

The Director General

Maisons-Alfort, 3 February 2022

OPINION

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

on the "relevance of reassessing the chronic oral TRV for perchlorate"

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 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 3 February 2022 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" (US EPA 2019a,b,c,d). A first deliverable, published on 16 March 2021, provided a response to this formal request.

However, following publication of the studies by Weterings *et al.* (2016), Bruce *et al.* (2018) and Haber *et al.* (2021), the Agency issued an internal request in order to determine the advisability of modifying ANSES's toxicity reference value (TRV) of $0.7 \mu\text{g.kg bw}^{-1}.\text{d}^{-1}$, which is the subject of this second deliverable.

1. BACKGROUND AND PURPOSE OF THE REQUEST

Since 2011, ANSES has been asked on several occasions to examine the health risks associated with perchlorate (ClO_4^-) 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 $15 \mu\text{g}\cdot\text{L}^{-1}$ for adult consumers, derived from the TRV of $0.7 \mu\text{g}\cdot\text{kg}\cdot\text{bw}^{-1}\cdot\text{d}^{-1}$ (ANSES, 2011), based on the inhibition of iodine uptake by the thyroid gland. ANSES had also advised against using water contaminated by perchlorate when preparing feeding bottles for infants aged up to 6 months, pending a national survey on perchlorate contamination of food, in particular to clarify the concentrations found in the powdered infant formula used for bottle preparation.

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." (ANSES, 2012).

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 human exposure to perchlorate and for interpreting the published epidemiological data.

In its opinion of 26 December 2018, the Agency had concluded that recent epidemiological studies, including the one by the French Institute for Public Health Surveillance¹ (InVS) published in 2016, did not provide any additional conclusive evidence on the biological or clinical effects of perchlorate versus 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 firstly on data on perchlorate contamination of food collected by the Directorate General for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF) as part of its national surveys, and secondly on data on DW contamination for the period 2014-2017 produced by the Regional Health Agencies (ARs) 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 data in the literature and was close to the 20% default percentage defined by the World Health Organization (WHO) in 2016, the Agency felt it necessary to lower to 20% the share of exposure via water (which had previously been set at 60%) used for calculating the GV of perchlorate in DW for adults. As a result, the proposed GV was lowered to $5 \mu\text{g}\cdot\text{L}^{-1}$ for the adult population.

¹ Became *Santé publique France* (SPF) on 1 May 2016

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. It therefore recommended that perchlorate be included in the third French Total Diet Study (TDS3).

In the absence of new data on the contamination of infant formula with perchlorate since the 2014 expert appraisal, the Agency also reiterated the conclusions of this earlier 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 $0.7 \mu\text{g.kg bw}^{-1}.\text{d}^{-1}$ for 95% of the population of children aged under 6 months consuming infant formula based on an average concentration of perchlorate of $1 \mu\text{g.L}^{-1}$ 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" (ERS EDCH) 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 would be necessary to re-examine the method for determining the critical dose and establishing the TRV for perchlorate."

All the agencies establishing chronic oral TRVs for perchlorate have chosen inhibition of iodine uptake by the thyroid as the critical effect (Table 1 on page 8).

In 2019, the US EPA adopted a different approach based on toxicokinetic-toxicodynamic modelling to assess the impact of perchlorate exposure on thyroid hormone (TH) production and the effect of a reduction in maternal plasma free thyroxine (fT4) concentrations during the first trimester of pregnancy on the child's neurodevelopment, as measured by a decrease in intelligence quotient. The US EPA suggested adopting a TRV of $2.2 \mu\text{g.kg bw}^{-1}.\text{d}^{-1}$, resulting in a maximum contaminant level of $56 \mu\text{g.L}^{-1}$ perchlorate in DW.

As mentioned previously, and in view of the management difficulties encountered, the DGS had formally asked ANSES to analyse the US EPA's work on assessing 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.

In view of this, ANSES was 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 first deliverable of this formal request therefore had the ultimate objective of determining whether the ANSES TRV of $0.7 \mu\text{g.kg bw}^{-1}.\text{d}^{-1}$ should be maintained. This first deliverable concluded that this TRV should not be called into question in light of the US EPA's work, mainly because of major uncertainties about the predictive ability of the model used.

The Agency therefore decided to retain its chronic oral TRV established in 2011, based on the no-effect level observed in the study by Greer *et al.* (2002). However, all the TRVs established since that date are based on a Benchmark Dose (BMD) approach, so the Agency therefore issued an internal request to assess the relevance of this approach, based in particular on recent publications (Weterings *et al.* 2016, Bruce *et al.* 2018, Haber *et al.* 2021).

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 "Health Reference Values" (VSR), the CES on "Water" and the CES on "Assessment of physico-chemical risks in food" (ERCA), whose members are listed in Annex 1. ANSES entrusted the expert appraisal to the *ad hoc* Working Group (WG) on "Perchlorate", reporting to the CES VSR. The conclusions of the WG on "Perchlorate" were adopted unanimously by its experts, with one abstention.

The work conducted for this opinion was presented to the CES VSR on 24 September 2021, to the CES on "Water" on 2 November 2021 and to the CES ERCA on 20 October and 9 December 2021. The work was validated unanimously by the CES VSR on 16 December 2021.

To ensure consistency between the activities of different expert groups, this work was also presented to the WG on "Assessment of the health risks associated with chemical parameters in drinking water" on 18 November 2021. The results were therefore produced by a group of experts with complementary skills.

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.

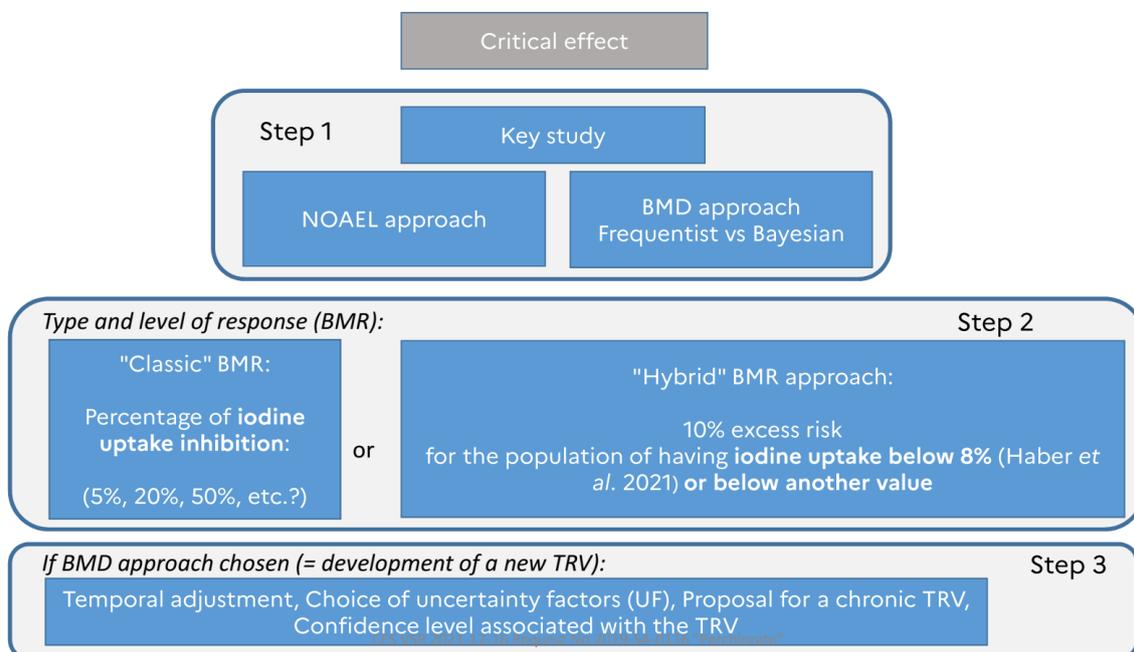
The experts' declarations of interests are published on the following website: <https://dpi.sante.gouv.fr/>.

