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Adopted: 25 March 2025

DOI: 10.2903/j.efsa.2025.9393

efsa JOURNAL

SCIENTIFIC OPINION

Update of the Scientific Opinion on the risks for human health related to the presence of perchlorate in food

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The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

Abstract

The European Commission asked EFSA to update its 2014 risk assessment on perchlorate in food. Perchlorate is a contaminant of both natural and anthropogenic sources present in food and drinking water. It is a substrate for the sodium iodide symporter (NIS) and competitively inhibits the uptake of iodide into the thyroid. Experimental animal studies show that perchlorate exposure during pregnancy can result in neurodevelopmental toxicity. The CONTAM Panel established a tolerable daily intake of 1.4 μg/kg body weight per day, based on the inhibition of thyroid iodine uptake in healthy adults. The tolerable daily intake (TDI) takes into account the sensitivity of the fetus to maternal thyroid hormone disturbance and uncertainty around the impact of iodine deficiency on the effects of perchlorate during fetal development. This TDI is applicable for both a short-term (approximately 2-week period) and chronic exposures based on the mode of action of perchlorate, its toxicokinetic properties and the key study used to derive the TDI. An acute reference dose (ARfD) was not deemed necessary. EFSA received a total of 40,356 analytical results, between 2016 and 2022, which were considered for the dietary exposure assessments. A chronic dietary exposure assessment for all age groups and a short-term dietary exposure assessment for pregnant women were calculated. The CONTAM Panel concluded that chronic and short-term dietary exposure estimates to perchlorate were below the TDI for all age groups including pregnant women, with the exception at the upper bound of the P95 for infants, breastfed infants and formula-fed infants. Even if the limitations in analytical methods, leading to a large difference between lower bound (LB) and upper bound (UB) dietary exposure, reduces the certainty in this conclusion for infants, breastfed infants and formula-fed infants, the uncertainty analysis indicates a higher (above 50%) likelihood of 'no concern' for all scenarios.

KEYWORDS

food, iodine, neurodevelopment, perchlorate, risk assessment, thyroid

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CONTENTS

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SUMMARY

The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) adopted in 2014 a Scientific Opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables, deriving a tolerable daily intake (TDI) of 0.3 μg/kg body weight per day, based on the inhibition of thyroid iodine uptake in healthy adults. In 2015 the CONTAM Panel also adopted a Scientific Opinion for the presence of chlorate in food, deriving a TDI as read across from the TDI set for the perchlorate, using a factor of 10 to account for the lower potency of chlorate. In 2023, the European Commission (EC) requested an update of the perchlorate Opinion, based on the 2017 update of the EFSA guidance on the use of the Benchmark Dose (BMD) modelling in risk assessment and other new scientific developments. The Opinion should also provide an assessment of the consequences for the Opinion on chlorate in food.

Perchlorate is an inorganic anion, generally occurring as salt which is highly soluble in both aqueous and non-aqueous environments. Perchlorate contamination in food and drinking water may be derived from several natural and anthropogenic sources. Methods of analysis for perchlorates include techniques such as ion chromatography or liquid chromatography-mass spectrometry. Some of them are recommended by regulatory bodies based on the type of matrices where perchlorates can be found.

A number of organisations have assessed the risk for the presence of perchlorate in food since EFSA's CONTAM Panel (2014) Opinion. In particular, in 2022 the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) revised its Opinion on the presence of perchlorate in drinking water, deriving a toxicity reference value (TRV) of 1.5 μg/kg bw per day using Greer et al. (2002), the same non-randomised human intervention study used by the CONTAM Panel in 2014 (ANSES, 2022). The Greer et al. (2002) study was also used to perform dose–response analyses by a number of different international organisations and researchers.

Maximum levels for certain contaminants in food, including perchlorate, were set by Commission Regulation (EU) 2023/915 of 25 April 2023. Maximum levels are set at 0.05 mg/kg for most fruits and vegetables, 0.75 mg/kg for tea and herbal and fruit infusions, 0.01 mg/kg for infant formulae and processed cereal-based food and 0.02 mg/kg for baby food.

Hazard identification and characterisation

A systematic literature review was conducted to retrieve relevant new evidence available since EFSA's CONTAM Panel 2014 Opinion. Regarding studies in experimental animals, numerous new oral repeated-dose toxicity studies, conducted mostly in rats showed dose-dependent effects of perchlorate, with the thyroid being the most sensitive organ. A decrease in T3 and T4 (thyroid hormones, THs) and an increase in TSH (thyroid stimulating hormone) were observed at doses as low as 0.01 mg/kg bw per day in rats. At a higher dose, perchlorate also led to changes in thyroid gland weight and histopathological findings in adult male and female animals. Exposure to perchlorate during critical developmental windows can disrupt thyroid homeostasis in fetuses and neonates thereby disturbing neurological development. Dose-dependent effects of perchlorate on the hypothalamus–pituitary–thyroid (HPT) axis have been documented in a series of studies with pregnant rats and in their offspring in terms of reduction in maternal and fetal T4 serum concentrations and the occurrence of periventricular heterotopia (PVH) in the brains of pups was observed. Direct oral administration of perchlorate to prenatally exposed rat pups from postnatal day (PND) 0 to PND 6 resulted in a significant reduction in serum and brain T4 levels. This treatment led to the development of PVH in the pups. Even a significantly lower amount of maternal perchlorate exposure (1 mg/L ~ 0.09 mg/kg bw per day) was enough to decrease TH synthesis in the thyroid gland in late pregnancy in the pups. However, decreases in gland synthesis of TH did not affect fetal blood TH levels, suggesting the existence of compensatory mechanisms. Only with greater doses, TH synthesis was reduced in the dam's gland, suggesting that selecting a no observed adverse effect level (NOAEL) for the dam based on the gland's TH synthesis is not protective for the fetus. Exacerbation of thyroidal and neurological effects in rats exposed to perchlorate during various stages of development was demonstrated under iodine deficiency. These findings, presented in this series of studies, show that perchlorate exposure in the prenatal and postnatal period of life can result in neurodevelopmental toxicity that may have long-term consequences. Even though it is difficult to extrapolate the rat TH perturbations to humans (because of the lengthy exposure time required to deplete iodine stores in the adult human thyroid), it is worth mentioning that the human fetus is reliant on its own production of TH in later stages of pregnancy and that, like the rat, the capacity for iodine storage in humans is much lower in the fetus compared to the maternal thyroid gland. The outcomes in experimental animals are in line with a sequence of events outlined in adverse outcome pathways (AOPs) for perchlorate which starts with inhibition of iodine uptake as molecular-initiating event (MIE). As the animal studies provide dose–response data and important mechanistic insights on the toxicity of perchlorate, they are used as supportive evidence in the assessment.

A total of 43 human observational studies (37 cross-sectional and 6 prospective studies) were retrieved covering additional health outcomes that were not assessed in the previous EFSA opinion (EFSA CONTAM Panel, 2014). These included studies were on thyroid hormones or thyroid disease ($n = 17$), cardiovascular disease and/or related risk factors ($n = 6$), cancer ($n = 3$), birth outcomes and children ($n = 8$) or other outcomes ($n = 9$). The accumulated epidemiological evidence suggests that exposure to perchlorate, at levels commonly found in the general population, may affect thyroid function. The absence of an association in some of the studies is not unexpected and should be interpreted in the context of both small sample size and uncertainties around timing of exposure assessment. Moreover, urinary perchlorate excretion is likely influenced by physiological changes during the course of pregnancy. The accumulated epidemiological evidence in adults and children supports an association between serum perchlorate and higher TSH and lower free thyroxine (FT4). Evidence

from one epidemiological study suggests that perchlorate may be adversely associated with neurodevelopment in the offspring, however, limited conclusions can be drawn from a single study and further replication in other settings would add more weight to these findings. Evidence from three cross-sectional studies on cancer was not sufficient to allow for conclusions on the association between perchlorate exposure and cancer in humans.

In appreciation of the fact that iodine deficiency (ID) is one of the main determinants of thyroid disorders and the potential for iodine deficiency to enhance susceptibility to perchlorate toxicity, the CONTAM Panel noted that population-based surveys from Europe suggest that the risk of either severe, moderate or mild iodine deficiency is potentially widespread as reflected by frequent reports of median urinary iodine concentrations below 100 µg/L. Iodine requirement for pregnant women is substantially increased, related to both physiological changes in pregnancy, including increased glomerular filtration rate, and increased demand to support fetal growth and development. Reduced iodine status may also result from plant-based diets without iodine supplementation, exposure to natural goitrogens and variability in genes coding for proteins involved in thyroid economy.

In terms of mode of action, experimental evidence supports the role of perchlorate in competing for iodine uptake into the thyroid gland (via the sodium iodide symporter (NIS)) and potentially uptake into other organs. The elemental form of 'iodine' is rarely found in food and water, while it generally occurs in the form of an iodide salt. In this Opinion, the term 'iodine' is to be understood as both 'iodine' and its reduced form 'iodide'.

Studies demonstrate an indirect, thyroid-mediated effect on reproduction and development with apparent interplay between the thyroid and androgen hormones as well as a potential direct interference of perchlorate with reproduction and development. Oxidative stress and indicators of an apoptotic mechanism of mammalian cell toxicity were evident. Mitochondrial dysfunction associated with oxidative stress may contribute to cytotoxicity as reported only in fish. Some studies also suggest perchlorate to affect thyroid peroxidase (TPO) and thyroglobulin (Tg) which are directly involved in the biosynthesis of thyroid hormones. AOPs 54 and 42, both endorsed by the OECD, support the biological plausibility of associations between inhibition of NIS function and of TPO during mammalian development, with decreased levels of TH in the blood and in the brain, and consequent potential adverse neurodevelopment outcomes such as learning and memory impairment.

Based on the available evidence, the CONTAM Panel concludes that the non-randomised human intervention study by Greer et al. (2002) assessing iodine inhibition at relatively low doses of perchlorate exposure in humans still provides the best evidence for characterising risk to human health.

BMD modelling was performed based on the study by Greer et al. (2002) adapting the 2022 EFSA Guidance on the use of the BMD approach in risk assessment for human data. To select an appropriate BMR, a biological reference interval was derived which reflects normal variation in radioactive iodine uptake (RAIU) at a population level. The lower cutoff value of the 95% confidence interval (95% CI) of RAIU was calculated at 14.6%. Exceedance of this threshold maybe considered abnormal and was therefore considered a suitable basis for defining the BMR for perchlorate. It was estimated that a 4.1% reduction in RAIU would correspond to an exceedance of the biological reference interval on a population basis. This value was rounded up to 5% and was used as the BMR.

Using this BMR, a benchmark dose lower credible limit ($BMDL_5$) of 7 mg/kg bw per day for reduction of RAIU was identified as the Reference Point for perchlorate.

To derive a HBGV, the CONTAM Panel considered the limitations associated with the study of Greer et al. (2002) used to derive the Reference Point, the sensitivity of the fetus to maternal thyroid disturbance and the uncertainty around the impact of ID on perchlorate effects during fetal development. The higher demand (approximately 50% increase) for iodine during pregnancy was also taken into account. Consequently, bearing in mind these limitations, it was decided that an overall uncertainty factor (UF) of 5 is warranted, leading to a TDI of 1.4 µg perchlorate/kg bw per day.

An acute reference dose (ARfD) was not deemed necessary.

In light of the amended TDI for perchlorate, a detailed assessment of the available literature on chlorate toxicity (including its potency for the inhibition of uptake of iodine) is necessary. This evaluation should determine the appropriateness of using a revised read across approach to derive a revised TDI for chlorate, to ensure a comprehensive assessment of the potential risk to public health associated with the presence of chlorate in food.

Occurrence and dietary exposure assessment for the European population

The Panel deemed relevant for this opinion to assess a chronic dietary exposure for all age groups and a short-term (2-week) dietary exposure assessment for pregnant women.

Food consumption data from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) were used for the dietary exposure assessments. Perchlorate occurrence data in food were extracted from the EFSA Occurrence database. After data validation and cleaning procedures a total of 40,356 analytical results submitted by 20 Member States plus Norway, Switzerland and United Kingdom, between 2016 and 2022, were available to be included in the dietary exposure assessments to perchlorate.

Mean **chronic dietary exposure** to perchlorate ranged across surveys and lower bound (LB) and upper bound (UB) estimates, from 0.02 µg/kg bw per day in Pregnant women, Adults, the Elderly and the Very elderly to 1.0 µg/kg bw per day in Infants. The 95th percentile (P95) chronic dietary exposure to perchlorate ranged across surveys and LB and UB estimates, from 0.04 µg/kg bw per day in the Pregnant women, Elderly and the Very elderly to 1.74 µg/kg bw per day in Infants.

The main food category contributing to the chronic dietary exposure were 'Vegetables and vegetable products' for all age groups (up to 65.5%), 'Milk and dairy products' for Infants, Toddlers and Other children (up to 48.5%), 'Water-based

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beverages' for Other children, Adolescents and Adults (up to 34.1%) and 'Food for the young population' for Infants (up to 71.6%).

Mean **short-term dietary exposure** to perchlorate ranged across Pregnant women surveys and LB and UB estimates, from 0.25 μg/kg bw per day to 0.6 μg/kg bw per day. P95 short-term dietary exposure to perchlorate ranged across Pregnant women surveys and LB and UB estimates, from 0.47 to 1.29 μg/kg bw per day.

Main contributors to the short-term exposure to perchlorate for Pregnant women were 'Vegetables and vegetable products' (contribution up to 50.3%), 'Starchy roots or tubers and products thereof, sugar plants' (up to 26.9%), 'Milk and dairy products' (up to 12.8%).

For the **breastfed infant** scenario, the exposure estimates were obtained using chronic dietary exposure data for Lactating women using mean and high (99th percentile (P99)) exposure in this population group, an excretion value of 54% of perchlorate in human milk and a daily human milk production of 0.8 L to 1.2 L. Infants at mean exposure ranged from 0.2 (LB) to 1.2 (UB) μg/kg bw per day, whereas infants at P95 exposure ranged from 0.5 (LB) to 2.1 (UB) μg/kg bw per day.

For **formula-fed infants**, the dietary exposure for infants with high (P95) infant formula consumption, dietary exposure estimates range from 0.07 to 0.5 μg/kg bw per day based on mean concentrations and from 0.7 to 1.7 μg/kg bw per day based on the highest reliable percentile (99th) concentrations.

The dietary exposure estimates to perchlorate were below the TDI for all age groups with the following exceptions: The upper bound (UB) of the P95 for infants, the UB of the P95 for breastfed infants and the UB of the P95 for formula-fed infants.

Risk characterisation

The CONTAM Panel evaluated the current chronic and short-term dietary exposure using mean LB and UB levels of perchlorate in various food groups and using the consumption surveys from European countries available in the Comprehensive Food Consumption database. The CONTAM Panel concluded that chronic and short-term dietary exposure estimates to perchlorate were below the TDI for all age groups including pregnant women, with the exception at the upper bound of the P95 for infants, breastfed infants and formula-fed infants. Of note, beside the well-known benefits of breastfeeding, human milk is the major source of iodine intake at this stage of life.

Uncertainty analysis

The uncertainty analysis performed resulted in the following conclusions: It is likely to very likely (no concern with at least 88% certainty) that mean or P95 chronic dietary exposure levels do not exceed the TDI for all age groups. For the short-term scenario, it is likely (no concern with at least 69% certainty) that mean or P95 exposure levels are below the TDI for pregnant women. It is almost certain (no concern with over 99% certainty) that the mean exposure level for breastfed infants is below the TDI. It is as likely as not (no concern with 62% certainty) that the P95 exposure level for breastfed infants does not exceed the TDI. It is likely (no concern with 88% certainty) that the P95 exposure level for formula-fed infants does not exceed the TDI.

Recommendations

More information is needed on concentrations of perchlorate in human milk in the European population. Improvement of the sensitivity of the analytical methods for perchlorate measurement in food is needed to reduce uncertainty in exposure assessments. More information on perchlorate exposure to the fetal thyroid gland and its impact on thyroid homeostasis and neurodevelopment is needed. A better characterisation of the possible effects of moderate iodine reduction caused by perchlorate (or other goitrogens) in populations with iodine deficiency/insufficiency would reduce uncertainty.

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1 | INTRODUCTION

1.1 | Background and Terms of Reference as provided by the requestor

Background

The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) adopted in 2014 a Scientific Opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables.[1] The CONTAM Panel established a tolerable daily intake of 0.3 µg/kg body weight (bw) per day, based on the inhibition of thyroid iodine uptake in healthy adults. The CONTAM Panel noted that a single acute exposure to perchlorate at levels found in food and water is unlikely to cause adverse effects on human health, including the more vulnerable groups of the population, and concluded that the establishment of an acute reference dose for perchlorate is not warranted.

The EFSA CONTAM Panel adopted in 2015 a scientific opinion on the risks for public health related to the presence of chlorate in food.[2] A tolerable daily intake (TDI) of 3 µg chlorate/kg bw was set by read-across from a TDI of 0.3 µg/kg bw derived for this effect for perchlorate, multiplied by a factor of 10 to account for the lower potency of chlorate. Formation of methaemoglobin was identified as the critical acute effect of chlorate. An acute reference dose (ARfD) of 36 µg chlorate/kg bw was derived from a no-observed- for chlorate in a controlled clinical study.

