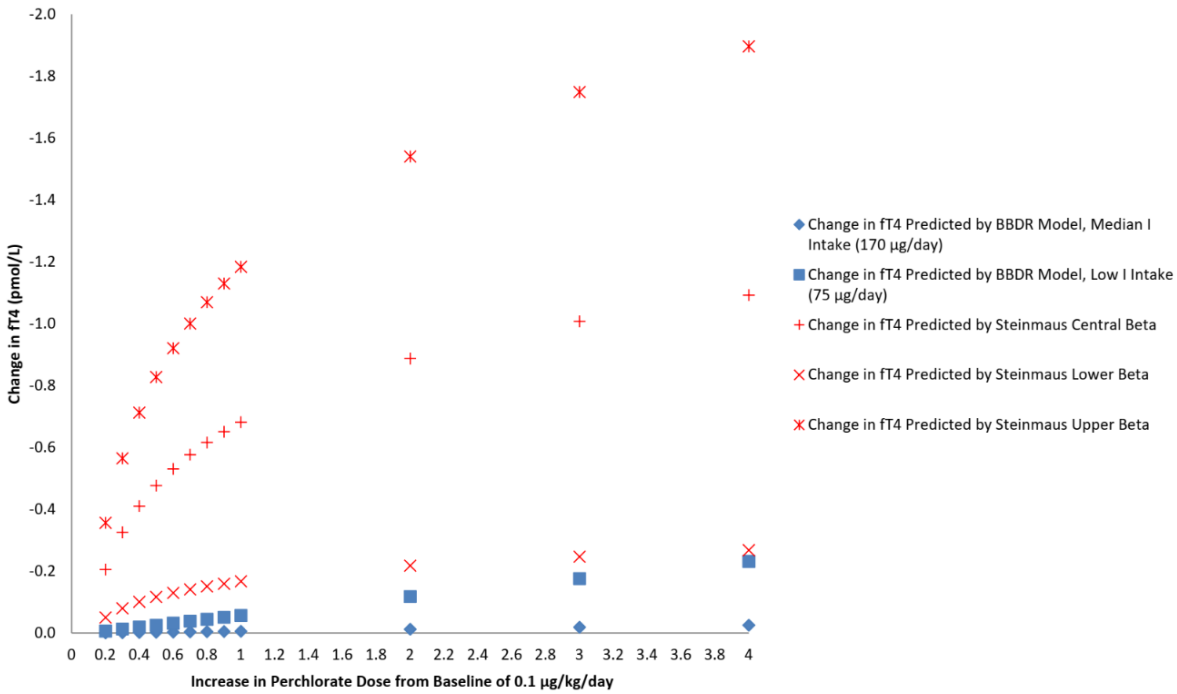
$$\text{Exposure to perchlorate} = \frac{\text{urinary concentration x daily urine volume}}{\text{weight}}$$

In this calculation, an average weight of 74 kg in the first trimester of pregnancy and an average daily urine volume of 1.82 L.d^{-1} were chosen by the US EPA. In addition, the US Agency assumed 100% oral absorption and urinary excretion of perchlorate.

The US EPA compared the changes in fT4 according to urinary perchlorate concentrations predicted by Steinmaus *et al*. (2016) with the changes in fT4 predicted by the BBDR model for the 16th week of pregnancy.

This comparison shows a considerable underestimation by the BBDR model of the perturbations in fT4 concentrations (Figure IV). Indeed, even for a low iodine intake scenario (75 µg.d^{-1}), the ratio between changes predicted from the data of Steinmaus *et al*. (2016) and changes predicted by the model is greater than 2.

Figure B-1. Comparing Predicted fT4 Changes from the BBDR Model and Steinmaus et al. (2016) due to Changes in Perchlorate Dose[2]



[2] Analogous changes in urinary perchlorate are presented in Table B-3.

Figure IV – Comparison of changes in fT4 from the BBDR model with those of Steinmaus *et al.* (2016) according to perchlorate exposure doses (US EPA 2019, Figure B-1)

This discrepancy between the measured data used to validate the model's predictions and the changes predicted by the model raises questions about the model's robustness and use in a regulatory context.

Besides the study by Steinmaus *et al.* (2016), the team of Clewell *et al.* (2019) compared the results of the US EPA's BBDR model with data measured in two studies in healthy volunteers: Greer *et al*. (2002) and Braverman *et al.* (2006), and in a longitudinal epidemiological study in pregnant women: Téllez-Téllez *et al.* (2005).

The WG stresses that these different available studies (Greer *et al.,* 2002; Braverman *et al*., 2006; Téllez-Téllez *et al.,* 2005) do not show a statistically significant impact of perchlorate exposure on fT4 concentration. On the other hand, in the absence of exposure to perchlorate, the fT4 concentration simulated by the model is lower than those measured in all the studies used by Clewell *et al*. (2019) to assess the model.

Similarly, the BBDR model cannot be used to predict significant changes in fT4 as a function of perchlorate exposure when simulating the conditions of the three studies mentioned above.

- **Uncertainties related to the toxicodynamic part of the model**

The major uncertainty in the toxicodynamic part is its poor predictive ability to link perchlorate exposure levels to the fT4 decrease in the population of interest, i.e. pregnant women in the first trimester.

Indeed, the uncertainties in this part call into question its use in predicting small changes in TH concentrations, such as a 1% change in fT4 (Clewell *et al*. 2019). As shown in Figure IV, the uncertainties increase with exposure to perchlorate (up to 4 µg.kg $bw^{-1}.d^{-1}$).

By considering a common placenta-foetus compartment, other key elements of thyroid physiology have been simplified in the model. Inter-individual and temporal variations in the expression of MCT8 and NIS proteins in the placenta prior to their expression in the foetal thyroid are not taken into account. Significantly, NIS expression in the developing foetal thyroid gland is dynamic during pregnancy, especially between 17 and 18 weeks of pregnancy, and varies between foetuses (Filis *et al.,* 2018). It would have been appropriate to consider the change in NIS expression during pregnancy in the model, as well as the conjugation of THs to sulphated hormones (the abundant form in the foetus-placenta compartment) and placental iodine clearance, although there is currently a lack of data on these parameters.

Conclusion on the toxicodynamic part of the model

The BBDR model was not validated by several studies showing an association between perchlorate and impaired maternal thyroid function (decreased fT4). Only one study on the population of interest was used by the US EPA to validate the model: Steinmaus *et al*. (2016). In addition, a comparison of changes in fT4 concentrations predicted by the study of Steinmaus *et al*. (2016) and by the BBDR model shows a considerable underestimation by the model.

Furthermore, while some of the uncertainties and approximations in the toxicodynamic part are inherent to the complex nature of thyroid function regulation (especially during pregnancy), some unfounded choices mean that it cannot be fully understood.

Under these conditions, the WG on "Perchlorate" considers that the BBDR model is not able to describe the relationship between exposure to perchlorate and the decrease in maternal fT4, and it does not validate the model.

3.2.2. Step 2: Identification of studies linking alterations in maternal thyroid hormone concentration to neurodevelopmental disorders

3.2.2.1. Assessment of the US EPA's literature search strategy

The literature search conducted by the US EPA was not a systematic review with weight-of-evidence evaluation. This is because the US EPA considered that the causal relationship between altered maternal TH levels and neurodevelopmental disorders had already been established by a strong body of scientific literature (Fetene *et al.,* 2018; Moog *et al*., 2017; Thompson *et al.,* 2018).

Therefore, in line with the SAB's recommendations, the purpose of the US EPA's literature search was to develop a methodological approach in order to:

- assess the available publications on this subject;
- identify studies that assessed incremental changes in fT4 as they relate to neurodevelopmental alterations, discarding those that showed no effect;
- select a study showing an appropriate dose-response relationship from among the studies establishing this relationship.

For this literature search, the US EPA used different keyword equations on two search engines (PubMed and Google Scholar) for an initial selection of available epidemiological studies:

- The choice of keywords defining neurodevelopment was not explained in the US EPA's argument, apart from the notion of a list based on the SAB's recommendations;
- The number of studies identified for each of the keyword equations with the two chosen search engines was not specified (Table 11 of Volume I of the US EPA's document);
- The key elements of the population, exposure, comparison group, outcome (PECO) principle, which should define the eligibility criteria for studies, were not given.

The US EPA's literature query is not detailed enough to enable the search to be replicated in order to find the studies identified by the first step and, among them, the 71 studies considered eligible. It is therefore relatively difficult to assess the reliability of the method and its ability to identify and select key studies that could have been used to refine the analysis, particularly with regard to the relationship between maternal fT4 and neurocognitive parameters in children.

3.2.2.2. Description of the procedure for selecting the epidemiological studies identified as eligible by the US EPA's literature search

The selection procedure for the epidemiological studies, which is detailed in Annex 7, was carried out in three steps:

1. identification and exclusion of studies that were not compatible with the BBDR model results (i.e. studies with fT4 concentrations not reported for the same population as the BBDR model target population, namely pregnant women in the general population between conception and gestational week 16);
2. identification and exclusion of studies that reported their results with fT4 concentrations presented as qualitative variables;
3. assessment of the risk of bias in the remaining studies and exclusion of studies by means of categorisation into "tiers" (term used in the US EPA document): i) studies classified as Tier 1 (studies with a "probably low" or "definitely low" risk of bias) or Tier 2 (studies not meeting the criteria for either Tier 1 or Tier 3) that did not observe a significant relationship between maternal fT4 concentration and the neurodevelopment measurement of interest and/or that did not provide information on the mathematical function explaining the relationship between neurodevelopment and maternal fT4, ii) studies classified as Tier 3 (studies with a "definitely high" or "probably high" risk of bias) according to the Office of Health Assessment and Translation (OHAT) criteria in the "Risk of Bias Rating Tool for Human and Animal Studies" (NTP, 2015).

Five studies were selected following this procedure: Pop *et al.* (1999), Pop *et al.* (2003), Finken *et al.* (2013), Korevaar *et al.* (2016) and Endendjik *et al.* (2017).

3.2.2.3. Analysis of studies selected by the US EPA

- **Assessment of the quality of the five epidemiological studies selected**

The WG assessed the risk of bias in the five selected studies using the same tools as the US EPA (i.e., the OHAT criteria in the "Risk of Bias Rating Tool for Human and Animal Studies"). The conclusions of the WG are in line with those of the US EPA (Table 1 in Annex 7): the WG also categorised the selected studies as Tier 1 or Tier 2, i.e. as high-quality epidemiological studies with a low risk of bias.

- **Assessment of the relevance of the final choice of the study by Korevaar *et al.* (2016) for defining the TRV**

The five studies chosen by the US EPA in the final selection phase are detailed in Table 2 in Annex 7.

In four of these five studies (Pop *et al.,* 1999; Pop *et al.,* 2003; Finken *et al*., 2013; Korevaar *et al.,* 2016), the alterations in child neurodevelopment concerned cognitive development, whereas the most recent study (Endendjik *et al.,* 2017) related to behavioural disorders.

Other alterations in child neurodevelopment such as hyperactivity, attention deficit disorder, autism or other psychiatric disorders reported in other studies are very difficult to assess and quantify, and cannot be selected as critical effects.

Intelligence quotient (IQ), used in children as a quantitative and comparative measure of neurocognitive abilities at a given age compared to a reference population, seems to be the most relevant tool for assessing a critical effect. It cannot be used in infants (before the age of 3), in whom it is replaced by Bayley[3] scales, which measure a developmental quotient. It should be interpreted with caution before the age of 5 and early schooling, and is acknowledged as having good stability from the age of 7 to 8 years. By integrating non-verbal and visual-spatial data, the IQ has the advantage of being independent of social background, making it the reference tool for analysing a population of varied origin.

Although the studies by Pop *et al.* (1999, 2003) specifically addressed the population of interest, i.e. hypothyroxinaemic women, these studies were small (60-200 subjects) and the results of the neurodevelopmental effect assessment (Bayley test) need to be interpreted with caution for children up to the age of 3 years. Lastly, the dose-response relationships were not determined by the authors: only the scatter plots (y-axis: Bayley test score; x-axis: maternal fT4) and the corresponding correlation coefficients were reported in the publications. The US EPA used the scatter plots to extract a mathematical relationship for each of the studies. These relationships reconstructed by the US EPA have not therefore been adjusted for the main confounding factors (maternal age, level of education, age of children at the time of testing).

As for the studies by Finken *et al*. (2013) and Endendjik *et al*. (2017), they showed very specific and non-objective effects that were assessed for all women participating in the study; the dose-response relationships described in these two studies were therefore not specific to the population of interest.

[3] Bayley score: a standard test to measure infant and young child development that takes all spheres of development into account and can identify children potentially at risk of development retardation compared to their peers.

Among the five studies selected, the one by Korevaar *et al*. (2016) best met the requirements of the US EPA's approach. In the context of this work, the main advantages of this study were:

- the large number of subjects (= 3839 mother-child pairs);
- the measurement of neurodevelopment by non-verbal IQ in 6-year-olds and by magnetic resonance imaging (MRI);
- the search for more in-depth modelling of the relationship between maternal fT4 and neurodevelopment than in the other four studies selected by the US EPA, which made it possible to determine a specific dose-response relationship for the population of interest.

3.2.2.4. Description of the key study selected: Korevaar *et al.* (2016)

The aim of this study was to examine the relationship between maternal thyroid function and child IQ (and for a subpopulation, the brain morphology of these children (White *et al.,* (2013)) in a prospective cohort of 3839 mother-infant pairs from the Generation R cohort (Rotterdam, the Netherlands), for which the authors had blood samples that were taken before the 18th week of a normal pregnancy.

The authors determined the form of the association between:

- fT4/TSH concentrations measured in maternal serum by chemiluminescence (median fT4 value: 14.9 pmol.L^{-1} [with 95% of fT4 values between 10.2 and 22.4 pmol.L^{-1}]);
- and non-verbal IQ assessed between the ages of 6 and 8 years, using the Snijders-Oomen Niet-Verbale Intelligentie Test, by investigators who were unaware of the maternal fT4 concentrations (mean IQ value of 101.5 [standard deviation: 14.9]; 13% of children with an IQ below 85);
- and brain morphology assessed by brain MRI in 646 of 3839 children, measuring volumes of grey matter, cortex, white matter, hippocampus and total brain volume.

The authors used the least-squares method to define linear regression functions whose independent variables were the log-transformed values of thyroid hormone concentrations between the minimum and 10th percentile, between the 10th and 50th percentile, between the 50th and 90th percentile, and above the 90th percentile (restricted cubic splines with 3 knots). The dependent variables, IQ and brain morphology parameters, were studied in independent models. The model for IQ was adjusted for gestational age at blood sampling, maternal age, smoking status, body mass index (BMI) at the start of pregnancy, parity, education, ethnic origin, foetal sex and birth weight. Models for MRI parameters were adjusted for gestational age at blood sampling, maternal age, BMI at the start of pregnancy, child age, birth weight and gestational age at birth.

The main results show a significant inverted U-shaped association between fT4 concentrations and child IQ, between fT4 concentrations and grey matter volume, and between fT4 concentrations and cortex volume. Secondary analyses showed that if the fT4 concentration between the 10th and 90th percentile is considered as the reference category, there is a significant 1.5 to 3.8 point reduction in the mean IQ of children whose mothers had fT4 concentrations between the 3rd and 11th percentile.

No significant relationship was observed between IQ or morphological parameters and TSH concentration.

Classifying this study as "Tier 1" (i.e. a study with a "definitely low" or "probably low" risk of bias) is justified for the examination of the relationship between fT4 concentration and IQ but not for the examination of the relationship between fT4 concentration and brain morphology, where there was no adjustment for intracranial volume, leading to a high risk of confounding bias.

In conclusion, the level of evidence for an inverted U-shaped association between fT4 concentration and child IQ is moderate (according to the OHAT criteria), bearing in mind that the level of evidence for an observational cohort study can only be low to moderate. While the shape of the relationship identified between IQ and fT4 concentration calls into question the linear relationships proposed over the entire panel of fT4 values in the articles by Finken *et al*. (2013) and Endendjik *et al*. (2017), this inverted U-shaped association is consistent with the work of Pop *et al.* (1999, 2003), which showed correlations (see Annex 7) between fT4 concentrations and neurodevelopmental scores when only hypothyroxinaemic women (fT4 concentrations below the 10th percentile) were considered. The level of evidence for an inverted U-shaped association between fT4 and brain morphology is however low.

In its assessment, the US EPA conducted an independent analysis of the raw data from the study. This sought to define a mathematical function that was more suited to the objectives of the US EPA's work than the function proposed in the publication.

The US EPA began by choosing a minimal set of adjustment factors for assessing the total effect of maternal fT4 concentration on child IQ. Factors such as gestational age or birth weight were not entered into the models. The US EPA's approach is relevant because it better meets the maximum contaminant level goal (MCLG) than the analysis by Korevaar's team.

Whereas Korevaar's team included log-transformed fT4 concentrations in the models without justifying this point, the US EPA compared the performance of the models with fT4 concentrations in log-transformed and crude form in order to justify its choice to use log-transformed fT4 concentrations.

Although the choice of the study by Korevaar *et al.* (2016) as the key study is justified, it has limitations that may (i) have influenced the estimated dose-response relationship, (ii) question the validity of extrapolating the identified dose-response relationship to the target population of the US EPA's work:

- The relationship between maternal fT4 and child IQ at 6-8 years of age was determined from a single measurement of fT4 concentration during the first trimester of pregnancy. This single sample is not necessarily representative of the average fT4 concentration in the mother during the first trimester of pregnancy. A non-differential classification bias between hypothyroxinaemic and non-hypothyroxinaemic women is therefore possible. The consequence of this potential bias would be to underestimate the strength of the effect;
  Moreover, the results of the study by Pop *et al.* (2003) suggest that hypothyroxinaemia in early pregnancy is not sufficient to explain the relationship between fT4 concentration and neurodevelopment but that the trajectory over the entire pregnancy should be taken into account. Indeed, in this study, women who were hypothyroxinaemic throughout pregnancy were most at risk of having children with neurodevelopmental

disorders. In contrast, women who were hypothyroxinaemic in the first trimester but had normal fT4 values in the third trimester were no longer at risk of having a child with neurodevelopmental disorders;

- The pregnant women in the study by Korevaar *et al*. (2016) come from a population in which iodine intake is considered adequate (Ghassabian *et al*., 2014), with fT4 values ranging from 7.4 pmol.L^{-1} (minimum value readable on the graphs in the publication by Korevaar *et al*. (2016)) to 11.92 pmol.L^{-1} (10^{th} percentile). In contrast, the target population selected by the US EPA is a low-iodine-intake population with weak TSH feedback, with fT4 values equal to 6.70 pmol.L^{-1} (10^{th} percentile), much lower than those in the study by Korevaar *et al*. (2016) (Table III).
  To model the effects of perchlorate on neurodevelopment, the US EPA therefore used for this target population a dose-response relationship determined on the population of the study by Korevaar *et al*. (2016).
  The US EPA therefore made the assumption that this dose-response relationship could apply to lower fT4 values. This assumption is questionable because it is not possible to rule out the possibility that the shape and/or strength of the dose-response relationship is at least slightly different with a lower range of values than those used to determine the dose-response relationship in the BBDR model.

Table III – Distribution of fT4 in the US EPA target population versus Korevaar *et al*. (2016) (Generation R cohort)

	fT4 in the US EPA target population (in pmol.L^{-1})	fT4 in the study population of Korevaar *et al*. (2016) (in pmol.L^{-1})
10^{th} percentile	6.70	11.92
50^{th} percentile	8.84	14.9

Conclusion on the epidemiology part of the model

Despite the lack of transparency on the initial selection of studies, the WG on "Perchlorate" agrees with the US EPA's assessment of the relevance of the selected studies and the final choice of the study by Korevaar *et al*. (2016) as the pivotal study to describe the relationship between maternal fT4 and neurodevelopment in the unborn child following the BBDR model.

However, even if this study is the most appropriate, uncertainties remain about the validity of extrapolating the relationship between maternal fT4 and child IQ at 6-8 years of age identified in the pregnant women of the "Generation R" cohort to the population targeted by the US EPA.