This expert appraisal was based on the publication by Haber *et al.* (2021), previous ANSES opinions and other scientific articles published since the last ANSES work.

The WG on "Perchlorate" analysed the different proposals for developing TRVs according to the BMD approach based on the data of Greer *et al.* (2002), reported in the scientific literature, in order to decide whether they justified reconsidering the chronic oral TRV used by the Agency since 2011, which was based on a NO(A)EL approach.

The WG therefore discussed the relevance of a BMD approach compared with the NO(A)EL approach previously used at the Agency to establish the TRV for perchlorate, by drawing mainly on a critical analysis of the publication by Haber *et al.* (2021) and following the decision tree below (Figure 1). In a first step, the WG analysed studies that could be used as key studies for developing a TRV for perchlorate. The relevance and *added value* of using the different approaches (NOAEL or BMD) were investigated. Then, in a second step, the type and level of response (benchmark response, BMR) were determined. Lastly, in the final step, the WG on "Perchlorate" reserved its right to adapt the calculation methods proposed by these publications and, if necessary, to recalculate a new TRV.

Figure 1 – Decision tree used by the WG on "Perchlorate"



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

3.1. Critical effect selected

3.1.1. Iodine uptake inhibition

The target organ for perchlorate in humans and animals is the thyroid, where it competitively inhibits iodine uptake through the sodium/iodide symporter (NIS), which ensures the entry of iodide together with sodium (two Na⁺ ions for one I⁻ ion) and the accumulation of iodide in thyrocytes.

With the exception of the US EPA's 2019 proposals (US EPA 2019a,b,c,d), the critical effect selected by agencies that have developed TRVs is inhibition of iodine uptake by the thyroid gland, as measured in controlled trials in volunteers (Greer *et al.*, 2002; Braverman *et al.*, 2006; Lawrence *et al.*, 2000 and 2001). This is an early biological effect that can lead to impaired thyroid function.

Despite the diversity of human epidemiological data in the literature seeking to establish a link between perchlorate exposure and disrupted thyroid function further downstream, the quality of these studies or the divergence between some of their results (see ANSES 2012, ANSES 2014, ANSES 2018) makes it impossible to select a critical effect downstream of iodine uptake inhibition. As a reminder, some of these studies have shown a link between perchlorate exposure and effects on TH in pregnant women, but divergent results and confounding factors, such as the iodine status of the subjects, have prevented a TRV from being established on the basis of these data.

Regarding animal data, the rat is a good qualitative model for the effects of perchlorate on thyroid function, but has proved to be a poor quantitative model due to interspecies differences in thyroid physiology² (ANSES 2011).

The WG experts also investigated the literature data mentioned in Adverse Outcome Pathway (AOP) 54 entitled *Inhibition of Na⁺/I⁻ symporter (NIS) decreases TH synthesis leading to learning and memory deficits in children*, published by the Organisation for Economic Co-operation and Development (OECD) in July 2019, which has undergone the full validation procedure as defined by the same organisation (Rolaki *et al.*, 2019). No other study was identified in the AOP 54 literature that could be used as a key study of an effect further downstream of the mode of action of perchlorate.

3.1.2. Neurodevelopmental disorders in the unborn child

As mentioned in the first deliverable of Request No 2019-SA-0116, which was published in the opinion of 16 March 2021 (ANSES, 2021), the WG on "Perchlorate" noted the quality of the work carried out by the US EPA, both on developing the biologically-based dose-response (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" noted 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 of the correlation between exposure and effect on THs.

The experts of the WG on "Perchlorate" considered that iodine uptake inhibition still represented the best choice of critical effect for the development of a TRV, in the absence of more suitable data. The WG experts point out that apart from the US EPA proposal in 2019, which was discussed in the first deliverable, iodine uptake inhibition is still currently the critical effect selected by the agencies that have developed chronic TRVs for perchlorate.

² ANSES, 2011: "The characteristics of thyroid function differ between rats and humans to such an extent that only the qualitative aspects of the toxic effects associated with exposure to perchlorate can be used in risk assessment (IARC, 1999; NAS, 2005). In particular, there is a difference between rats and humans concerning the proteins related to the tri- and tetraiodothyronine THs (T3 and T4) and their binding affinities. In humans, THs bind mainly to thyroxin-binding globulin (TBG) with high affinity. Conversely, in rats, THs bind to albumin and transthyretin with lower affinities, by a factor of at least 100, compared with TBG (Connors, 1997)." This results in a significantly shorter half-life of T4 in rodents.

3.2. Choice of the key study

With regard to the choice of key study, as the critical effect selected was iodine uptake inhibition, the experts of the WG on "Perchlorate" analysed the various key studies selected by the agencies proposing TRVs.

As reported in Table 1, all the agencies establishing oral TRVs for perchlorate chose the study by Greer *et al.* (2002) as the key study.

In 2018, Bruce *et al.* conducted a BMD analysis of the effects of perchlorate exposure on iodine uptake inhibition 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].

However, the studies by Lawrence *et al.* (2000 and 2001) only investigated one dose, and in fact served as preliminary trials to define the doses to be tested in the study by Greer *et al.* (2002); they are therefore less robust.

The study by Braverman *et al.* (2006) had several methodological limitations, including a lack of information on the body weight of the study volunteers and the withdrawal of some of them during the study.

Moreover, apart from the study by Greer *et al.* (2002), the raw results of the aforementioned studies were not available, which explains the choice of the WG on "Perchlorate" and the CES VSR to select the study by Greer *et al.* (2002) as the key study.