Since the adoption of the EFSA opinion in 2014, there have been scientific developments which are relevant to the assessment of risks to public health related to the presence of perchlorate in food. In particular:

- An update of the EFSA guidance on the use of the Benchmark Dose (BMD) modelling in risk assessment[3] has been published in 2017.[4] According to a scientific publication[5] this update would have an impact on the derivation of the health-based guidance for perchlorate (and for chlorate).
- In February 2022, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) conducted a re-assessment of the chronic oral toxicity reference value (TRV)[6] and derived a TRV for perchlorate different from the TDI derived by EFSA in the 2014 opinion.

Therefore, it is appropriate that EFSA based on these new scientific developments re-assesses the risk related to the presence of perchlorate in food, and in case of an update to assess the consequences for the opinion on chlorate in food.

Terms of Reference

In accordance with Art. 29 (1) (a) of Regulation (EC) No 178/2002, the Commission asks EFSA for a re-assessment of the risks related to the presence of perchlorate in food, taking into account new scientific developments and information since the adoption of its earlier scientific opinion on the risks related to the presence of perchlorate in food.

In case of a change to the current risk assessment related to the presence of perchlorate in food, the Commission asks also to assess the consequences for the scientific opinion on the risks for public health related to the presence of chlorate in food.

1.2 | Additional information

1.2.1 | Chemistry

Perchlorate is an inorganic anion (Figure 1) comprising a chlorine atom in a +7 valence state bound to four oxygen atoms, forming a characteristic tetrahedral geometry (Brown & Gu, 2006). Represented by the chemical formula (ClO_4^-) perchlorate embodies the highest oxidised state of chlorine, rendering it a potent oxidising agent (Urbansky, 1998, 2002).

The reduction potential of the overall reaction from perchlorate to chloride anion shown below is 1.39 V (1M solution of acid at 25°C).

$$ClO_4^- + 8e^- + 8H^+ \rightarrow Cl^- + 4H_2O$$

[1]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*, *12*(10), 3869. doi:10.2903/j.efsa.2014.3869.

[2]EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain). (2015). Scientific Opinion on risks for public health related to the presence of chlorate in food. *EFSA Journal*, *13*(6), 4135. 10.2903/j.efsa.2015.4135.

[3]EFSA Scientific Committee. (2017). Update: Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2017;15(1):4658, 41 pp. doi:10.2903/j.efsa.2017.4658.

[4]The 2017 EFSA Guidance on benchmark dose was superseded by the 2022 EFSA Guidance on the use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2022).

[5]Toxicology Letters, 2021, Volume 340: p. 89–100: Impact of updated BMD modelling methods on perchlorate and chlorate assessments of human health hazard. https://doi.org/10.1016/j.toxlet.2021.01.001.

[6]Opinion of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on the "relevance of reassessing the chronic oral TRV for perchlorate", 2022: https://www.anses.fr/en/system/files/VSR2019SA0116EN-1.pdf.

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Despite its strong oxidative properties, the perchlorate anion exhibits remarkable stability, typically necessitating substantial activation energy to initiate its reduction process (Urbansky, 1998, 2002).

Perchlorate anion's ability to evenly distribute its negative charge across the four oxygen atoms contributes to its low propensity to bind with cations. This makes perchlorate's salt highly soluble in both aqueous and non-aqueous environments (Urbansky, 1998, 2002).

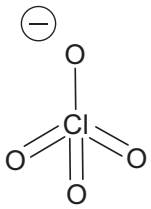

FIGURE 1 The perchlorate anion.

1.2.2 | Sources of contamination

Perchlorate contamination in food and drinking water may be derived from several natural and anthropogenic sources.

1.2.2.1 | *Natural sources*

Naturally occurring perchlorate has been recognised in various environments (Hu et al., 2021).

In the Earth's atmosphere, perchlorate primarily exists in the form of an aerosol in the troposphere and stratosphere. Detection efforts have revealed perchlorate presence in stratospheric aerosols, initially predicted by Jaeglé et al. (1996), using a photochemical model, then confirmed a few years later at a concentration in the range of 0.5–5 ng/kg (Murphy & Thomson, 2000). Further studies suggested ClO_4^- origin from ozone chemical oxidation reactions (Trumpolt et al., 2005) and ultraviolet photooxidation processes (Jackson et al., 2010).

Major perchlorate deposits are found in South America and Death Valley, USA, often mixed with other minerals (Murray & Bolger, 2014). The Atacama Desert in Chile, renowned for its nitrate deposits, emerges as significant reservoirs of natural perchlorate. The mining of fertilisers from Chilean deposits has facilitated the exportation of perchlorate-rich materials worldwide, further emphasising the global significance of such natural reservoir (Duncan et al., 2005).

Other natural occurrences have been identified in the snow of the Arctic, the waters of the Great Lakes, and the soil of Death Valley and Dry Valley in Antarctica (Kounaves et al., 2010; Poghosyan et al., 2014; Rao et al., 2007; Van Stempvoort et al., 2019), suggesting widespread distribution of perchlorate.

To conclude, the contribution of naturally occurring perchlorate to food and drinking water contamination is complex to quantify, nevertheless it is deemed small.

1.2.2.2 | *Anthropogenic sources*

Anthropogenic sources represent a primary contributor to perchlorate contamination in environmental matrices (Hu et al., 2021).

Evidence suggests that primarily human activities have contributed to the presence of perchlorate in drinking water. In the US, the reported median concentration in drinking water is 1.16 µg/L (Blount et al., 2010). Mean concentrations in groundwater range from 0.1 to 22.1 µg/L, and in surface water from 0.1 to 51.3 µg/L (Wu et al., 2010). In China, the reported mean concentration of perchlorate in soil is 3.9 µg/kg (Jackson et al., 2010; Ye et al., 2013).

Significant sources of perchlorate contamination in ground and surface water include the military, aerospace and explosives industries, as well as fireworks, which mainly contain potassium perchlorate ($KClO_4$) or ammonium perchlorate (NH_4ClO_4) among other chemicals (Gu & Coates, 2006; Kumarathilaka et al., 2016; Ucar et al., 2017).

Perchlorate is additionally found in various salt formulations used in fertilisers, herbicides, polyvinyl chloride (PVC), lithium-ion batteries, LCD screen production, automotive airbag inflators, matches, dyes, rubber, lubricants and other commercial materials (Kumarathilaka et al., 2016; Maffini et al., 2016). While precise production figures remain unknown, estimates suggest that global perchlorate production reaches several hundred thousand tons annually, with major production plants located in the USA, France, Germany, Italy, China and Brazil (Trumpolt et al., 2005).

Fertiliers are an important source of perchlorate in agricultural soils with the potential to be transferred into plants. In 2013, EFSA gathered data on perchlorate levels in soils and fertilisers, reporting mean concentrations of 150 µg/kg in soil samples and 100 mg/kg in fertiliser samples collected in Germany and the Netherlands. Despite efforts to reduce perchlorate content in fertilisers, with Fertilizer Europe members limiting perchlorate levels to 100 mg/kg fertiliser (EFSA CONTAM Panel, 2014), the use of such fertilisers remains a relevant pathway for perchlorate presence in vegetables due to its rapid uptake through plant roots.

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In a greenhouse study (Bloem & Panten, 2021) perchlorate uptake and transfer were investigated in different plant species. This study involved applying fertiliser with varying amounts of perchlorate during early growth stages of the plants. Results showed that leafy vegetables absorbed most of the perchlorate, primarily storing it in the leaves, while root vegetables showed lower levels and no perchlorate was detected in fruits. This indicates that fertilisers can pose a risk of perchlorate contamination in food.

Sodium and calcium hypochlorite solutions, used for water disinfection and potabilisation, could also be a plausible source of perchlorate. While there is no evidence in the literature on reaction mechanisms implying the conversion of hypochlorite (ClO^-) to perchlorate (Brown & Gu, 2006), presence of perchlorate has been observed in aged solutions of hypochlorite salts (Greiner et al., 2008; Stanford et al., 2011). The use of such products may indirectly contribute to the presence of perchlorate in food.

Overall, human activities are an important source of perchlorate contamination in water, soil and indirectly in food, with significant contributions from industrial processes and commercial products.

1.2.2.3 | *Medicinal use*

Historically, perchlorate has been widely utilised in clinical medicine for treating medical disorders like hyperthyroidism and to help diagnose disorders related to iodine metabolism (Murray & Bolger, 2014). Its use has largely been discontinued with the availability of alternative treatments. Currently, sodium and/or potassium perchlorate are authorised in Slovakia, Austria and Germany but has never been assessed by the European Medical Agency.

1.2.3 | Analytical methods

Methods of analysis for perchlorate use similar approaches as for polar pesticides. Some of them are recommended by regulatory bodies based on the type of matrices where perchlorate can be found.

The most frequently used methods for sample preparation include quick polar pesticides (QuPPe), QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe), dispersive solid phase extraction (dSPE) and solid phase extraction (SPE). The most frequently used techniques for characterisation are ion chromatography (IC) or liquid chromatography (LC) coupled with either mass spectrometry (MS) or tandem mass spectrometry (MS/MS) (Hakme et al., 2022; Li, Huang et al., 2023; Liao et al., 2022).

The United States Environmental Protection Agency (US-EPA) suggests METHOD 332.0 for perchlorate in drinking water based on ion chromatography with suppressed conductivity electron spray ionisation–mass spectrometry (IC–ESI/MS) (Hedrick et al., 2005). This method can achieve the lowest concentration minimum reporting level (LCMRL) of 0.1 µg/kg, with relative standard deviations (RSDs) < 10% at concentrations ≥ 0.2 µg/L perchlorate and recoveries between 90% and 110% (Hedrick et al., 2005).

The European Union Reference Laboratory (EURL) for pesticides uses of QuPPe Method to collect occurrence data of perchlorate in food (Anastassiades et al., 2021; Hepperle et al., 2013). QuPPe involves perchlorate extraction with acidified methanol and analysis using LC–MS/MS. This method features a limit of quantification (LOQ) of 2 µg/kg in fruits and vegetables and demonstrates acceptable recoveries between 70% and 120% and low RSDs < 10% across various fruits and vegetables (Hepperle et al., 2013). More details are given in the EURL report (Anastassiades et al., 2021).

1.2.4 | Previous human health risk assessments

The German Federal Institute for Risk Assessment (BfR) issued several opinions since 2013 regarding perchlorate in the food chain.

In the opinion No. 015/2013 dated 6th June 2013, BfR recommended to use the provisional maximum tolerable daily intake (PMTDI) value of 0.01 mg/kg body weight (bw) set by JECFA (Joint FAO/WHO Expert Committee on Food Additives) for acute risk assessment (BfR, 2013a). BfR stressed that the residues of perchlorate are not equally distributed among single units of food, high variability is present due to different exposure levels during spray application and other agricultural practices. BfR advised the usage of variability factors as implemented in EFSA Pesticide Residue Intake Model (PRIMo) in the acute consumer risk assessment for perchlorate in order to provide more reliable and realistic risk assessment and avoid underestimation (ingested portion might contain higher amount of perchlorate).

In its opinion No. 022/2013, BfR discussed the entry pathways of perchlorate in the food chain (BfR, 2013b). Perchlorate residues reported from more than 15 different countries were found in various food commodities, such as: citrus fruits, berries, root vegetables, leaf vegetables, fresh herbs. BfR warned that large consumption of certain foods could potentially lead to harmful effects triggered by inhibition of iodine uptake in the thyroid gland. BfR identified entry routes of perchlorate in food via migration from fertilisers, industrial wastewater and chlorination from drinking water when used for irrigation (which is not permitted but cannot be ruled out). Additionally, it was highlighted that perchlorate may be released from rocket fuels and fireworks and formed from hypochlorites, chlorites and chlorates. BfR raised the concern about the potential perchlorate transfer from food packaging, which may be also an entry pathway for perchlorate in the food chain.

In 2014, EFSA's CONTAM Panel performed a risk assessment for the presence of perchlorate in food, in particular fruits and vegetables, on a mandate from the European Commission (EC) (EFSA CONTAM Panel, 2014). The CONTAM Panel established

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a TDI of 0.3 μg perchlorate/kg bw per day, based on inhibition of thyroid iodine uptake in healthy adults. The CONTAM Panel noted that a single acute exposure to perchlorate at levels found in food and water is unlikely to cause adverse effects on human health, including the more vulnerable groups of the population and concluded that the establishment of an acute reference dose for perchlorate is not warranted.

EFSA's CONTAM Panel also received a mandate from the European Commission (EC) to perform a risk assessment for the presence of chlorate in food, which was published in 2015 (EFSA CONTAM Panel, 2015). A TDI of 3 μg chlorate/kg bw per day was set by read across derived from the perchlorate TDI (on inhibition of thyroid iodine uptake in healthy adults), multiplied by a factor of 10 to account for the lower potency of chlorate, based on a number of in vitro and animal studies (EFSA CONTAM Panel, 2015). Formation of methaemoglobin was identified as the critical acute effect of chlorate and an acute reference dose (ARfD) of 36 μg chlorate/kg bw per day was derived in a controlled clinical study.

In 2017, EFSA assessed the dietary exposure assessment to perchlorate in the European population, taking into account occurrence data in the EFSA database (EFSA, 2017). Relatively high mean middle-bound occurrence values were found in dried products, like 'Tea and herbs for infusion' (324 μg/kg) and 'Herbs, spices and condiments' (63 μg/kg), and in some fresh vegetables, like 'Radishes' (117 μg/kg), 'Rocket salad, rucola' (75 μg/kg) and 'Spinach (fresh)' (132 μg/kg). The mean and the 95th percentile (P95) exposure to perchlorate across dietary surveys were estimated using chronic and short-term scenarios across different population groups. 'Vegetable and vegetable products', 'Milk and dairy products' and 'Fruit and fruit products' were found to be important contributors to the exposure across all population groups.

In its 2018 opinion, BfR was involved with the discussion related to the risk assessment of perchlorate in the food chain (including drinking water) and agreed with EFSA's health risk assessment for perchlorate (BfR, 2018). The BfR emphasised that the level of perchlorate in the food commodities should be as low as reasonably achievable.

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) revised its Opinion on the presence of perchlorate in drinking water in 2022 (ANSES, 2022). ANSES emphasised the divergence among studies. The result of the study by Greer et al. (2002) was used by ANSES as well as by many other agencies due to its suitability to be utilised for benchmark dose analysis in order to derive a more reliable toxicity reference value for perchlorate than that obtained with the NOAEL approach. The frequentist approach was chosen for BMD modelling due to its simplicity of implementation and ease of interpretation by the users of these health values. A toxicity reference value (TRV) of 1.5 μg/kg bw per day was obtained from the BMDL using an uncertainty factor of 10 for inter-individual variability.

1.2.5 | Legislation

An EC Statement as regards the presence of perchlorate in food was endorsed by the Standing Committee on Plants, Animals, Food and Feed (SCPAFF) on 10 March 2015, and updated on 23 June 2015. This Statement identified the need for monitoring of perchlorate in food and also set a harmonised provisional enforcement approach for intra-Union trade.

Commission Recommendation (EU) 2015/682 of 29 April 2015 recommended monitoring at Member State level for the presence of perchlorate in food. In particular in fruits, vegetables and processed products thereof, including juices, foods intended for consumption by infants and children, dried herbs and spices, beverages, including drinking water. The EC Recommendation (EU) 2015/682 also provided details on the analytical methods to be used to quantify perchlorate in food and drinking water.

Commission Regulation (EU) 2023/915[7] of 25 April 2023 set maximum levels for certain contaminants in food, including perchlorate, as per Table 1 below.

TABLE 1 Maximum levels for perchlorate in food as set in Annex I to Commission Regulation (EU) 2023/915.

6.3	Perchlorate	Maximum level (mg/kg)	Remarks
6.3.1	Fruits and vegetable except of products listed in 6.3.1.1 and 6.3.1.2	0.05	
6.3.1.1	Cucurbitaceae and kale	0.10	
6.3.1.2	Leaf vegetables and herbs	0.50	
6.3.2	Tea (Camellia sinensis) (dried product) Herbal and fruit infusions (dried product) and ingredients used for herbal and fruit infusions (dried products)	0.75	'Herbal infusions (dried product)' refers to: — herbal infusions (dried product) from flowers, leaves, stalks, roots and any other parts of the plant (in sachets or in bulk) used for the preparation of herbal infusion (liquid product); and — instant herbal infusions. In the case of powdered extracts, a concentration factor of 4 has to be applied.

[7]Commission Regulation (EU) 2023/915 of 25 April 2023 on maximum levels for certain contaminants in food and repealing Regulation (EC) No 1881/2006 C/2023/35 OJ L 119, 5/5/2023, p. 103–157.

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TABLE 1 (Continued)

6.3	Perchlorate	Maximum level (mg/kg)	Remarks
6.3.3	Infant formulae, follow-on formulae, food for special medical purposes intended for infants and young children[8] and young-child formulae[9]	0.01	The maximum level applies to the products ready-to-use (placed on the market as such or after reconstitution as instructed by the manufacturer).
6.3.4	Baby food[8]	0.02	The maximum level applies to the products ready-to-use (placed on the market as such or after reconstitution as instructed by the manufacturer).
6.3.5	Processed cereal-based food[8]	0.01	The maximum level applies to the product as placed on the market.