3.2.2.5. Studies published since the US EPA's literature search

The WG identified two studies published by Korevaar *et al*. (2016) since the work of the US EPA (2019), investigating the potential link between impaired neurodevelopment and maternal fT4 concentration.

An initial study by Levie *et al*. (2018), aimed to assess the association between maternal thyroid function in early pregnancy and child neurodevelopment in countries with different iodine status. An analysis of pooled individual data from 9036 mother-infant pairs from three cohorts – Generation R (Rotterdam, Netherlands), INMA (Spain) and ALSPAC (UK) – showed that maternal fT4 concentrations below the 2.5th percentile were associated with a 3.9 point decrease in non-verbal IQ ($CI_{95\%}$: -5.7 / -2.2) and a 2.1 point decrease in verbal IQ (95% CI: -4 / -0.1). The results of this pooled data analysis are consistent with those obtained by Korevaar *et al*. (2016) in the Generation R cohort alone.

In a second study by Jansen *et al.* (2019), also conducted on the Generation R cohort (Rotterdam, The Netherlands), the relationship between maternal thyroid function and brain morphology in children at the age of 10 years was investigated. No significant relationship was observed between brain morphological parameters and maternal fT4 concentration. The results of the study by Korevaar *et al.* (2016), however, appear to be more robust than those of Jansen *et al*. (2019), in which neurodevelopment was assessed by a single point of measurement of rather "coarse" imaging data (total grey matter volume, cortical grey matter volume), whereas a "whole brain" analysis at the voxel level would have provided a better understanding of the effect on children's brain morphology of a decrease in maternal fT4 concentration. In addition, the cross-sectional relationship between global grey matter volume/cortical volume and IQ is uncertain: cortical grey matter volume has a dynamic trajectory during development, with an increase up to the age of 5 years and then a decrease until late adolescence (Ostby *et al.,* 2009; Paus *et al*., 2001). A longitudinal study would have been more relevant than a single measurement point.

3.2.3. Critical analysis of the establishment of the US EPA's TRV

3.2.3.1. Choice of critical effect and its magnitude

Due to inter- and intra-individual variability in IQ measurement, a one-point drop in IQ cannot be regarded as significant at the individual level. On the other hand, at the level of the general population, even a small drop in IQ can be meaningful if it is statistically significant. While a decrease in IQ is not in itself a disease, an IQ below 70 defines mental retardation, which is a condition that warrants specific medical and social care. As shown in the work of Fewtrell *et al*. (2003), an exposure factor able to decrease IQ by one point at the population level results in an overall shift of the Gaussian IQ distribution curve to the left. Therefore, an exposure factor resulting in a loss of one IQ point in an exposed population implies that all those whose IQ was *a priori* between 71 and 70 join the cohort of people with mental retardation, which constitutes a public health problem[4]. Korevaar *et al.* (2018) calculated that for a hypothetical population of 100 million people, a decrease of one IQ point in the vulnerable population representing 10% of the general population would result in an additional 37,127 people with an intellectual

[4] Quantitatively, this represents about 0.4% of the population: 0.24% of the population has an IQ between 70 and 70.65 and 0.8% an IQ between 70 and 71.95 (Fewtrell *et al.,* 2003).

disability (IQ < 70). These calculations are applicable to the TRV proposed by the US EPA for which hypothyroxinaemic pregnant women (fT4 concentrations below the 10th percentile, i.e. 10%) were taken into consideration. Since health effects are measurable for a one-point change in IQ at the population level, it is difficult to argue that a two-point drop should be selected as the critical effect.

The WG therefore agrees with the US EPA's proposal to consider lowered IQ as the critical effect for deriving the TRV. On the other hand, the US EPA's preferred proposal[5] of a two-point rather than a one-point drop seems difficult to justify, since health effects can be measured from a one-point drop in IQ at the population level.

3.2.3.2. Review of the uncertainty factors selected by the US EPA

The US EPA used an uncertainty factor of 3 for the inter-individual variability instead of 10 (default value) because the dose-response relationship was modelled on a population considered to be particularly sensitive to the effects of exposure to perchlorate (i.e. foetuses of pregnant mothers exposed in the first trimester of pregnancy). In addition, the parameters used in this modelling were those that correspond to the physiological characteristics of the women who would be most at risk in this sensitive population. These parameters were:

- Pregnant women with low fT4 values in early pregnancy and thus more vulnerable to variation. The US EPA selected the 10th percentile of the distribution around the mean fT4 as the limit for modelling exposure to perchlorate. The choice of the 10th percentile, which may seem arbitrary for defining hypothyroxinaemia since it does not correspond to a pathological clinical situation, was made by the US EPA because it covers inter-individual changes in fT4 or changes in the first few weeks of pregnancy. This choice is conservative and provides greater protection, particularly for populations that may have low iodine intakes;
- Low daily iodine intake (75 µg.d^{-1});
- Weak TSH feedback.

The US EPA believes that protecting the unborn child of a hypothyroxinaemic woman will also protect other identified sensitive populations (breastfed or bottle-fed infants).

Even if uncertainties remain with regard to the lack of available information linking incremental changes in thyroid test results in infants to neurodevelopmental disorders, the WG on "Perchlorate" considers that the choice of the UF_H of 3 is justified, in accordance with the ANSES guidance document on establishing TRVs (ANSES, 2017).

3.3. Step 3 – Update of the literature since the ANSES opinion of 26 December 2018 on the adverse effects associated with perchlorate

As mentioned above, the WG carried out a literature search to identify data on associations between exposure to perchlorate and adverse effects or changes in thyroid parameters, published since the ANSES opinion of 26 December 2018. This search was conducted using

[5] US EPA proposal submitted for comment in May 2019. The US EPA's final decision in June 2020 was not to regulate perchlorate in DW, given the recent reduction in resource contamination levels in the US: https://www.epa.gov/newsreleases/epa-issues-final-action-perchlorate-drinking-water.

the PubMed and SCOPUS search engines over the period 1 January 2018 to 1 October 2020. The details of this literature search can be found in Annex 8.

From the seven full-text articles reviewed for eligibility, the publication by Bruce *et al.* (2018) was chosen. The authors' objective was to carry out a more robust analysis of the effects of perchlorate exposure on iodine uptake inhibition (IUI) using pooled data from four clinical trials [Lawrence *et al*. (2000) n = 9, Lawrence *et al.* (2001) n = 8, Greer *et al.* (2002) n = 37 and Braverman *et al*. (2006) n = 19]. To establish a response threshold, the data were analysed using segmented linear regression and a BMD approach assuming a 20% decrease in radiolabelled iodine uptake. A threshold dose for iodine uptake inhibition by perchlorate of 0.021 and 0.038 mg.kg $bw^{-1}.d^{-1}$ was estimated using the BMD approach and linear regression, respectively.

It should be noted that the BMDL (lower limit of the 95% confidence interval of the BMD) of 0.021 mg.kg $bw^{-1}.d^{-1}$ is close to the lowest observed effect level (LOEL) of 0.020 mg.kg $bw^{-1}.d^{-1}$ established in the study by Greer *et al.* (2002).

With regard to iodine uptake inhibition, Bruce *et al*. (2018) used a BMR response level of 20%, which the authors believe represents a biologically significant change in iodine uptake that accounts for intra-individual variability in the RAIU test. This value of 20% was established by Weterings *et al.* (2016) based on an analysis of data from four published trials in which measurements of 24-hour radiolabelled iodine uptake (^{123}I, ^{131}I, ^{132}I) were repeated in the same untreated subjects (100 subjects). In view of this intra-individual variability, Weterings *et al*. (2016) concluded that iodine uptake inhibition during the RAIU test can only be attributed to perchlorate exposure if the difference from the initial value of iodine uptake exceeds 20%. Indeed, the authors consider that response levels below this threshold can be explained simply by natural intra-individual variations in iodine uptake.

As mentioned in Table I in Section 3.3 of this opinion, this same BMR value of 20% was recently adopted in 2020 by Health Canada, which, by modelling the data of Greer *et al.* (2002), established a $BMD_{20}L$ of 0.0109 mg.kg $bw^{-1}.d^{-1}$ (Table I).

It should be noted that JECFA (WHO, 2011) had adopted a BMR value of 50% of thyroid iodide uptake, a value that is assumed to have no impact on serum TH concentrations in adults, based on clinical data in healthy adults (JECFA, 2011). In contrast, EFSA (EFSA, 2014) had retained a BMR of 5% (default value used for modelling continuous variables). This is because EFSA had concluded that the chronic adaptive changes to compensate for sustained inhibition of thyroid iodine uptake could lead to long-term effects, particularly in populations with mild to moderate iodine deficiency.

In a new study currently being published (Haber *et al.,* 2021), the authors refute the adequacy of the software ("PROAST" and "BMDS") used so far to model the dose response of the data from Greer *et al*. (2002) and suggest Bayesian modelling leading to a BMDL value of 30 µg.kg $bw^{-1}.d^{-1}$.

Once the Haber *et al*. study has been published, the experts consider that further expert appraisal is needed on the different BMR proposals and modelling of the data from Greer *et al*. (2002) reported in the above-mentioned publications, in order to decide whether they call into question the TRV used by the experts since 2011, based on the no observed effect level from the study by Greer *et al*. (2002).

3.4. Conclusions and recommendations of the WG on "Perchlorate" and the CES VSR

The WG on "Perchlorate" and the CES VSR note the quality of the work carried out by the US EPA both on developing the BBDR model and on the literature search for epidemiological studies, in order to estimate the perchlorate concentrations that can lead to neurodevelopmental disorders in the unborn child. The WG on "Perchlorate" and the CES VSR also note the relevance of this innovative two-step approach to consider an adverse effect rather than an early biological effect in order to refine the health risk assessment of perchlorate.

With regard to the US EPA's BBDR model, the robustness of the toxicokinetic part of the model was rigorously assessed by the US Agency itself. This assessment showed that the kinetic model of perchlorate effectively reproduces the different data available in the literature, such as the changes in plasma concentration and cumulative urinary excretion in adults. In addition, this part of the model fulfils the IPCS (WHO, 2010) requirements for use in risk assessment.

On the other hand, the toxicodynamic part of the BBDR model is not able to describe the relationship between perchlorate exposure and the decrease in maternal fT4, mainly due to the lack of available data (only one study: Steinmaus *et al.,* 2016) for a robust validation of this part. In addition, a comparison of changes in fT4 concentrations predicted by the study of Steinmaus *et al*. (2016) and by the BBDR model showed that the model induces a considerable underestimation.

The WG on "Perchlorate" and the CES VSR stress that some of the uncertainties in the toxicodynamic part are inherent to the complex nature of thyroid function regulation.

In addition, a notable limitation of the NHANES study used by the US EPA is the lack of matched intra-individual data between TSH and the other THs (total T3, total T4 and fT4), which calls into question the values considered for the strength of the feedback of THs on TSH (values of 0.398 and 1 for the pTSH coefficient).

The WG and the CES therefore consider that in view of the above-mentioned uncertainties, the BBDR model cannot be used in the context of TRV development and health risk assessment.

The WG and the CES note that the impact of these uncertainties on the applicability of the BBDR model also led Clewell *et al*. to recommend that the US EPA continue referring to the RfD established in 2005 that was based on inhibition of thyroid iodide uptake (Clewell *et al*., 2019).

With regard to the part on epidemiology, the WG on "Perchlorate" endorses the US EPA's literature evaluation and the choice of the study by Korevaar *et al*. (2016) as the pivotal study to describe the relationship between maternal fT4 and neurodevelopment in the unborn child following the BBDR model. Indeed, the WG and the CES consider that the US EPA's work to determine a relationship between maternal fT4 concentration and child neurodevelopment was carried out properly.

However, even if this study is the most appropriate, uncertainties remain about the validity of extrapolating the dose-response relationship identified in the pregnant non-iodine deficient women of the study by Korevaar *et al*. (2016) to the US EPA's target population of women with low daily iodine intake (75 $\mu g.d^{-1}$).

This uncertainty, added to those about the BBDR model validated on the single study of Steinmaus *et al*. (2016), therefore limits the degree of confidence that can be placed in the TRVs proposed by the US EPA.

The WG on "Perchlorate" and the CES VSR therefore suggest keeping ANSES's current TRV of 0.7 µg.kg $bw^{-1}.d^{-1}$, which was selected by the Agency in 2011 based on the study by Greer *et al.* (2002) (Figure V). This choice is conservative in the sense that the effect is not based on a clinical observation (hypothyroidism) or a biological alteration (decrease in TH levels), but on an early indicator of a change in thyroid function.

As with other TRVs calculated using the same type of approach, it is therefore difficult to estimate the health risk of exceeding this TRV in terms of clinically observable effects (ANSES 2014, 2018). Indeed, as shown previously, estimating the health risk requires knowledge of both the iodine status of the study population, in this case pregnant women, and the levels of exposure to perchlorate via water and food.

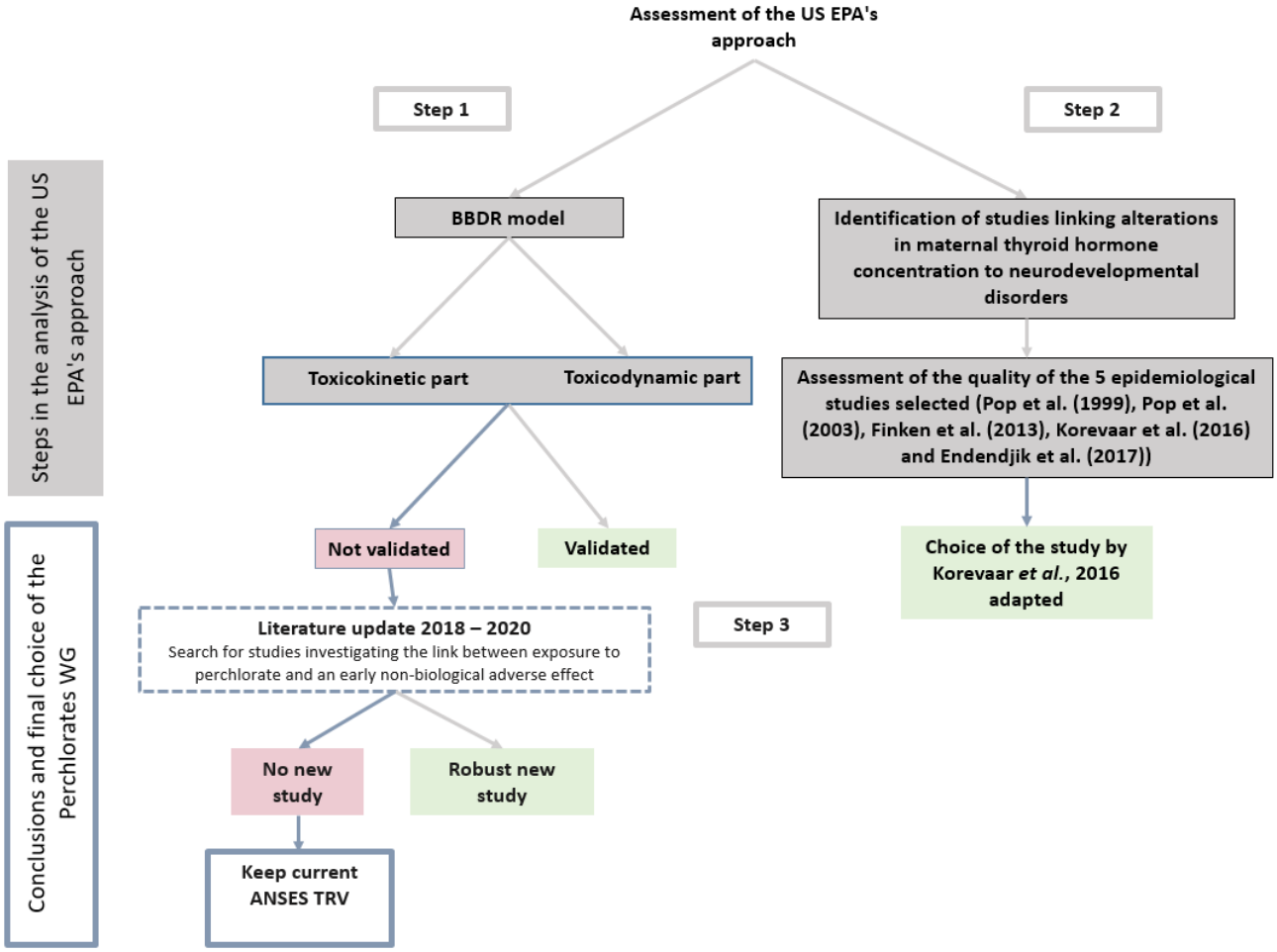


Figure V – Decision tree and conclusions of the WG on "Perchlorate" and the CES VSR

In order to consider a revision of the current TRV on the basis of the effects of perchlorate on neurodevelopment in children, the WG on "Perchlorate" and the CES VSR believe it would be necessary to rely on data from epidemiological studies:

- conducted in general population birth cohorts, and including geographical areas where exposure to perchlorate is known to occur;
- collecting biological samples with a protocol to reflect perchlorate exposure as well as iodine intake and maternal thyroid function;
- monitoring the neurodevelopment of children up to at least 6 years of age using neuropsychological tests conducted by health professionals.

Until further data are available to calibrate and validate the toxicodynamic part of the BBDR model with respect to the population of interest, the study by Greer *et al*. (2002) is therefore a preferable choice to the US EPA's proposals for developing a TRV. The WG on "Perchlorate" and the CES VSR therefore consider that there is no justification for challenging the current ANSES TRV in light of the US EPA's work.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of the WG on "Perchlorate" and the CES VSR regarding a reassessment of the chronic oral TRV for perchlorate.

The chronic oral TRV adopted by the Agency since 2011, based on the no observed effect level in the study by Greer *et al*. (2002), is therefore still recommended by the Agency. ANSES reiterates that this TRV is based on an early indicator of a change in thyroid function and that in this respect it constitutes a protective choice.

Table IV: Chronic TRV by the oral route for perchlorate

Type of TRV	Critical effect (key study)	Critical dose	UF	TRV
Chronic oral TRV	Inhibition of radiolabelled iodide uptake by the thyroid gland Greer *et al.,* 2002	NOEL = 7 µg.kg $bw^{-1}.d^{-1}$	10 UF_H = 10	**0.7 µg.kg $bw^{-1}.d^{-1}$**

In addition, the Agency indicates that it has decided to continue its expert appraisal work, with a view to analysing the publication by Haber *et al*., which examines different proposals for the Benchmark Response (BMR) and modelling of the data of Greer *et al*. (2002), in order to decide whether this TRV should be reconsidered as a result.

However, ANSES believes that a fundamental revision of the TRV, mainly on the basis of the effects of perchlorate on neurodevelopment in children, would require new data from epidemiological studies:

- conducted in general population birth cohorts, and including geographical areas where exposure to perchlorate is known to occur;
- collecting biological samples with a protocol to reflect perchlorate exposure as well as iodine intake and maternal thyroid function;
- monitoring the neurodevelopment of children up to at least 6 years of age using neuropsychological tests conducted by health professionals.

ANSES stresses that the critical effect of perchlorate is based on impaired thyroid function, and therefore a change in an endocrine regulation. A decision on the hazard characterisation of perchlorate as an endocrine disruptor (ED) would require a full assessment of this specific hazard. Work is currently being carried out at European level under the Regulation on Registration Evaluation and Authorisation of Chemicals (REACh) by the German agency: based on its assessment report (BAuA, 2016), a dossier identifying perchlorate as a substance of very high concern (SVHC) is being finalised with regard to its ED characterisation for the environment and ecosystems; this will be followed by a report – expected in the coming weeks – on the analysis of the best risk management options (RMOA) to limit emissions of perchlorate into the environment. Once this work has been completed, ANSES will analyse it and determine what additional expert appraisals are needed to protect humans from exposure to perchlorate.

Dr Roger Genet

KEYWORDS

Perchlorates, ions, risques sanitaires, valeur toxicologique de référence, eaux destinées à la consommation humaine (EDCH).