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Request No 2019-SA-0116

Related requests Nos 2011-SA-0024; 2011-SA-0208; 2011-SA-0336; 2012-SA-0119; 2016-SA-0155 and 2017-SA-0170

Table 1: Chronic oral TRVs for perchlorate published by North American, European and international health risk assessment agencies or proposed by authors

Agency or author	Key study	Point of departure ($\mu\text{g.kg bw}^{-1}.\text{d}^{-1}$)	Effect Level of response	BMD software	Uncertainty factor(s)	TRV ($\mu\text{g.kg bw}^{-1}.\text{d}^{-1}$)
US EPA 2005, ATSDR 2008, ANSES 2011	Greer <i>et al.</i> (2002)	NOEL 7	RAIU ³ inhibition /	/	10	0.7
JECFA 2011	Greer <i>et al.</i> (2002)	BMDL 114	RAIU inhibition BMR 50%	PROAST v23.2	10	10
EFSA 2015	Greer <i>et al.</i> (2002)	BMDL 1.2	RAIU inhibition BMR 5%	PROAST v38.9	4	0.3
OEHHA 2015	Greer <i>et al.</i> (2002)	BMDL 3.7	RAIU inhibition BMR 5%	BMDS v 2.0.0.33	10	0.37
WHO 2016⁴	Greer <i>et al.</i> (2002)	BMDL 114	RAIU inhibition BMR 50%	PROAST v23.2	10	11
Weterings <i>et al.</i> 2016	Greer <i>et al.</i> (2002)	BMDL 16.6	RAIU inhibition BMR 20%	PROAST v38.9	4	4
Bruce <i>et al.</i> 2018	Lawrence <i>et al.</i> (2000 and 2001), Braverman <i>et al.</i> (2006), Greer <i>et al.</i> (2002)	BMDL 21	RAIU inhibition BMR 20%	BMDS v 2.6.0.1	NA ⁵	NA
Health Canada 2020	Greer <i>et al.</i> (2002)	BMDL 10.9	RAIU inhibition BMR 2 standard deviations	BMDS v 2.18	10	1.09
Haber <i>et al.</i> 2021⁶	Greer <i>et al.</i> (2002)	BMDL 30	RAIU inhibition "Hybrid" BMR: 10% excess risk of iodine uptake < 8%	<i>Ad hoc</i> modelling	4 10	7.5 3

³ RAIU test: Radioiodine uptake test.

⁴ Same approach as JECFA, but the rounding was performed by the organisation in a different way.

⁵ NA: Not applicable.

⁶ Two TRV values proposed by the authors, considering two different values for the overall uncertainty factor.

3.3. Approach adopted by the WG on "Perchlorate" and the CES VSR

The number of doses tested and the level of effects obtained in the study by Greer *et al.* (2002) meant that a BMD approach was possible.

This approach, recommended by the "TRV development guide" (ANSES, 2017) when the available data allow it, was therefore selected by the WG on "Perchlorate". This was also the approach taken by all the most recent assessments (including the one by Haber *et al.* (2021).

3.4. Modelling a benchmark dose

Several steps are necessary to calculate a BMD, especially for the choices of:

- a theoretical model of the dose-response relationship;
- a method of fitting the model to available experimental data;
- the level of response (BMR).

Tools such as the US EPA's BMD software (BMDS) and RIVM's PROAST have been developed specifically for estimating BMDs and are used by health agencies.

The model can be fitted to the experimental data using either frequentist or Bayesian inference.

3.4.1. Analysis of the estimation method used by Haber *et al.* versus the frequentist approach

The frequentist approach is the most commonly used in BMD calculations.

Haber *et al.* (2021) believed that the data from the study by Greer *et al.* (2002) could not be processed sufficiently rigorously by the BMDS and PROAST modelling software, for two main reasons. Firstly, the protocol used in this study included repeated measures on the same individuals, such that it is unrealistic to assume that the data collected on the same individual are independent (the effect of the individuals' characteristics on the observed response generates correlations). Secondly, PROAST and BMDS use normal or lognormal probability distributions to estimate the parameters of the response models. These distributions are not ideal here because radioiodine uptake (RAIU) is bounded between 0 and 1, whereas variables with normal and lognormal distributions can take values beyond these bounds.

To overcome these limitations, Haber *et al.* (2021) used a Bayesian hierarchical approach that was able to take into account the correlations between observations collected on the same individuals and to use a likelihood based on a Beta distribution compatible with a range of variation of observations between 0 and 1. This approach was applied to four standard response models based on different equations, also available in PROAST and BMDS for modelling continuous effects.

Haber *et al.* (2021) estimated the parameters of the four response models with R software, using a Markov chain Monte Carlo method based on the *RStan* v.2.19 package, often used in Bayesian inference. For each model, four Markov chains of 5000 iterations each – i.e. 20,000 in total – were generated with *RStan*. The last 10,000 iterations were used with each model to estimate the mean and credibility intervals of the RAIU response as a function of the dose. The authors did not identify any convergence problems based on standard verification criteria. The dose-response curves fit the data very well and led to very similar BMDs and BMDLs from one

model to another, with the most conservative values being given by the "Hill" model with a $BMD_{10\%L_{95\%}}$ of 0.030 mg.kg bw⁻¹.d⁻¹.

Haber *et al.* (2021) chose to consider the lower end of the range for RAIU accepted as clinically normal in the United States as the biologically relevant response level (see Section 3.4.2) (UCLA Health, 2020; MedLine Plus, 2020). An RAIU of 8% for a 24-hour measurement was therefore defined by these authors as the BMR and a "hybrid" approach was adopted. For continuous response parameters, this hybrid approach enables the risk measurement to be expressed in terms of response probability, and in this case can be used to define a BMD for which there is an estimated 10% additional risk in the population of having an RAIU of 8% or less.

The use of Bayesian inference has increased since the development of numerical computation. It is more informative than frequentist modelling in that it leads directly to a probability distribution of the parameter values of the model under consideration, which is useful for uncertainty analysis. It also enables modelling assumptions to be formalised precisely and is particularly useful when few observations are available or when prior distributions of plausible parameter values can be established on the basis of previously acquired knowledge.

In their work, Haber *et al.* (2021) compared previous assessments (which did not take into account correlations of observations, nor the restricted range of the RAIU metric) with those obtained using the Bayesian approach based on the 5%, 20% and 50% decreases in RAIU used respectively by EFSA (2015), Weterings *et al.* (2016) and JECFA (2011). The authors concluded that the results were very similar in all cases; the difference between all these assessments was mainly due to the definition of the BMR rather than the modelling method (Bayesian versus frequentist inference).

Because of the limited *added value* of the Bayesian approach due to a lack of information on the *a priori* distribution of the modelling parameters, as well as the frequentist approach's simplicity of implementation and ease of interpretation by the users of these health values, the latter was chosen by the WG on "Perchlorate".

3.4.2. Choice of the type of response level (BMR)

The benchmark dose is a dose producing a measurable effect corresponding to a given response level (BMR) compared with a control group. This BMR can be defined in several ways depending on the type of data, and can be based on:

- a percentage increase or decrease compared with the mean value of the control group;
- the value corresponding to the mean of the control group plus or minus one time the standard deviation of the control group;
- a threshold value, if knowledge is available with which to define an effect as harmful or not;
- a percentage increase or decrease compared with the probability of observing an adverse effect in the control group (the "hybrid" approach in the event of continuous data).

Several alternatives for the type of BMR were identified by the WG experts:

a) Percentage of iodine uptake inhibition

The agencies proposing TRVs and the scientific community hold different positions regarding this parameter. Table 2 shows that several BMR values have been established based on the data of Greer *et al.* (2002).