2 | DATA AND METHODOLOGIES

The current update of the EFSA risk assessment on perchlorate in food, was developed applying a structured methodological approach, which implied developing a priori the protocol or strategy of the full risk assessment (EFSA Scientific Committee, 2023). The protocol in Annex A of this Opinion contains the method that was proposed for covering all the steps of the risk assessment process. The CONTAM Panel used its previous risk assessment on Perchlorate in food (EFSA CONTAM Panel, 2014) as a starting point for drafting the current Opinion.

2.1 | Evidence collection and study appraisal

Information on physicochemical properties, natural and anthropological sources, medicinal use, previous assessments and legislation was gathered from the previous EFSA Opinion on perchlorate in food (EFSA CONTAM Panel, 2014), assessment by other international and national bodies (by checking the original websites of the relevant organisations) and from current EU legislation.

A systematic literature review was conducted to retrieve new information available in reviews and peer-reviewed original studies on the effects of perchlorate on human health and in experimental animals. Search strings were designed to identify potentially relevant studies published between 1/1/2013 (to cover the period since the previous literature search had been performed for the previous Opinion; EFSA CONTAM Panel, 2014) and 29/1/2024 (the date when the actual search was performed) within the following five areas: (1) Analytical methods, (2) Data on toxicity in experimental animals, (3) Occurrence in food and exposure, (4) Data on toxicokinetics in experimental animals, in humans and in vitro studies, and (5) Data on observations in humans (including epidemiological studies, case reports and biomarkers of exposure). Web of Science and PubMed were identified as the databases appropriate for retrieving literature for the present evaluation. An overview of the search terms and the result of the search is given in Appendix A. After removal of duplicates and applying inclusion/exclusion criteria, potentially relevant references were identified.

An additional literature search was performed to identify studies published from January 2024 to January 2025 as reported in Appendix A.

The selection of the scientific papers for inclusion or exclusion was based on consideration of the extent to which the study was relevant to the assessment (inclusion/exclusion criteria are detailed in Section 3.3 of the protocol in Annex A), irrespective of the results. Limitations in the information used are documented in this Scientific Opinion.

For human studies and studies in experimental animals that are directly relevant to the risk assessment question, a tailored OHAT Risk of Bias Tool (as included in the NTP-OHAT Approach for Systematic Review; Rooney et al., 2014) was used as a critical appraisal tool, as detailed in Annex C. Included studies that are not directly relevant to the risk assessment question, but contribute to the risk assessment as auxiliary evidence, were described narratively.

The draft Scientific Opinion underwent a public consultation from 17 December 2024 to 11 February 2025. The comments received were taken into account when finalising the Scientific Opinion and are presented and addressed in Annex D.

2.2 | Hazard identification and characterisation

Information relevant for the sections under hazard identification and characterisation was identified by a literature search and study appraisal which were conducted as described above.

[8]Food as defined in Article 2 of Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009 (OJ L181, 29.6.2013, p. 35).

[9]'Young-child formulae' refers to milk-based drinks and similar protein-based products intended for young children. These products are outside the scope of Regulation (EU) No 609/2013 (Report from the Commission to the European Parliament and the Council on young-child formulae (COM(2016) 169 final)). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52016DC0169&qid=1620902871447.

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Benchmark dose (BMD) analyses were carried out according to the most recent EFSA Scientific Committee Guidance on BMD modelling at the time of this assessment (EFSA Scientific Committee, 2022).

Since this guidance addresses the analysis of dose–response data from toxicity studies in experimental animals, an adaptation of the approach for human data was performed taking into consideration more recent guidance on epidemiological studies and how such adaptations could be made (EFSA Scientific Committee, 2024).

The BMD analyses were carried out using the Bayesian BMD Modelling web-app (https://zenodo.org/record/7334435#.Y5osYXbMLD4) available at the EFSA R4EU platform (https://r4eu.efsa.europa.eu/). This tool, developed and maintained by EFSA, is freely available and extensively documented (Hasselt University, 2022; Verlinden et al., 2024).

For the derivation of the HBGV, the CONTAM Panel considered that an ARfD was not necessary for perchlorate based on the short half-life, the storage capacity of thyroid hormone and compensatory mechanisms and the availability of reliable human data on radioactive iodine uptake (RAIU) (see Section 3.1.3). However, a chronic dietary exposure assessment was deemed necessary for the entire population and in particular for vulnerable groups (e.g. breastfed and formula-fed infants) (see Section 2.6), while a short-term assessment was performed for pregnant women.

2.3 | Occurrence data

2.3.1 | Occurrence data submitted to EFSA

2.3.1.1 | *Data collection*

Following a mandate from the European Commission, a call for annual collection of chemical contaminant occurrence data in food was issued by EFSA in December 2010. Since then, data have been submitted every year by a deadline agreed with the EFSA Scientific Network on Chemical Monitoring Data collection.[10]

The data submission to EFSA follows the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed (EFSA, 2010a) and the EFSA Guidance on Standard Sample Description 2 (EFSA, 2013). Occurrence data are managed following the EFSA standard operational procedures (SOPs) on 'Data collection and validation' and on 'Data analysis of food consumption and occurrence data'.

2.3.1.2 | *Data validation and analysis*

Following EFSA's Technical Report on handling of occurrence data for dietary exposure assessment (EFSA, 2021) to guarantee an appropriate quality of the data used in the exposure assessment, the initial dataset was carefully evaluated by applying several data cleaning and validation steps. Special attention was paid to the identification of duplicates and to the accuracy of different parameters, such as 'Sampling strategy', 'Sampling year', 'Sampling country', 'Analytical methods', 'Result express' (expression of results, e.g. fat weight), 'Reporting unit', 'Limit of detection/quantification' and the codification of analytical results under FoodEx2 classification (EFSA, 2011a, 2011b, 2015).

Left-censored data were treated using the substitution method as recommended in the 'Principles and Methods for the Risk Assessment of Chemicals in Food' (WHO/IPCS, 2009, updated in 2020). This is the same method as indicated in the EFSA scientific report 'Management of left-censored data in dietary exposure assessment of chemical substances' (EFSA, 2010b). The guidance suggests that the LB and UB approach should be used for chemicals likely to be present in the food (e.g. naturally occurring contaminants, nutrients and mycotoxins). The LB is obtained by assigning a value of zero (minimum possible value) to all samples reported as lower than the < LOD or < LOQ. The UB is obtained by assigning the numerical value of LOD to values reported as < LOD and LOQ to values reported as < LOQ (maximum possible value), depending on whether LOD or LOQ is reported by the laboratory.

Mean and the highest reliable percentile LB and UB occurrence values were then calculated at each level of the FoodEx2 classification (EFSA, 2015).

Means for specific food categories calculated on less than six analytical results, were not used in the dietary exposure assessment as mean calculated on less than six samples are not considered reliable. However, these analytical results were included in the calculation of averages for categories at higher levels of the FoodEx2 classification where this would allow to calculate a mean concentration on more than six samples. For the percentiles, the minimum number of analytical results to consider them reliable was $n = 5$ for P50, $n = 11$ for P75, $n = 29$ for P90, $n = 59$ for P95, $n = 119$ for P97.5 and $n = 299$ for P99 (EFSA, 2011c).

Specific food subcategories with 100% left-censored results and less than 30 analytical results available were included with mean and P95 LB and UB concentration of the closest parent FoodEx2 category for which quantified results were available, if there was no reason to exclude the presence of the compound in the subcategory. For example, cherry tomatoes, for which there were available 15 samples 100% left censored (LC), were assigned the mean concentration of the parent category 'Tomatoes' calculated on 1195 samples.

[10]Current call: https://www.efsa.europa.eu/en/call/annual-call-continuous-collection-chemical-contaminants-occurrence-data-food-and-feed-0.

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Similarly, specific food subcategories for which there were no occurrence data available were attributed with the concentration of the parent FoodEx2 category if there was no reason to exclude the presence of the compound in the subcategory, e.g. the mean concentration for 'Marine fish' was attributed to 'Sea bass', subcategory for which there were no specific occurrence data.

In the cases in which there were no suitable analytical results available for derivatives, the perchlorate mean concentration for the food derivative was obtained from the concentration in the raw primary commodity if available, e.g. perchlorate concentration in processed eggs was calculated from perchlorate concentration in whole eggs, applying the reverse yield factor available in EFSA raw primary commodity (RPC) model (EFSA, 2019a).

Composite foods documented to contain ingredients belonging to the food categories for which data were available (e.g. foods belonging to the 'Fine bakery wares' category) were also included in the dietary exposure assessment of perchlorate, with LB and UB mean and P95 concentration calculated using the available LB and UB mean and P95 concentration of the ingredients based on simplified assumptions.

Dilution factors suggested in EFSA guidelines (EFSA, 2018) were also used to calculate LB and UB perchlorate concentrations for ready-to-eat foods or ready-to-drink beverages from the available concentrations in the dry ingredients, and vice versa.

2.3.2 | Occurrence data from the literature

As part of the comprehensive literature search, potentially relevant studies and reviews relating Occurrence in food were identified, as per details included in Appendix A. Occurrence data from literature is discussed on Section 3.2.1.2.

2.4 | Food consumption data

2.4.1 | Food consumption data

Food consumption data from the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) were used for the dietary exposure assessment. This database contains national data on food consumption at the individual level, which are the most complete and detailed data currently available in the EU.

The food consumption data gathered in the Comprehensive Database were collected using repeated 24-h or 48-h dietary recalls or dietary records covering 3–9 days per individual. Owing to the differences in the methods used for data collection, direct country-to-country comparisons of the exposure estimates should be avoided.

Details of how the Comprehensive Database is used to assess the dietary exposure to food chemicals are published in a 2011 EFSA Guidance (EFSA, 2011b). The latest version of the Comprehensive Database was published in October 2024 and contains results from 58 dietary surveys carried out in 24 Member States covering 98,014 individuals. Seven surveys provide information on 'Pregnant women' and on 'Lactating women' and 3 surveys provided information on Vegetarians.

A chronic dietary exposure assessment and a short-term dietary exposure assessment were deemed relevant for perchlorate in the context of the Terms of Reference and the available evidence for critical windows of exposure during development (see Section 2.6.2).

For such assessments, surveys in which food consumption data were collected over only 1 day are not considered appropriate. Exclusion of these surveys resulted in a total of 55 dietary surveys carried out in 23 Member States covering 93,844 individuals available to be used in the chronic dietary exposure assessment. Table 2 provides an overview of the population groups and countries included in the dietary exposure assessment.

According to the EFSA Scientific Committee Guidance on the risk assessment of substances present in food intended for infants under 16 weeks of age, the exposure assessment for these infants should be carried out separately from that for older infants, following the procedure described in the guidance (EFSA Scientific Committee, 2017). Based on this guidance, infants under 16 weeks of age should be excluded from the dietary exposure estimation of the infants age group. However, due to uncertainty in the reported individual ages of infants in the Comprehensive Database, the cutoff age was based on a validated existing age group in this database corresponding to 12 weeks of age. Thus, food consumption data of infants between 12 and 16 weeks of age were also included in the exposure assessment. As the number of children within this age range in the database is limited, it is not expected that this will have affected the exposure estimate for infants of 16 weeks up to 12 months of age.

Annex B (Table B.1) provides details on the dietary surveys included in the dietary exposure assessments.

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TABLE 2 Population groups and countries included in the chronic and short-term dietary exposure assessment.

Population group	Age range	Countries with food consumption surveys covering more than 1 day
Infants	> 12 weeks to < 12 months	Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Italy, Latvia, Poland, Portugal, Slovenia, Spain
Toddlers	≥ 12 months to < 36 months	Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Netherlands, Poland, Portugal, Slovenia, Spain
Other children	≥ 36 months to < 10 years	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Netherlands, Poland, Portugal, Spain, Sweden
Adolescents	≥ 10 years to < 18 years	Austria, Belgium, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden
Adults	≥ 18 years to <65 years	Austria, Belgium, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden
Elderly	≥ 65 years to < 75 years	Austria, Belgium, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden
Very elderly	≥ 75 years	Austria, Belgium, Croatia, Denmark, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Sweden
Pregnant women		Austria, Cyprus, Latvia, Poland, Portugal, Romania, Spain

2.5 | Food classification

Consumption and occurrence data were codified according to the FoodEx2 classification system (EFSA, 2011a, 2011b). Since 2018, all consumption records in the Comprehensive Database as well as all occurrence data submitted to EFSA have been codified according to the FoodEx2 classification system (EFSA, 2015). The FoodEx2 classification system consists of a large number of standardised basic food items aggregated into broader food categories in a hierarchical parent–child relationship. Additional descriptors, called facets, are used to provide additional information about the codified foods (e.g. information on food processing and packaging material).

2.6 | Dietary exposure assessment

2.6.1 | Human chronic dietary exposure assessment

For calculating the chronic dietary exposure to perchlorate, food consumption and body weight data at the individual level were retrieved from the Comprehensive Database. Occurrence data and consumption data were linked at the relevant FoodEx2 level.

Chronic dietary exposures were calculated by combining mean perchlorate occurrence values for food samples collected in different countries (pooled European occurrence data) with the average daily consumption for each food at the individual level in each dietary survey and age class. Consequently, individual average exposures per day and body weight were obtained for all individuals. The following formula describes the calculation made:

$$\bar{e}_i = \frac{\sum_{d \in D_i} \sum_{f \in F} \bar{x}_f \cdot c_{f,d,i}}{|D_i| \cdot bw_i}$$

where:

- $\bar{e}_i$ is the average exposure of individual *i*
- $\bar{x}_f$ is the mean perchlorate concentration in each food or food group *f* (belonging to set of foods F_i for individual *i*)
- $c_{f,d,i}$ is the consumed amount of food f by individual *i* on day *d*
- bw_i is individual body weight of individual *i*
- *d* is the survey day (belonging to the set of survey days D_i for individual *i*)
- $|D_i|$ represents the number of survey days of individual *i*

The distributions of individual exposures were then used to calculate the mean and high (95th percentile) exposure per survey and per age class. These exposure estimates were obtained using the LB and UB mean concentrations of perchlorate. The number of surveys in which food categories have contributed more than 10% to the total dietary exposure to perchlorate was used to rank main contributors to the overall exposure and for each age group. Contribution of different

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food categories to the total chronic dietary exposure was calculated over LB exposure estimates to avoid that the high contribution of certain food groups could be artificially driven by the treatment of the left-censored data.

All analyses were run using the SAS Statistical Software (SAS enterprise guide 8.3 Update 5).

2.6.2 | Short-term dietary exposure assessment for pregnant woman

The CONTAM Panel firstly considered that an acute dietary exposure assessment would not be needed for perchlorate based on the short half-life, the storage capacity of thyroid hormone and compensatory mechanisms and the availability of reliable human data on radioactive iodine uptake (RAIU) (see Section 3.1.3). However, the Panel deemed relevant to assess a short-term dietary exposure to perchlorate for the special population group of pregnant women. The CONTAM Panel developed a 'short-term' exposure assessment to take into account the possibility of being exposed to relatively high levels of perchlorate during a short period of time (of approximately 2 weeks) during pregnancy, longer than 1 day or one eating occasion but shorter than lifetime. This scenario has been considered because higher levels of thyroid iodine uptake inhibition for short periods could induce adverse effects in vulnerable groups of the population, in particular developing fetuses and neonates. The selection of a 2 weeks period is also supported by the findings of Greer et al. (2002), in which effects on RAIU were observed within 14 days.

For calculating the short-term dietary exposure to perchlorate for pregnant woman, the same method used for calculating chronic diet exposure was applied, but for the occurrence values the highest reliable percentile of the perchlorate occurrence was used instead of the mean. The distributions of individual short-term exposures were used to calculate the mean and high (95th percentile) dietary exposure for the pregnant women for each of the 7 available surveys.

2.6.3 | Specific exposure scenarios

In addition to the general exposure assessment, the CONTAM Panel acknowledged the importance of estimating exposure specifically for infants. Accordingly, two targeted exposure scenarios were developed and calculated for infants below the age of 16 weeks, i.e. exposure via human milk consumption and exposure via infant food formula, as described below.

Exposure via human milk consumption

To assess the dietary exposure to perchlorate of breastfed infants below 6 months of age, a scenario considering a median age of 3 months was selected, equivalent to a body weight of about 6.1 kg, with an estimated average daily milk consumption of about 800 mL and a high consumption of 1200 mL (EFSA Scientific Committee, 2012, 2017).

Since the previous EFSA CONTAM Panel Opinion on perchlorate, four new studies published after 2013 containing occurrence data in human milk were identified as possibly relevant (one from Türkiye, one from Canada and two from China) covering sampling years from 2008 to 2020. Considering that the applicability of these non-EU studies to the European Union populations remains uncertain and considering that no occurrence data on perchlorate in human milk within the EU were identified, neither from data submitted to EFSA nor from EU available literature, the CONTAM Panel decided to estimate the concentration of perchlorate in human milk of the EU lactating women population based on dietary exposure results calculated in this Opinion together with human milk perchlorate excretion data from the literature. When perchlorate levels were reported as μg/kg, they were converted to μg/L assuming a human milk density of 1 (Neville et al., 1988; Woolridge et al., 1985).