Perchlorates, ions, health risks, toxicity reference value, drinking water.

REFERENCES

Ain, K. B., Y. Mori and S. Refetoff. 1987. "Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. " *The Journal of clinical endocrinology and metabolism* 65(4), 689–696. https://doi.org/10.1210/jcem-65-4-689

Andersen, S. L., P. A. Christensen, L. Knøsgaard, S. Andersen, A. Handberg, A. B. Hansen and P. Vestergaard. 2020. "Classification of Thyroid Dysfunction in Pregnant Women Differs by Analytical Method and Type of Thyroid Function Test. " *The Journal of clinical endocrinology and metabolism* 105(11), dgaa567. https://doi.org/10.1210/clinem/dgaa567

Anses. 2011. Avis du 18 juillet 2011 relatif à l'évaluation des risques sanitaires liés à la présence d'ions perchlorate dans les eaux destinées à la consommation humaine (saisine 2011-SA-0024). Maisons-Alfort : Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail.

Anses. 2012. Avis du 20 juillet 2012 relatif aux études épidémiologiques portant sur les associations entre une exposition aux ions perchlorate dans l'eau de boisson et la fonction thyroïdienne dans des populations spécifiques (saisine 2011-SA-0119). Maisons-Alfort : Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail.

Anses. 2014. Avis du 8 avril 2014 relatif à la présence d'ions perchlorate dans le lait infantile et dans l'eau destinée à la consommation humaine en France (saisines n° 2011-SA-0208 et n° 2011-SA-0336). Maisons-Alfort : Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail.

Anses. 2018. Avis du 26 décembre 2018 relatif à la « Pertinence de la ré-évaluation de la valeur guide pour les ions perchlorate dans l'eau destinée à la consommation humaine » (saisines n° 2016-SA-0155 et 2017-SA-0170). Maisons-Alfort : Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail.

Ansm. 2020. Référentiel des ATU nominatives. IRENAT 300 mg/ml, solution buvable en gouttes.

ATSDR. 2009. *Toxicological profile for perchlorates*. U.S. Department of Health and Human Services. Public Health Service Agency for Toxic Substances and Disease Registry.

Attanasio R., F. Scinicariello, B. C. Blount, L. Valentin-Blasini, K. A. Rogers, D. C. Nguyen and H. E. Murray. 2011. "Pendrin mediates uptake of perchlorate in a mammalian in vitro system." *Chemosphere* 84(10):1484-1488. doi: 10.1016/j.chemosphere.2011.04.038.

Bartalena, L., S. Brogioni, L. Grasso, F. Bogazzi, A. Burelli and E. Martino. 1996. "Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. " *The Journal of clinical endocrinology and metabolism* 81(8), 2930–2933. https://doi.org/10.1210/jcem.81.8.8768854;

BAuA. 2016. *Substance evaluation conclusion document as required by Reach Article 48 and*

Evaluation Report for sodium perchlorate - EC N°231-511-9, CAS N°7601-89-0. Federal Institute for Occupational Safety and Health. Accessible from the ECHA website via the following link: https://echa.europa.eu/fr/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807ea4f2

Bernal, J. and F. Pekonen. 1984. "Ontogenesis of the nuclear 3,5,30-triio- dothyronine receptor in the human fetal brain. " *Endocrinology*. 114(2):677-9

Biondi B. 2012. "Natural history, diagnosis and management of subclinical thyroid dysfunction. " *Best Pract Res Clin Endocrinol Metab*. 26(4):431-46.

Braverman, L. E., E. N. Pearce, X. He, S. Pino, M. Seeley, B. Beck, B. Magnani, B. C. Blount, and A. Firek. 2006. "Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers." *J Clin Endocrinol Metab* 91 (7):2721-4. doi: 10.1210/jc.2006-0184.

Bruce, G. M., L. M. Corey, E. N. Pearce, L. E. Braverman and R. C. Pleus. 2018. "Determination of Thresholds of Radioactive Iodine Uptake Response With Clinical Exposure to Perchlorate: A Pooled Analysis." *Journal of occupational and environmental medicine* 60(4), e199–e206.

Budenhofer, B. K., N. Ditsch, U. Jeschke, R. Gärtner and B. Toth. "Thyroid (dys-)function in normal and disturbed pregnancy. " *Arch Gynecol Obstet* 2013;287(1):1-7.

Clewell, H. J., 3rd, P. R. Gentry, C. E. Hack, T. Greene and R. A. Clewell. 2019. "An evaluation of the USEPA Proposed Approaches for applying a biologically based dose-response model in a risk assessment for perchlorate in drinking water." *Regul Toxicol Pharmacol* 103:237-252. doi: 10.1016/j.yrtph.2019.01.028.

Clewell, R. A., E. A. Merrill, J. M. Gearhart, P. J. Robinson, T. R. Sterner, D. R. Mattie and H. J. Clewell, 3rd. 2007. "Perchlorate and radioiodide kinetics across life stages in the human: using PBPK models to predict dosimetry and thyroid inhibition and sensitive subpopulations based on developmental stage." *J Toxicol Environ Health A* 70 (5):408-28. doi: 10.1080/15287390600755216.

Concilio, S. C., H. R. Zhekova, S. Y. Koskov and S. T. Russell. 2020. “Inter-species variation in monovalent anion substrate selectivity and inhibitor sensitivity in the sodium iodide symporter (NIS).” *PloS one vol*. 15,2 e0229085. doi:10.1371/journal.pone.0229085.

Cotzias, C., S. J. Wong, E. Taylor, P. Seed and J. Girling. 2008. "A study to establish gestationspecific reference intervals for thyroid function tests in normal singleton pregnancy." *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 137(1), 61-66. doi: 10.1016/j.ejogrb.2007.10.007.

Durand, M. J. 1938. "Recherches sur l'élimination des perchlorates, sur leur répartition dans les organes et sur leur toxicité." *Bulletin de la Société de Chimie Biologique* 20:422-433.

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2014. *Scientific Opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables*. EFSA Journal 2014;12(10):3869, 117 pp. doi:10.2903/j.efsa.2014.3869.

Eichler, O. 1929. "Zur Pharmakologie der Perchloratwikung [The pharmacology of the perchlorate effect]." *Naunyn-Schmiedeberg's Archives of Pharmacology* 144:251-260.

Elhaj, E. T., I. Adam, M. A. Ahmed, and M. F. Lutfi. 2016. "Trimester-specific thyroid hormone reference ranges in Sudanese women." *BMC Physiology*, 16(1), 5. doi: 10.1186/s12899-016-0025-0

Endendijk, J. J., H. A. A. Wijnen, V. J. M. Pop, and A. L. van Baar. 2017. "Maternal thyroid hormone trajectories during pregnancy and child behavioral problems." *Horm Behav* 94:84-92. doi: 10.1016/j.yhbeh.2017.06.007.

Fetene, D. M., K. S. Betts and R. Alati. 2017. "Mechanisms in endocrinology: Maternal thyroid dysfunction during pregnancy and behavioural and psychiatric disorders of children: a systematic review." *European Journal of Endocrinology* 177(5), R261-R273.

Fewtrell, L., R. Kaufmann and A. Lead Prüss-Üshin. 2003. "Assessing the environmental burden of disease at national and local levels." *Environmental burden of diseases series* n°2. Who, Geneva; 65p

https://www.who.int/quantifying_ehimpacts/publications/en/leadebd2.pdf?ua=1

Filis, P., S. Hombach-Klonisch, P. Ayotte, N. Nagrath, U. Soffientini, T. Klonisch, P. O'Shaughnessy and P.A. Fowler. 2018. "Maternal smoking and high BMI disrupt thyroid gland development." *BMC medicine* 16(1), 194.

Finken, M. J., M. van Eijsden, E. M. Loomans, T. G. Vrijkotte and J. Rotteveel. 2013. "Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring." *J Clin Endocrinol Metab* 98 (4):1417-26. doi: 10.1210/jc.2012-3389.

Garber, J. R., R. H. Cobin, H. Gharib, J. V. Hennessey, I. Klein, J. I. Mechanick, R. Pessah-Pollack, P. A. Singer and K. A. Woeber. 2012. "Clinical Practice Guidelines for Hypothyroidism in Adults : Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association." *Thyroid* 2012;22(12):1200-51.

Ghassabian, A., J. Steenweg-de Graaff, R. P. Peeters, H. A. Ross, V. W. Jaddoe, A. Hofman, F. C. Verhulst, T. White and T. Tiemeier. 2014. "Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area." *BMJ open* 4(6), e005520. https://doi.org/10.1136/bmjopen-2014-005520

Giannocco, G., M. M. L. Kizys., R. M. Maciel and J. Sena de Souza. 2020. “Thyroid hormone, gene expression, and Central Nervous System: Where we are”. *Seminars in cell and developmental biology.* doi.org/10.1016/j.semcdb.2020.09.007.

Glinoer, D. 1997. “The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology.” *Endocrine reviews* vol. 18,3 : 404-33. doi:10.1210/edrv.18.3.0300

Greer, M. A., G. Goodman, R. C. Pleus and S. E. Greer. 2002. "Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans." *Environmental health perspectives* 110(9), 927–937. https://doi.org/10.1289/ehp.02110927

Haber, L. T., R. S. Schoeny and B. C. Allen. 2021. "Impact of updated BMD modeling methods on perchlorate and chlorate assessments of human health hazard." *Toxicology letters* 340, 89–100. https://doi.org/10.1016/j.toxlet.2021.01.001

Hadlow, N. C., K. M. Rothacker, R. Wardrop, S. J. Brown, E. M. Lim and J. P. Walsh. 2013. “The relationship between TSH and free T4 in a large population is complex and nonlinear and differs by age and sex.” *J Clin Endocrinol Metab* 98 (7):2936-43. Doi:10.1210/jc.2012-4223.

Häggström, M. 2014. "Medical gallery of Mikael Häggström 2014." *WikiJournal of Medicine*, 1 (2), doi:10.15347/WJM/2014.008.

Health Canada. 2020. Drinking water screening value for perchlorate – Technical summary https://www.canada.ca/en/services/health/publications/healthy-living/drinking-water-screening-value-perchlorate.html

Howdeshell, K. L. 2002. "A model of the development of the brain as a construct of the thyroid system." *Environ Health Perspect*. PMID: 12060827**.**

INERIS. 2011. Profil toxicologique et choix de valeur de référence pour le perchlorate lors d'expositions chroniques par voie orale. Rapport d'étude n° DRC-11-119475-02737A. pp. 24

IPCS (International Program on Chemical Safety), 2010. "Characterization and application of physiologically based pharmacokinetic models in risk assessment." World Health Organization, International Programme on Chemical Safety, Geneva, Switzerland.

Jansen, T. A., T. Korevaar, T. A. Mulder, T. White, R. L. Muetzel, R. P. Peeters and H. Tiemeier. 2019. "Maternal thyroid function during pregnancy and child brain morphology: a time window-specific analysis of a prospective cohort." *Lancet Diabetes Endocrinol* 7 (8):629-637. doi: 10.1016/s2213-8587(19)30153-6.

JECFA. 2011. "Safety evaluation of certain contaminants in food." FAO JECFA monographs 8, in WHO Food Additives Series 63 : Food and Agriculture Organisation of the United Nations / World Health Organisation

Kamm, G. and G. Drescher. 1973. "Demonstration of perchlorate in the urine." *Beitr Gerichtl Med* 30:206-10.

Karthikprabua B., A.Palanimurugana, A.Dhanalakshmib, K.Kannana and S.Thangadurai. 2020. "Perchlorate contamination assessment and hypothyroidism in rat studies using water samples collected around Kovil Patti, Tuticorin District of Tamil Nadu, India." *Microchemical journal* : 154 (104570). https://doi.org/10.1016/j.microc.2019.104570

Khalid, A. S., Z. Marchocki, K. Hayes, J. E. Lutomski, C. Joyce, M. Stapleton, J. O'Mullane and K. O'Donoghue. 2014. "Establishing trimester-specific maternal thyroid function reference intervals." *Annals of Clinical Biochemistry* 51(2), 277-283. doi: 10.1177/0004563213496394

Kim, Y. A. and Y. J. Park. 2014. "Prevalence and risk factors of subclinical thyroid disease." *Endocrinology and metabolism*, 29(1), 20–29. https://doi.org/10.3803/EnM.2014.29.1.20

Korevaar, T., R. Muetzel, M. Medici, L. Chaker, V. W. Jaddoe, Y. B. de Rijke, E. A. Steegers, , T. J. Visser, T. White, H. Tiemeier and R. P. Peeters. 2016. "Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study." *The lancet. Diabetes & endocrinology* 4(1), 35–43. https://doi.org/10.1016/S2213-8587(15)00327-7

Korevaar, T., H. Tiemeier and R. P. Peeters. 2018. "Clinical associations of maternal thyroid function with foetal brain development: Epidemiological interpretation and overview of available evidence." *Clinical endocrinology* 89(2), 129–138. https://doi.org/10.1111/cen.13724

Lawrence, J. E., S. H. Lamm, S. Pino, K. Richman and L. E. Braverman. 2000. " The effect of short-term low-dose perchlorate on various aspects of thyroid function." *Thyroid : official journal of the American Thyroid Association* 10(8), 659–663. https://doi.org/10.1089/10507250050137734

Lawrence, J., S. Lamm and L. E. Braverman. 2001. " Low dose perchlorate (3 mg daily) and thyroid function." *Thyroid : official journal of the American Thyroid Association* 11(3), 295. https://doi.org/10.1089/105072501750159796

Levie, D., T. Korevaar, S. C. Bath, A. Dalmau-Bueno, M. Murcia, M. Espada, M. Dineva, J. M. Ibarluzea, J. Sunyer, H. Tiemeier, M. Rebagliato, M. P. Rayman, R. P. Peeters and M. Guxens. 2018. "Thyroid Function in Early Pregnancy, Child IQ, and Autistic Traits: A Meta-Analysis of Individual Participant Data." *The Journal of clinical endocrinology and metabolism* 103(8), 2967–2979. https://doi.org/10.1210/jc.2018-00224

Li, C., Z. Shan, J. Mao., W. Wang, X. Xie, W. Zhou and W. Teng. 2014. "Assessment of thyroid function during first-trimester pregnancy: What is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women?" *Journal of Clinical Endocrinology and Metabolism* 99(1), 73-79. doi: 10.1210/jc.2013-1674

Lisco, G., A. De Tullio, V. A. Giagulli, G. De Pergola and V. Triggiani. "Interference on Iodine Uptake and Human Thyroid Function by Perchlorate-Contaminated Water and Food." *Nutrients.* 2020 Jun 4;12(6):1669. doi: 10.3390/nu12061669.

Lumen, A., D. R. Mattie and J. W. Fisher. 2013. "Evaluation of perturbations in serum thyroid hormones during human pregnancy due to dietary iodide and perchlorate exposure using a biologically based dose-response model." *Toxicol Sci* 133 (2):320-41. doi: 10.1093/toxsci/kft078.

Männistö, T., H. M. Surcel, A. Ruokonen, M. Vääräsmäki, A. Pouta, A. Bloigu, M-J. Järvelin, A-L. Hartikainen and E. Suvanto. 2011. "Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population." *Thyroid* 21(3), 291-298. doi: 10.1089/thy.2010.0337

McCanlies, E. C., C. C. Ma, J. K. Gu, D. Fekedulegn, W. T. Sanderson, Y. J. Ludeña-Rodriguez, and I. Hertz-Picciotto. 2019. "The CHARGE study: an assessment of parental occupational exposures and autism spectrum disorder." *Occup Environ Med* Sep;76(9):644-651. doi: 10.1136/oemed-2018-105395.

Medici, M., Y. B. de Rijke, R. P. Peeters, E. W. Visser, S. M. de Muinck Keizer-Schrama, V. V. Jaddoe, A. Hofman, H. Hoojikaas, Y. B. De Rijke, H. Tiemer, J. J. Bongers-Schokking, T. J. Visser, R. P. Peeters and E. A. P. Steegers. 2012. "Maternal early pregnancy and newborn thyroid hormone parameters: The Generation R study." *Journal of Clinical Endocrinology and Metabolism* 97(2), 646-652. doi: 10.1210/jc.2011-2398

Medici, M., T. Korevaar, E. W. Visser, T. J. Visser, R. P. Peeters. "Thyroid function in pregnancy: What is normal?" *Biochim Clin* 2016;40 (4):383-92.

Merrill, E. A., R. A. Clewell, P. J. Robinson, A. M. Jarabek, J. M. Gearhart, T. R. Sterner and J. W. Fisher. 2005. "PBPK model for radioactive iodide and perchlorate kinetics and perchlorate-induced inhibition of iodide uptake in humans." *Toxicol Sci* 83 (1):25-43. doi: 10.1093/toxsci/kfi017.

Moleti, M., B. Di Bella, G. Giorgianni, A. Mancuso, A. De Vivo, A. Alibrandi, F. Vermiglio. 2011. "Maternal thyroid function in different conditions of iodine nutrition in pregnant women exposed to mild-moderate iodine deficiency: an observational study." *Clinical Endocrinology*, 74(6), 762-768. doi: 10.1111/j.1365-2265.2011.04007.x

Moncayo, R., B. Zanon, K. Heim, K. Ortner and H. Moncayo. 2015. "Thyroid function parameters in normal pregnancies in an iodine sufficient population." *BBA Clinical* 3, 90-95. doi: 10.1016/j.bbacli.2014.12.006

Moog, N. K., S. Entringer, C. Heim, P.D. Wadhwa, N. Kathmann and C. Buss. 2017. "Influence of maternal thyroid hormones during gestation on fetal brain development." *Neuroscience, 342*, 68-100.

Moon, H. W., H. J. Chung, C. M. Park, M. Hur and Y. Yun. 2015. "Establishment of trimesterspecific reference intervals for thyroid hormones in Korean pregnant women." *Annals of Laboratory Medicine* 35(2), 198-204. doi: 10.3343/alm.2015.35.2.198

Morreale de Escobar, G., M. J. Obregón and F. E. Del Rey. 2004a. "Maternal thyroid hormones early in pregnancy and fetal brain development." *Best practice & research. Clinical endocrinology & metabolism* 18(2), 225–248. https://doi.org/10.1016/j.beem.2004.03.012

Morreale De Escobar G., M. J. Obregon and F. Escobar Del Rey. "Role of thyroid hormone during early brain development." *Eur J Endocrinol* 2004b;151 Suppl:U25-37.

National Toxicology Program. 2015. *OHAT risk of bias rating tool for human and animal studies*.

NRC. 2005. *Health Implications of Perchlorate Ingestion*. Washington, DC: National research council of the national academies.

OEHHA. 2015. *Public health goal : Perchlorate in drinking water*. Office of environmental health hazard assessment.

Orathel, S. P., R. Thomas, N. Chandramohanakumar, J. J. Kulavelil, K. G. Kumar, V. U. Menon, P. Jayaprakash, S. Krishnan, P. S. Manju, S. Param, M. G. Rajamanickam, U. G. Unnikrishnan, J. Thomas J and P. Jose. 2020. "Possible Effects of Perchlorate Contamination of Drinking Water on Thyroid Health." *J Thyroid Res* 13;2020:5208657. doi: 10.1155/2020/5208657.

Ostby, Y., C. K. Tamnes, A. M. Fjell, L. T. Westlye, P. Due-Tønnessen and K. B. Walhovd. 2009. "Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years." *The Journal of neuroscience : the official journal of the Society for Neuroscience* 29(38), 11772–11782. https://doi.org/10.1523/JNEUROSCI.1242-09.2009

Panesar, N. S., C. Y. Li and M. S. Rogers. 2001. "Reference intervals for thyroid hormones in pregnant Chinese women." *Annals of Clinical Biochemistry* 38(Pt 4), 329-332. doi: 10.1258/0004563011900830

Paus, T., D. L. Collins, A. C. Evans, G. Leonard, B. Pike and A. Zijdenbos. 2001. "Maturation of white matter in the human brain: a review of magnetic resonance studies." *Brain research bulletin* 54(3), 255–266. https://doi.org/10.1016/s0361-9230(00)00434-2

Peeters, R. P. and T. J. Visser. Mis à jour en 2017. "Metabolism of Thyroid Hormone." *Feingold KR, Anawalt B, Boyce A, et al., editors*. https://www.ncbi.nlm.nih.gov/books/NBK285545/

Pop, V. J., E. P. Brouwers, H. L. Vader, T. Vulsma, A. L. van Baar and J. J. de Vijlder. 2003. "Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study." *Clin Endocrinol (Oxf)* 59 (3):282-8. doi: 10.1046/j.1365-2265.2003.01822.x.