Table 2: BMR values used by different agencies or authors

Agency or author	Iodine uptake inhibition value taken as the BMR level	Justification
JECFA (2011)	50%	Lack of severity of the critical effect
EFSA (2014)	5%	Default BMR value taken for modelling of continuous data when it is not possible to establish a biologically relevant BMR
Weterings <i>et al.</i> (2016)	20%	Intra-individual variability
Health Canada (2020)	20%	2 standard deviations

In 2011, JECFA had adopted a BMR value of 50% of thyroid iodide uptake, a value considered to have no impact on serum TH concentrations, based on clinical data in healthy adults (JECFA, 2011).

However, as pointed out by EFSA (EFSA, 2015) and mentioned in ANSES's opinion of 26 December 2018 (ANSES, 2018), the possibility that prolonged inhibition of 50% of iodine uptake by the thyroid could increase the risk of toxic multinodular goitre cannot be ruled out. Furthermore, the experts of the WG on "Perchlorate" underline the lack of assessment of the impact of such a reduction in iodine uptake on populations at risk such as pregnant women and newborns.

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 processes designed to compensate for sustained inhibition of thyroid iodine uptake could lead to long-term effects, particularly in populations with mild to moderate iodine deficiency. As this value is a default value, the WG on "Perchlorate" chose to examine the alternative BMRs proposed in the literature.

More recently, Weterings *et al.* (2016) proposed a BMR value of 20% based on an analysis of data from four trials conducted in 1955, 1959, 2000 and 2002 (Hare and Haigh, 1955; Levy *et al.*, 1959; Lambers *et al.*, 2000 and Greer *et al.*, 2002) in which 24-hour radioiodine uptake measurements (¹²³I or ¹³¹I) were repeated in the same untreated subjects (100 subjects).

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 iodine uptake value exceeds 20% (75th percentile of intra-individual variability in the population in question). Indeed,

the authors considered that response levels below this threshold can be explained simply by natural intra-individual variations in iodine uptake.

However, the WG on "Perchlorate" considers that the variation in a physiological parameter has greater consequences if it is considered at a population level rather than an individual level. In other words, an impact at the population level can occur for far lower intra-population variability than intra-individual variability (Korevaar, Tiemeier and Peeters, 2018). The WG on "Perchlorate" considers that it is not appropriate to adopt a BMR value based on intra-individual variability.

In 2020, Health Canada also selected a BMR of 20% based on two standard deviations (SDs), defending the choice of this value on the basis that 20% represents the intra-individual variation in iodine uptake established by Weterings *et al.* (2016). Like the value proposed by EFSA, this is a default value, and therefore the WG on "Perchlorate" did not adopt this BMR.

Given the lack of international consensus and the above criticisms, the WG on "Perchlorate" sought to find an alternative BMR, based on all the data available in the literature.

The function of NIS and its essential role in TH synthesis are well known across species. However, quantitative information on the relationship between two key events in AOP 54, mentioned above, is limited. It is therefore difficult to decide on a percentage of iodine uptake inhibition that can be regarded as toxicologically relevant and consequently to identify a robust BMR.

b) "Hybrid" approach

An alternative is to identify the dose resulting in iodine uptake below a certain value of the percentage of iodine uptake in a given fraction of the population.

This assumes knowledge of a range of RAIU values described as "physiological". For adult euthyroid individuals, outside of pregnancy and any acute pathological situation, a certain range of RAIU values is expected and is regarded as physiological. When this value is abnormal, it reflects a proximal biological effect that may be the cause of thyroid dysfunction. Based on the lower bound of this physiological range, the expert group then determined the $BMD_{10\%L_{95\%}}$ value on the basis of the study by Greer *et al.* (2002) (see Section 3.4.4).

It should be noted that in France, there is no established recommendation for the clinical use of RAIU values, regardless of the population⁷. It is therefore not possible to rely on a value recognised nationally by a health agency or scientific organisations such as the French Society for Nuclear Medicine (SFMN). Similarly, there is no international consensus on a range of RAIU values that could be considered physiological, regardless of the population.

The experts of the WG on "Perchlorate" therefore investigated the data available in the scientific literature through a literature search, whose results are available in Annex 3.

⁷ However, due to the risks of exposure to radioiodide and malformations in unborn children, the experts reiterate that the RAIU test should not be performed on pregnant women.

The range of physiological RAIU values of 8-25% established by the University of California, Los Angeles (UCLA) was identified because it is mentioned in the publication of Haber *et al.* (2021), but could not be further analysed by the WG⁸.

The experts of the WG on "Perchlorate" therefore analysed the publications identified by the literature search to determine the range of RAIU values that can be regarded as physiological in euthyroid individuals, taking possible variation factors into account:

- The iodine status of individuals, depending mainly on possible iodine deficiency or supplementation, was not reported in the studies. However, this is a key factor in interpreting the RAIU test results;
- The results in the published studies may be influenced by dietary iodine intakes, which changed considerably from the 1970s to the present day, due to the supplementation of certain foods such as table salt and bread (Robertson *et al.* 1975; Milakovic *et al.* 2006);
- There may be a gender difference in values, as women appear to have slightly higher physiological RAIU values than men (González *et al.* 2008; Culp *et al.* 1978; Wassie *et al.* 1990; Atkins *et al.* 1971).

Despite the different geographical origins of the subjects and the varying age of the studies, as well as the factors documented above, the experts were able to filter the publications on the basis of other exclusion criteria. The exclusion criteria used were a lack of data on the number of samples in the publications, and a lack of information on the standard deviation of the sample distribution (absence of distribution parameters). Publications prior to 1970 were also excluded from the results, for the above-mentioned reasons relating to diet and iodine intake.

Of the publications identified, only four were ultimately selected (Table 3): Ballal *et al.* (2017), Al-Muqbel *et al.* (2010), Gonzalez *et al.* (2008) and Culp *et al.* (1978, in which results for women and men were reported separately). They were selected by the experts for their quality and the completeness of the available data.

⁸ The WG on "Perchlorate" sent a request for information about this range to the American university, but there was no response as to the origin of the selected values.

Table 3: Publications selected for the determination of a range of physiological RAIU values

Publication	Location	Number of subjects (and gender)	Average age of individuals (and range)	Thyroid status	Range of physiological RAIU values (in %)	Average RAIU in the study (in %)	Standard deviation (in %)
Ballal et al. 2017	India	110 (56 men and 54 women)	38 (18-88)	Euthyroid UIE _{mean} ⁹ = 9 µg.dL ⁻¹ (range: 6.0-12.8)	7-18	12.75	5.51
Al-Muqbel et al. 2010	Jordan	102 (25 men and 77 women)	42 (17-72)	Euthyroid Suspected thyroid disease before testing	2-56	15	7
Gonzalez et al. 2008	Chile	105 (52 men and 53 women)	45 (20-68)	Euthyroid Clinical and physiological examination (TSH and anti-TPO antibodies)	6.5-30.1	16.2	4.8
Culp et al. 1978	USA	25 men	30 (18-69)	Subjects with no history of thyroid disease but no TH measurements	11-23	15.9	3.1
		28 women			13-32	21.2	4.9

For each of the selected publications, a lognormal distribution of the RAIU values was calculated from the published mean and standard deviation values.