Despite the number of studies on the modelling of perchlorate in the human body (pharmacokinetic models) including placental transfer and elimination via human milk of perchlorate, it was not possible to determine with certainty the relationship between oral exposure to perchlorate in pregnant women and concentration in human milk.

Clewell et al. (2003a, 2003b) assumed that at low levels of maternal exposure to perchlorate, a nursing rat pup would receive up to 50% of the maternal intake of perchlorate. Another study carried out by Dasgupta et al. (2008) showed that 54% of perchlorate intake were excreted in human milk.

The CONTAM Panel decided to use the value of 54% excretion of perchlorate in milk to estimate the human milk concentration of perchlorate in the European population based on a daily human milk production of 0.8–1.2 L and on the distribution of individual oral exposure of perchlorate in lactating women population.

The calculation was performed using the results from the chronic exposure reported in Table B.10 within Annex B.

Human milk perchlorate concentration was estimated using the biomonitoring equivalent equation (Hays et al., 2018):

$$bmP = \frac{Chronic\ exposureP \times pme}{V24}$$

Where bmP = human milk perchlorate concentration (μg/L), chronic exposureP = total perchlorate intake (μg/day), pme = human milk excretion fraction of perchlorate (54%) and V24 = daily milk production (0.8–1.2 L/day).

The total perchlorate intakes (μg/day) were calculated using the individual body weight of the 444 lactating women for whom chronic exposure to perchlorate had been derived as explained in Section 2.6.1. To complete the exposure assessment of breastfed infants, an age of 3 months was selected. Milk production in women can be quite variable nevertheless it

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generally meets the infant consumption. Concentration data of perchlorate in human milk used in the exposure calculation for breastfed infants, together with exposure calculations, are summarised in Table 23 (Section 3.3.3).

Exposure via infant food formula

To better characterise the contribution of infant formula to the dietary exposure of infants below 16 weeks of age to perchlorate, and given the limited data on infant formula consumption across Europe, the CONTAM Panel applied an exposure scenario using 200 mL/kg bw per day and 260 mL/kg bw per day for mean and P95 consumption, respectively, as recommended by the Guidance of the EFSA Scientific Committee (SC) on the risk assessment of substances present in food intended for infants below 16 weeks of age, for substances that do not accumulate in the body (EFSA Scientific Committee, 2017). For infants around 2 months and using a default body weight of 5 kg as per the EFSA SC Guidance on default values (EFSA Scientific Committee, 2012), these values correspond to daily intakes of 1000 mL for mean consumption and 1300 mL for high consumption.

For this scenario of formula-fed infants, the CONTAM Panel used the mean and the highest reliable percentile of perchlorate occurrence in infant formula from the occurrence data submitted to EFSA. These data, reported in both solid (powder) and liquid forms were combined for the current assessment. For data reported in solid form, the concentrations were converted to liquid form by applying a dilution factor of 8 (EFSA, 2018) to align with consumption data. Additionally, the concentration of perchlorate in the drinking water used for reconstituting the formula was included in the calculation. If the concentration of perchlorate was provided in µg/kg, it was converted to µg/L assuming an infant formula density of 1. Concentration data of perchlorate used in the exposure calculation for formula-fed infants are summarised in Table 15 (Section 3.2.1.1).

3 | ASSESSMENT

Perchlorate is known to be a substrate for the sodium iodide symporter (NIS) and thereby (competitively) 'inhibits' the uptake of iodide into the thyroid follicles (EFSA CONTAM Panel, 2014). The elemental form of 'iodine' (I_2) is rarely found in food and water, while it generally occurs in the form of an iodide salt. In this Opinion, the term 'iodine' is to be understood as both 'iodine' and its reduced form 'iodide'.

3.1 | Hazard identification and characterisation

3.1.1 | Toxicokinetics

In the previous EFSA Opinion on perchlorate (EFSA CONTAM Panel, 2014) it was concluded that in rats and humans perchlorate is rapidly absorbed following oral ingestion, widely distributed in the body and readily excreted in urine with very little, if any, metabolism. The pattern of distribution in the thyroid of the rat was similar to that of iodide, consistent with the concept of their active uptake by the sodium iodide symporter (NIS) and competitive inhibition of the ions' transport (see Section 3.1.4 on Mode of Action).

Few toxicokinetic studies have been published since EFSA's summary of studies in experimental animals and humans in 2014 (EFSA CONTAM Panel, 2014). Pertinent data on aspects such as dose-related excretion of perchlorate in rat urine (Chen et al. 2015), kinetics of single oral dosing in rats (Zhang et al., 2023) and on bioaccessibility/bioavailability (Tian et al., 2020; Liu et al., 2021) have been reviewed and are included in the summary of toxicokinetics below.

3.1.1.1 | *Absorption, distribution, metabolism and excretion (ADME)*

Absorption

Following oral exposure, perchlorate has been shown to be readily absorbed from the gastrointestinal (GI) tract, in both human and animal studies (ATSDR, 2008). Human studies suggest that a rapid and almost complete absorption of perchlorate occurs through the GI tract, with subsequent excretion in the urine (ATSDR, 2008). In a 14-day human volunteer study, the serum half-life of perchlorate was calculated as 6.0–9.3 h (mean 8.1 h), following oral dosing of perchlorate in drinking water at 0.5 mg/kg bw per day (Greer et al., 2002). The half-life was later re-calculated by Crump and Gibbs (2005) to be on average 7.5 h. In rats, peak blood concentrations of orally administered radiolabelled perchlorate were observed at 3 h and half-lives range from less than 8 h to approximately 20 h (Wolff, 1998). A recent study observed similar kinetics with the highest concentration (C_{max} 0.02 mg/mL at 1 h) in blood plasma of rats after gavage with 10 mg/kg bw perchlorate and a half-life of about 8 h (Zhang et al., 2023).

In a study by Selivanova et al. (1986), absorption of ammonium perchlorate was investigated in rats and calves following single oral doses of 2, 20, 200 or 600 mg/kg bw. The maximum concentrations of perchlorate in blood occurred at 30–60 min in rats and at 5 h in calves, with 8.5% of the dose eliminated in faeces and the rest eliminated in urine, suggesting absorption of > 90% of the dose.

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Distribution

As noted in the 2014 CONTAM Panel Opinion, perchlorate is found in human serum, plasma, urine, saliva and human milk (Dasgupta et al., 2008; Kannan et al., 2009; Kirk et al., 2005, 2007; Leung et al., 2009; Oldi & Kannan, 2009a, 2009b; Pearce et al., 2007; Tellez et al., 2005). In female rhesus monkeys, after oral exposure to perchlorate during lactation, perchlorate was detected in the blood, milk and urine of dams and in infant blood (Ozpinar et al., 2011). In rats, perchlorate has been observed to cross the placenta, and is found in maternal milk, serum, skin and in gastrointestinal (GI) content of neonatal rats (Clewell, Merrill, Yu, Mahle, Sterner, Fisher, & Gearhart, 2003; Clewell, Merrill, Yu, Mahle, Sterner, Mattie, et al., 2003). Following oral administration, in the rat, perchlorate is concentrated in the thyroid, GI contents, skin, mammary gland and milk (Clewell et al., 2004; Dohan et al., 2007; Yu et al., 2002). From investigations in rabbits and rats, concentrations of perchlorate in most soft tissues (kidney, liver, skeletal muscle) are similar to serum perchlorate concentrations, yet considerably higher in the thyroid (Durand, 1938; Yu et al., 2002; Zhang et al., 2023). Perchlorate binds to bovine and human serum albumin and has high non-specific binding to albumin and prealbumin (transthyretin) in rat plasma, with saturation occurring at perchlorate doses of 1.0 and 10.0 mg/kg bw per day in the rat (Carr, 1952; Clewell, Merrill, Yu, Mahle, Sterner, Mattie, et al., 2003; Merrill et al., 2003; Scatchard & Black, 1949). Perchlorate uptake in the thyroid gland occur through a saturable active transport process (peak uptake 2 to 4 h in rats following oral exposure), during which it is concentrated in the lumen of the thyroid. The pattern of distribution of perchlorate within the rat thyroid (between the follicular cells, stroma and lumen) is comparable to that for iodine (Wolff, 1998). In the lactating breast, NIS mediates the translocation of iodide and perchlorate from the blood to milk as shown in vitro and in vivo in rats (Dohan et al., 2007).

Metabolism

Evidence indicates that very little if any of the perchlorate anion is metabolised in rats or humans (ASTDR, 2008; Fisher et al., 2000; Wolff, 1998). Potential metabolites of potassium perchlorate (radiolabelled with ^{36}Cl and $^{18}O4$) were investigated in a study in humans by Anbar et al. (1959) analysing urine samples collected 3 h after a single oral dose (200 mg/kg bw). In the excreted perchlorate, no isotopic exchange of oxygen atoms occurred and the authors concluded that 3 h after dosing, perchlorate was excreted unmodified in the urine. In a study by Yu et al. (2002), almost all radiolabelled perchlorate (99.5%) was recovered from urine within 48 h following intravenous administration in rats, with the majority excreted within a day.

Excretion

Oral studies conducted in humans and experimental animals (rats and calves) indicate that urinary excretion is the main pathway for elimination of perchlorate from the body (Selivanova et al., 1986; Fisher et al., 2000; Lawrence et al., 2000; Zhang et al., 2023). A repeat-dose study in rats (130, 260, 520 mg/kg bw) found that perchlorate concentrations in urine increased proportionally in a dose-related manner and thus it is a useful biomarker of exposure (Chen et al., 2015). This was also observed in a small study with rhesus macaque monkeys receiving daily doses of 0.05, 2.38 or 82.6 mg/kg bw ammonium perchlorate for 14 days (Ozpinar et al., 2011). Human milk is also considered as an excretion route for rhesus macaque monkeys, rats and humans (Clewell, Merrill, Yu, Mahle, Sterner, Fisher, & Gearhart, 2003; Kirk et al., 2005; Ozpinar et al., 2011; Pearce et al., 2007; Tellez et al., 2005). Perchlorate present in human milk can be a relevant source of exposure for nursing infants (see Section 3.3 on Dietary exposure assessment).

Bioaccessibility and bioavailability of perchlorate from food

To explore how different food commodities (lettuce, milk powder, rice, soybean or pork) may affect the absorption and bioavailability of perchlorate, a Caco-2 cell model and a 7-day mice feeding study have been used (Tian et al. 2020; Liu et al., 2021). These studies indicate varying bioaccessibility and bioavailability of perchlorate in the in vitro model and also in mice receiving chow to which five types of foods (see above) were added. The estimated in vivo perchlorate bioavailability ranged from 18% (soybean) to 46% (lettuce), and 36% in fortified mice chow (control), i.e. a lower bioavailability than observed upon administration of an aqueous solution (93.5%) in mice. The authors measured also concentrations in blood, tissues, urine and faeces; yet reporting is limited, and some data are inconsistent with perchlorate tissue distribution in rats. Some data on 'accumulation' in both brain and faeces presented in the Liu et al. (2021) paper are inconsistent regarding perchlorate distribution in rats. For these reasons, the CONTAM Panel noted this study but did not consider it further.

3.1.1.2 | *PBPK modelling*

In the previous opinion (EFSA CONTAM Panel, 2014), several human PBPK models for the simultaneous kinetics of iodine and perchlorate, had been described, including those by Merrill et al. (2005), Clewell et al. (2007) and McLanahan et al. (2014). A biologically-based Dose–Response (BBDR) was also developed by Lumen et al. (2013) based on previous PBPK models (Clewell et al., 2007; Fisher et al., 2016; McLanahan et al., 2014; Merrill et al., 2005).

Since the previous opinion (EFSA CONTAM Panel, 2014), the US EPA (2017), Fisher et al. (2016) and Clewell et al. (2019) have modified the BBDR model (a full description of these models is presented in Appendix B).

The BBDR model was developed for the uptake and disposition of iodide and perchlorate, and the synthesis and disposition of thyroid hormones in a woman prior to conception and through early pregnancy (until gestational week 16).

The assessment of the toxicokinetic part of the BBDR model (perchlorate) showed 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/IPCS, 2010) requirements for use in health risk assessment.

The assessment of the toxicodynamic part of the BBDR (effects of perchlorate on thyroid function) showed an inadequate predictive ability to link perchlorate exposure levels to the fT4 decrease in the population of interest, i.e. pregnant women in the first trimester. This part of the model does not fulfil the IPCS (WHO/IPCS, 2010) requirements for use in health risk assessment.

The CONTAM Panel concluded that these models were not applicable to predict the effects of perchlorate on thyroid hormones in iodine-deficient individuals or in those with thyroid dysfunction (hypothyroid, hyperthyroid and other thyroid disease states).

3.1.1.3 | *Biomarkers of exposure*

Analysis of perchlorate levels in human urine samples, serum samples and in human milk samples has been used to investigate the exposure of various population groups, including pregnant women and infants. An overview of such data reported in the literature can be found in Appendix D of the previous EFSA opinion (EFSA CONTAM Panel, 2014; section 5.3.1). More recent studies support the usefulness of biomonitoring approaches for assessing the extent of perchlorate exposure and related risks (Steinmaus et al., 2016; Zhang et al., 2016; Ucal et al., 2018; Chen et al., 2023; Guan et al., 2023). No further human biomonitoring studies from the EU could be identified.

3.1.2 | Adverse effects in experimental animals

Studies on experimental animals are summarised in Table 3, while non-mammalian species are included in Table D.1 within Appendix D.

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TABLE 3 Experimental animal studies.

Authors	Animal species	Substance	Exposure (doses)	Duration	Way of dosing	Critical endpoint	Association signal	Results
Chen et al. (2014)	Male Sprague–Dawley rats	Ammonium perchlorate	0, 130, 260 and 520 mg/kg bw per day	13 weeks	Oral administration via gavage	Thyroid toxicity	↑TSH (high-dose group) ↓ FT3 (low-dose group) ↓ FT4	At the highest dose increased urinary iodine levels after 6th week, with subsequent normalisation at the 13th week. Decreased total iodine and relative iodine content in thyroid tissues was observed at all doses. Lower total protein levels in thyroid tissue were observed in the medium- and high-exposure groups.
ECHA (2014)	Female Sprague–Dawley rats	Ammonium Perchlorate	Single dose of 300 mg/kg bw or 2000 mg/kg bw	Observation period of 14 days	Oral administration via gavage	Acute toxicity		Low acute oral toxicity, with only mild, transient clinical signs (hypoactivity) at the highest dose (2000 mg/kg bw)
Chen et al. (2015)	Male Sprague–Dawley rats	Ammonium perchlorate	0, 130, 260 and 520 mg/kg per day	13 weeks	Oral administration via gavage	Thyroid toxicity	↑ TSH ↓ FT3 (low-dose group) ↓ FT4 (medium-, high-dose group)	The rats treated with medium and high doses experienced a significant decrease in bw gain. Urine perchlorate levels significantly increased in rats exposed to medium- and high doses, suggesting its potential as a biomarker for quantifying actual perchlorate exposure intensity.
Serrano-Nascimento et al. (2018)	Male Wistar Rats	Sodium Perchlorate	0, 35 mg/kg bw per day	60 days	Oral administration	Thyroid toxicity	↑ TSH ↓ T3, T4 ↓ expression of dio1 ↑ pro-inflammatory cytokines	Significant effects of perchlorate on the hypothalamus-pituitary-thyroid axis. Changes in thyrotropin-releasing hormone mRNA and protein content suggested regulatory effects of perchlorate on the hypothalamus.

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TABLE 3 (Continued)

Authors	Animal species	Substance	Exposure (doses)	Duration	Way of dosing	Critical endpoint	Association signal	Results
Suarez et al. (2018)	ICR mice	Ammonium perchlorate	0, 0.35, 0.7, 1.4, 3.5, 7 μg/kg bw per day	14 days	Oral administration via drinking water	Immunotoxicity	↓ weight	Notable changes in leukocyte counts, especially among lymphocytes. Both male and female mice experienced alterations in their white blood cell counts, with males showing a greater incidence of changes, including lymphocytopenia. Exposure to ammonium perchlorate can result in leukopenia and other leukocyte abnormalities in mice, underscoring its immunotoxic effects
Yu et al. (2019)	Wistar rats	Sodium perchlorate	0, 0.05, 1 or 10 mg/kg bw per day (expressed as perchlorate)	8 weeks	Oral administration via gavage	Reproductive toxicity	↓ T3	Rats treated with perchlorate exhibited decreased indexes of live birth, viability and weaning in comparison with the negative control group. In addition, there was a reduction in sperm quality at 10 mg/kg bw.
Chakraborty (2021)	Male Wistar albino rats	Ammonium perchlorate	0 or 130 mg/kg bw (with and without iodine) per day	45 days	Oral administration via gavage	Reproductive toxicity	↑ ROS ↓ serum testosterone	Significant decrease in gain percentage of bw in the perchlorate groups (with and without iodine). Organs were significantly decreased in the perchlorate groups (with and without iodine) in comparison to the control group.
Gilbert et al. (2022)	Female Long–Evans rats	Ammonium perchlorate	0, 0.09, 2.7, 27, 90 mg/kg bw (expressed as perchlorate)	Gestational days (GD) 6 to 20	Oral administration via drinking water	Reproductive and thyroid toxicity	↑ TSH (in the 27 and 90 mg/kg bw dose groups) ↓ T4, T3 (dams on day 20 of gestation) ↓ T4, T3 (fetuses, in the 300 and 1000 mg/L dose groups)	Exposure to perchlorate did not significantly affect the dams' bw or the litter's size. However, the thyroid weights of the dams were increased at the two highest perchlorate concentrations.