Pop, V. J., J. L. Kuijpens, A. L. Van Baar, G. Verkerk, M. M. Van Son, J. J. De Vijlder, T. Vulsma, W. M. Wiersinga, H. A. Drexhage and H. L. Vader. 1999. "Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy." *Clinical Endocrinology* 50 (2):149-155. doi: 10.1046/j.1365-2265.1999.00602.x.

Schlosser, P. M. 2016. "Revision of the affinity constant for perchlorate binding to the sodium-iodide symporter based on in vitro and human in vivo data." *J. Appl. Toxicol*. 36: 1531–1535. doi: 10.1002/jat.3337.

Serrano-Nascimento, C., J. Calil-Silveira, R. Dalbosco, T. T. Zorn, M. T. Nunes. 2018. "Evaluation of hypothalamus-pituitary-thyroid axis function by chronic perchlorate exposure in male rats. Environmental Toxicology." (2):209-219. DOI: 10.1002/tox.22509.

Slominski, A., J. Wortsman, L. Kohn, K. B. Ain, M. G. M. Venkataraman, A. Pisarchik, J. Hoon Chung, C. Giuliani, M. Thornton, G. Slugocki and J. Tobin 2002. "Expression of hypothalamic-pituitary-thyroid axis related genes in the human skin." *The Journal of Investigative Dermatology*. 119(6):1449-1455. DOI: 10.1046/j.1523-1747.2002.19617.x.

Soldin, O. P., R. E. Tractenberg, J. G. Hollowell, J. Jonklaas, N. Janicic and S. J. Soldin. 2004. "Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations during gestation: trends and associations across trimesters in iodine sufficiency." *Thyroid* 14(12), 1084-1090. doi: 10.1089/thy.2004.14.1084.

Springer, D., J. Jiskra, Z. Limanova, T. Zima, E. Potlukova. 2017. "Thyroid in pregnancy: From physiology to screening." *Crit Rev Clin Lab Sci* 0(0):1-15

Steinmaus, C., M. Pearl, M. Kharrazi, B. C. Blount, M. D. Miller, E. N. Pearce, L. Valentin-Blasini, G. DeLorenze, A. N. Hoofnagle and J. Liaw. 2016. "Thyroid Hormones and Moderate Exposure to Perchlorate during Pregnancy in Women in Southern California." *Environ Health Perspect* 124 (6):861-7. doi: 10.1289/ehp.1409614.

Stricker, R., M. Echenard, R. Eberhart, M. C. Chevailler, V. Perez, F. A. Quinn and R. Stricker. 2007. "Evaluation of maternal thyroid function during pregnancy: the importance of using gestational age-specific reference intervals." *European Journal of Endocrinology* 157(4), 509- 514. doi: 10.1530/eje-07-0249.

Szinnai, G., L. Lacroix, A. Carré, F. Guimiot, M. Talbot, J. Martinovic., A. L. Delezoide, M. Vekemans, S. Michiels, B. Caillou, M. Schlumberger, J. M. Bidart and M. Polak. 2007. "Sodium/iodide symporter (NIS) gene expression is the limiting step for the onset of thyroid function in the human fetus." *The Journal of clinical endocrinology and metabolism* 92(1), 70–76. https://doi.org/10.1210/jc.2006-1450.

Téllez, R. T., P. M. Chacón, C. R. Abarca, B. C. Blount, C. B. Van Landingham, K. S. Crump, and J. P. Gibbs. 2005. "Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period." *Thyroid* 15 (9):963-975. doi: 10.1089/thy.2005.15.963.

Thompson, W., G. Russell, G. Baragwanath, J. Matthews, B. Vaidya and J. Thompson-Coon. 2018. "Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis." *Clin Endocrinol (Oxf)* 88 (4):575-584. doi: 10.1111/cen.13550.

US EPA. 2005. *Perchlorate and perchlorate salts*. Dans Integrated Risk Information System. Washington, DC: U.S. Environmental protection agency.

US EPA. 2017. *External Peer Review for EPA's Draft Biologically Based Dose-Response (BBDR) Model and Draft BBDR Model Report for Perchlorate in Drinking Water*. Washington, DC: U.S. Environmental protection agency.

US EPA. 2018. *External peer review for EPA's proposed approaches to inform the derivation of a maximum contaminant level goal for perchlorate in drinking water*. Dans Post-meeting peer review summary report. Washington, DC: U.S. Environmental protection agency.

US EPA. 2019a. *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water*. Volume I, May 2019. Washington, DC: U.S. Environmental protection agency.

US EPA. 2019b. *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water – BBDR Modeling*. Volume II Appendix A, May 2019. Washington, DC: U.S. Environmental protection agency.

US EPA. 2019c. *Proposed Approaches to Inform the Derivation of a Maximum Contaminant Level Goal for Perchlorate in Drinking Water*. Volume III Appendices B-J, May 2019. Washington, DC: U.S. Environmental protection agency.

US EPA. 2019d. *Technical Support Document : Deriving a Maximum Contaminant Level Goal for Perchlorate in Drinking Water*. Volume III Appendices B-J, May 2019. Washington, DC: U.S. Environmental protection agency.

US EPA. 2020. *Drinking Water: Final Action on Perchlorate* https://www.govinfo.gov/content/pkg/FR-2020-07-21/pdf/2020-13462.pdf

Visser, T. J. 1996. "Pathways of thyroid hormone metabolism." *Acta medica Austriaca* 23(1-2), 10–16.

Weterings, P. J., C. Loftus and T. A. Lewandowski. 2016. "Derivation of the critical effect size/benchmark response for the dose-response analysis of the uptake of radioactive iodine in the human thyroid." *Toxicology letters* 257, 38–43. https://doi.org/10.1016/j.toxlet.2016.06.004

White, T., H. E. Marroun, I. Nijs, M. Schmidt, A. van der Lugt, P. A. Wielopolki, V. W. V. Jaddoe, A. Hofman, G. P. Krestin, H. Tiemeier and F. C. Verhulst. 2013. "Pediatric population-based neuroimaging and the Generation R Study: the intersection of developmental neuroscience and epidemiology." *Eur J Epidemiol* 28, 99–111. https://doi.org/10.1007/s10654-013-9768-0

Williams, G.R. 2008. "Neurodevelopmental and neurophysiological actions of thyroid hormone." *J Neuroendocrinol* 20(6):784-94.

WHO. 2007. *Reaching optimal Iodine Nutrition in Pregnant and Lactating Women and Young Children*. Joint statement by the World Health Organization and the United Nations Children's Fund.

"https://www.who.int/nutrition/publications/micronutrients/WHOStatement__IDD_pregnancy.pdf?ua=1"

WHO. 2016. *Perchlorate in drinking water. Background document for development of WHO Guidelines for Drinking-Water Quality*. World Health Organization.

Yan, Y. Q., D. Z. Dong, L. Dong, F. R. Wang, X. M. Yang, X. Y. Jin, L-X. Lin, Y-N. Sun and Z-P. Chen. 2011. "Trimester- and method-specific reference intervals for thyroid tests in pregnant Chinese women: Methodology, euthyroid definition and iodine status can influence the setting of reference intervals." *Clinical Endocrinology* 74, 262-269.

Yu, J., H. W. Dong, L.T. Shi, X. Y. Tang, J. R. Liu, J. H. Shi. 2019. "Reproductive toxicity of perchlorate in rats." *Food Chem Toxicol* 128:212-222. doi: 10.1016/j.fct.2019.04.014.

Zhang, X., B. Yao, C. Li, J. Mao., W. Wang, X. Xie, X. Teng , C. Han , W. Zhou, C. Li , B. Xu, L. Bi, T. Meng, J. Du, S. Zhang, Z. Gao, L. Yang, C. Fan, W. Teng and Z. Shan. 2016. "Reference Intervals of Thyroid Function During Pregnancy: Self-Sequential Longitudinal Study Versus Cross-Sectional Study." *Thyroid* 26(12), 1786-1793. doi: 10.1089/thy.2016.0002

Zhu, F., M. Huang, J. Jiao, P. Zhuang, L. Mao and Y. Zhang. 2019. "Environmental exposure to perchlorate, nitrate, and thiocyanate in relation to obesity: A population-based study." *Environ Int* 133(Pt B):105191. doi: 10.1016/j.envint.2019.105191.

Zoeller, R. T. and J. Rovet. 2004. "Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings." *Journal of neuroendocrinology* 16(10), 809–818. https://doi.org/10.1111/j.1365-2826.2004.01243.x

SUGGESTED CITATION

ANSES. (2021). Avis de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à la « Pertinence de la ré-évaluation des risques sanitaires liés à la présence d'ions perchlorate dans les eaux destinées à la consommation humaine à la lumière des travaux de l'US EPA publiés le 23 mai 2019 »

[Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the "relevance of reassessing the health risks associated with the presence of perchlorate in drinking water, in light of the work by the US EPA published on 23 May 2019"] (Request No 2019-SA-0116). Maisons-Alfort: ANSES, 78 p.

ANNEX 1 – PARTICIPANTS

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP ON "PERCHLORATE"

Chair

Mr Nicolas CHEVALIER – Endocrinologist, Nice University Hospital – Expertise: endocrinology, thyroid specialist, clinical epidemiologist.

Members

Mr Laurent BODIN – Research engineer, French Alternative Energies and Atomic Energy Commission (CEA) – Expertise: PBPK modelling, basic and clinical toxicology.

Ms Céline BROCHOT – Head of the Models for Ecotoxicology and Toxicology Unit, INERIS – Expertise: toxicokinetics, PBPK modelling.

Mr Jean-Baptiste FINI – CNRS, French Natural History Museum (MNHN) – Expertise: endocrine disruptors, thyroid, ecotoxicology, reproduction, testing.

Mr Robert GARNIER – Medical toxicologist, Paris Poison Control Centre – Expertise: medical toxicology, occupational health – environmental health.

Mr Michel LAURENTIE – Research Director – ANSES Fougères Laboratory – Expertise: PBPK modelling, methodology, biostatistics, statistics.

Ms Sakina MHAOUTY-KODJA – Research Director – CNRS – Expertise: environmental health, neurodevelopment, endocrinology, reproductive biology, toxicology.

Ms Marion MORTAMAIS – Veterinarian, postdoctoral researcher, Inserm Occitanie Méditerranée – Expertise: epidemiology, environmental epidemiology, statistics.

Ms Isabelle OLIVER-PETIT – Paediatrician, Toulouse University Hospital – Expertise: paediatrics, neonatology, growth and development retardation.

Ms Catherine VIGUIÉ – Veterinarian, Director of Research, INRAE – Expertise: toxicology, endocrine disruptors, thyroid, reproductive biology.

Mr Jean-Louis WÉMEAU – Professor Emeritus of Endocrinology, Endocrinologist, Lille University Hospital, Full Member of the Academy of Medicine – Expertise: internal medicine, endocrinology, thyroid, iodine symporter, endocrine disruptors, perchlorate.

EXPERT COMMITTEE

The work covered in this report was monitored and adopted by the following CES VSR (2021-2023):

EXPERT COMMITTEE ON "HEALTH REFERENCE VALUES" (CES VSR) (2021-2023)

Chair

Mr Fabrice MICHIELS – Occupational physician/toxicologist – Inter-company Association for Occupational Health (Corrèze) – Expertise: occupational medicine, toxicology.

Vice-Chair

Ms Anne MAITRE – University Professor-Hospital Practitioner at the Laboratory of Occupational and Environmental Toxicology, Grenoble University Hospital; Manager of the "Environment and population health forecasting" team, TIMC Laboratory, Grenoble-Alpes University – Expertise: medicine, toxicology, BMEs, pollutant metrology, industrial hygiene.

Members

Mr Luc BELZUNCES – Research Director and Director of the Laboratory of Environmental Toxicology at INRAE – Expertise: general toxicology, neurotoxicology, ecotoxicology, analytical chemistry, risk assessment.

Ms Michèle BISSON – Toxicologist and Research Manager at INERIS – Expertise: Pharmacist toxicologist, TRV, health risk assessment.

Ms Céline BOTINEAU – Engineer in Chemical Risk Prevention at the CEA – Expertise: Industrial hygiene, chemistry, risk assessment.

Ms Anne CHEVALIER – Retired from the French Institute for Public Health Surveillance – Expertise: epidemiology.

Mr François CLINARD – Epidemiologist at *Santé Publique France* – Expertise: pharmacy-toxicology, epidemiology, health risk assessment.

Ms Fatiha EL-GHISSASSI – Scientist, Monographs Programme. Evidence Synthesis and Classification Branch. International Agency for Research on Cancer – Expertise: biochemistry specialising in carcinogenesis and genotoxicity

Mr Claude EMOND – Associate Professor – School of Public Health, University of Montréal – Department of Environmental and Occupational Health – Expertise: toxicology, PBPK modelling, toxicokinetics, nanotoxicology, endocrine disruptors.

Mr Robert GARNIER – Medical toxicologist, Paris Poison Control Centre – Expertise: medical toxicology, occupational health – environmental health.

Ms Perrine HOET – Professor at the Catholic University of Louvain. IREC – Expertise: occupational medicine, occupational and environmental toxicology.

Mr Kevin HOGEVEEN – Toxicologist, ANSES – Fougères, Toxicology of Contaminants – Expertise: toxicology, genotoxicity, hepatotoxicity, *in vitro* toxicology.

Ms Yuriko IWATSUBO – Doctor-epidemiologist at *Santé Publique France* – Expertise: Epidemiology of occupational risks.

Mr Frédéric LIRUSSI – University Professor-Hospital Practitioner at the UFR of Health Sciences & Besançon University Hospital – Expertise: clinical toxicology, analytical toxicology, innate immunity, reprotoxicity.

Mr Luc MULTIGNER – Research Director, INSERM U1085 – IRSET – Expertise: epidemiology, endocrine disruptors, diseases of reproductive functions and organs.

Ms Nadia NIKOLOVA-PAVAGEAU – Medical advisor at INRS – Expertise: occupational medicine, medical toxicology, IBE.

Mr Benoît OURY – Research Manager at INRS – Expertise: atmospheric metrology, workplace air, occupational exposure assessment.

Mr Henri SCHROEDER – Associate Professor at the Faculty of Sciences and Technologies of University of Lorraine – CALBINOTOX Laboratory, EA 7488 – Pharmacist-neurobiologist – Expertise: neurotoxicity, environmental pollutants, animal behaviour, cerebral development, perinatal exposure.

Mr Olivier SORG – Head of research group at University of Geneva – Expertise: doctor of science in biochemistry, experimental toxicology, dermatotoxicology.

Mr Jérôme THIREAU – PhD, CNRS Research Manager – Expertise: animal physiology, electrophysiology, cell biology, cardiotoxicity.

Ms Maeva WENDREMAIRE – Lecturer at the University of Burgundy – Expertise: toxicology, reprotoxicity, pharmacology, analytical toxicology.

Before validation by the CES VSR (2021-2023), the work was presented to the following CESs:

EXPERT COMMITTEE ON "HEALTH REFERENCE VALUES" (CES VSR) (2017-2020)

Chair

Mr Fabrice MICHIELS – Occupational physician/toxicologist at the Inter-company Association for Occupational Health (Corrèze) – Expertise: occupational medicine, toxicology.

Vice-Chair

Mr Raymond VINCENT – Retired (formerly Project Officer in the Applications Division (INRS)) – Expertise: chemistry, pollutant metrology, occupational risk assessment.

Members

Mr Marc BARIL – Associate Professor at University of Montreal – Expertise: chemical toxicology, industrial hygiene.

Mr Stéphane BINET – Pharmacist-toxicologist in the Research and Studies Department (INRS) – Expertise: general and industrial toxicology.

Ms Michèle BISSON – Research Manager at INERIS – Expertise: pharmaceutical toxicology, general toxicology.

Ms Anne CHEVALIER – Retired from the French Institute for Public Health Surveillance – Expertise: epidemiology.

Ms Fatiha EL-GHISSASSI – Scientist, IARC Monographs Group (IMO). International Agency for Research on Cancer – Expertise: biochemistry specialist in carcinogenesis and genotoxicity.

Mr Claude EMOND – Associate Professor – School of Public Health, University of Montréal – Department of Environmental and Occupational Health – Expertise: toxicology, PBPK modelling, toxicokinetics, nanotoxicology, endocrine disruptors.

Mr Rex FITZGERALD – Expert in Regulatory Toxicology at the Swiss Centre for Applied Human Toxicology – Expertise: reproductive toxicology, developmental neurotoxicity, human risk assessment.

Mr Robert GARNIER – Medical toxicologist, Paris Poison Control Centre – Expertise: medical toxicology, occupational health – environmental health.

Ms Perrine HOET – Professor at the Catholic University of Louvain. IREC – Expertise: Medicine, industrial and environmental toxicology.

Ms Yuriko IWATSUBO – Doctor-epidemiologist at *Santé Publique France* – Expertise: Epidemiology of occupational risks.

Ms Cécile KAIRO – Health risk assessor at *Santé Publique France* – Expertise: doctor of pharmacy specialising in the environment, general toxicology and risk assessment.

Ms Laila LAKHAL – INRA Engineer, Toxalim unit – Expertise: toxicology, metabolism, endocrine disruptors.

Mr Frédéric LIRUSSI – University Professor-Hospital Practitioner at the UFR of Health Sciences & Besançon University Hospital – Expertise: clinical toxicology, analytical toxicology, innate immunity, reprotoxicity.

Ms Anne MAITRE – University Professor-Hospital Practitioner at the Laboratory of Occupational and Environmental Toxicology, Grenoble University Hospital; Manager of the "Environment and population health forecasting" team, TIMC Laboratory, Grenoble-Alpes University – Expertise: medicine, toxicology, BMEs, pollutant metrology, industrial hygiene.

Ms Anne PLATEL – Lecturer at the Lille Faculty of Pharmaceutical and Biological Sciences – Genetic Toxicology Laboratory, Institut Pasteur, Lille – Expertise: toxicology, genotoxicity, QSAR.

Mr Henri SCHROEDER – Associate Professor at the Faculty of Sciences and Technologies of University of Lorraine – CALBINOTOX Laboratory, EA 7488 – Pharmacist-neurobiologist – Expertise: neurotoxicity, environmental pollutants, animal behaviour, cerebral development, perinatal exposure.

Mr Olivier SORG – Head of research group at University of Geneva – Expertise: doctor of science in biochemistry, experimental toxicology, dermatotoxicology.

Mr Jérôme THIREAU – CNRS Research Manager – Expertise: doctor of science, animal physiology, cellular biology, cardiotoxicity.

EXPERT COMMITTEE ON "WATER" (2021-2023)

Chair

Mr Gilles BORNERT – Head of Department, Armed Forces Veterinary Group of Rennes – Expertise: microbiology, regulation, degraded situations, water defence.

Vice-Chair

Mr Jean-François HUMBERT – Research Director / Doctor authorised to supervise research – BIOENCO UMR, INRAE, Paris – Expertise: water microbiology including cyanobacteria, microbial ecology.

Ms Anne TOGOLA – Research Project Manager, BRGM – Expertise: organic micropollutants, analytical chemistry, groundwater.

Members

Mr Jean BARON – Head of Department / Research Engineer, *Eau de Paris* – Expertise: Materials in contact with water, water treatment products and processes (treatment systems), corrosion.

Mr Jean-Luc BOUDENNE – Professor – University of Aix-Marseille – Environmental Chemistry Laboratory – Expertise: water metrology, chemistry and quality.

Mr Nicolas CIMETIÈRE – Research Professor – National School for Chemistry, Rennes (ENSCR) – Expertise: water analysis and treatment (DW, organic micropollutants).