From each of these distributions, a random selection was made to numerically create individual values equivalent in number to those in the selected publications. The samples obtained from each publication were then pooled into a set of 370 data. This dataset was fitted to a lognormal distribution, from which the mean (15.18%) and standard deviation (6.60%) were extracted.

⁹ UIE: Urinary Iodine Estimation (WHO reference value = 10 µg.dL⁻¹)

The lower bound of the RAIU ($RAIU_{\text{threshold}}$) was set at 1 standard deviation from the mean¹⁰, or 9.1%. This value was then used as a threshold value for dichotomising the data (see next section 3.4.3).

However, several uncertainties related to the studies used were noted by the WG:

- Despite the large number of studies initially identified, few publications could be used for calculating the $RAIU_{\text{threshold}}$;
- The populations in these studies, although clinically euthyroid, were quite heterogeneous in terms of ethnicity, age and even exact thyroid status (some just had no thyroid disease while others had undergone extensive biological investigations);
- The individual data had to be generated numerically (in this case from a lognormal distribution).

Moreover, an alternative approach to determining a range of physiological RAIU values from the four selected publications (i.e. a meta-analysis) was explored and led to similar results.

3.4.3. Dichotomisation of data

Unlike the US EPA's BMDS software, the PROASTweb¹¹ v70.1 software does not allow the direct use of a hybrid approach on continuous data. The data from Greer *et al.* (2002) at 24h – D14 for non-zero doses and at 24h – D0 for the zero dose were therefore dichotomised.

Thus, for each dose, the RAIU data were fitted to a normal distribution. The percentage of this distribution with an RAIU below the 9.1% threshold was then calculated.

Lastly, the number of subjects per dose with an RAIU below the threshold was calculated by multiplying the number of samples per dose by the previously calculated percentage. This number was rounded to the nearest whole number.

¹⁰ BMD modelling with the lower bound of the RAIU equal to the mean minus two standard deviations (i.e. 3%) was also considered. However, dichotomising the data of Greer *et al.* 2002, taking into account a threshold of 3%, leads to a curve that is not very conducive to BMD modelling (individual numbers of 0, 0, 0, 1 and 1 at doses of 0, 0.007, 0.02, 0.1 and 0.5 mg.kg bw⁻¹.d⁻¹ respectively), leading to very high uncertainty (BMD/BMDL ratio of the order of 30).

¹¹ PROASTweb (RIVM): <https://proastweb.rivm.nl>

The calculations by dose have been grouped together in the following table:

Table 4: Dichotomisation of the data from Greer *et al.* (2002) as a function of the probability of an RAIU below 9.1%

Dose (mg.kg bw ⁻¹ .d ⁻¹)	Normal distribution		Probability of an RAIU below 9.1%	Number of subjects	Number of subjects with an RAIU < 9.1% (rounded to the nearest whole number)
	mean	standard deviation			
0	mean	0.1961	0.0429	37	1.6 (2)
	standard deviation	0.0611			
0.007	mean	0.1646	0.0317	7	0.2 (0)
	standard deviation	0.0396			
0.02	mean	0.1522	0.0262	10	0.3 (0)
	standard deviation	0.0315			
0.1	mean	0.1097	0.3476	10	3.5 (4)
	standard deviation	0.0477			
0.5	mean	0.0690	0.7951	10	7.9 (8)
	standard deviation	0.0267			

One of the uncertainties in these calculations was the small number of individuals per dose. Other uncertainties included the numerical generation of samples and the assumptions made about the type of distribution.

3.4.4. Calculation of the BMD and BMD_{10%}L_{95%}

Next, the BMD and BMD_{10%}L_{95%} for this scenario were calculated by considering a 10% excess (extra) risk of exceeding the threshold, classically used for quantal data, recommended by both EFSA and ANSES guidelines and used by Haber *et al.* (2021). No experimental data were available to refine this value.

In addition, choosing a percentage lower than 10%, when the number of samples per dose was 10 on average, would mean considering a single sample as statistically representative of an event. However, it is not possible to extrapolate from a single event.

The RIVM's PROASTweb software (v70.1), which is equivalent to the PROAST version available on the EFSA website¹², was used for these calculations.

¹² EFSA: <https://r4eu.efsa.europa.eu/app/bmd>

Based on the number of subjects with an RAIU below the lower bound of 9.1% for each dose of perchlorate received, the PROASTweb v70.1 software gives the following results for a 10% excess risk (Table 5).

Table 5: Comparison of model results when using the RIVM PROAST software (v70.1)

Model	BMD _{10%} L _{95%}	BMD	BMDU	loglik	AIC
<i>full</i>	NA	NA	NA	-19.51	49.02
<i>two.stage</i>	0.0195	0.0325	0.0591	-21.30	48.60
<i>log.logist</i>	0.0136	0.0435	0.0963	-20.87	47.74
<i>Weibull</i>	0.0097	0.0406	0.1070	-21.24	48.48
<i>log.probit</i>	0.0152	0.0443	0.0933	-20.69	47.38
<i>gamma</i>	0.0097	0.0439	0.1060	-21.19	48.38
<i>LVM: Expon. m3-</i>	0.0065	0.0366	0.1220	-21.60	49.20
<i>LVM: Hill m3-</i>	0.0065	0.0366	0.1220	-21.60	49.20

The best fit, which results in the highest maximum likelihood (and in this case the lowest Akaike index (AIC)), was obtained with a log-probit model. The excess risk selected (hybrid BMR) was 10%; this takes into account the variability of the experimental test, the small number of subjects in the tested groups and the early nature of the observed effect.

The corresponding BMD is 0.0443 mg.kg bw⁻¹.d⁻¹ and the lower limit of the 95% confidence interval (BMD_{10%}L_{95%}) is 0.0152 mg.kg bw⁻¹.d⁻¹ (Table 5).

These results are in line with ANSES's "TRV Development Guide" (ANSES, 2017):

- BMD and BMDL from the model that best fits the experimental data;
- Range of BMD and BMDL values from different models less than 10;
- BMD/BMDL ratio from the log-probit model less than 3.

3.5. TRV

3.5.1. Choice of uncertainty factors

The TRV was calculated from the above-mentioned BMD_{10%}L_{95%}, derived from the study by Greer *et al.* (2002), using the following uncertainty factors (ANSES, 2017):

- **Inter-species variability (UF_A): 1.**

The value of 1 can be used to calculate the TRV because the study by Greer *et al.* (2002) was conducted in humans.

- **Inter-individual variability (UF_H): 10.**

In addition to the various diverging BMR values adopted by the different agencies proposing TRVs (JECFA 2011; EFSA 2014) and authors (Weterings *et al.* 2016), it is important to remember first of all that the study by Greer *et al.* (2002) was carried out in healthy volunteers

and that not all observable compensation phenomena will necessarily be the same for all individuals and for longer exposure periods.