(Continues)

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TABLE 3 (Continued)

Authors	Animal species	Substance	Exposure (doses)	Duration	Way of dosing	Critical endpoint	Association signal	Results
Wang, Song et al. (2022)	Male C57BL/6J mice	Sodium perchlorate	0.1, 1 and 10 mg/kg bw per day (expressed as perchlorate)	12 weeks	Oral administration (sodium perchlorate was dissolved in physiological saline)	Hepatic lipid profile (lipid metabolism)	↑ lipid metabolic markers(TC, TG, HDL)	Based on targeted lipidomics, perchlorate had a significant effect on glycerophospholipid metabolic pathways in mice on a high-fat diet.
Gilbert et al. (2023) (exp. 1)	Female Long–Evans rats	Ammonium perchlorate	0, 2.7, 27, 90 mg/kg bw (expressed as perchlorate)	Gestational day (GD) 6 to postnatal day (PND) 21	Oral administration via drinking water	Reproductive and thyroid toxicity	↓ T4 (dams and fetuses in late gestation)	Small PVHs were evident in the brains of offspring when assessed on PND 14.
Gilbert et al. (2023) (exp. 2)	Long–Evans rats (pups)	Ammonium perchlorate	90 mg/kg bw (expressed as perchlorate)	Postnatal day (PND) 0 to 6	Oral administration via drinking water	Reproductive, developmental toxicity	↓ T4	This treatment led to the development of PVH in the pups.
Gilbert et al. (2023) (exp. 3)	Female Long–Evans rats	Ammonium perchlorate + iodine (in feed)	27 mg/kg bw (expressed as perchlorate)	Gestational day (GD) 6 to postnatal day (PND) 21	Oral administration via drinking water	Reproductive, developmental toxicity	↓ T4 (in pregnant & lactating dams) ↑ PVH (brains of pups from dams with iodine deficiency)	Perchlorate exposure, in combination with other chemicals/ environmental stressors, can cause significant neurodevelopmental impact also associated with thyroid hormone disruption.
Gilbert et al. (2024)	Female Long–Evans rats and pups	Ammonium perchlorate + iodine (in feed)	0, 2.7, 9, 27, 90 mg/kg bw (expressed as perchlorate)	Gestational day (GD) 6 to postnatal day (PND) 21	Oral administration via drinking water	Reproductive, developmental toxicity	↑ TSH ↓ T4 (in dams) T3: – ↑ expression of Nis	Reduction in iodine content (from 1000 ng I/g to 225 ng I/g) did not have a major impact on serum hormone profiles or neurobehavioral outcomes.
Gilbert et al. (2024)	Female Long–Evans rats and pups	Ammonium perchlorate 300 mg/L in drinking water	~23 mg/kg bw/day (expressed as perchlorate), given to dams on iodine (I) replete or I-deficient diets	Gestational day (GD) 6 to postnatal day (PND) 21	Oral administration via drinking water	Developmental toxicity	Pregnant & lactating dams:↓T4, but ↓T3 and ↑TSH only in ID-ClO4; in pup serum: ↓T4 but ↓T3 and ↑ TSH sign. Only in ID-ClO4; Thyroid gland of pups: ↑ expression of Nis; in pups' brain: ↓ presence of Pvalb+ neurons	Iodine deficiency (ID) in combination with developmental perchlorate (ClO4) exposure exacerbates the thyroidal and neurological effects induced by either one of these conditions alone. Treatments have an impact on some brain and behavioural parameters in pups and adult offspring.

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TABLE 3 (Continued)

Authors	Animal species	Substance	Exposure (doses)	Duration	Way of dosing	Critical endpoint	Association signal	Results
Sakamaki et al. (2025)	Pregnant Sprague–Dawley rats	Ammonium perchlorate	0, 22.9 and 76.2 mg/kg bw (expressed as perchlorate)	Gestational day (GD) 6 to postnatal day (PND) 21	Oral administration via drinking water	Developmental toxicity	In the pups: ↓T3 and ↓T4, ↑ SST+ interneurons and CCK+ interneurons (76.2 mg/kg bw); thyroid follicular epithelial cell hyperplasia (at 22.9 mg/kg bw)	Neurotoxic effects of ammonium perchlorate are associated with hypothyroidism, impacting both hippocampal neurogenesis and the maturation of oligodendrocytes.

Abbreviations: bw, body weight; Dio1, type 1 iodothyronine deiodinase; ECHA, European Chemicals Agency; FT3, free triiodothyronine; FT4, free thyroxine; GD, gestational day; HDL, high-density lipoprotein; ICR, Institute of Cancer Research; mRNA, messenger ribonucleic acid; Nis, sodium iodide symporter; PND, postnatal day; PVH, periventricular heterotopia; ROS, reactive oxygen species; T3, triiodothyronine, T4, thyroxine; TC, total cholesterol; TG, total triglyceride; TSH, thyroid stimulating hormone.

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3.1.2.1 | *Acute toxicity*

The acute toxicity of perchlorate was discussed in the previous EFSA Opinion (2014), specifically examining the effects of a single dose of ammonium perchlorate administered to female Sprague–Dawley rats. The report concluded that perchlorate has low acute oral toxicity in rats, with only mild transient clinical signs (hypoactivity) at the highest dose (2000 mg/kg bw in rats).

No recent studies have been identified by the CONTAM Panel with regard to acute toxicity of perchlorate in experimental animals.

3.1.2.2 | *Repeated-dose toxicity*

Thyroid toxicity

The 2014 EFSA Opinion identified studies where repeated exposure to perchlorate caused changes in thyroid hormone and TSH levels, increased thyroid weight and histological alterations in the thyroid (colloid depletion, follicular cell hypertrophy and hyperplasia) in rats.

Following the 2014 Opinion, two additional studies were published regarding thyroid toxicity of perchlorate in experimental animals.

The study by Chen et al. (2014) involved 24 male Sprague–Dawley rats divided into four groups: a control group and three exposure groups receiving different doses of ammonium perchlorate by gavage for 13 weeks. The doses administered were 0, 130, 260 and 520 mg ammonium perchlorate/kg bw per day (corresponding to 0, 111, 222 and 444 mg perchlorate/kg bw per day). The rats were monitored for changes in urinary iodine, serum thyroid hormones, total iodine, relative iodine, total protein and antioxidant enzyme activities in thyroid tissues. The study revealed that the highest dose increased urinary iodine levels 6 weeks after the initiation of administration, with subsequent normalisation and elevated catalase activity. Decreased total iodine and iodine thyroid concentration relative to thyroid tissue mass was observed at all doses. Lower total protein levels in thyroid tissue were observed in the medium- and high-exposure groups. Free thyroxine levels decreased at all doses, while serum TSH levels increased significantly only in the high-dose group. In another following study, rats were divided into control groups and three exposure groups received doses of ammonium perchlorate (130, 260 and 520 mg/kg bw per day) by oral gavage in tap water for 13 consecutive weeks (Chen et al., 2015). The study observed changes in the body weight of rats exposed to ammonium perchlorate over the period of 13 weeks, compared to the control group: the rats treated with medium and high doses of perchlorate by gavage experienced what the study reports as 'a significant decrease' in body weight gain. The body weight gain decreased dose-dependently with perchlorate exposure, with the weight gain dose–response to be stabilised at week six. Urinary perchlorate levels were significantly increased in rats exposed to medium and high perchlorate doses in a dose-dependent manner, suggesting its potential as a biomarker of exposure. Additionally, the study revealed significant effects on thyroid hormones, with decreased FT4 levels (at all doses) and increased TSH levels in rats exposed to the highest dose.

Male Wistar rats treated with sodium perchlorate in drinking water at a concentration of 35 mg sodium perchlorate/kg bw per day (corresponding to 28.44 mg perchlorate/kg bw per day) for 60 days had statistically significant increased serum TSH and decreased T4/T3 compared to controls (Serrano-Nascimento et al., 2018). The study authors suggested that perchlorate induces thyroid and systemic inflammation through the increased production of cytokines (see Section 3.1.3.2).

Reproductive and developmental toxicity

The 2014 EFSA Opinion on perchlorate indicated that exposure to perchlorate can affect some reproductive endpoints, such as a decrease in the number of litters born. It was also noted that exposure to perchlorate, in utero and via lactation resulted in findings in fetuses and pups which were similar to those noted in adults, i.e. changes in thyroid hormone and TSH levels and effects on the thyroid (increased weights and histological changes). Studies have suggested that perchlorate exposure during critical developmental windows can disrupt thyroid function and potentially impact neurodevelopment. However, also due to the limitations of the available studies, the CONTAM Panel concluded in 2014 that it was not possible to determine an association between exposure to perchlorate and developmental neurotoxicity from the studies in rats.

Following the 2014 Opinion, two additional articles were published regarding the reproductive toxicity of perchlorates. In Yu et al. (2019) male and female Wistar rats were administered perchlorate orally by gavage 0.05, 1 or 10 mg/kg bw daily for 8 weeks. The results revealed notable reductions in the rates of live birth and weaning index at doses of 1 and 10 mg/kg and a reduction in the viability index (the ratio between the survival number of offspring after 4 days lactation and the number of born alive offspring) at a dose of 10 mg/kg. Exposure to perchlorate resulted in a notable decrease in blood T3 levels in male rats at daily doses of 1 and 10 mg/kg bw. Additionally, it led to an increased sperm abnormality at 10 mg/kg bw per day and DNA strand breaks, as assessed by the Comet assay in testicular cells, were noted. Furthermore, changes in oxidative stress indicators and increased levels of apoptosis-related proteins (fas and c-fos observed by immunohistochemistry) were seen in the testicular tissues. The findings indicate that exposure to perchlorate can lead to DNA damage, impair spermatogenesis and result in reproductive toxicity in male rats.

Chakraborty (2021) examined the impact of simultaneous exposure to excessive amounts of iodine and perchlorate on the reproductive system of male rats. A cohort of male Wistar albino rats was categorised into three distinct groups:

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a control group, a group subjected to perchlorate oral treatment at a dosage of 130 mg ammonium perchlorate/kg bw per day (corresponding to 110 mg perchlorate/kg bw per day) and a group treated with both perchlorate dose and excess iodine at a dosage of 7 mg potassium iodine per kg bw. The treatment duration for all groups was 45 days and rats received oral treatment. The study showed that simultaneous exposure to perchlorate and iodine decreased the amount of perchlorate and iodine excreted in urine. Additionally, an increase in the production of reactive oxygen species (ROS) was observed. Notable decreases in the testicular weight, the accessory sex organs and the sperm count in the epididymis, and blood levels of testosterone were observed. These findings were also combined with reduced functioning of enzymes involved in the steroid production. The presence of perchlorate alone did not cause reproductive toxicity. However, when combined with excessive iodine, it significantly damaged the testicular structure and function and sperm quality. The authors' suggestion of a potential interaction and a synergistic effect of high iodine and perchlorate in the reproductive toxicity is discussed under the Mode of Action (Section 3.1.4).

Recent investigations corroborate the conclusions of Yu et al. (2019) and Chakraborty (2021), suggesting that exposure to perchlorate can affect reproduction.

In the study on gestational exposure to perchlorate in Long–Evans rats, gravid rats were exposed to perchlorate via drinking water at doses of 0, 0.09, 2.7, 27, 90 mg/kg bw per day from gestation days 6 to 20 (Gilbert et al., 2022). Blood, thyroid and brain samples were taken from both the fetuses and the mothers on day 20 of gestation. The study results showed that exposure to perchlorate did not significantly affect the dams' body weights or the litter's size. However, the thyroid weights of the dams were increased at the two highest perchlorate doses. Serum T4 levels were reduced in the dams on day 16 of gestation at the two highest dose levels, while T3 concentrations remained unchanged. On day 20 of gestation, maternal serum T4 and T3 concentrations decreased, and TSH was elevated in the 27 and 90 mg/kg bw per day dose groups. Fetal serum concentrations of T4 were also reduced at these higher doses (see Section 3.1.3.2). The fetal thyroid gland was found to be more sensitive to TH-action abnormalities than the dam's thyroid, with decreased thyroid hormone levels and changes in thyroid hormone-responsive gene expression observed in the fetal cortex, suggesting potential implications for brain development. These results are the first quantitative evaluations of the fetal thyroid gland and fetal brain deficiencies caused by perchlorate.

Gilbert et al. (2023) investigated the effects of perchlorate exposure, both alone and in combination with dietary iodine deficiency, on thyroid hormone levels and brain development, particularly the formation of periventricular heterotopia (PVH) in newborn rats (a brain malformation characterised by neurons abnormally located in or near the periventricular region rather than in their typical positions within the cortical layer). The study consisted of three experiments; the first was a dose–response analysis in gravid rats. The rats received five dose levels of perchlorate (0, 2.7, 9, 27, 90 mg/kg bw per day) in drinking water from the sixth day of gestation until the pups were weaned on the 21st day. Serum and brain T4 concentrations were measured at different time points across pregnancy and lactation in dams (GD16, GD20 and PN21) and in pups (PN0, PN2, PN6 and PN14); in the offspring also the occurrence of PVH, a brain malformation associated with neurodevelopmental disorders, resulting also from T4 insufficiency, was evaluated. Perchlorate reduced T4 levels in pregnant dams and pups depending on age and dose. Dams' serum T4 decreased dose-dependently during pregnancy and breastfeeding. Newborn pups' serum T4 levels dropped considerably at the highest dose level but recovered to or exceeded control levels by PN2. Like serum data, late-term fetuses and newborn pups had significantly and dose-dependently lower whole brain T4 and T3 levels, which PN2 restored. Only the two highest perchlorate doses lowered brain T3 and T4 levels. PVHs were observed in the brains of the offspring when assessed on PN14, but restricted to the highest dose treatment, highlighting the effects of perchlorate on thyroid hormone levels and neurodevelopment of the pups. The second experiment focused on postnatal perchlorate exposure. The pups from perchlorate-exposed dams received a direct oral dose of perchlorate (three dose groups: vehicle control, 114 mg/kg/day equivalent and 285 mg/kg per day equivalent) via drinking water from day 0 to postnatal day 6 in conjunction with a maternal perchlorate exposure of approximately 90 mg/kg bw per day from GD6 and throughout lactation. The experiment lasted until PN14, although on the mornings of PN2 and PN6, one pup from each group was euthanized. The results showed that direct oral administration of perchlorate to pups from postnatal day 0 to postnatal day 6 resulted in a significant reduction in serum and brain T4 levels. This treatment led to the development of PVH in the pups. In the third experiment, pregnant rats were administered 27 mg perchlorate/kg bw per day via drinking water and a low iodine diet from day 6 of gestation. The results indicated that the combination of dietary iodine deficiency and 27 mg perchlorate/kg bw per day significantly reduced serum T4 levels in pregnant and lactating dams. While no reduction in thyroid hormones was observed in the offspring on postnatal day 0 or 2, large PVH occurred in the brains of pups from dams with iodine deficiency and perchlorate exposure. The study concluded that perchlorate exposure can cause PVH in the offspring, which, according to the authors, was 'a significant neurodevelopmental defect' associated with thyroid hormone disruption.