Mr Christophe DAGOT – University of Limoges – UMR Inserm 1092, RESINFIT – Expertise: antibiotic resistance: integrons – process engineering – effluent quality (antibiotics and resistant bacteria).

Ms Sabine DENOOZ – Process and Water Quality Expert – Wallonia Water Company (SWDE) – Expertise: water treatment products and processes (DW), water safety plans, technical expertise.

Ms Isabelle DUBLINEAU – Project Officer for the Director of Human Radiological Protection / Doctor authorised to supervise research – IRSN, Fontenay-aux-Roses – Expertise: toxicology, radioelements.

Mr Frédéric FEDER – Director of the "Recycling and Risk" unit – CIRAD – Expertise: geochemistry, water/soil/plant contaminant transfer, environmental risk assessment, water, soil and plant analysis, reuse.

Mr Matthieu FOURNIER – Lecturer, Authorised to supervise research in Geosciences – University of Rouen Normandy – Expertise: hydrogeology, hydrology, DW, transfer and fate of micro-organisms in the environment, modelling, health risks.

Mr Stéphane GARNAUD-CORBEL – Research officer for "Water, biodiversity and urban development" – French Biodiversity Agency (OFB) – Expertise: Sanitation, integrated rainwater management, sludge treatment, use of non-conventional sources of water.

Ms Nathalie GARREC – Research and Expertise Engineer – CSTB – Expertise: microbiology of alternative water sources/*Legionella*, opportunistic pathogens, biocidal efficacy.

Mr Johnny GASPÉRI – Researcher – Gustave Eiffel University – Expertise: organic micropollutants, urban water, surface water, wastewater treatment.

Mr Julio GONÇALVÈS – Professor – CEREGE, Aix en Provence – Expertise: hydrogeology, water resources, transfer of contaminants in groundwater, modelling, recharge.

Mr Jean-Louis GONZALEZ – Researcher authorised to supervise research – IFREMER – Expertise: marine environment, chemical contaminants, speciation, modelling, passive sampling.

Mr Olivier HORNER – Director of Research and Innovation – EPF – Expertise: water chemistry, water treatment.

Mr Michel JOYEUX – Retired, Doctor of Medicine, Doctor of Science – Expertise: medicine, toxicology, quantitative health risk assessment, hazard analysis methods, water chemistry, DW treatment products and processes, environmental health.

Mr Jérôme LABANOWSKI – University of Poitiers – UMR CNRS 7285 IC2MP – National Engineering School (ENSI) Poitiers – Expertise: effluent quality, river biofilm, sediments, fate of effluent-river contaminants.

Ms Sophie LARDY-FONTAN – Metrology Project Manager – LNE, Paris – Expertise: metrology, analytical chemistry, micropollutants, ultratrace elements, QA/QC.

Ms Françoise LUCAS – Lecturer-Researcher, University of Paris-Est Créteil – Expertise: virology, microbial ecology, indicators of faecal contamination, bacteriophages, mycobacteria, enteric viruses, wastewater and rainwater.

Mr Christophe MECHOUK – Head of the "Studies and Construction" Division – Water Department of the City of Lausanne – Expertise: water engineering (drinking water, wastewater, process water, swimming pools), water treatment (processes), physical chemistry and microbiology of water, micropollutants.

Mr Laurent MOULIN – Head of the Research and Development Department – *Eau de Paris* – Expertise: microbiology, virology, disinfection treatments, amoebae.

Mr Damien MOULY – Epidemiologist, Unit Manager, in charge of surveillance of waterborne illness outbreaks – *Santé Publique France* – Expertise: infectious risks, chemical risks, water safety plans, epidemiology, health risk assessment, exposure assessment, surveillance, alert.

Ms Fabienne PETIT – Teacher-researcher / Professor – Rouen University / CNRS UMR M2C – Expertise: microbial ecology.

Ms Catherine QUIBLIER – Lecturer at the University of Paris Diderot – Authorised to supervise research, French Natural History Museum – Expertise: ecology and toxicity of planktonic and benthic cyanobacteria, monitoring.

Ms Pauline ROUSSEAU-GUEUTIN – Researcher in hydrogeology – EHESP – Expertise: hydrogeology, hydrology, contaminant transfer, catchment protection areas, water safety plans.

Ms Marie-Pierre SAUVANT-ROCHAT – Professor – University of Clermont-Auvergne / Faculty of Pharmacy, Clermont-Ferrand – Expertise: public and environmental health, epidemiology, health risk assessment.

Ms Michèle TREMBLAY – Doctor of Medicine specialising in community health / Medical advisor for occupational health and infectious diseases – Public Health Institute of Quebec / Montreal Directorate for Public Health – Expertise: occupational health, water microbiology.

EXPERT COMMITTEE ON "WATER" (2017-2020)

Chair

Mr Gilles BORNERT – Head of Department, Armed Forces Veterinary Group of Rennes – microbiology, regulations, degraded situations, water defence.

Members

Ms Claire ALBASI – Research director / Doctor of Engineering – UMR 5503, Chemical engineering laboratory, CNRS-INPT-UPS, Toulouse – water treatment products and processes including membranes, sanitation, water chemistry, use of alternative water resources.

Ms Sophie AYRAULT – Team Leader / Doctor authorised to supervise research, CEA, Gif-sur-Yvette – geochemistry of metals in the environment.

Mr Jean BARON – Department Head / Research engineer – *Eau de Paris* – materials in contact with water, water treatment products and processes (treatment systems), corrosion.

Mr Jean-Luc BOUDENNE – Professor – Aix-Marseille University – water metrology, chemistry and water quality. Laboratory for Environmental Chemistry.

Ms Corinne CABASSUD – Professor – INSA, Toulouse – Laboratory for the engineering of biological systems and processes, INSA-CNRS-INRAE UMR – water treatment products and processes including membranes, water chemistry.

Ms Véronique CARON – Medical expert in occupational health – INRS – Occupational physician in charge of biological (zoonotic) risk and work environment (resigned on 1 September 2020).

Mr Jean CARRÉ – Retired Doctor of Science – hydrogeology, water resources, catchment protection areas and field experience.

Ms Hélène CELLE-JEANTON – Professor – University Franche Comté – hydrogeology, hydrogeochemistry.

Mr Nicolas CIMETIÈRE – Teacher-researcher – National School for Chemistry, Rennes (ENSCR) – water analysis and treatment (DW, organic micropollutants).

Mr Christophe DAGOT – University of Limoges – UMR Inserm 1092, RESINFIT – antimicrobial resistance: integrons – process engineering – effluent quality (antibiotics and resistant bacteria)

Ms Isabelle DUBLINEAU – Project Officer for the Director of Human Radiological Protection / Doctor authorised to supervise research – IRSN, Fontenay-aux-Roses – toxicology, radioelements.

Mr Johnny GASPÉRI – Researcher – Gustave Eiffel University – organic micropollutants, urban water, surface water, wastewater treatment.

Mr Jean-Louis GONZALEZ – Researcher authorised to supervise research – IFREMER – marine environment, chemical contaminants, speciation, modelling, passive sampling.

Mr Jean-François HUMBERT – Research Director / Doctor authorised to supervise research – BIOENCO UMR, INRAE, Paris – microbiology of water including cyanobacteria, microbial ecology.

Mr Frédéric HUNEAU – Head of the Geology-Hydrogeology Department – University of Corsica – hydrogeology, hydrogeochemistry.

Mr Yves LÉVI – Professor of Public Health and the Environment – Paris Sud University – public health, environmental health, emerging pollutants, health risk assessment, microbial ecology.

Mr Laurent MOULIN – Head of Research and Development Department – *Eau de Paris* – microbiology, virology, disinfection treatments, amoebae.

Mr Daniel PERDIZ – Lecturer / Pharmacist-toxicologist – Paris 11 Sud University – toxicology, genotoxicity, endocrine disruptors in water.

Ms Fabienne PETIT – Teacher-researcher / Professor – Rouen University / CNRS UMR M2C – microbial ecology.

Mr Mohamed SARAKHA – Professor – Clermont-Ferrand Institute of Chemistry, Blaise Pascal University – water treatment products and processes, photochemistry, advanced oxidation, reaction chemistry of water.

Ms Marie-Pierre SAUVANT-ROCHAT – Professor – Clermont-Auvergne University / School of Pharmacy, Clermont-Ferrand – public health and the environment, epidemiology, health risk assessment.

Ms Anne TOGOLA – Research Project Manager, BRGM – organic micropollutants, analytical chemistry, groundwater

Ms Michèle TREMBLAY – Doctor of Medicine specialising in community health / Medical advisor for occupational health and infectious diseases – Public Health Institute of Quebec / Montreal Directorate for Public Health – Occupational health, microbiology of water.

Ms Michèle VIALETTE – Department Head / Doctor authorised to supervise research – Institut Pasteur of Lille – Microbiology of water including virology.

Ms Bénédicte WELTÉ – Retired, Doctor of Science – Water treatment products and processes (all processes, treatment plants).

ANSES PARTICIPATION

Scientific coordination

Ms Karine ANGELI – Coordinator of studies and scientific support in toxicology – Chemicals Assessment Unit, Risk Assessment Department – ANSES

Mr Nicolas FARION – Scientific and Technical Project Leader – Water Risk Assessment Unit, Risk Assessment Department – ANSES

Scientific contribution

Ms Pascale PANETIER – Head of the Water Risk Assessment Unit, Risk Assessment Department – ANSES

Ms Cécile MICHEL – Head of the Chemicals Assessment Unit, Risk Assessment Department – ANSES

Mr Christophe ROUSSELLE – Deputy Coordinator of the Partnership for the Assessment of Risk from Chemicals (PARC) project – ANSES

Administrative secretariat

Ms Virginie SADÉ – Risk Assessment Department – ANSES

CONTRIBUTIONS FROM OUTSIDE THE GROUP(S)

Purpose of the contribution: "Additional data"; Mr Tim KOREVAAR – Postdoctoral Research Fellow – Erasmus University Medical Centre of Rotterdam

ANNEX 2 – ACRONYMS AND ABBREVIATIONS

ADD: Acceptable daily dose
ADME: Absorption, distribution, metabolism and excretion
ANSES: French Agency for Food, Environmental and Occupational Health & Safety
TDI: Tolerable daily intake
ATSDR: US Agency for Toxic Substances and Diseases Registry
ARS: French Regional Health Agency
BAuA: German Federal Institute for Occupational Safety and Health
BBDR: Biologically based dose-response
BMD: Benchmark dose
BMDL: Lower limit of the 95% confidence interval of the BMD
BMR: Benchmark response
CES: Expert Committee
SC: Sensitivity coefficient
DGS: French Directorate General for Health
DGCCRF: French Directorate General for Competition, Consumer Affairs and Fraud Control
NOEL: No observed effect level
TDS: Total diet study
ECHA: European Chemicals Agency
DW: Drinking water
EFSA: European Food Safety Authority
HRA: Health risk assessment
UF: Uncertainty factor
fT4: Free thyroxine
WG: Working Group
HBM4EU: European Human Biomonitoring Initiative
CH: Clinical hypothyroidism
hCG: Human chorionic gonadotropin
SCH: Subclinical hypothyroidism
TH: Thyroid hormone(s)
BMI Body mass index
InVS: French Institute for Public Health Surveillance
IPCS: International Programme on Chemical Safety
MRI: Magnetic resonance imaging
JECFA: Joint FAO/WHO Expert Committee on Food Additives
IQ: Intelligence quotient
LOEL: Lowest observed effect level
MCLG: Maximum contaminant level goal
MCT: Monocarboxylate transporter
MDI: Mental development index
MRL: Minimal risk level
NHANES: National Health and Nutrition Examination Survey
NIS: Sodium-iodide symporter
NRC: US National Research Council of the National Academies
OATP: Organic anion transporting polypeptide
OEHHA: Office of Environmental Health Hazard Assessment (California, USA)
OHAT: Office of Health Assessment and Translation

WHO: World Health Organization
PBPK: Physiologically-based pharmacokinetic
PDI: Psychomotor development index
PECO: Population, exposure, comparison group, outcome
PMTDI: Provisional maximum tolerable daily intake
pTSH: TSH feedback
REACh: Registration, evaluation and authorisation of chemicals
RfD: Reference dose
RMOA: Regulatory management option analysis
ROB: Rest of body
rT3: Reverse T3
SAB: Science Advisory Board
SD: Standard deviation
SISE-Eaux: Environmental health information system
CNS: Central nervous system
SVHC: Substance of very high concern
T3: Triiodothyronine
T4: Thyroxine
TBG: Thyroxine-binding globulin or Transthyretin
TR: Thyroid hormone receptor
TRH: Thyrotropin-releasing hormone
TTR: Transthyretin
TSH: Thyroid-stimulating hormone
US EPA: United States Environmental Protection Agency
VCHNG: Parameters controlling changes in iodide uptake
HCGreg: Parameters controlling hCG hormone levels
GV: Guideline value
V_{max}: Maximum velocity
VSR: Health reference value
TRV: Toxicity reference value

ANNEX 3 – FORMAL REQUEST LETTER

ANSES Reçu le
28 JUIN 2019

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

2019-SA-0116

MINISTERE DES SOLIDARITES ET DE LA SANTE

DIRECTION GENERALE DE LA SANTE
SD/Prévention des risques liés à l'environnement
et à l'alimentation
Bureau Qualité des eaux
DGS/EA4 n°154
Nathalie FRANQUES
☎ : 01.40.56.69.18
nathalie.franques@sante.gouv.fr
Pégase n° D-19-015621

Paris, le 25 JUIN 2019

Le Directeur général de la santé

à

Monsieur le Directeur général de l'Agence
nationale de sécurité sanitaire de l'alimentation,
de l'environnement et du travail
Direction Evaluation des Risques (D.E.R.)
UERE
14 rue Pierre et Marie Curie
94701 MAISONS-ALFORT Cedex

OBJET : Ions perchlorate dans les eaux destinées à la consommation humaine (EDCH)

N/Réf : Saisines DGS EA4 n°160007 (2016-SA-0155) et DGS EA4 n°170013 (2017-SA-0170) (numéro de dossier à rappeler dans toute correspondance)

L'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (Anses) a été saisie en juillet 2016 et juillet 2017 par la Direction générale de la santé (DGS) pour la réalisation de travaux d'expertise relatifs à la pertinence de la ré-évaluation des risques sanitaires liés à la présence d'ions perchlorate dans l'EDCH, à la lumière notamment de la valeur guide proposée par l'Organisation mondiale de la santé (70 µg/L) en 2017. L'Anses a présenté les conclusions de ses travaux d'expertise dans son avis du 26 décembre 2018 en recommandant d'abaisser les valeurs de gestion actuelles préconisées[1], sur la base des différentes expertises, par la DGS aux Agences régionales de santé (ARS), et retient ainsi notamment la valeur de gestion de 5 µg/L en ions perchlorate dans l'EDCH pour la population adulte.

L'Anses indique dans son avis, au paragraphe 3.2.8 relatif aux conclusions sur le choix de la valeur toxicologique de référence (VTR), que *« le groupe de travail « ERS EDCH » et le comité d'expert spécialisé « Eaux » estiment qu'en cas de future évaluation des risques sanitaires liés à l'ingestion d'ions perchlorate postérieure à la publication des travaux en cours de l'US EPA (agence de protection de l'environnement américaine), il sera nécessaire de réexaminer le mode de détermination de la dose critique et de construction de la VTR des ions perchlorate ».*

[1] 15 µg/L : valeur au-delà de laquelle il est recommandé de limiter la consommation d'eau pour les femmes enceintes et allaitantes ;
4 µg/L : valeur au-delà de laquelle il est recommandé de limiter l'utilisation de l'eau pour la préparation des biberons des nourrissons de moins de 6 mois.

14, AVENUE DUQUESNE – 75350 PARIS 07 SP
TÉLÉPHONE : 01 40 56 60 00

Le 23 mai 2019, l'US EPA a lancé une consultation publique sur son projet d'avis relatif à une valeur de gestion pour les ions perchlorate dans les EDCH. Ayant adopté une méthodologie différente (modélisation toxicocinétique de la relation dose-réponse), l'US EPA propose de retenir une valeur de gestion de 56 µg/L en ions perchlorate dans les EDCH.

Comme rappelé dans mon précédent courrier du 29 mars dernier sollicitant vos services pour un temps d'échanges approfondi sur ce sujet sensible, l'étendue des territoires concernés par cette problématique n'est pas négligeable.

Aussi, compte tenu de ces éléments et afin de donner aux ARS des orientations adaptées et proportionnées au risque sanitaire, je souhaite que l'Anses examine à nouveau l'évaluation des risques sanitaires liés à l'ingestion d'ions perchlorate, à la lumière des récents travaux de l'US EPA en cours de publication, et me rende un avis dans un délai de 6 mois.

Jérôme SALOMON

2

ANNEX 4 – DIAGRAMS ON THYROID FUNCTION AND MODE OF ACTION OF PERCHLORATE

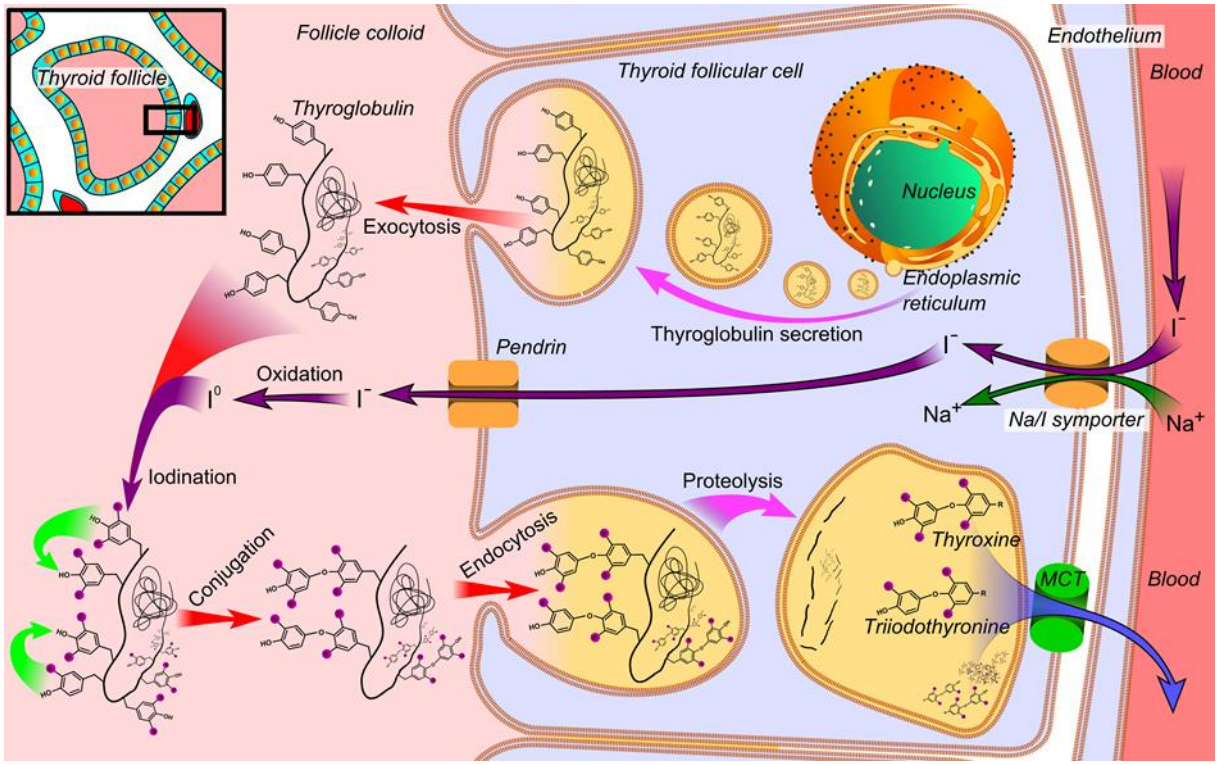


Figure 1 – Thyroid hormone synthesis in a follicular cell (thyrocyte) (Häggström 2014)

- Thyroglobulin synthesised in the rough endoplasmic reticulum is secreted by exocytosis into the colloidal substance in the lumen of the thyroid follicle.