The experts of the WG on "Perchlorate" point out that the human data support the existence of population groups – such as pregnant women – that are susceptible to the thyroid toxicity of perchlorate. These susceptible populations may have different RAIU values. The lack of data on the RAIU values of these susceptible populations also leads to uncertainty. The uncertainty factor of 10 for inter-individual variability is therefore justified.

- **Subchronic to chronic transposition (UF_S): 1.**

The observed iodine uptake inhibition occurred relatively quickly after the onset of exposure in the study by Greer *et al.* (2002) and varied only slightly as exposure continued. These data are from a subacute exposure study, but the kinetics of perchlorate and the mechanism of action indicate that there is unlikely to be a risk of bioaccumulation of perchlorate and/or cumulative effects.

- **Use of a NOAEL/C (UF_{B/L}): 1**

The value of 1 can be used because the key study allows for the use of a BMD_{10%}L_{95%}.

- **Inadequacy of the data (UF_D): 1.**

The UF_D reflects the quantitative and/or qualitative inadequacy of the data available for the hazard assessment and/or the severity of the selected critical effect. The inadequacy of the scientific literature in terms of studies that could be used to develop a TRV could argue for a UF_D greater than 1. However, here the severity of the critical effect is very low, as it is not an adverse effect but an early effect. In addition, human and animal data on the effects of perchlorate are generally consistent.

An overall uncertainty factor of 10 was thus used to develop the TRV.

3.5.2. Proposed chronic oral TRV

$$\text{TRV} = \text{BMD}_{10\%L_{95\%}} / \text{UF} = 0.0152 / 10 = 0.00152 \text{ mg.kg bw}^{-1}.\text{d}^{-1} \approx 1.5 \text{ }\mu\text{g.kg bw}^{-1}.\text{d}^{-1}$$

3.5.3. Confidence level

The overall confidence level **moderate** was assigned to this TRV based on the following criteria:

- Level of confidence in the type and quality of the data: **moderate**.

The available human data on the health effects of perchlorate, in particular its thyroid effects, are quite extensive. Despite their number, however, the quality of the studies or the divergence between some of their results (see the ANSES opinions of 2012, 2014 and 2018), mean that it is not possible to characterise a critical effect downstream of iodine uptake inhibition. Regarding animal data, the rat is a good qualitative model for the effects of perchlorate on thyroid function, but has proved to be a poor quantitative model due to interspecies differences in thyroid physiology (ANSES 2011).

- Level of confidence in the choice of the critical effect and the mode of action: **moderate**.

The critical effect selected is inhibition of iodine uptake by the thyroid gland, which represents an early biological effect upstream of impaired thyroid function. However, as previously indicated, the available human data, although converging to identify the thyroid as the target organ for perchlorate, cannot be used to characterise a critical effect downstream of iodine uptake inhibition.

Despite the existence of a validated adverse outcome pathway (AOP) between an initiating event "iodine uptake inhibition" and "cognitive deficits in children" (AOP 54) (Rolaki *et al.* 2019), the WG on "Perchlorate" considers that some events in this AOP are unmeasured and difficult to quantify with the techniques currently used. It is therefore not possible to assign the highest level of confidence.

- Level of confidence in the choice of the key study: **moderate**.

There are very few studies that could be used for calculating the TRV, which makes it impossible to judge the quality of the response. The study by Greer *et al.* (2002) is of good quality. Its main limitation is that it involves healthy volunteers (due to the constraints associated with the RAIU test), a population that is not particularly susceptible to the adverse effects of perchlorate on thyroid function.

- Level of confidence in the choice of the critical dose: **high**.

The data used are numerically suitable for calculating the BMDL with low (computational) uncertainty. In addition, comparisons of calculation methods (Bayesian method, BMD on continuous data) all gave results of the same order of magnitude.

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

The experts of the WG on "Perchlorate" and the CES VSR, like many other agencies and authors, considered the results of the study by Greer *et al.* (2002) to be well suited to the use of a BMD approach, in order to develop a more relevant TRV for perchlorate than that obtained with the NO(A)EL approach.

Due to a lack of information on the *a priori* distribution of the modelling parameters, as well as the frequentist approach's simplicity of implementation and ease of interpretation by the users of these health values, this approach was chosen by the WG, rather than the study by Haber *et al.* (2021), which used a Bayesian approach.

With regard to the BMR, the experts recognised the value of the hybrid approach proposed by Haber *et al.* (2021), based on the excess risk of having an RAIU below a given value. Because the lower bound of the RAIU selected by Haber *et al.* (2021) was not documented, the experts of the WG on "Perchlorate" conducted a literature search and set the lower bound value of the RAIU at 9.1%.

On the basis of the aforementioned approaches and selected parameter values, the WG on "Perchlorate" calculated a new $BMD_{10\%L_{95\%}}$ value of $15.2 \mu\text{g.kg bw}^{-1}$ and developed a TRV of $1.5 \mu\text{g.kg bw}^{-1}.\text{d}^{-1}$ for perchlorate.

In order to consider revising this TRV and developing a new value on the basis of the adverse effects of perchlorate downstream of iodine uptake inhibition (mainly on neurodevelopment in children), the WG on "Perchlorate" and the CES VSR reiterate the need to draw on data from epidemiological studies:

- conducted in general population mother-child 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 thyroid function of the mother of the newborn and infant;
- monitoring the neurodevelopment of children up to at least 6 years of age using neuropsychological tests conducted by health professionals.

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 the proposed chronic oral TRV for perchlorate, whose characteristics are summarised in Table 6 below.

Table 6: Chronic oral TRV for perchlorate

Critical effect (key study)	Critical dose	UF	TRV
Inhibition of radioiodide uptake by the thyroid gland Greer <i>et al.</i> (2002)	BMD _{10%} L _{95%} = 0.0152 mg.kg bw ⁻¹ .d ⁻¹	10 UFA: 1 UFH: 10 UFLB: 1 UFS: 1 UFD: 1	TRV = 1.5 µg.kg bw ⁻¹ .d ⁻¹
			Confidence level Moderate

UFA: Inter-species variability (toxicokinetics/toxicodynamics), UFH: Inter-individual variability (toxicokinetics/toxicodynamics), UFLB: Use of a BMDL, LOAEL/C or NOAEL/C, UFS: Transposition from subchronic to chronic exposure, UFD: Data sufficiency (quality and quantity)

The Agency points out that in the absence of more suitable data, the critical effect selected corresponds to iodine uptake inhibition. It stresses the need to acquire knowledge to consider revising this TRV on the basis of the adverse effects of perchlorate downstream of this inhibition, as expressed above and in the first deliverable of the formal request, published in the opinion of 16 March 2021 (ANSES, 2021), as well as in the Agency's previous work.

Lastly, the Agency also points out that until studies of sufficient quality to meet these needs are available, it reserves the right to consider as inadmissible any future request for an expert appraisal on the advisability of revising the TRV for perchlorate.