Gilbert et al. (2024) conducted a study on pregnant Long–Evans rats with a controlled iodine supply (225 mg/kg potassium iodate) from GD2, resulting in a mean daily intake of 5.5 mg during gestation and lactation. On GD6, rats were assigned to one of five dose groups receiving perchlorate (0, 30, 100, 300 or 1000 mg/L) via deionised drinking water from GD6 to PN 21 (corresponding to 2.7, 9, 27, 90 mg perchlorate/kg bw per day). Serum T4 levels in dams were reduced dose-dependently on GD16, GD20 and PN21, with significant reductions observed at all dose levels on GD20. T3 levels remained largely unchanged, except for a significant decrease at the highest dose on GD20. Serum TSH levels were significantly elevated in dams on GD20 at the two highest dose levels and remained high at the time of pup weaning, particularly in the highest dose group. TSH levels were increased in fetal, pup, and dam serum in all dose groups at all tested ages, with the most significant increase observed in the fetus on GD20. Although TSH levels decreased in pups by PN2, PN6 and PN14, they

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remained elevated in the high-dose group. Serum T4 was reduced in fetuses at the two highest dose levels and remained low on PN0 but recovered by PN2. T3 was below detection limits in fetal serum. There were significant changes in the expression of genes associated with thyroid hormone regulation in the neonatal thyroid gland. Specifically, the expression of the *NIS* gene was upregulated in the thyroid gland of newborn pups compared to late-term fetuses. This upregulation may have contributed to the rapid normalisation of serum thyroid hormone levels in neonates. Despite the normalisation of serum thyroid hormones by PN2, modest reductions in the relative expression of several thyroid hormone-responsive genes were observed in the brains of pups assessed on PN14. This suggests that while serum hormone levels returned to control levels, the underlying gene expression related to thyroid hormone responsiveness in the brain was still affected. The study highlighted that gene expression profiles in the neonatal thyroid gland and serum profiles of TSH and perchlorate changed dramatically within the first few days of life, indicating a dynamic response to maternal exposure to perchlorate. Gilbert et al. (2024) examined the impact of maternal exposure to perchlorate under conditions of dietary iodine deficiency (ID) on the brain and behaviour of the offspring in a study covering four treatment conditions: female rats were kept for 4 weeks on an iodine-replete or an iodine-deficient diet (providing a mean daily intake of 4.0 vs. 0.47 μg I/kg bw) prior to mating and maintained thereafter. Pregnant rats from each diet group then received drinking water without or with 300 mg ammonium perchlorate/L (equal to an intake of ~23 mg/kg bw per day) from GD6 until weaning of the pups on PN21. Dam blood was collected for thyroid hormone (TH) analysis, and thyroid glands were collected from pups at sacrifice on PN0, PN2, PN6 and PN14 and from dams on PN21 for gene expression, hormone and perchlorate analyses. Perchlorate was also determined in serum of pregnant or lactating dams, of pups and in milk bands. Several neurobehavioral tests were conducted with adult offspring of the four treatment groups (Con-Con; ID-Con; Con-ClO_4, ID-ClO_4) 1 to 2 months after cessation of exposure to perchlorate and return to iodine-sufficient diets to assess long-lasting effects.

The iodine deficient diet caused a significant decline in serum T4 levels before and after breeding; T4 serum levels were lowest in dams kept on this diet and exposed to perchlorate at GD20 and PN21 but also reduced in dams on iodine-replete diet exposed to perchlorate. Serum T3 did not differ significantly among groups in late gestation but was clearly lowest on PN21 in the ID-ClO_4 group which also presented the highest increase in TSH levels. In the offspring, reductions in serum T4 and T3 were seen at all ages (PN0 to PN14) and limited to pups of the ID-ClO_4 group relative to the Con-Con group, along with significant increases in TSH levels. Pup serum TSH was also elevated temporarily at PN0 in the Con-ClO_4 animals, whilst ID alone did not affect TSH at any time point. Significant increases in thyroid gland weight were seen in dams limited to the ID-ClO_4 group, and small but significant increases in PN14 pup thyroid gland weight were found in the ID-Con and the ID-ClO_4 group. With regard to gene expression in this organ, the most prominent change was found for *Nis* transcript levels, with a 20- and 30-fold increase in newborns of the Con-ClO_4 and the ID-ClO_4 group, respectively. As pups aged the upregulation of *Nis* subsided but remained elevated in the ID-ClO_4 animals throughout the neonatal period. Relative to *Nis*, with a 10-fold increase in ID-ClO_4 dams on PN21, the magnitude of changes was comparatively small in 6 other transcripts of genes involved in TH synthesis, and the predominant pattern in pups and dams was downregulation.

Perchlorate was present in pup serum during the first 2 weeks of life, but at much lower levels than those found in dams during late gestation and at the end of lactation. Pup serum ClO4 was at its highest at PN0 and declined over the next 2 weeks, despite continued exposure with dam milk.

To assess TH action in the brain, the expression of a set of genes were analysed in the cortex, hippocampus and cerebellum of the PN14 pups: More genes expression was altered in the cortex than the other two brain areas and reductions in relative gene expression were largely limited to the ID-ClO4 treatment group. Furthermore, several cortical regions in the anterior forebrain of pups were examined by immunohistochemistry for parvalbumin (Pvalb), a calcium-binding protein expressed in a sub-set of inhibitory neurons. Pvalb+ staining was not visibly altered by ClO4 or ID alone, whilst a more diminished presence of Pvalb+ neurons was observed in pups of the ID-ClO4 group.

The neurobehavioral tests performed with adult male and female offspring revealed some sex-specific differences, with trace fear conditioning being altered in females of the ID-ClO4 group, but not in males. In tests for the acoustic startle response and prepulse inhibition, male offspring were more affected than females, with the strongest alterations observed in the ID-ClO4 and the Con-ClO4 group. The authors discuss these effects in the context of structural changes observed in the neonatal brain.

Overall, the results provide evidence that iodine deficiency exacerbates thyroidal and neurological effects of developmental perchlorate exposure in rats.

The study by Sakamaki et al. (2025) investigated the effects of developmental exposure to ammonium perchlorate on hippocampal neurogenesis and oligodendrocyte (OL) development in rats. Pregnant Sprague–Dawley rats were administered ammonium perchlorate in drinking water at 0, 300 and 1000 mg/L (corresponding to perchlorate in doses of 0, 22.9 and 76.2 mg/kg bw per day) from gestation day 6 until postnatal day 21. Offspring were examined at postnatal days 21 and 77 for serum thyroid hormone levels, thyroid histopathology, immunohistochemistry and apoptosis in the hippocampus, gene expression analysis and oxidative stress markers. On postnatal day 21, the offspring exposed to perchlorate at a concentration of 76.2 mg/kg bw per day exhibited significantly reduced levels of serum T3 and T4. Thyroid follicular epithelial cell hyperplasia was observed at ≥ 22.9 mg/kg bw per day r. Furthermore, there was a suppression of hippocampal neurogenesis, indicated by decreased proliferation of neurogenic cells at ≥ 22.9 mg/kg bw per day, resulting in reductions in type-1 neural stem cells (NSCs) and type-2a neural progenitor cells (NPCs). By postnatal day 77, while thyroid abnormalities had resolved, the reductions in type-1 NSCs persisted. Additionally, there was an increase in SST+ (somatostatin-positive) interneurons and CCK+ (cholecystokinin-positive) interneurons, accompanied by a decrease in white matter area at the 76.2 mg/kg bw per day exposure level. The study concludes that developmental exposure to ammonium perchlorate induces

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hypothyroidism in rats, which becomes noticeable at weaning. This exposure suppresses NSCs and NPCs proliferation and reduces synaptic plasticity of granule cells during weaning, with neurogenesis suppression persisting into adulthood. The neurotoxic effects of ammonium perchlorate are associated with hypothyroidism, impacting both hippocampal neurogenesis and oligodendrocytes maturation.

Other endpoints

The study by Wang, Song et al. (2022) investigated the effects of perchlorate on lipid metabolism in the liver of high-fat diet mice. During the 12-week study period, 24 male C57BL/6J mice were orally (assumed to be by gavage) given daily perchlorate doses. The experimental groups, including low-dose group (0.1 mg/kg bw), medium dose group (1 mg/kg bw) and high-dose group (10 mg/kg bw), received different concentrations of perchlorate while the control group was treated with an equivalent volume of normal saline. Exposure to perchlorate resulted in alterations in lipid metabolic markers in serum, including notable increases in total cholesterol (TC) and triglycerides (TG) in the medium- and high-dose groups compared to the control group. Significant elevations in high-density lipoprotein cholesterol (HDL-c) levels in the experimental groups indicated disruptions in lipid metabolism induced by perchlorate. Although there were no significant changes in low-density lipoprotein (LDL) cholesterol levels, the study suggested that perchlorate influenced lipid metabolism. Histopathological assessment of liver sections exposed to perchlorate revealed vacuolisation, inflammatory cell infiltration and dilated congested central veins. These observations, in conjunction with serum biochemical parameters, suggested that perchlorate impacted lipid accumulation and metabolism in the liver, leading to disorders in lipid metabolism. During the perchlorate exposure period, body weight gradually increased, with notable differences observed in the low-dose group compared to the control group. The liver weight relative to body weight did not show significant variances between the treatment and control groups, except for a reduction in the high-dose group, indicating the potential effects of prolonged high-dose perchlorate consumption on liver coefficients. Targeted lipidomics analysis identified significant effects of perchlorate on glycerophospholipid metabolic pathways in mice fed a high-fat diet (see Section 3.1.3).

Suarez et al. (2018) investigated the leukocyte alterations and potential immunotoxic effects caused by exposure to ammonium perchlorate in ICR mice. The mice were divided into six groups receiving different doses of ammonium perchlorate: a negative control group, a group receiving the safe dose recommended by the U.S. Environmental Protection Agency (0.7 µg/kg bw per day), a half dose group (0.35 µg/kg bw per day), a duplicate dose group (1.4 µg/kg bw per day), a 5-fold dose group (3.5 µg/kg bw per day) and a 10-fold dose group (7 µg/kg bw per day). These doses were administered orally using micropipettes and were monitored throughout the 14-day treatment period. The research demonstrated notable changes in leukocyte counts, especially among lymphocytes. Alterations in white blood cell counts was seen in both males and females, with higher incidence of changes in males, including lymphocytopenia. These results suggest that exposure to ammonium perchlorate can result in leukopenia and other leukocyte abnormalities in mice, underscoring its immunotoxic effects.

3.1.2.3 | *Genotoxicity*

In the previous EFSA Opinion on Perchlorate (2014), it was noted that negative tests had been reported for perchlorate in in vitro tests for bacterial mutagenicity, DNA crosslinks or mutagenicity in human lymphocytes with or without metabolic activation. In vivo, there were also negative test outcomes in bone marrow micronucleus assays following administration in drinking water in rats and after intra-peritoneal injection in mice. Consequently, it was concluded that perchlorate is not a concern with respect to genotoxicity.

Since the 2014 Opinion, no new publications have been retrieved regarding the genotoxicity of perchlorate, apart from evidence of DNA strand breaks (measured by the Comet assay) associated with production of reactive oxygen species (See Section MoA 3.1.4). Therefore, the conclusion that perchlorate poses no concern for genotoxicity remains unchanged.

3.1.2.4 | *Carcinogenicity*

Thyroid tumours (papillary and/or follicular adenomas and/or carcinomas) have been reported to be produced by perchlorate in rats and mice as summarised in the previous Opinion (EFSA CONTAM Panel, 2014).

Since the 2014 Opinion, no new carcinogenicity studies on perchlorate have been identified by EFSA. The CONTAM Panel considers that evidence from three cross-sectional human studies on cancer was inconclusive.

3.1.2.5 | *Overview on animal toxicity studies*

Numerous oral repeated-dose toxicity studies, mostly in rats and described above or summarised in EFSA's previous Opinion (EFSA CONTAM Panel, 2014) showed dose-dependent effects of perchlorate, with the thyroid being the most sensitive organ. A decrease in T3 and T4 and an increase TSH were observed in some studies at daily perchlorate doses as low as 0.01 mg/kg bw (Chen et al., 2014; EFSA CONTAM Panel, 2014; Siglin et al., 2000; York et al., 2004). High(er) perchlorate doses (≥ 10 mg/kg bw per day) also led to changes in thyroid gland weight and histopathological findings in adult male and female animals.

Furthermore, exposure to perchlorate during critical developmental windows can disrupt thyroid function in fetuses and neonates thereby disturbing neurological development. Dose-dependent effects of perchlorate on the

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hypothalamus–pituitary–thyroid (HPT) axis *(as found in adult animals)* have been documented in a series of studies with pregnant rats and in their offspring (Gilbert et al., 2022, 2023, 2024, 2024): reductions in maternal and fetal T4 serum concentrations and the occurrence of periventricular heterotopias (PVH) in the brain of pups were observed. Furthermore, direct oral administration of perchlorate to prenatally exposed pups from PND 0 to PND 6 resulted in a significant reduction in serum and brain T4 levels. This treatment led to the development of PVH in the pups. Maternal perchlorate exposure of 1 mg/L ~ 90 μg/kg bw per day was enough to decrease TH synthesis in the fetal thyroid gland in late pregnancy, although decreases in the gland's synthesis of TH did not affect the fetus's blood TH levels, indicating that TSH stimulation upregulated NIS in the fetus and was able to make up for the decreased synthesis. Only with greater doses in the dam gland's, TH synthesis was reduced suggesting that selecting a NOAEL for the dam based on the gland's TH synthesis is not protective for the fetus. These findings, presented in this series of studies, show that perchlorate exposure in the prenatal and postnatal period of life can result in changes indicative of neurodevelopmental toxicity that might have long-term consequences. Overall, the outcomes are in line with a sequence of events as outlined in Section 3.1.4.2 on an adverse outcome pathway for perchlorate which starts with inhibition of iodine uptake as molecular-initiating event (MIE). As the animal studies provide dose–response data and important mechanistic insights on the toxicity of perchlorate, they will be used as supportive evidence in this assessment.

3.1.3 | Observations in humans

Background information

Historically, perchlorate has been used for treating hyperthyroidism; however, its use has largely discontinued since the 1960s due to the availability of alternative treatments (Soldin et al., 2001). As a result, both older pharmaceutical trials and more recent interventions in humans are available. Eleven of them were reviewed in the previous EFSA Opinion on perchlorate (EFSA CONTAM Panel, 2014). Among those studies, an interventional study in 37 healthy volunteers by Greer et al. (2002) is described in Section 3.1.5. In the previous EFSA Opinion (EFSA CONTAM Panel, 2014) that study was used as the critical study and a $BMDL_5$ for the effect of perchlorate on thyroidal iodide uptake was used as a Reference Point for setting a health-based guidance value (HBGV).

Several ($n = 23$) observational studies on thyroid function or thyroid disease, and one study on school performance, were also reviewed in the previous EFSA Opinion (EFSA CONTAM Panel, 2014). At that time, the CONTAM Panel concluded that these studies did not provide consistent evidence for an association between perchlorate exposure and thyroid hormones' levels or thyroid disease in occupational settings (two studies) or at non-occupational exposure levels.

Assessment of new studies since 2014

Concerning new evidence identified for this Opinion, no new intervention study in humans was identified. A total of 43 human observational studies (37 cross sectional and 6 prospective studies) were retrieved covering additional health outcomes that were not assessed in the previous EFSA opinion (EFSA CONTAM Panel, 2014). These included studies on thyroid hormones or thyroid disease ($n = 17$), cardiovascular disease and/or related risk factors ($n = 6$), cancer ($n = 3$), gestational exposure, birth outcomes and early neurodevelopmental outcomes ($n = 8$) or other outcomes ($n = 9$). These studies are summarised below. Biomarkers of exposure for perchlorate are discussed in Section 3.1.1.3 of this Opinion.

3.1.3.1 | *Thyroid toxicity*

Thyroid toxicity in pregnancy and neonates

One prospective and six cross-sectional studies were identified that examined the association between urinary concentration of perchlorate and thyroid hormones' levels in pregnant women. Two studies examined the association between levels of perchlorate in drinking water and TSH levels in neonates (Chamot et al., 2023; Javidi et al., 2015). Four studies had a sample size of ~200–300 individuals while two studies were considerably larger ($n > 1800$) (Chamot et al., 2023; Steinmaus et al., 2016). The mean or median urinary perchlorate levels ranged from 2.0 to 6.5 μg/L across studies with six out of seven studies reporting levels below 4 μg/L. All studies measuring exposure in urine relied on one or more spot urine samples. Five studies measured both TSH and FT4 that allows for better characterisation of thyroid function compared to the studies where these combined measurements were lacking.

The main study characteristics and results of these studies are summarised in Table 4.

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TABLE 4 Summary of studies examining associations between exposure to perchlorate during pregnancy with maternal or offspring thyroid hormones.