- The NIS actively pumps iodide (I^-) from the blood across the basal membrane of the thyrocytes.

- This iodide enters the follicular lumen from the cytoplasm via the pendrin transporter (apical membrane) of the thyrocytes.

- In the colloid, iodide (I^-) is oxidised to iodine (I^0) by an enzyme called thyroid peroxidase (TPO).

- Iodine (I^0) reacts with the tyrosine residues of thyroglobulin (about 120 tyrosine residues).

- Adjacent iodotyrosine residues are condensed to produce iodothyronines, including THs.

- Iodinated thyroglobulin is taken up by endocytosis in the thyrocytes.

- Proteolysis of iodinated thyroglobulin by various proteases releases thyroxine (T4) and triiodothyronine (T3) molecules.

- T4 and T3 seem to pass into the bloodstream largely via monocarboxylate transporters (MCTs).

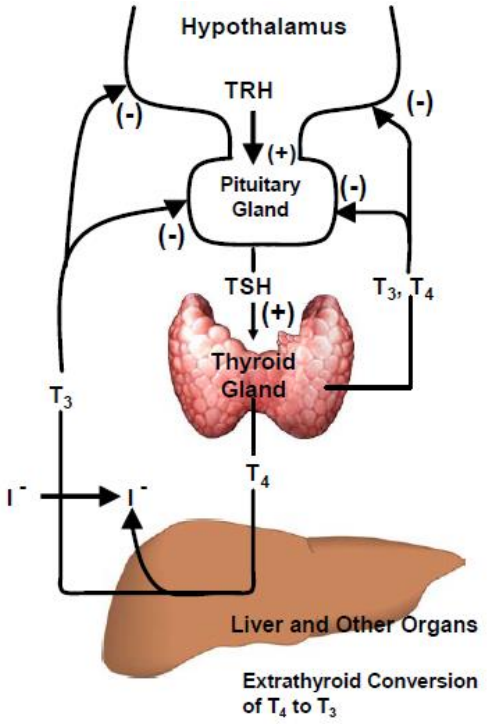


Figure 2 – Schematic representation of the thyroid axis (from NRC, 2005)

Thyroid autoregulation; low circulating levels of THs stimulate hypothalamic secretion of TRH, which in turn stimulates the endocrine cells of the anterior pituitary gland to release TSH into the circulatory system. TSH acts on the thyroid gland to stimulate the various stages of TH production.

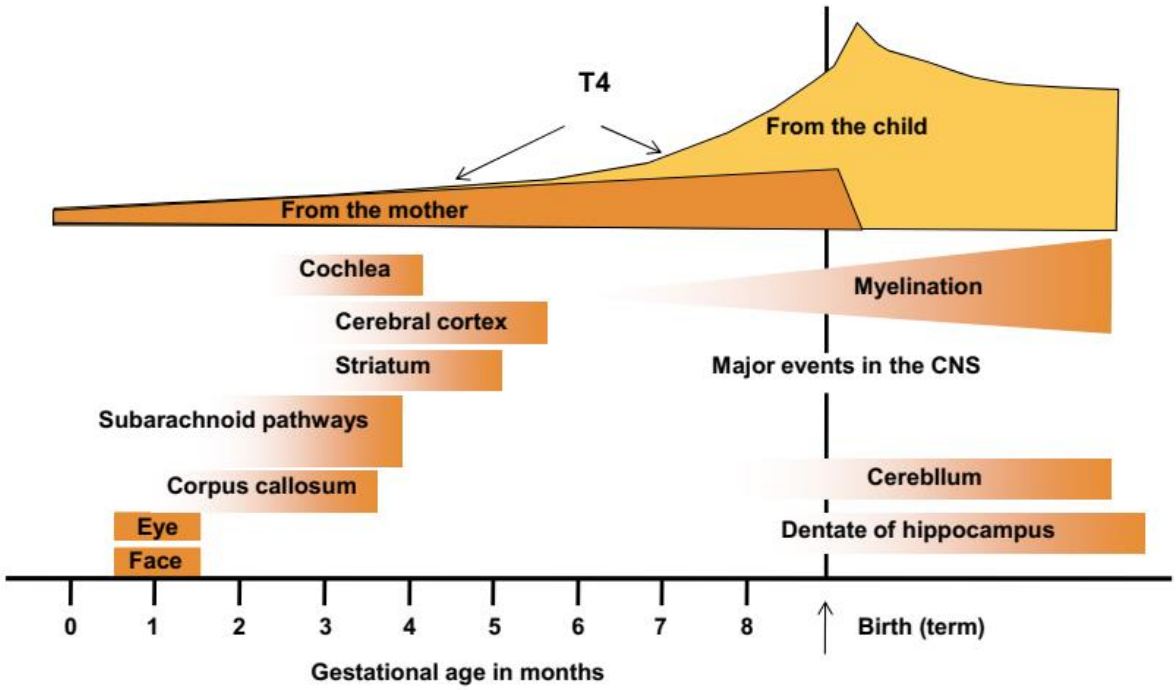


Figure 3 – Foetal brain development from Morreale de Escobar *et al*. (2000)

The foetal thyroid gland appears in the second month and becomes progressively functional from the fourth month. The brain ontogeny of the foetus and the development of fine structures depends on maternal THs, and therefore on the transplacental transfer of adequate quantities of hormones.

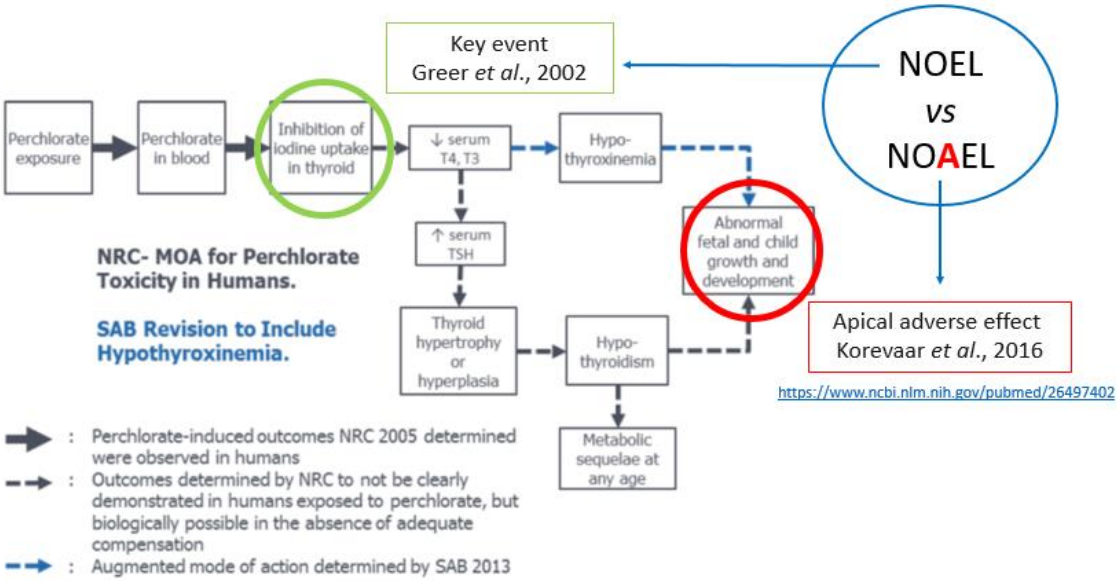


Figure 4 – Mode of action of perchlorate on thyroid function in pregnant women and consequences for neurodevelopment in children (from US EPA, 2019)

ANNEX 5 – ANALYSIS OF THE US EPA'S BBDR MODEL ACCORDING TO THE ROADMAP DRAWN UP BY ANSES DURING THE HBM4EU PROJECT – NOVEMBER 2020

1 – Description of the model

1.1 Description of the model (toxicokinetic part)

Description of the BBDR model (toxicokinetic part)			
Type of information	**Responses**	**Comments**	**Suggestions for improving the model**
Substance name	Perchlorate Iodide	nil	nil
Authors + year of publication	US EPA (May 2019)	nil	nil
Model objective	BBDR model: Relationship between perchlorate exposure and THs at sensitive life stages and the approach seeking to link BBDR model results to neurodevelopmental outcomes using the epidemiological literature	nil	nil
Model codes	acslX, MCsim Codes available on the website of the US EPA[6]	nil	Could be coded in R or Berkeley Madonna
Target population	Women before conception and early pregnancy (first trimester)	nil	nil
Route of exposure	Oral route	nil	nil

[6] https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/3352518

Measurements selected and consistency with formulation of the problem	Perchlorate: plasma and urine Iodide: plasma and urine	nil	nil
Number, description and types of compartments	**Perchlorate:** 3 compartments Plasma + 2 sub-compartments (erythrocytes, protein) Thyroid (plasma + tissue) Rest of body **Iodide:** 3 compartments Plasma Thyroid (plasma + tissue) Rest of body T3-T4 model: 1 compartment for T3 and T4 (non-physiological – volume of distribution)	nil	nil
Metabolic pattern	Perchlorate and iodide: no metabolism	nil	nil
<u>Physiological parameters</u> **Type of parameters (e.g. tissue volumes, body weight, glomerular filtration rate, etc.)** **Parametrisation methods**	See Tables 1 and 2 below (US EPA assessment page 3-5 to 3-8 Volume I, and Section 1.4 Volume II) Constant parameters and parameters that change with pregnancy (e.g. body weight, plasma volume, $fT4/T4_{total}$ ratio, etc.)	nil	nil
<u>Physico-chemical parameter</u> **Partition coefficient**	Tables 1 and 2 below (US EPA assessment page 3-5 Volume I, and Section 1.4 Volume II)	nil	nil

<u>Biochemical parameters</u> **Type of parameters (e.g. metabolic rates such as Vmax, Km, etc.) Parametrisation methods**	Tables 1 and 2 below (US EPA assessment page 3-5 Volume I, and Section 1.4 Volume II) The US EPA used a Bayesian methodology to estimate iodine uptake by the thyroid.	The biochemical parameters used are described by the US EPA. Four parameters were calibrated by the US EPA with toxicokinetic data from the study by Greer *et al*. (2002). These parameters are: - urinary clearance of perchlorate: the US EPA defined a value of 0.105 L/hour/kg$^{0.75}$, which corresponds to the 2.5th percentile of the general population distribution for the median. This value is more than twice as high as the values used in the PBPK models of Lumen *et al*. (2013) and Merrill *et al.* (2005), which correspond to estimated urinary clearance values in women in the third trimester of pregnancy. - urinary clearance of iodide: this parameter was estimated because the modelling of urinary elimination in the US EPA model is different from that of Lumen *et al* (2013), which linked iodide clearance to ingested dose. - the affinity constant (Km) in the Michaelis-Menten equation governing perchlorate transport by the NIS: the value used is 3 times lower than Lumen *et al*. (2013). This value is based on the US EPA's re-analysis of Greer *et al*. (2002). This value makes perchlorate three times more effective at competitive inhibition of the NIS compared to Lumen *et al*. (2013). - the maximum velocity (V_{max}) of iodide in the Michaelis-Menten equation governing iodide entry into the thyroid: the current model uses a value (690 nmol/h/kg$^{0.75}$) 5.6 times lower than that of Lumen *et al*. (2013). This is based on adjustment to data on the female subjects in Greer *et al*. (2002).	- NB: It is true that the Km value is three times higher than that used by Lumen but it corresponds to the 50th percentile of the study by Schlosser *et al.*, 2016.
Model calibration	(US EPA Evaluation Section 2 Volume II)	The studies used for the calibration are detailed.	nil
Additional information	T3-T4 cycle	nil	nil

Model plausibility	Despite some uncertainties, the model has physiological plausibility.
Remarks	The influence of the NIS was incorporated into the model via a Mickaelis-Menten type equation (Vmax, Km), based on *in vitro* studies and correlated with *in vivo* studies, which seems consistent. The new values for the four parameters result in perchlorate having a far greater predicted effect on iodide uptake by the thyroid compared to previous models. In particular, the US EPA defined a value of 0.105 L/hour/kg$^{0.75}$ for urinary clearance of perchlorate, corresponding to the 2.5th percentile of the general population distribution for the median, which is an uncertainty because this value is more than twice as high as the values used in the third trimester of pregnancy. This is not consistent with the increased glomerular filtration rate (GFR) in pregnant women.

1.2 Description of the model (toxicodynamic part)

Description of the BBDR model (toxicokinetic part)		
Type of information	**Responses**	**Comments**
Substance name	Perchlorate Iodide	nil
Authors + year of publication	US EPA (2019)	
Model objective	Describe the combined effect of varying blood concentrations of perchlorate and iodide on thyroid iodide uptake and subsequent production of THs, including T4	nil
Mode of action (MOA) fully understood	Action on the thyroid gland Plasma T3 and T4 concentrations	nil
Toxicodynamic events appropriate according to the MOA	Measurement in T4 and T3	nil
Type of toxicodynamic events	Secretion	nil
Selected unit of measurement appropriate to the toxicodynamic event	nil	To date, there are not many models that take the kinetic and dynamic aspect into account. However, the selected dose measurement unit seems consistent.

Toxicodynamic events / calibration	Iodide sub-model T3-T4 sub-model - The parameter values and their sources are detailed by the US EPA and listed in Table A-2. - 14 studies (Cotzias *et al.*, 2008; Elhaj *et al.*, 2016; Khalid *et al.*, 2014; Li *et al*., 2014; Männistö *et al*., 2011; Medici *et al*., 2012; Moleti *et al*., 2011; Moncayo *et al*., 2015; Moon *et al*. 2015; Panesar *et al*., 2001; Soldin *et al*., 2004; Stricker *et al*., 2007; Yan *et al.,* 2011; Zhang et *al*., 2016) were selected by the US EPA to calibrate the relationship between plasma TSH and fT4 concentrations. - The theoretical curves were adjusted to the experimental data for modelling THs.	Compared to the model developed previously, some parameters have been re-estimated (e.g. T4 production rate) without sufficient justification (Annex 4). Calibration of the rate of basal T4 hormone production is a parameter taken into account in the model calibration. The use of a lower T4 production rate (6.25×10^{-7}/hr/kg$^{0.75}$) than the value published in the model of Lumen *et al*., 2013 (2.45×10^{-6}/hr/kg$^{0.75}$) is not sufficiently justified, as mentioned by Clewell *et al*. (2019).

The model parameters were described in Table A-2 of Volume II of the US EPA assessment and are detailed in Tables 1 and 2 below:

Table 1 – Physiological parameters of the model

Parameters	Values	References	Confidence level assigned to the value according to the method of determination
Body weight for non-pregnant woman - BW0 (kg)	70	Default value	High
Hematocrit, red blood cell fraction - Hct0	0.394	Value for non-pregnant women	Moderate
Cardiac output constant - QFC0 (L/(h·kg$^{0.75}$))	13.8	Non-pregnant women, scaled to body weight by allometric adjustment	High
Fraction of cardiac output going to thyroid - QFthy0	0.015	Non-pregnant (Leggett & Williams, 1995)	High
Fractional volume of blood plasma - VFpls	0.0539	Default value	Moderate
Fractional volume of entire thyroid - VFthy	1.34 10^{-4}	Default value	Moderate
Fractional volume of thyroid blood - VFthyB	0.276	(Lumen, *et al*., 2013)	Low
Fractional volume of thyroid tissue - VFthyT	0.724	Calculated, 1 - VFthyB	Low
Sensitivity constant for increase in T4 and T3 production per unit hCG - khCG (L/kIU)	$3.54 \cdot 10^{-3}$	Calculated	Low
Target TSH level, at which iodine uptake Vmax and thyroid hormone production are at calibrated levels – TSHtar (mIU/L)	1.37	TSH equation normalised to yield TSH = TSHtar when CFT4 = CFT4tar	Low
Abndmax0 (ng)	$17 \cdot 10^{6}$	Maximum capacity for thyroidal bound iodide in the non-pregnant woman (start of pregnancy)	High

Table 2 – Specific parameters for perchlorate and iodide, T4, T3

Parameters	Values	References	Confidence level assigned to the value according to the method of determination
Perchlorate			
Rest of body : plasma partition coefficient - Prob_P	0.558	The current model uses a weighted average of the tissue-specific partition coefficients (PCs) for the new ROB compartment and takes into account the presence of the NIS in the skin and mammary glands. The inclusion of skin and breast NIS increased the PC by 80%.	Low
Red blood cell : plasma partition coefficient - PRBC_P	0.8	(Clewell, *et al*., 2007)	High
Thyroid tissue : plasma partition coefficient - Pthy_P	0.13	(Merrill, *et al*., 2005)	High
PA product, red blood cells-plasma - PARBCc_P (L/(h·kg$^{0.75}$))	10	(US EPA, 2009) Scaled to body weight by allometric adjustment	High
Permeability-area (PA) product for thyroid tissue : plasma - PAthyC_P (L/(h·kg$^{0.75}$)	10^{-4}	(Lumen, *et al*., 2013) Scaled to body weight by allometric adjustment	High
Km for perchlorate binding in serum - Km_Bp (nM)	181	(Merrill *et al*., 2005)	High
Vmax, perchlorate binding in serum - VmaxC_Bp (nmol/(h·kg$^{0.75}$))	5.9	(Clewell, *et al*., 2007) Scaled to body weight by allometric adjustment	High
First order constant for unbinding of perchlorate from plasma protein binding - KunbC_P (L/(h·kg$^{0.75}$))	0.03	(US EPA, 2009) Scaled to body weight by allometric adjustment	High
Uptake into thyroid via NIS - VmaxNISF_thy_P (nmol/h/kg$^{0.75}$)	650	Value for non-pregnant women; scaled for pregnancy (Lumen, *et al*., 2013)	High
Km for NIS - uptake in thyroid - KmNIS_P (nM)	489	Based on a re-analysis of Greer *et al*. (2002) by the US EPA 2.5th percentile of sampling distribution for the median	High
Elimination to urine - CLFUP (L/hr/kg$^{0.75}$)	0.105	Value for non-pregnant women; scaled for pregnancy. Based on a re-analysis of Greer *et al*. (2002)	High

Iodide			
Plasma protein binding of iodide = N/A		Not modelled in the current version of the BBDR (nor in the 2017 version).	
Rest of body : plasma partition coefficient - Prob_I,	0.243	The current model uses a weighted average of the tissue-specific PCs for the new ROB compartment that takes into account the presence of the NIS (Slominski *et al*., 2002) and mammary glands. The adjustment for skin and mammary NIS increased the PC by 20%. Lumen *et al.* (2013) reported PCs for iodide for individual tissues ranging from 0.15 to 0.4, which were used as is in the January 2017 model.	Low
Thyroid tissue : plasma partition coefficient - Pthy_I	0.15	(Merrill, *et al*., 2005)	High
Permeability-area (PA) product for thyroid tissue-plasma - PAthyC_I (L/(h·kg$^{0.75}$)	10^{-4}	Lumen *et al.* (2013); scaled to body weight by allometric adjustment.	High
Thyroid Iodide Uptake via NIS - VmaxNISF_thy_I (nmol/h/kg$^{0.75}$)	690	Value for non-pregnant women, scaled for pregnancy. This value is based on an adjustment to data on the female subjects in Greer *et al*. (2002). In addition, the VmaxC is scaled to increase with pregnancy based on an empirical relationship between gestational age and radioactive iodide uptake. The current model uses a VmaxC 5.6 times lower than that of Lumen *et al*. (2013).	High
Km for NIS-uptake in thyroid - KmNIS_I (nM)	3.15×10^{4}	Lumen *et al*. (2013)	High
Iodide from T4 deiodination based upon degradation rate of T4 - KdegT4F (L/hr/kg$^{0.75}$)	1.9×10^{-5}	1st order T4 degradation constant (scaled). This value decreases KdegT4F by a factor of 10 compared to the values of Lumen *et al*. (2013). The decrease allows the model to be adjusted to the NHANES data range, taking into account uncertainties in other model parameters, with the procedure used by the US EPA.	High
Iodide from T3 deiodination based upon degradation rate of T3 (KdegT3F) KdegT3F (L/hr/kg$^{0.75}$)	1.7×10^{-4}	This value decreases KdegT3F by a factor of 10 compared to the values of Lumen *et al*. (2013). The decrease allows the model to be adjusted to the NHANES data range, taking into account uncertainties in other model parameters, with the procedure used by the US EPA.	High
Elimination to urine - CLFUI (L/hr/kg$^{0.75}$)	0.0653	Value for non-pregnant women, scaled for pregnancy.	High