Roger Genet

KEYWORDS

Perchlorates, ions, valeur toxicologique de référence, benchmark dose.

Perchlorates, ions, toxicity reference value, benchmark dose.

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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" (SECOND DELIVERABLE)

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.

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

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

Ms Isabelle OLIVER-PETIT – Paediatrician and endocrinologist, Toulouse University Hospital – Expertise: Paediatrics, endocrinology, newborn and child thyroid diseases.

Mr Alain-Claude ROUDOT – University Professor, University of Western Brittany. Mathematical modelling and exposure assessment.

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 opinion 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 HOGVEEN – 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 "ASSESSMENT OF PHYSICAL-CHEMICAL RISKS IN FOOD" (CES ERCA) (2018-2023)

Chair

Mr Bruno LE BIZEC – University Professor – Expertise in analytical chemistry

Vice-Chair

Mr Fabrice NESSLANY – Laboratory Director – Expertise in toxicology

Members

Mr Claude ATGIE – University Professor – Expertise in toxicology

Mr Pierre-Marie BADOT – University Professor – Expertise in contaminant transfer and ecotoxicology

Ms Marie-Yasmine DECHRAOUI BOTTEIN – Researcher in environmental toxicology – Expertise in marine biotoxins

Ms Martine CLAUW – University Professor – Expertise in toxicology

Mr Nicolas DELCOURT – University Lecturer, Hospital Pharmacist – Expertise in biochemistry and clinical toxicology

Ms Christine DEMEILLIERS – University Lecturer – Expertise in toxicology

Mr Erwan ENGEL – Research Director – Expertise in analytical chemistry

Mr Jérôme GAY-QUEHEILLARD – University Lecturer – Expertise in digestive impacts, metabolism, immunity; health impacts of pesticides

Mr Petru JITARU – Laboratory Manager – Expertise in analytical chemistry

Ms Sonia KHIER – University Lecturer – Expertise in pharmacokinetics

Ms Emilie LANCE – University Lecturer – Expertise in ecotoxicology and cyanotoxins

Ms Caroline LANIER – University Lecturer – Expertise in the assessment of health risks associated with the environment and food

Mr Ludovic LE HEGARAT – Laboratory Manager – Expertise in toxicology

Mr Nicolas LOISEAU – Researcher – Expertise in toxicology

Mr David MAKOWSKI – Research Director – Expertise in statistics and modelling

Mr Eric MARCHIONI – University Professor – Expertise in analytical chemistry

Mr Jean-François MASFARAUD – University Lecturer – Expertise in contaminant transfer and ecotoxicology

Mr César MATTEI – University Lecturer – Expertise in toxicology

Mr Alain-Claude ROUDOT – University Professor – Expertise in mathematical modelling, exposure assessment

Mr Yann SIVRY – University Lecturer – Expertise in analytical chemistry

Ms Paule VASSEUR – Professor Emeritus – Expertise in toxicology

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 DENOZ – 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 of treated wastewater.

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.

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 Éléonore NEY – Head of the Water Risk Assessment Unit, Risk Assessment Department – ANSES

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

Ms Aurélie MATHIEU-HUART – Deputy Head of the Chemicals Assessment Unit, Risk Assessment Department – ANSES

Administrative secretariat

Ms Virginie SADÉ – Risk Assessment Department – ANSES

ANNEX 2 – ACRONYMS AND ABBREVIATIONS

AIC: Akaike information criterion
ANSES: French Agency for Food, Environmental and Occupational Health & Safety
AOP: Adverse outcome pathway
ATSDR: US Agency for Toxic Substances and Disease Registry
ARS: French Regional Health Agency
BBDR: Biologically-based dose-response
BMD: Benchmark dose
BMDxLy: Lower limit of the y% confidence interval of the benchmark dose associated with x%
BMR: Benchmark response
BMDS: BMD Software
BMDU: Upper limit of the 95% confidence interval of the BMD
CES: Expert Committee
DGS: Directorate General for Health
DGCCRF: Directorate General for Competition, Consumer Affairs and Fraud Control
TDS: Total diet study
DW: Drinking water
EFSA: European Food Safety Authority
ERS EDCH: Assessment of the health risks associated with chemical parameters in drinking water
HRA: Health risk assessment
fT4: Free thyroxine
WG: Working Group
TH: Thyroid hormone(s)
InVS: French Institute for Public Health Surveillance
IPCS: International Programme on Chemical Safety
JECFA: Joint FAO/WHO Expert Committee on Food Additives
NIS: Sodium/iodide symporter
NOAEL: No observed adverse effect level
OECD: Organisation for Economic Co-operation and Development
OEHHA: Office of Environmental Health Hazard Assessment (California, USA)
WHO: World Health Organization
PBPK: Physiologically-based pharmacokinetic
RAIU: Radioiodine uptake test
RIVM: *Rijksinstituut voor Volksgezondheid en Milieu* (Netherlands National Institute for Public Health and the Environment)
SD: Standard deviation
SFMN: French Society for Nuclear Medicine
SISE-Eaux: Environmental health information system
T3: Triiodothyronine
T4: Thyroxine
TBG: Thyroxine-binding globulin or Transthyretin
TSH: Thyroid-stimulating hormone
UCLA: University of California, Los Angeles
UF: Uncertainty factor