Study	Aim	Setting	Perchlorate (ClO_4^-) conc.[1]	Thyroid hormones conc. as reported	Statistical analyses	Association signal[2]	Results (effect estimate)
Thyroid hormones in early infancy							
Suh, Abraham, Hixon, and Proctor (2014)	To examine the **cross-sectional** association between ClO_4^- in pregnancy with maternal thyroid function	92 pregnant women from the US NHANES study (2001–2002) provided urine and serum and urine samples in pregnancy (timing not specified)	Mean in urine: 2.7 µg/L	Mean FT4 ~ 0.6 ng/dL	Slope (β) reflecting change in absolute FT4 per 1-unit increase in log-transformed ClO_4^- (base of log not reported) Adjusted for thiocyanate, creatinine and gestational age	FT4: ↑	Regression coefficient, *p*-value FT4: 0.040 ($p=0.002$)
Charatcharoenwitthaya et al. (2014)	To examine the **cross-sectional** association between ClO_4^- in pregnancy and maternal thyroid function	Pregnant women from Thailand ($n=200$). 1st trimester creatinine adjusted urinary ClO_4^- and maternal serum TSH, fT4 and fT3	Mean (SD) in urine 3.0 µg/L (3.9)	Mean (SD) TSH (mIU/dL): 1.6 (1.3) FT4 (ng/dL): 1.2 (0.2) FT3 (ng/dL): 0.3 (0.1)	Univariate Spearman correlations (r) between ClO_4^-, TSH, fT3 and fT4 Slope (β) reflecting change in log-transformed TSH per 1-unit change in log-transformed ClO_4^-; or absolute change in FT4 per 1-unit increase in ClO_4^-	TSH: ↑ FT4: ↓ FT3: – TSH: ↑ FT4: ↓ FT3: –	Spearman correlation coefficient: TSH, $r=0.20$ ($p=0.05$) FT4, $r=-0.18$ ($p=0.01$) FT3, $r=-0.04$ ($p=0.59$) Regression analyses: TSH: $\beta=0.31$ ($p=0.002$) FT4: $\beta=-0.04$ ($p=0.002$) FT3: $\beta=-0.02$ ($p=0.11$)
Mortensen et al. (2016)	To examine the **cross-sectional** association between ClO_4^- in pregnancy with maternal thyroid function	330 pregnant women from the US provided urine and serum samples in 3rd trimester	Median (interquartile range) in urine 4.0 µg/L (4.4)	Median (interquartile range) TSH: 1.5 mIU/L (1.03) FT4: 1.1 ng/dL (0.3)	Slope (β) reflecting absolute change in FT4 and % change in TSH in thyroid hormones per 1-unit increase in ClO_4^- Adjusted for urinary creatinine concentrations	TSH: – FT4: –	Regression coefficient (95% CI) TSH: −0.00008 (p=0.10) FT4: 0.00007 ($p=0.10$)
Steinmaus et al. (2016)	To examine the **prospective** association between ClO_4^- in pregnancy with maternal thyroid function	1880 pregnant women from the US providing urine samples in gestational week ~7 (ClO_4^-) and serum samples at gestation week ~20 (thyroid hormones)	Median (p25, p75[1]) in urine 6.5 µg/L (4.0, 10.0)	Median (p25, p75) TSH: 1.2 mIU/L (0.8, 1.7) T4: 12.3 µg/dL (11.2, 13.4) FT4: 0.85 ng/dL (0.77, 093)	Slope (β) reflecting absolute change in T4 and FT4; and % change in TSH in thyroid hormones per 1-unit increase in ClO_4^- Adjusted for urinary creatinine, maternal age, maternal education, ethnicity gestational age at serum collection and urinary thiocyanate	TSH: ↑ T4: ↓ FT4: ↓	Regression coefficient (95%CI) TSH: 7.1% (0.8%, 13.3%) T4: −0.70 (−1.06, −0.34) FT4: −0.053 (−0.092, −0.013)
Javidi et al. (2015)	To examine the **cross-sectional** relationship between ClO_4^- in drinking water with thyroid hormones in cord blood	Thyroid hormones in 25 neonates from Iran were compared relative to ClO_4^- in drinking water around the area where they were born	Mean (SD) in drinking water 3.6 µg/L (5.1)	Mean (SD) TSH (mIU/m): 7.8 (4.1) T4: 6.1 mg/dL (0.9) T3: 63.5 mg/dL (17.5) **Note:** T4 and T3 reported as mg/dL (questionable)	Mean concentration of thyroid hormones compared relative to drinking water ClO_4^- < 5 or ≥5 µg/L	TSH: – T4: – T3: –	Mean thyroid conc. between low versus high drinking water areas (< 5 vs. ≥ 5 µg/L): TSH (7.8, 7.9) T4 (6.1 vs. 6.0) T3 (67.1 vs. 57.0)
Horton et al. (2015)	To examine the **cross-sectional** association between ClO_4^- in pregnancy with maternal thyroid function	Pregnant women living in New York city ($n=248$) creatinine adjusted urinary ClO_4^- and maternal serum TSH, fT4 measured in first half of pregnancy	Mean (SD) in urine 3.4 µg/L (3.1)	Mean (SD) TSH (mU/L): 1.5 (1.1) FT4 (ng/dL): 1.0 (0.2)	Mean % change in serum thyroid hormones was estimated across quartiles of creatinine adjusted ClO_4^- exposure adjusting for ethnicity, smoking, BMI, gestational week and urinary iodide.	TSH: – FT4: –	Pairwise comparison across quartiles of perchlorate exposure: TSH: A non-significant increase of 18% when comparing the highest versus lowest quartile or urinary ClO_4^- conc ($p=0.11$). FT4: the corresponding estimate for FT4 was −2.9% ($p=0.13$)

(Continues)

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TABLE 4 (Continued)

Study	Aim	Setting	Perchlorate (ClO_4^-) conc.[1]	Thyroid hormones conc. as reported	Statistical analyses	Association signal[2]	Results (effect estimate)
Knight et al. (2018)	To examine the **cross-sectional** association between ClO_4^- in pregnancy with maternal thyroid function	306 pregnant women from the UK. Maternal urinary ClO_4^- and serum TSH measured in week 36–38 of gestation	Median (p25, p75) in urine 2.1 μg/L (1.4, 3.8)	Median (p25, p75) TSH (mIU/L): 1.9 (1.4, 2.6) Mean (SD) FT4 (pmol/L*): 12.0 (1.6)	Slope (β) and 95%CI reflecting % change in thyroid hormones per unit increase in ClO_4^- Adjusted for urinary iodine, thiocyanate and being TPO antibody positive. Additional adjustment for smoking was not influential	TSH: – FT4: ↓	Regression coefficient (95% CI) TSH: β = 0.008 (−0.06, 0.07) FT4: β = −0.29 (−0.52, −0.07)
Chamot et al. (2023)	To examine the association between maternal exposure to ClO_4^- from geospatial data in drinking tap water in pregnancy and offspring TSH.	ClO_4^- based on drinking water monitoring was linked by geolocation for 6249 mothers giving birth at the Amiens' University Hospital (FR). TSH in the offspring was measured at day 3 as a part of routine screening *N* = 1910	Median (p25th, p75th) Drinking water (μg/L): 2.0 (0.7–4.5)	Median (p25, p75) TSH (mIU/L): 1.7 (1.0, 1.8)	Slope (β) and 95%CI reflecting %change in TSH for each interquartile (3.6 μg/L) increase in drinking water concentrations Adjustment: Model 1: Gestational age and sex Model 2: Model 1 plus water nitrate and airborne $PM_{2.5}$	TSH: ↑ TSH: ↑	Regression coefficient (95% CI) Model 1: β = 2.3% (95%CI: 1.0, 3.7) Model 2: β = 1.6% (95%CI: 0.2, 3.0)

Abbreviations: BMI, body mass index; CI, confidence interval; FR, France; FT3, free triiodothyronine; FT4, free thyroxine; PM, particulate matter; SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; TPO, thyroid peroxidase; US, United States.

[1]All studies measuring exposure in urine relied on one or more spot urine samples.

[2]The arrows reflect statistically significant positive or inverse association. The use of '–' indicates non-significant association. The direction of the association ('significant or non-significant' is reflected by the effect estimates reported in the right most column).

*Conversion factor between pmol/L to ng/dL is 12.87.

Chamot et al. (2023) examined the association between geospatial data on perchlorate levels in drinking tap water with TSH status in 3-day old neonates. Information on maternal exposure to perchlorate via drinking water was based on perchlorate concentration as measured by the water supplier linked to participants residency during pregnancy. Offspring TSH status was measured at day 3 after birth during routine screening for congenital hypothyroidism. The median (25th to 75th) percentile for perchlorate in drinking water was 2.0 μg/L (0.7–4.5) and a statistically significant association with offspring TSH at day three was observed. The observed effect size corresponded to around 2.3% mean increase in TSH per one interquartile increment (~3.6 mg/L) in perchlorate concentrations in drinking water.

Four studies examined the association between urinary concentrations of perchlorate in pregnancy with maternal serum concentrations of TSH and FT4. Steinmaus et al. (2016) recruited 1880 pregnant women from San Diego County in California in 1st trimester. The median (25th, 75th percentile) urinary concentrations were 6.5 μg/L (4.0, 10.0). These concentrations are higher compared to those reported in the other included studies (or ~ 2–4 μg/L, see Table 4). Serum thyroid hormones were quantified in samples collected in 2nd trimester and after adjustment for covariates each 1-mg/L increase in creatinine adjusted urinary perchlorate concentration was statistically significantly associated with 7.1% (95% CI: 0.8%, 13.3%) higher serum TSH and 0.05 ng/dL (95% CI: 0.01, 0.09) lower FT4. Serum T4 was also statistically significantly inversely associated with perchlorate urinary concentrations. These associations were slightly more pronounced in subjects with relatively high urinary iodine concentrations (> 300 mg/L) and among those being positive to anti-thyroid antibodies.

Similarly, a study of 306 pregnant women from the UK with median (25th, 75th percentile) concentrations of perchlorate in urine of 2.1 μg/L (1.4, 2.8 μg/L) reported an inverse association between maternal urinary perchlorate concentrations and maternal FT4 concentrations, while no association was observed for TSH (Knight et al., 2018). Another study of 200 pregnant women from Thailand with mean (SD) concentrations in urine of 3.0 μg/L (SD 3.9) also reported statistically significant associations of urinary perchlorate concentrations with lower FT4 and higher TSH (Charatcharoenwitthaya et al., 2014). However, due to the use of log-transformation for both exposure and outcome (Knight et al., 2018) and correlation coefficients (Charatcharoenwitthaya et al., 2014), the effect sizes from these studies cannot be directly compared with those reported by Steinmaus et al. (2016). Two other studies in 248 pregnant women from New York (Horton et al., 2015) and 330 pregnant women recruited across the US (Mortensen et al., 2016) found no statistically significant associations with serum TSH and FT4. In these two studies the maternal urinary concentrations for perchlorate were ~ 3–4 μg/L.

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Finally, a small study from Iran compared TSH and T4 concentrations between 16 women exposed to perchlorate in drinking water at concentrations below 5 μg/L and 9 women exposed to concentrations ≥5 μg/L (Javidi et al., 2015). No differences in mean TSH, T4 and T3 were observed. Another small study found no association between urinary perchlorate (mean of 2.7 μg/L) and FT4 among 92 pregnant US women participating in the 2001–2002 NHANES survey (Suh, Abraham, Hixon, & Proctor, 2014).

Overall, the relatively large ($n = 1880$) prospective study by Steinmaus et al. (2016) reported significant association between urinary perchlorate in early gestation with higher TSH and lower FT4 in mid gestation. This provides some evidence to suggest that background exposure to perchlorate may be adversely associated with maternal thyroid function. Of note is that the exposure levels observed in this study were slightly higher compared to those reported in other studies (see Table 4). The observed effect size in this study requires careful interpretation; however, assuming that the association is approximately linear as modelled, a 5 mg/L increase in urinary perchlorate concentrations (corresponding to a shift from the 25th to the 75th percentile) would be associated with approximately 35% increase in mean TSH and a 2.5 ng/dL decrease in mean FT4. In the case of FT4, this change would represent a reduction of more than 1-standard deviation from the mean.

Similar findings to those reported by Steinmaus were reported in two cross-sectional studies (Charatcharoenwitthaya et al., 2014; Knight et al., 2018). A similar association with TSH in young infants was also observed for exposure to perchlorate in utero through maternal exposure via drinking water, which is a direct measure of external exposure that is less prone to day to day variability compared to spot urine samples but does not account for dietary exposure to perchlorate (Chamot et al., 2023). However, four cross-sectional studies reported no associations (Suh et al. 2014; Horton et al., 2015; Javidi et al., 2015; Mortensen et al., 2016) although two of those where too small to draw any meaningful conclusion (Suh et al. 2014; Javidi et al., 2015).

Taken together, the accumulated epidemiological evidence suggests that exposure to perchlorate during pregnancy, at levels commonly found in the general population, may affect maternal thyroid function. The absence of an association in some of the studies is not unexpected and should be interpreted in the context of both small sample size and uncertainties around timing of exposure assessment. In the case of urinary perchlorate measures, these are influenced by physiological changes during pregnancy.

Thyroid toxicity in children and adults

Eight cross-sectional and one ecological study examined the association between either urinary ($n = 7$), serum ($n = 1$) or drinking water ($n = 1$) concentrations of perchlorate and thyroid hormones in children or adults. The sample size in these studies ranged from 127 to 7598 and seven out of nine studies measured both TSH and FT4.

The main study characteristics and results of these studies are summarised in Table 5.

TABLE 5 Summary of studies examining associations between exposure to perchlorate with thyroid hormones in children and adults.

Study	Design/ population	Setting	Perchlorate (ClO_4^-) conc.[1]	Thyroid hormones conc. as reported	Statistical analyses	Association signal[2]	Results (effect estimate)
Eguchi et al. (2014)	Cross-sectional Vietnamese adults ($n = 127$). Mean (SD) age of 36 years (12)	Subjects were either living in a contaminated e-waste recycling site ($n = 83$) or a control rural ($n = 43$) area	Median (25th, 75th) in **serum** E-waste site: 0.12 μg/L (0.09, 0.16) Rural site: 0.09 μg/L (0.07, 0.12)	Median (P25, P75) E-waste site: T3 (ng/mL): 1.2 (1.1, 1.3) FT3 (pg/mL): 3.3 (3.0, 3.5) T4 (ng/mL): 71 (61, 81) FT4 (ng/mL): 1.3 (1.2, 1.4) TSH (μUI/mL) 1.5 (1.0, 2.2) Rural site: T3: 1.3 (1.2, 1.4) FT3: 3.4 (3.2, 3.5) T4 79 (69, 87) FT4: 1.3 (1.4, 1.7) TSH 1.4 (1.0, 2.1)	Comparing the concentrations in thyroid hormones between the two sites. Multiple linear regression analyses Adjustments made for age, BMI, pregnancy status (yes/no), living site (e-waste/reference) and habit of eating freshwater fish, marine fish and meat	T3: – FT3: – T4: – FT4: – TSH: –	No significant difference in thyroid hormones between the two sites. No association when examining the association between ClO_4^- and thyroid hormones in all subjects combined
McMullen et al. (2017)	Cross-sectional 3151 US children and adults. Age: 12–21 years: 26% 22–49 years: 43% 50–80 years: 31%	Subjects were participants, in the US NHANES 2009–2012 study NOTE: Partly overlapping study population with King et al. (2022) below	Median (P25, P75) in **urine** creatinine adjusted 3.0 μg/L (1.83, 5.09)	Median (P25, P75): TSH (μIU/L): 1.42 (0.98, 2.04) FT4 (ng/mL): 0.8 (0.72, 0.9)	Linear regression analyses examining the association between Log10-transfromed ClO_4^- with FT4 or Log10-transformed TSH. Adjusted for: urinary thiocyanate and nitrate, serum cotinine BMI and total energy intake race/ethnicity and poverty-to-income ratio.	TSH: – FT4: ↓	Slope (β) and 95%CI TSH: −0.01 (−0.05, 0.04) FT4: −0.03 (−0.04, −0.008) Effect estimate for FT4 corresponds to % increase per 10-fold increase in exposure. Interpretation for TSH less clear

(Continues)

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TABLE 5 (Continued)

Study	Design/ population	Setting	Perchlorate (ClO_4^-) conc.[1]	Thyroid hormones conc. as reported	Statistical analyses	Association signal[2]	Results (effect estimate)
Von Oettingen et al. (2017)	Cross-sectional 299 children from Haiti aged 9 months to 6 years (mean: 3.3 years)	A survey, conducted in 2015 screening healthy children for iodine deficiency and to assess influence of environmental chemicals on their thyroid function	Median (P25, P75) in **urine** 1.7 µg/L (1.0, 3.3)	Median (P25, P75) in **urine**: TSH (IU/mL): 1.9 (1.3, 2.6) Iodine (µg/L): 145 (97, 241)	Association between perchlorate and iodine were examined in both simple bivariate correlations and multiple linear regression analyses. Mean differences in TSH levels were assessed across three recruitment areas. Adjusted for age, sex, height and weight for age, family income, region, breastfeeding, urinary thiocyanate and selected dietary variables.	Urinary iodine[11] ↑	Urinary iodine and perchlorate were positively correlated: Pearson $r = 0.22$ ($p < 0.001$). The positive association between urinary perchlorate and iodine concentration remained strongly significant after adjustment for covariates in linear regression analyses. Mean TSH levels were not significantly different between the three recruitment areas ($p = 0.31$). However, the mean urinary perchlorate concentrations were relatively comparable across those sites ranging from 1.4 to 1.9 µg/L
Przybyla et al. (2018)	Cross-sectional 1560 US children (12–19 years) and adults. Mean age of 45.5 years (SD) not reported	Subjects were participants, in the US NHANES 2007–2008 study	Mean in **urine** creatinine adjusted Males: 4.4 µg/L Females: 3.5 µg/L (SD) not reported	Mean TSH (mIU/mL): Males: 1.63 T3 (ng/dL): 115 T4 (µg/L): 7.35 Females: TSH: 1.57 T3: 112 T4 7.58 (SD) not reported	Multivariate linear regression reporting standardised slope (β) and 95%CI Adjusted for age, race and urinary creatinine in addition to the following set of co-exposure measured in urine: bisphenol-A, benzophenone-3 (only in females), mono-2ethyl5carboxypentyl phthalate, mono-n-butyl phthalate, mono-(3-carboxypropyl) phthalate, mono(2ethyl5hydroxyhexyl) phthalate, mono-benzyl phthalate and mono-isobutyl phthalate	T4: ↓ Results for TSH and T3 not reported (assumed to be non-significant)	Based on their regression models the authors reported that the combined chemical exposure was negatively associated with T4 and perchlorate appears to have had some contribution. Unclear how to interpret the effect estimate as reported by the authors
Ucal et al. (2018)	Cross sectional 185 lactating Turkish mothers and their offspring Mean (SD) age Mother: 27.1 (5.6)	Women giving birth in 2013. Urinary perchlorate concentrations were measured in urine samples within 48 h from birth. Samples collected in neonates within 72 h from birth for routine screening for congenital hypothyroidism abnormalities	Mean (SD) creatinine adjusted perchlorate in **Urine:** 5.6 µg/L (5.7) **Colostrum:** 4.1 µg/L (4.8)	Mean (SD) TSH (µIU/mL): 2.6 (1.9) FT4 (pmol/L): 12.1 (2.0) FT3 (pmol/L): 4.5 (0.8)	Combined exposure to perchlorate, thiocyanate and nitrate was explored. Only simple univariate correlation between perchlorate and TSH was reported.	TSH: ↑	Pearson's r between perchlorate in colostrum and neonatal TSH: 0.21 ($p < 0.015$). Results reported selectively and difficult to evaluate this study
Orathel et al. (2020)	Cross-sectional study from India 542 children and adults from India Age: 0–20 years: 30% 21–40: 30% 41–60: 28% 61–80: 12% Exact age range not reported but means (SD): ~34 years (20)	272 subjects recruited from an area surrounding an ammonium perchlorate enrichment plant and to 270 study subjects recruited from a control area.	Range in **groundwater samples** collected around the two areas: Contaminated area: 1.6–57 µg/L (10 samples) Control area: < 0.02 µg/L	See results column	Comparison in mean thyroid hormone levels (TSH and FT4) between contaminated and control area No adjustment for covariates Subjects with urinary iodine < 100 mg/L were excluded from the analyses.	TSH: – FT4: –	Contaminated vs. control area: Mean (SD) TSH: 2.05 (1.19) vs. 2.91 (1.16), $p = 0.66$ FT4: 1.08 (0.14) vs. 1.08 (0.18), $p = 0.70$ Hypothyroid: 4.1% vs. 3.3% Hyperthyroid: 1.5% vs. 2.5%

[11]TSH was not examined in this study, in which the levels across the three recruitment sites and discussed the results.