2nd order constant for iodide binding in thyroid - KBIND_I (nmol·h)-1	$3.12 \cdot 10^{-3}$	Calibrated from NHANES data (non-pregnant women)	Moderate
T3			
T3 urinary clearance - CLUFT3 (L/(h·kg0.75))	$2.7 \cdot 10^{-3}$	Scaled, non-pregnant women (Lumen *et al*., 2013)	High
Ratio of free to total T3 – FRT30	$2.77 \cdot 10^{-3}$	Non-pregnant women	High
First order T3 degradation constant - KdegT3F (h·kg0.75)-1	$1.7 \cdot 10^{-4}$	Calibrated – reduced by 10% compared to Lumen *et al*. (2013)	High
First order T3 production constant - KPRODT3F (h·kg0.75)-1	$5.83 \cdot 10^{-8}$	Calibrated from NHANES data (non-pregnant women)	High
T3 volume of distribution - VDFT30 (L/kg)	0.603	Non-pregnant women	Moderate
T4			
Second order/first order term for change in fT4 : T4 with GW - AobT4	-0.07782	Calibrated from NHANES data (non-pregnant women)	High
First order term for change in fT4 : T4 with GW - bT4	0.01845	Calibrated from NHANES data (non-pregnant women)	High
T4 urinary clearance CLUFT4 (L/(h·kg0.75))	$2.83\ 10^{-4}$	Calibrated from NHANES data (non-pregnant women)	High
Ratio of free to total T4 - FRT40	$1.03 \cdot 10^{-4}$	Non-pregnant women	High
Target" T4 serum concentration, at which TSH feedback term = 1, neither stimulating nor inhibiting hormone production - CT4tar (mIU/L)	99.1	CFT4tar = FRT40·CT4TAR·10^3	Low
1st order T4 degradation constant – KdegT4F (h·kg0.75)-1	$1.9 \cdot 10^{-4}$	Calibrated – reduced by 10% compared to Lumen *et al*. (2013)	High
1st order T4 production constant – KPRODT4F (h·kg0.75)-1	$6.25 \cdot 10^{-7}$	Calibrated from NHANES data (non-pregnant women)	High
T4 volume of distribution - VDFT40 (L/kg)	0.162	Non-pregnant women	Moderate

Note: the last column represents the level of confidence assigned to the value of the parameter according to the method of determination, as shown below:

Indicative confidence level for model parameter values	
High	Data **measured** in *in vivo/in vitro* studies (animal, human tissue)
Moderate	Data **estimated** by optimisation/adjustment of the curve
Low	Data **estimated** by other *in silico* methods (QSAR, etc.)

2- Parameter verification and model analysis

Parameter verification and model analysis		
Type of information	**Responses**	**Comments – suggestions for improving the model**
Information required	PBTK: Toxicokinetic data for perchlorate in adults (i.e. measurements of plasma/urinary concentrations under controlled conditions) are limited and no appropriate data in pregnant women have been identified. Biomonitoring data were excluded. The body of data for assessing the perchlorate sub-model is as follows: •Greer *et al*. (2002) (also used for calibration) •Kamm & Drescher (1973) The model's predictions are considered satisfactory.	Comment: The predictions generally agree with the experimental data. It should be noted that the data from Greer *et al*. (2002) were used to calibrate 4 parameters of the perchlorate and iodide sub-models.
	PBTD: Comparison with Steinmaus *et al*. (2016) by the US EPA and comparisons with data from Greer *et al*. (2002), Braverman *et al*. (2006) and Téllez-Téllez *et al*. (2005a, 2005b) by Clewell *et al.* (2019). See below.	
Model analysis		
Sensitivity analysis conducted for all parameters	This was carried out by the authors and is presented in the next section. The local sensitivity analysis was carried out to assess the influence of model parameters on a measure of perchlorate dose-response, i.e. the decrease in plasma fT4 concentration. A local normalised sensitivity coefficient was calculated for a 1% increase or decrease in the value of the parameter. Sensitivity was assessed at GW -1 (pre-pregnancy), 12 and 16	
Uncertainty analysis conducted for the most influential parameters	This was carried out by the authors. Monte Carlo simulations were carried out.	

3- Assessment of the model

Apart from the study by Steinmaus *et al.,* the model seems to reproduce the experimental data, i.e. predicted values/reported values < 2, in accordance with the International Program on Chemical Safety (IPCS) (WHO, 2010) for the studies by Greer *et al*. (2002), Braverman *et al.* (2006) and Téllez-Téllez *et al*. (2005).

However, these studies available to assess the model do not show any impact of perchlorate exposure on fT4 concentration.

As an example, Table 3 below shows the comparison from the publication of Clewell *et al*. (2019) between the model estimates (fT4) and the data measured in the study by Greer *et al*. (2002).

Table 3 – Comparison of model-simulated data with data measured by Greer *et al*. (2002) – Clewell *et al.* (2019)

Dose	RAIU (%)		fT4 (pM)	
(µg/kg/d)	Simulated	Measured	Simulated	Measured
0	100	100	10.33	–
7	89	98.2	10.33	–
20	74	83.6	10.32	16.09
100	37	55.3	10.31	15.26
500	11	32.9	10.30	15.44

3.1 Results of the sensitivity analysis

The sensitivity analysis performed by the authors was presented in Table A-8 of the US EPA document and is shown below (Table 4).

As a reminder, a parameter is considered to have "high" sensitivity if the sensitivity coefficient (SC) is greater than 0.5, "moderate" if its coefficient is between 0.2 and 0.5, and "low" if its coefficient is less than 0.2.

This analysis was performed taking three different time periods into account (one week before pregnancy, and at 12 and 16 weeks of pregnancy) for women with a median fT4 value and efficient TSH feedback (pTSH = 1) and for women with a 10th percentile fT4 value and weak TSH feedback (pTSH = 0.398)

Table 4 – Significant local sensitivity factors (Table A-8, US EPA Volume II)

Parameters	**Median individual pTSH = 1**			**10th percentile individual pTSH = 0.398**		
	Gestation week (GW) -1	**GW 12**	**GW 16**	**GW -1**	**GW 12**	**GW 16**
BW0	-0.90	-0.71	-0.64	0.57	0.66	0.70
VDFT40	-0.28	-0.36	-0.30	0.09	0.18	0.18
QFC0, QFTHY0	0.16	0.14	0.12	0.02	0.00	0.00

VMAXNISF_THY_I (-KMNIS_I)	0.65	0.53	0.47	-0.37	-0.41	-0.42
KMNIS_P	-0.96	-0.96	-0.96	-0.98	-0.98	-0.98
KDEGT4F	-0.28	-0.22	-0.24	0.09	0.10	0.13
CLFUI	-0.82	-0.67	-0.60	0.36	0.41	0.43
CLFUP	-0.95	-0.96	-0.96	-0.98	-0.98	-0.98
CLUFT4	-0.91	-0.63	-0.59	0.22	0.20	0.22
FRT40	1.94	1.58	1.42	-1.14	-1.30	-1.32
AOBT4	0.00	-0.14	-0.24	0.00	0.07	0.12
PTSHV	-0.38	-0.38	-0.41	-0.72	-0.69	-0.67
KHCG	0.00	0.13	0.08	0.00	-0.08	-0.06
CT4TAR	0.75	0.60	0.53	-0.84	-0.92	-0.93

Normalised sensitivity coefficients for the effect of the parameter on perchlorate dose-response. A positive value means that increasing the parameter increases the relative change in fT4 concentration vs. perchlorate exposure and vice versa.

3.2 Analysis of uncertainty

The uncertainty was analysed by the US EPA. According to the IPCS document (WHO, 2010), a parameter is considered to have "high" uncertainty if its value is greater than 2, "moderate" if its value is between 0.3 and 2, and "low" if its value is less than 0.3.

Table 5 below also presents the values from the sensitivity analysis (SC).

Table 5 – Summary of uncertainty and variability with their potential impact on dose-response (Table A-11, US EPA Volume II)

Parameters with maximum |SC| > 0.1 (Table A-8)	**Absolute SC (Table A-8) ***	**Variability**		**Uncertainty**		***Analysis of uncertainty***
		Variability parameters	**Potential impact**	**Uncertainty parameters**	**Potential impact**	
KMNIS_P‡	0.96-0.98 (0.97)	~ 0	~ 0	0.86	**0.8**	*Moderate*
CLFUP‡	0.95-0.98 (0.97)	0.82	**0.8**	0.16	0.2	*Low*
FRT40	1.14-1.94 (1.45)	0.34	**0.7**	0.2	0.3	*Low*
CT4TAR	0.6-0.93 (0.76)	0.26	0.2	~ 0	< 0.1	*Low*
PTSHV, PTSHK‡†	0.38-0.72 (0.54)	1.35	**1**	1.35	**0.7**	*Moderate*
CLFUI	0.36-0.82 (0.55)	0.82	**0.7**	0.2	0.1	*Low*
VMAXNISF_THY_I (-KMNIS_I)	0.37-0.65 (0.48)	(~ 0) 0.4	(~ 0) 0.3	(~ 0) 0.27	(~ 0) 0.1	*Low*
CLUFT4	0.2-0.91 (0.46)	0.41	0.4	~ 0	~ 0	*Low*
KDEGT4F†	0.09-0.28 (0.18)	0.52	0.1	0.52	< 0.1	*Moderate*
BW0	0.57-0.9 (0.7)	0.4	0.4	~ 0	~ 0	*Low*
VDFT40	0.09-0.36 (0.23)	0.28	0.1	0.5	0.1	*Moderate*
AOBT4	0-0.24 (0.1)	0.25	< 0.1	0.25	< 0.1	*Low*
QFC0, QFTHY0	0-0.16 (0.07)	0.4	< 0.1	0.2	< 0.1	*Low*
KHCG	0-0.13 (0.06)	0.85	0.1	0.26	< 0.1	*Low*

* Values are ranges of absolute sensitivity coefficients (SCs) across iodine intake and gestation times evaluated (numerical average of absolute sensitivities)

‡ Lower bound estimates of KMNIS_P and CLFUP (5th percentile of the estimated distribution for the median) and PTSHV and PTSHK (approximate lower bound = 0.4), which result in higher sensitivity to perchlorate than median estimates, were evaluated and used to derive the limit value for DW.

The likelihood that KMNIS_P or CLFUP are significantly less than the 5th percentiles used is considered low. Likewise, the likelihood that PTSHV and PTSHK are less than 0.4 is considered low. Hence the remaining uncertainty is qualified as low.

3.3 Coupling the results of the sensitivity and uncertainty analyses

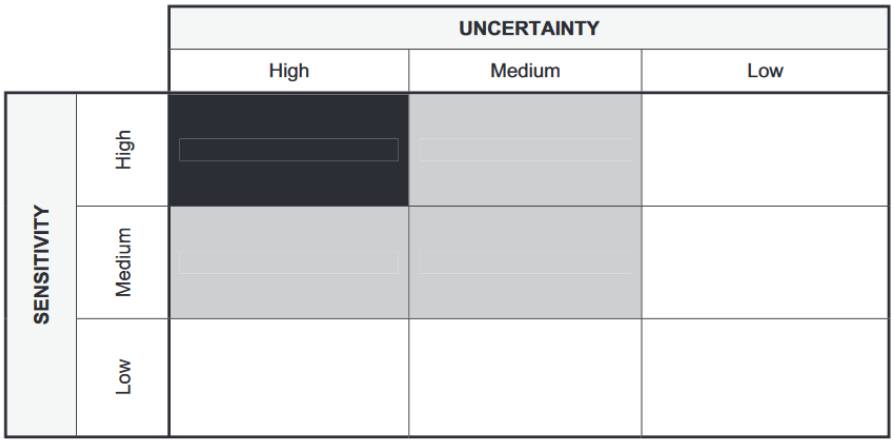


Figure 1 – Illustration of the role of sensitivity and uncertainty analyses in determining the reliability of the model's dose measurement predictions for risk assessment. Low reliability (black box); Moderate reliability (grey boxes); High reliability (white boxes) (see IPCS 2010)

In conclusion, the coupled uncertainty and sensitivity analysis (Table A-11) reveals that only two parameters are in the grey boxes: KMNIS and PSTHV. The other parameters are in the white boxes, indicating high to moderate reliability of the model.

4- Conclusion

The toxicokinetic part of the BBDR model for perchlorate has been rigorously assessed by the US EPA. This assessment shows that the kinetic model of perchlorate effectively reproduces the different data available in the literature, i.e. the changes in plasma concentration and cumulative urinary excretion in adults.

This part of the model fulfils the WHO/IPCS requirements for use in risk assessment.

The analysis of the US EPA model according to the IPCS methodology (WHO 2010) and the roadmap (drawn up as part of the HMB4EU project) led to the conclusion that:

- the studies used to calibrate the model are detailed, and a confidence level was assigned to the selected values according to the recommendations of the HBM4EU roadmap;

- the sensitivity and uncertainty analyses indicate high to moderate reliability of the model;

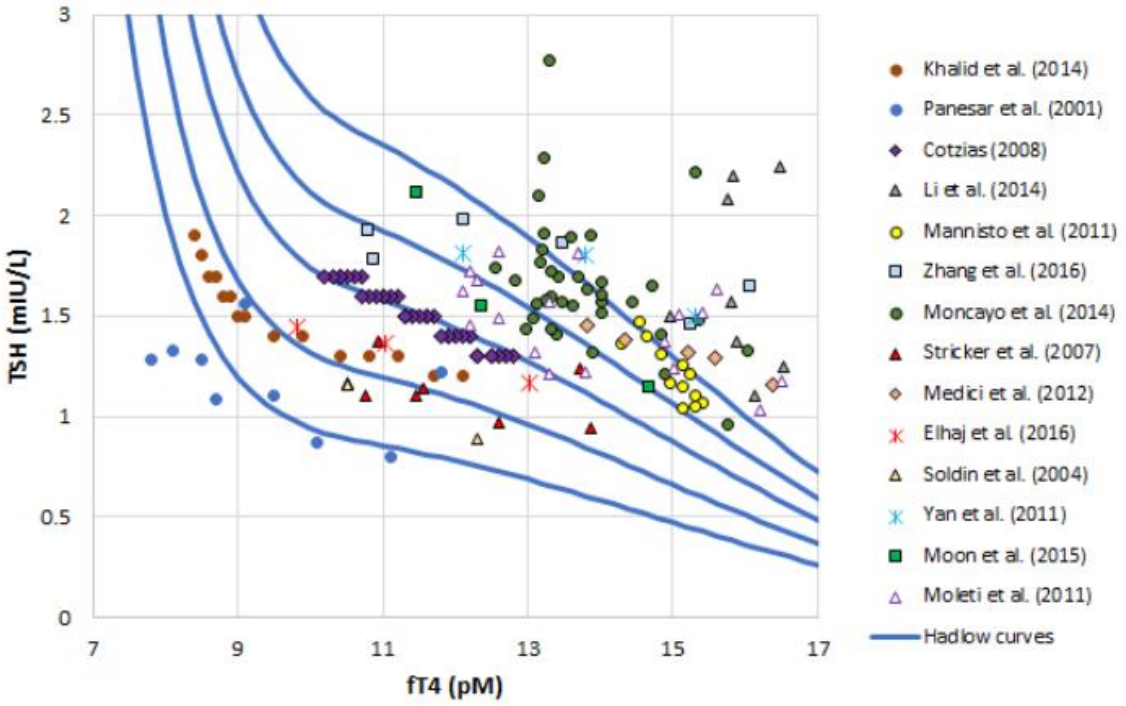
- with the exception of the study by Steinmaus *et al*. 2016, the model appears to reproduce the experimental data (i.e. predicted values/reported values < 2).

However, the comparison with the different studies available (Greer *et al*. (2002), Braverman *et al.* (2006) and Téllez-Téllez *et al*. (2005)) used by Clewell *et al*. (2019) to assess the model does not show any impact of perchlorate exposure on fT4 concentration.

In conclusion, due mainly to the lack of data available for conducting a robust validation, the US EPA model does not allow the relationship between perchlorate exposure and the

decrease in fT4 to be assessed. Through its validation by comparison with a single study (Steinmaus *et al.*, 2016), it seems difficult to identify significant variations between perchlorate exposure and THs.

ANNEX 6 – RELATIONSHIP BETWEEN TSH AND fT4 ACROSS MULTIPLE STUDIES (FIGURE A-46 US EPA 2019)



[a] The curves are roughly adjusted in this example to show the range of behavior. Data sources are listed in legend of Figure A-44.

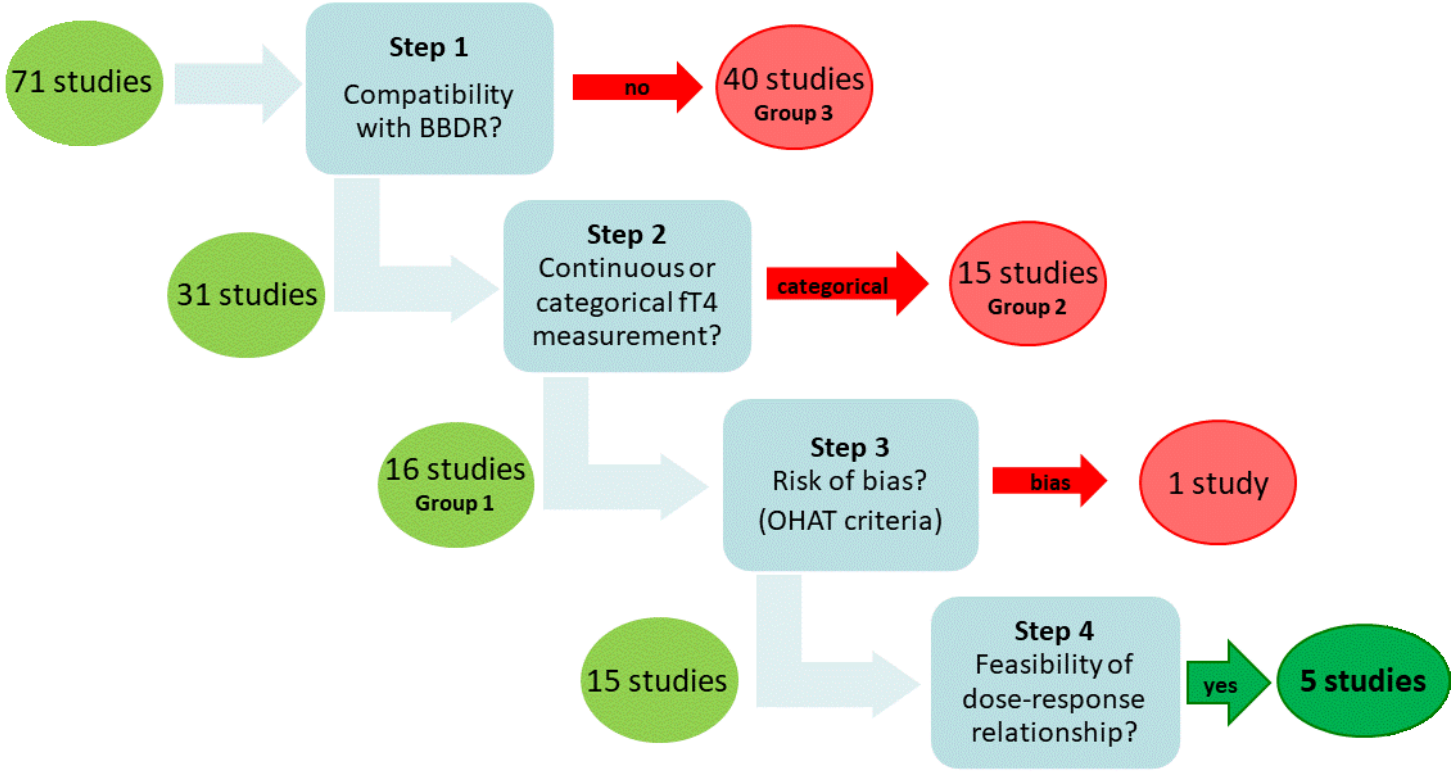
Figure 1 – Relationship between TSH and fT4

(curves from Figure A-46 of Volume II of US EPA 2019)

The relationship curves according to Hadlow *et al*. (2013) corresponding to different studies tend to show an association. However, there is a high variability between plasma TSH and fT4 concentrations in the 14 available studies.