UF_A: Inter-species uncertainty factor

UF_D: Database uncertainty factor

UF_H: Inter-individual uncertainty factor

UF_{H-TK}: Toxicokinetic component of the inter-individual uncertainty factor

UF_{H-TD}: Toxicodynamic component of the inter-individual uncertainty factor

UF_{B/L}: Uncertainty factor related to the use of a LOAEL or BMD

UF_S: Uncertainty factor related to subchronic to chronic transposition

US EPA: US Environmental Protection Agency

GV: Guideline value

TRV: Toxicity reference value

VSR: Health Reference Values

ANNEX 3 – LITERATURE SEARCH ON THE RAIU RANGE

QUERIES

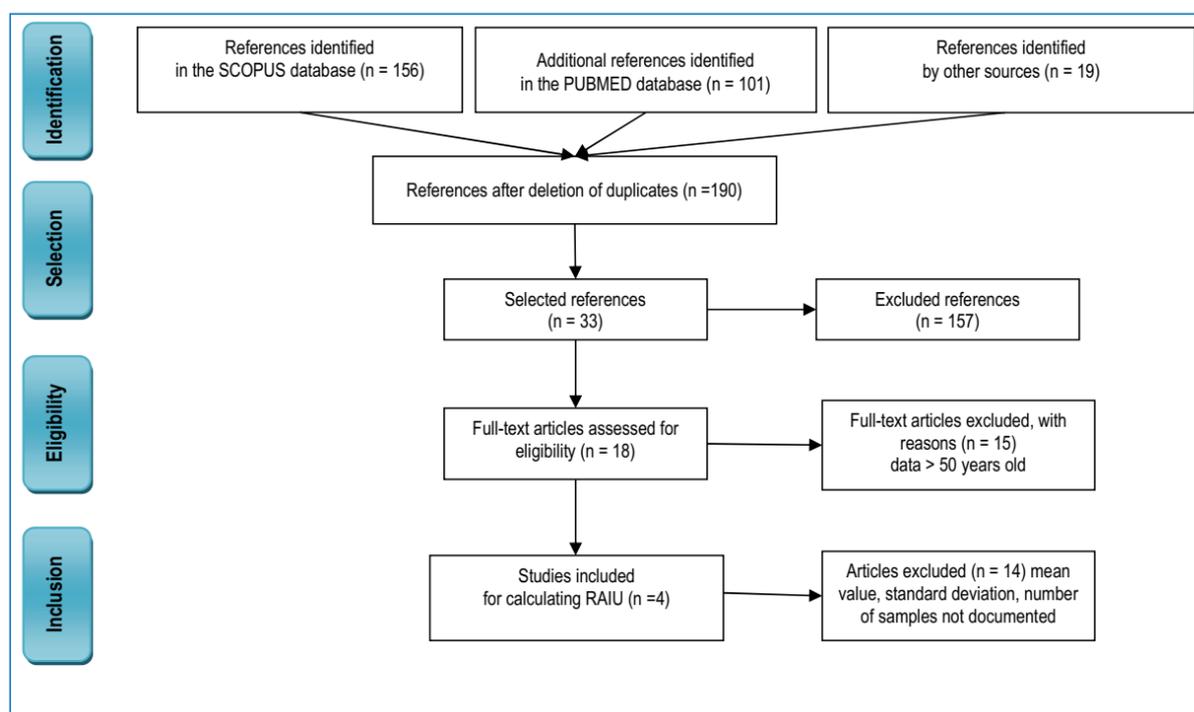
Date: 15 June 2021

Search equations:

Scopus: TITLE-ABS-KEY ("radioiodine uptake" OR "radioactive iodine uptake" OR "RAIU") AND ("normal range" OR "abnormal range" OR "reference range" OR "distribution")

PubMed: All fields ("radioiodine uptake" OR "radioactive iodine uptake" OR RAIU) AND ("normal range" OR "abnormal range" OR "reference range" OR distribution))

PRISMA diagram:



ANNEX 4 – CALCULATION OF THE LOWER BOUND OF THE PHYSIOLOGICAL RAIU RANGE

The mean and standard deviation values from the publications by Ballal *et al.* (2017), Al-Muqbel *et al.* (2010), Gonzalez *et al.* (2008) and Culp *et al.* (1978) were used to reconstruct a lognormal sample equal to the number of subjects in each study using @RISK software.

Table 1 – Mean and standard deviation of the RAIU from the different publications selected

	Mean	Standard deviation	N
Ballal <i>et al.</i>	12.75	5.51	110
Al-Muqbel <i>et al.</i>	15	7	102
Gonzalez <i>et al.</i>	16.2	4.8	105
Culp <i>et al.</i> (♂)	15.9	3.1	25
Culp <i>et al.</i> (♀)	21.2	4.9	28

For each of these publications a lognormal distribution of the RAIU values was modelled and then N individual values corresponding to N samples were randomly selected for the data of Culp *et al.* (1978) relating to 28 women.

The subjects were then all grouped together giving a set of 370 data (110 + 102 + 105 + 25 + 28) to define a common lognormal distribution, whose mean was s around 15.18 and standard deviation was 6.1.

The lower bound of the RAIU range is set at 1 standard deviation below the mean, i.e. 9.1%.

ANNEX 5 – CALCULATION OF THE BMD

Based on the number of subjects with an RAIU below the lower bound of 9.1% according to the dose (in $\text{mg.kg bw}^{-1}.\text{d}^{-1}$) of perchlorate received, the PROAST v70.1 software <https://proast-web.rivm.nl/> gives the following results for a 10% excess risk:

Input values

Removed data No

Type of response data Quantal

Dose column(s) Dose

Response column(s) RAIU<9.1%

Group size column(s) N

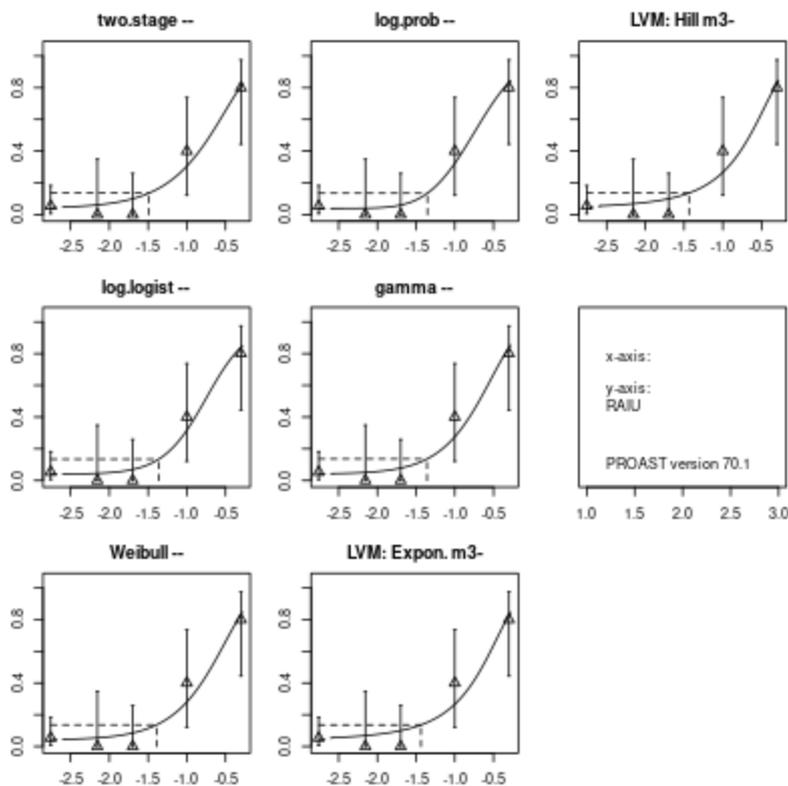
Covariate column none

Litter effect No

BMR (CES) 0.1

Model averaging No

AIC criterion 2

Graphical output

Fitted models

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
null	1	-35.89	73.78	NA	NA	NA	NA	NA
full	5	-19.51	49.02	NA	NA	NA	NA	NA
two.stage	3	-21.3	48.6	yes	0.0195	0.0591	0.0325	yes
log.logist	3	-20.87	47.74	yes	0.0136	0.0963	0.0435	yes
Weibull	3	-21.24	48.48	yes	0.00978	0.107	0.0406	yes
log.prob	3	-20.69	47.38	yes	0.0152	0.0933	0.0443	yes
gamma	3	-21.19	48.38	yes	0.00977	0.106	0.0439	yes
LVM: Expon. m3-	3	-21.6	49.2	yes	0.0065	0.122	0.0366	yes
LVM: Hill m3-	3	-21.6	49.2	yes	0.00651	0.122	0.0366	yes