ANNEX 7 – EPIDEMIOLOGICAL STUDIES SELECTED BY THE US EPA

Selection procedure and assessment of epidemiological studies (see Volume I Section 5 and Volume III Appendices E, F, G, I, J)



Assessment of the US EPA's conclusions on the quality of the selected studies:

The US EPA assessed the quality of the studies with a "risk of bias" analysis using an approach inspired by the OHAT methodology. The risk of bias was assessed qualitatively and a rating for each study was proposed according to three levels. For this purpose, the tool detailed in Appendix E Volume III (pages E5 – E12) was used. It consists of a series of questions to consider relating to five types of bias (confounders, attrition/exclusion, exposure characterisation, outcome assessment, reporting). An answer was given in terms of risk of bias (definitely low, probably low, probably high, definitely high). The studies were then classified into three tiers (Tier 1, 2 or 3) according to the number of low or high risk-of-bias responses.

The US EPA's analysis of the risk of bias of the five selected studies (as well as that of the other 11 Group 1 studies from the US EPA selection process) is available in Table E-2 on page E-13 of Volume III.

Risk of bias

Definitely low	Probably low	Probably high	Definitely high
++	+	-	--

Study classification:

Tier 1	Tier 2	Tier 3
"Probably low" or "definitely low" risk of bias for the majority of questions asked and no risk of bias rated as "definitely high"	Study does not meet the criteria for either Tier 1 or Tier 3	"Probably high" or "definitely high" risk of bias for the majority of questions asked

Table 1 – Risks of bias according to the US EPA

	Risk of bias related to:					Dose-response[6]	Iodine intake[7]	Opinion of the WG on the conclusions of the US EPA
	Confounders[1]	Attrition/ exclusion[2]	Exposure[3]	Outcome[4]	Data presentation[5]			
Endendijk *et al*. (2017)	-	-	+	+	++	N	N	Agreement on the assessment of the risks of outcome and exposure bias, as the assessment of the primary decision criterion is based on a test completed by parents and not by a neutral observer.
Finken *et al*. (2013)	-	-	+	++	++	N	N	Agreement on the assessment of the risks of bias except for that of exposure. The standardisation of maternal fT4 on the day of pregnancy was carried out according to an arbitrary formula that is not justified by the authors: this may enhance the study or may induce additional noise. Furthermore, there is no correlation for the multiplicity of tests (risk of analysis bias).
Korevaar *et al*. (2016)	+	-	+	++	++	N	N (Urinary Iodine measured on some of the subjects)	Agreement on the analysis of the risks of bias carried out by the US EPA.

Pop *et al*. (2003)	-	++	+	++	++	Y	N	Agreement on the assessment of the risks of bias except for that of attrition/exclusion, which is defined as "very low" (++) and is not justified by the US EPA.
Pop *et al*. (1999)	-	-	-	++	++	Y	N	Agreement on the analysis of the risks of bias carried out by the US EPA. Apart from the risk of bias in the measurement of the effect, which is probably overestimated given the number of participants considered.

[1]: Did the study design or analysis account for important confounding and modifying variables?
[2]: Were outcome data complete without attrition or exclusion from analysis?
[3]: Can we be confident in the exposure characterisation?
[4]: Can we be confident in the outcome assessment?
[5]: Were all measured outcomes reported?
[6]: Did the study provide dose-response information specific to children of hypothyroxinaemic pregnant women?
[7]: Did the study measure iodine intake in participants?

Table 2 – Critical analysis of the dose-response of the five studies retained by the US EPA

Study	Population	Participants (woman-child pairs)	Endpoint considered	fT4 ranges	Dose-response relationship determined in the article	Study's suitability for the US EPA's requirements
Pop *et al.* 1999	Women recruited at the 12th week of pregnancy	220	**PDI**: Psychomotor development index and **MDI**: Mental development index assessed by the Bayley Scales of Infant Development.	fT4 below the 5th percentile (< 9.8 pmol/L): n=11 fT4 below the 10th percentile (< 10.4 pmol/L): n=22 fT4 below the 15th percentile (< 10.9 pmol/L): n=34 fT4 below the 20th percentile (< 11.4 pmol/L): n=45	Effect observed only on **PDI** and not MDI. Mean PDI scores were significantly lower in children whose mothers had fT4 concentrations in the 5th or 10th percentile at the 12th week of pregnancy than in the rest of the children. **The dose-response relationship was not described**. Only a correlation coefficient R = 0.46 (P = 0.03) is given but there is no mathematical function describing the relationship between fT4 concentration and PDI score for women with fT4 concentrations below the 10th percentile. Only a **scatter** plot is visible.	Interesting study with a view to the US EPA work because a specific study of the relationship between maternal fT4 and neurodevelopment was carried out in hypothyroxinaemic women. The US EPA used the figures and the scatter plots in the figures to extract a mathematical relationship (linear regression): they used the "WebPlotDigitizer Extension" for Google Chrome and the linear regression function in Excel. **ΔPDI = × ΔfT4** $(95\%\ \mathrm{CI}) = 8.5\ (0.01\text{-}17.04)$ The raw data were not made available to the US EPA.
Pop *et al.* 2003	Women recruited at the 12th week of pregnancy	125	**PDI:** Psychomotor development index and **MDI**: Mental development index Bayley Scales of Infant Development. Assessed at 1 and 2 years	fT4 10th percentile = 12.4 pmol/L with normal TSH fT4 50th percentile = 15.6 pmol/L with normal TSH fT4 90th percentile = 19.1 pmol/L with normal TSH	Small but significant correlations between **MDI** at 2 years and fT4, and **PDI** at 2 years and fT4 in children of women in the group below the 10th percentile. R = 0.48 (P = 0.001) and R = 0.38 (P = 0.006), respectively. **The dose-response relationship was not described**. Only a correlation coefficient is given but there is no mathematical function describing the relationship between [fT4] concentration and DPDI score for women with [fT4] concentrations below the 10th percentile. Only a scatter plot is visible.	Interesting study with a view to the US EPA work because a specific study of the relationship between maternal fT4 and neurodevelopment was carried out in hypothyroxinaemic women. The US EPA used the figures and the scatter plots in the figures to extract a mathematical relationship (linear regression): they used the "WebPlotDigitizer Extension" for Google Chrome and the linear regression function in Excel. **ΔMDI = × ΔfT4** (95% CI) = 6.3 (1.92-10.6) **ΔPDI = × ΔfT4**

						(95% CI) = 8.4 (4.0-12.8) The raw data were not made available to the US EPA.
Finken *et al.* 2013	83rd to 100th day of pregnancy	1765 (175 women with fT4 below the 10th percentile, < 7.7 pmol/L)	**Reaction time standard deviation (SD)** 4 tasks **of the *Amsterdam Neuropsychological Test*** (ANT) at age 5. Cognitive domains tested: attention, information processing, executive function and visuospatial perception.	6.5; 10.4 (mean: 9.6 pmol/L)	Linear regression results when fT4 is considered as a quantitative variable: the only significant results concerned the intra-individual SD for task 1. For a 1pmol/L increase in fT4 concentration, there was a decrease of just over 3% in the intra-individual variability of reaction time during the 32 trials. **ΔSD Reaction Time (ms) = β × ΔfT4** =-4.9 (-9.5; -0.2), p=0.04	Study based on an objective criterion (computerised standardised assessment) but with unknown predictive value. Due to the lack of correction for the multiplicity of tests, there is a low level of evidence for a relationship between maternal fT4 and an adverse effect on neurodevelopment (according to the OHAT criteria). The value of this study comes from the number of hypothyroxinaemic women: n=175. However, the US EPA did not exploit these data. The US EPA used the linear relationship described in this paper for the entire population.
Endendjik *et al.* 2017	10th to 12th week of pregnancy	442	**Anxiety/Depression score** *Child Behavior Check List* (CBCL 1.5-5). Assessment of children's behaviour at an average age of 30 months.	8.7 – 19.6 pmol/L 5th percentile: fT4 < 12.40 pmol/L 10th percentile: fT4 < 13.30 pmol/L.	- Correlation between fT4 in the first trimester and anxiety/depression in girls only (r=0.17, p<0.05). - Correlation between TSH concentration in the first trimester and attention problems in boys only (r=0.21, p<0.05). - No association between behavioural problems and hormone levels in other trimesters regardless of sex. - Linear regression: the relationship between fT4 concentration and anxiety/depression was significant regardless of sex in a model adjusted for maternal psychopathological symptoms during pregnancy. **$\Delta AD = (1/ \times fT4_2) - (1/ \times fT4_1)$** = 0.12 (0.11; 0.13), p<0.05	Dose-response relationship given for the whole population. Several possible biases, notably selection bias (few hypothyroxinaemic women), classification bias (CBCL completed by parents; disparate ages of children) and confounding bias. Considering the results of the linear regressions, the level of evidence for a relationship between maternal fT4 and the risk of anxiety/depression is moderate (according to the OHAT criteria).

Korevaar *et al*., 2016	Before the 18th week of pregnancy Median: 13.2 Range 95%: 9.8 – 17.5	3839	**Non-verbal IQ assessed with the *Snijders-Oomen Niet-Verbale Intelligentie Test*.** Assessment of children aged 6 (median 6 years; range 95%: 5.6 – 7.9 years)	Median: 14.9 pmol/L Range 95%: 10.2–22.4 pmol/L	- Linear regression with log-transformed values of TH concentrations as independent variables. Determination of the shape of the relationship by defining the mathematical functions between the minimum and the 10th percentile, between the 10th and the 50th, between the 50th and the 90th, and then above the 90th percentile with polynomials of the 1st, 2nd or 3rd degree maximum ("restricted cubic splines with 3 knots"). - Significant inverted U-shaped association between fT4 concentrations and IQ. $\Delta IQ = (_1 \times lnfT4_2 + _2 \times ln(fT4_2)^2) - (_1 \times lnfT4_1 + _2 \times ln(fT4_1)^2)$ β_1 = 33.81 (95% CI: 9.8; 57.82) β_2 = -6.235 (95% CI: -10.567; -1.903) Significant 1.5 to 3.8 reduction in IQ in children whose mothers had fT4 concentrations between the 3rd and 11th percentile compared to the reference category (fT4 concentration between the 10th and 90th percentile)	Interesting study due to the large number of subjects and the well-developed dose-response modelling. The level of evidence for an inverted U-shaped association between maternal fT4 and IQ is moderate (according to the OHAT criteria). Independent analysis of the raw study data by the US EPA to establish a mathematical function better suited to development of the TRV for perchlorate: - No adjustment for the factors that might explain the observed relationship between maternal fT4 concentration and child IQ in order not to understate the strength of the observed effect - Concentrations of fT4 in their raw form, and not log-transformed $\Delta IQ = (_1 \times ln(fT4_2)) - (_1 \times ln(fT4_1))$ β1 = 17.26 (3.77; 30.75)

ANNEX 8 – ANSES LITERATURE SEARCH

Search: Articles on perchlorate exposure and adverse effects with a particular focus on thyroid function and neurodevelopmental disorders (children) published since the ANSES opinion of 31 December 2018.

PECO:

Population* (or subjects investigated)	Keywords from the thesaurus	*Other terms*
Population (or subjects investigated)	All populations	Infant, child, newborn, breastfed, pregnant, lactation
Exposition	Perchlorate	Perchloric acids, perchloric acid derivatives
Comparator	Non exposed	
Outcome (result of interest, event measured, judgment criteria. i.e: mortality, health effect, psysocial effects, perception, economic results	Toxicity, Thyroid, Neurodevelopment	Health effects, adverse effects Throxine, T4, hypothroxinemia, "thyroid hormones" "neurodevelopmental effects" OR "mental ability" OR "intelligence quotient" OR cognition OR cognitive OR motor OR language OR behaviour OR autism OR ADHD
Temporality (research period)	01/01/2018 – 10/01/2020	

Query

Logiciel bibliographique	Requête bibliographique	Nombre de résultats de la requête
Scopus	TITLE-ABS-KEY (perchlorate AND (toxicity OR {adverse effect} OR {health effect} OR disease OR cancer OR thyroid OR thyroxine OR t4 OR hypothyroxinemia OR "thyroid hormones")) AND PUBYEAR > 2017	177
Scopus	TITLE-ABS-KEY (perchlorate AND (neurodevelopment OR "neurodevelopment effects" OR "mental ability" OR intelligence OR cognition OR cognitive OR motor OR language OR behavior OR autism OR adhd) AND (infant OR child*)) AND PUBYEAR > 2017	4
Pubmed	All fields Perchlorate AND (Toxicity OR {adverse effect} OR {health effect} OR Thyroid OR disease OR cancer OR thyroxine OR T4 OR hypothyroxinemia OR "thyroid hormones") Filters: from 2018 - 2020	161
Pubmed	All fields Perchlorate AND (Neurodevelopment OR "Neurodevelopmental effects" OR "mental ability" OR intelligence OR cognition OR cognitive OR motor OR language OR behavior OR autism OR ADHD) AND (infant OR child) Filters: from 2018 - 2020	4

Number of results of the query in *SCOPUS:* 179 on 01/10/2020

Number of results of the query in *PUBMED:* 163 on 01/10/2020

After removing duplicates: 243

PRISMA flow diagram

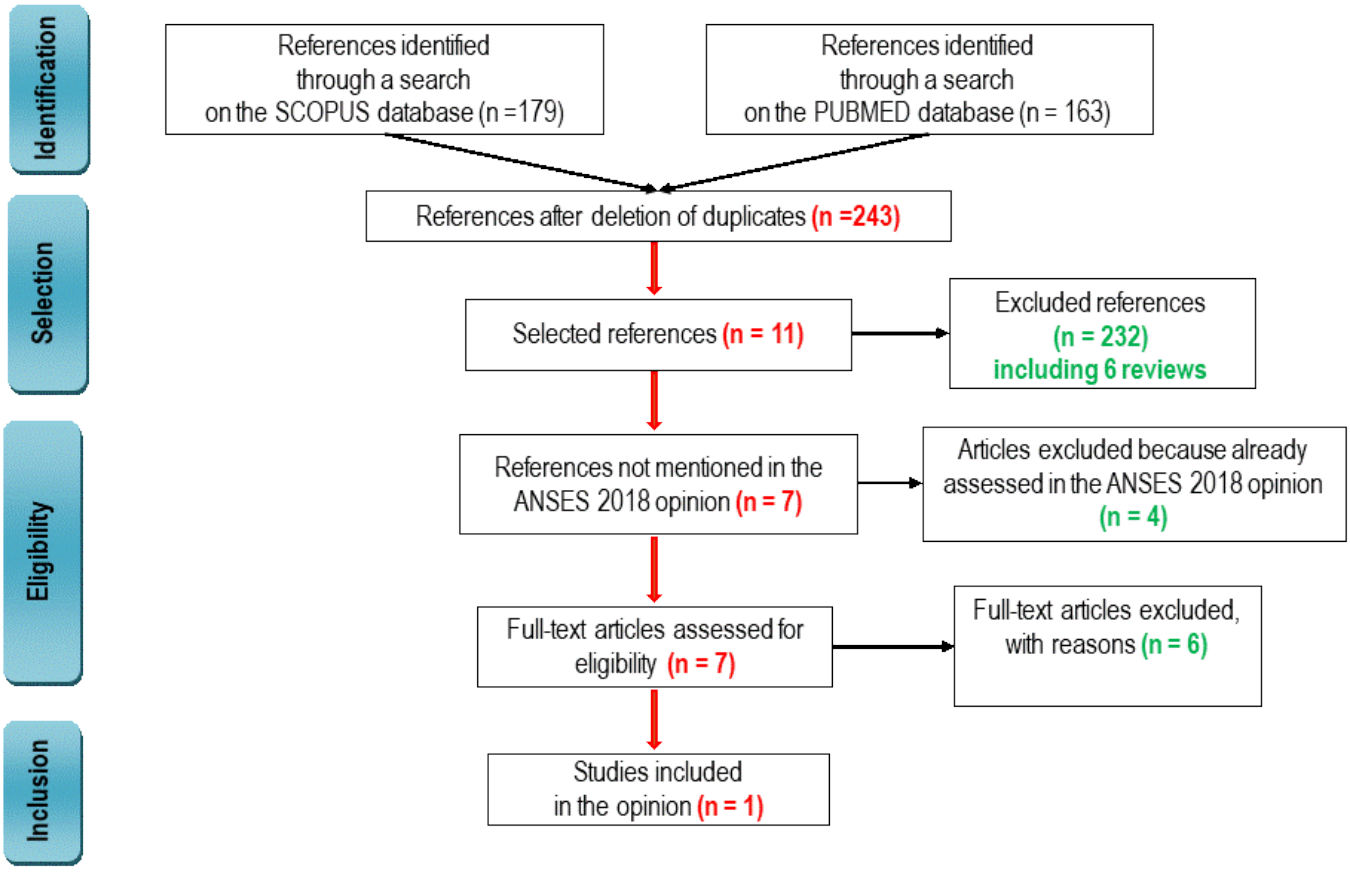


Table 1 – Articles whose text was assessed in full

Reference	Type of study	Title	Result	Eligibility
Zhu *et al.*, 2019	Cross-sectional epidemiological	*Environmental exposure to perchlorate, nitrate, and thiocyanate in relation to obesity: A population-based study*	**No association between $UClO_4$-** and obesity (BMI) or abdominal obesity (waist circumference)	Protocol with low evidentiary force → **No**
McCanlies *et al.*, 2019	Case-control epidemiological	*The CHARGE study: An assessment of parental occupational exposures and autism spectrum disorder*	**No occupational exposure** to perchlorate in the CHARGE study	Perchlorate not studied → **No**
Orathel *et al.,* 2020	Ecological epidemiological	*Possible Effects of Perchlorate Contamination of Drinking Water on Thyroid Health*	**No significant difference** in TSH, T4, number of hypothyroid patients	Protocol with low evidentiary force → **No**
Bruce *et al.*, 2018	BMD modelling	*Determination of Thresholds of Radioactive Iodine Uptake Response with Clinical Exposure to Perchlorate*	$BMD_{20}L$: 0.021 mg.kg $bw^{-1}.d^{-1}$	→ **Yes**
Serrano-Nascimento, C., 2018	60 d subchronic toxicological in rats	*Evaluation of hypothalamus-pituitary-thyroid axis function by chronic perchlorate exposure in male rats*	Thyroid alteration and inflammation (0 and 35 mg.kg $bw^{-1}.d^{-1}$)	TRT*: 3 1 high dose only → **No**
Yu *et al.*, 2019	Toxicological, reprotoxicity in rats	*Reproductive toxicity of perchlorate in rats*	0; 0.5; 1 and 10 mg.kg $bw^{-1}.d^{-1}$ gavage NOAEL 0.5 mg	TRT: 1 NOAEL 100 ~ times higher than NOEL in Greer *et al*. (2002) → **No**
Karthikprabu *et al.*, 2020	20 d subacute toxicological in rats	*Perchlorate contamination assessment and hypothyroidism in rat studies using water samples collected around Kovil Patti, Tuticorin District of Tamil Nadu, India*	↓ T4 contaminated water (98.8 $mg.L^{-1}$) 3 mL. $^{-1}rat^{-1}.d^{-1}$ IV for 20 days	TRT: 4 numerous limitations → **No**

*TRT: ToxRTool scoring