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TABLE 5 (Continued)

Study	Design/ population	Setting	Perchlorate (ClO_4^-) conc.[1]	Thyroid hormones conc. as reported	Statistical analyses	Association signal[2]	Results (effect estimate)
King et al. (2022)	Cross-sectional 7598 US adults Mean age of 45.5 years (SD) not reported	Subjects were participants, in the US NHANES 2007–2012 study	Mean in **urine** creatinine adjusted 5.5 μg/L	Mean (standard error) FT4 (pmol/L): 10.23 (0.07) TSH (μIU/L): 1.95 (0.05)	Mean changes in thyroid hormones across quartiles of urinary ClO_4^- concentrations was examined Adjusted for: urinary creatinine, age, race/ethnicity, sex, smoking, alcohol, physical activity, BMI, medication usage, serum albumin, total energy intake, C-reactive protein; and urinary iodine, nitrate and thiocyanate.	TSH: - FT4: ↓	Mean difference (standard error comparing highest versus lowest quartile) and p-for linear trend across quartiles: −0.03 (0.13), $p = 0.88$ −0.33 (0.12), $p = 0.006$
Yue et al. (2023)	Cross-sectional 177 Chinese adults Mean (SD) age: 42 years (10)	Participants were adults, without any severe underlying diseases, who attended a health physical examination at Beijing Hospital in mid-2017	Median (P25, P75) creatinine adjusted perchlorate in **urine**: 8.8 ng/mL (6.3, 15.3)	Median (P25, P75) THS (mIU/mL): 1.83 (1.35, 2.45) T4 (mg/dL): 8.2 (7.2, 9.3) FT4 (ng/dL): 1.37 (1.26, 1.48) T3 (mg/dL): 1.00 (0.92, 1.24) FT3 (ng/dL): 3.25 (2.95, 3.97)	Slope (β) and 95% CI Multivariable-adjusted linear regression examining associations between several mutually adjusted urinary substances with thyroid hormones Adjusted for age, gender, BMI, smoking status, urinary iodine, education level, thiocyanate, MBP, MEP, MEHP, MEOHP, MECPP, MEHNP, BPF, BPA and BPS	TSH: – T4: – FT4: – T3: – FT3: –	TSH 0.07 (−0.19, 0.33) T4: −0.23 (−0.62, 0.16) FT4: −0.02 (−0.06, 0.01) T3: −0.01 (−0.04, 0.04) FT3: −0.04 (−0.06, 0.01)
King et al. (2023)	Cross-sectional 2441 Chinese adults Mean (SD) age of 50.4 years (12.2)	Sub-set of participants from Tongji-Shenzhen Cohort recruited in Shenzhen, China in 2018 to 2019	Median (P25, P75) in **urine** creatinine adjusted 16.6 μg/L (11.0, 25.7)	Mean (SD) TSH (mIU/L): 2.2 (2.5) FT4 (pmol/L*): 12.6 (1.5) TT4 (nmol/L): 97.2 (16.7) FT3 (pmol/L): 2.8 (0.4) TT3 (nmol/L): 1.0 (0.2)	Concentrations of thyroid hormones were examined across tertiles of $ClO4^-$ concentrations Linear regression estimating the slope (β) reflecting change in thyroid hormones per 1-log increase in ClO_4^- (base of log not reported) All analyses were adjusted age, sex, BMI, smoking (yes, no), alcohol, serum albumin, hypertension, diabetes, urinary iodine; and urinary nitrate and thiocyanate.	TSH: ↑ FT4: ↓ TT4: – FT3: ↑ TT3: ↓	Mean difference (95% CI) in thyroid hormones comparing tertile 3 versus 1 TSH: 0.37 (0.10, 0.64) FT4: −0.34 (−0.50, −0.18) TT4: −3.70 (−5.51, −1.90) FT3: 0.07 (0.03, 0.11) TT3: −0.02 (−0.04, −0.01)

Abbreviations: BMI, body mass index; BPA, bisphenol A; BPF, bisphenol F; BFS, bisphenol S; FT3, free triiodothyronine; FT4, free thyroxine; MBP, mono-n-butyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHP, mono-2-ethylhexyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; NHANES, National Health and Nutrition Examination Survey; P25, the 25th percentile; P75, the 75th percentile; PM, particulate matter; SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; US, United States.

[1]All studies measuring exposure in urine relied on one or more spot urine samples.

[2]The arrows reflect statistically significant positive or inverse association. The use of '–' indicates non-significant association. The direction of the association ('significant or non-significant' is reflected by the effect estimates reported in the right most column).

*Conversion factor for FT4 between pmol/L to ng/dL is 12.87.

Two studies were conducted in areas where recruited participants were likely to be highly exposed to perchlorate compared to the other studies conducted in the general population. One of these was a cross-sectional study comparing thyroid hormone concentrations between 83 subjects living near an e-waste recycling site in Vietnam and 43 subjects living in a rural control area (Eguchi et al., 2014). A modest but significant difference in serum perchlorate concentration was observed between those living in the contaminated versus control area (0.12 vs. 0.9 ng/mL). No significant differences in serum TSH, FT4, T4, FT3 or T3 were observed. Similarly, an ecological study of 542 children and adults (aged 0 to 80 years) of which 272 were recruited from an area with perchlorate concentration in groundwater ranging from 1.6 to 57 μg/L ($n = 10$ samples) and 270 children from a control area concentration < 20 μg/L found no significant difference in serum TSH or FT4 concentrations (Orathel et al., 2020).

Concerning larger cross-sectional studies conducted in a study of 2441 Chinese adults reported a 0.37 mIU/L higher TSH (17% of the mean) and 0.34 pmol/L lower FT4 concentrations (~3% of the mean) when comparing subjects in the highest versus lowest tertile of urinary perchlorate concentrations. A significant higher total triiodothyronine (TT3) and lower FT3 was also observed (King et al., 2023). The median (P25, P75) urinary perchlorate concentration in that study was 17 μg/L (11, 26). Similarly, a study of 7598 adults from the US 2007–2012 NHANES participants reported a 0.33 pmol/L lower (or 3% of the mean) FT4 concentrations among those in the highest versus lowest quartile of urinary perchlorate concentrations [mean (SD): 5.5 μg/L (0.2)] (King et al., 2022). In that study, no significant differences were observed for TSH. Another partly overlapping study based on 3151 children and adults recruited into the NHANES survey in 2009–2012 also reported significant lower FT4 and no significant change in TSH with higher urinary perchlorate exposure (McMullen et al., 2017). Another study of 1560 children and adults from the 2007–2008 NHANES survey reported significantly lower T4 after mutual adjustment, in a multi-pollutant model, for 9 other organic environmental contaminants (Przybyla et al., 2018). Results for other thyroid hormones were not reported.

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Concerning the smaller cross-sectional studies ($n < 300$) a study in 185 lactating women from Türkiye reported a positive correlation ($r = 0.21$, $p < 0.02$) between perchlorate concentrations measured in colostrum and maternal TSH levels (Ucal et al., 2018). No significant correlation was observed for perchlorate in urine [mean (SD): 5.6 µg/L (5.7)]. Conversely, no association between urinary perchlorate concentrations (median: 8.8 ng/mL) were observed with thyroid hormones in 177 Chinese adults who attended a health physical examination at Beijing Hospital in 2017 (Yue et al., 2023).

Only one study examined associations between urinary perchlorate and urinary iodine concentrations (Von Oettingen et al., 2017). In that study, a modest correlation was found between the two ($r = 0.22$, $p < 0.01$), potentially supporting mediation by urinary iodine.

In summary, similar to the studies in pregnant women, large ($n > 2000$) cross-sectional studies in adults from both China (King et al., 2023) and the US (King et al., 2022) reported a modest but significant association of perchlorate exposure with higher TSH and lower FT4 in adults. Two other studies, partly overlapping in terms of recruited participants with King et al. (2022) from the same NHANES database also provided some support to these findings (McMullen et al., 2017; Przybyla et al., 2018). Comparison by King et al. (2022) of results from the two studies (McMullen et al., 2017; Przybyla et al., 2018) is hampered by differences in statistical analyses grouping the children together with adults. This may have some influence on findings as children's thyroid hormone concentrations vary more with age compared to adults.

Although the larger cross-sectional studies in background exposed population reported relatively consistent findings on increase in TSH and decrease in FT4 such findings were not observed in two studies from Vietnam and India conducted in adults living in perchlorate contaminated versus control area (Eguchi et al., 2014; Orathel et al., 2020). Although these studies may seem contradictory, caution is needed in terms of study limitations. Firstly, in the cross-sectional study from Vietnam (Eguchi et al., 2014) the mean difference in serum perchlorate concentrations was modest as was the exposure gradient between those living in the contaminated versus control area (40% of the mean). This may suggest the exposure in the contaminated area was only modestly elevated compared to the background or that both areas were contaminated. Secondly, although the ecological study from India compared thyroid hormones in subjects living in an area with quite elevated concentrations of perchlorate in ground water (1.6–57 µg/L) compared to subjects living in the control area (< 0.02–7 µg/L) no individual measure of perchlorate in serum or urine or some other form of validation of exposure was provided (Orathel et al., 2020). Although concentrations in groundwater may very well reflect levels which participants were exposed to, it is also possible that those living in very contaminated sites may seek to access less contaminated water. Lack of reflection on this in the paper is a source of considerable uncertainty.

In summary, similar to the findings in pregnant women, the accumulated epidemiological evidence in other adults and children supports an association between serum perchlorate and higher TSH and lower FT4. This evidence primarily comes from large cross-sectional studies from the US and China, which are consistent in terms of both the direction and magnitude of the effect. Of note, in the studies that did not report a statistically significant association, the direction and magnitude of the association were consistent with those found in the studies yielding statistically significant results.

3.1.3.2 | *Studies on cancer*

Two case–control studies from China and one cross-sectional study from the US (NHANES) assessed associations between urinary perchlorate concentrations and cancer outcomes (Shiue, 2015a; Zhang et al., 2018; Wang et al., 2022).

Zhang et al. recruited in a Chinese hospital setting 116 cases of papillary thyroid cancer (PTC) (~75% females) and 116 age and sex-matched controls who also visited the hospital during the recruitment period. Mean (range) urinary perchlorate concentrations were significantly lower among PTC cases compared to controls: 6.1 µg/L (0.4–28.4) versus 9.8 µg/L (1.4–54.4). This difference persisted after adjustment for creatinine. In their fully adjusted models, however, the authors reported a significant association between perchlorate and papillary thyroid cancer (OR: 2.27; 95% CI: 1.03, 5.03).

In another case–control study from China, 184 individuals diagnosed with nodular goitre (NG), papillary thyroid microcarcinoma (PTMC) or PTC were recruited from two hospitals (Wang, Jiang et al., 2022). These cases (~65% females) were compared with age and sex-matched controls (limited description on control selection was provided by the authors). Urinary perchlorate concentrations were significantly lower in cases compared to controls (~9 vs. 14 µg/L), with similar differences observed for each-subtype (NG, PTMC and PTC). However, after adjusting for covariates, a positive association was observed between urinary perchlorate concentrations and thyroid disease (NG, PTMC and PTC) (OR: 1.04; 95% CI: 1.02, 1.07), with similar positive association observed for each disease subtype (NG, PTMC and PTC).

A cross-sectional study from the NHANES (2009–2012, $n = 18{,}169$) reported no significant association (OR: 0.99; 95% CI: 0.78, 1.25) between urinary perchlorate concentrations and any prevalent cancer in covariate adjusted analyses (Shiue, 2015a). However, the results from this study are difficult to evaluate, as the number of cancer cases and specific cancer sub-types were not reported.

Evidence from these three cross-sectional studies on cancer was inconclusive.

3.1.3.3 | *Cardiovascular diseases (CVD) and related risk factors*

In a study of 16,570 participants from NHANES cycles from 2001 to 2014, Wang et al. (2022) examined the cross-sectional association between urinary perchlorate concentrations (mean: 3.4 mg/L) and CVD, or specific sub-types, including coronary heart disease, angina, heart failure and stroke. No association with prevalent CVD or its specific sub-types were observed.

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Another cross-sectional study of 12,007 participants from the NHANES cycles 2005 to 2018 by Guo, Zong, et al. (2023) examined the association between urinary perchlorate concentrations (mean: 3.0 mg/L) and the metabolic syndrome. After adjusting for covariates, each 3-fold increase in urinary perchlorate concentrations was associated with around 7% higher odds of being classified with metabolic syndrome (OR: 1.07; 95% CI: 1.01, 1.14).

Another study of 11,443 NHANES participants from cycles 2001 to 2014, explored the associations between urinary perchlorate concentrations (median: 3.3 mg/L) with measures of glucose homeostasis and the prevalence of diabetes (Liu et al., 2017). After adjusting for covariates, higher urinary perchlorate concentrations were associated with higher prevalence of diabetes with an OR of 1.53 (95% CI: 1.21, 1.93) when comparing those in the highest versus lowest quintile of urinary perchlorate exposure.

In contrast, another study among 7028 participants from the NHANES cycles 2005 to 2008, found no association between urinary perchlorate and fasting blood glucose (Schreinemachers et al., 2015). However, in this study urinary perchlorate (mean: 3.9 μg/L) was inversely associated with blood urea nitrogen, serum iron and red blood cell count while a positive association with serum uric acid was observed.

In a study of 15,717 adults from the NHANES cycles 2005 to 2016, urinary perchlorate concentrations (median: 3.2 μg/L) were significantly associated with lower risk of hypertension when comparing the highest versus lowest quartile of exposure (OR: 0.83; 95%CI: 0.73, 0.93) (Xu et al., 2023). In this study, hypertension was defined as systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 80 mm Hg, which is different from the normal definition of hypertension (140/90 mm Hg).

Finally, a study of 959 participants in the NHANES study cycle 2013 to 2014 found no association between urinary perchlorate (mean: 2.47 μg/L) and abdominal aortic calcification (Yuan et al., 2023).

In summary, the six cross-sectional studies conducted using data from different NHANES cycles showed some associations, reflecting both benefits and possible adversity, with different cardiovascular diseases and related risk factors. While some studies suggested potential associations with conditions like metabolic syndrome, diabetes and hypertension, others showed no significant relationships. Overall, the evidence for an adverse association between urinary perchlorate concentrations and cardiovascular diseases and related risk factors is inconclusive.

3.1.3.4 | *Gestational exposure, birth outcomes and early neurodevelopmental outcomes*

Two prospective cohort studies from the US examined the associations between maternal urinary concentrations of perchlorate in pregnancy with birth weight and length of gestation.

The first study recruited 107 pregnant women between gestation week 9 to 39 (Evans et al., 2015). The mean perchlorate concentrations in maternal urine ranged between 4.5 to 5.5 mg/L, depending on the gestation week of sampling. In this small study no association with birth weight or length of gestation was observed. The other study recruited 1957 pregnant women from San Diego County between 2000 and 2003 also found no clear association between maternal urinary concentrations [median (25th to 75th percentile): 6.5 μg/L (2.9, 100)] of perchlorate (gestation weeks 15–20) and birth weight or pre-term deliveries (Rubin et al., 2017).[12] The available limited epidemiological evidence does not support an association between perchlorate exposure and either birth weight or pre-term delivery.

Two prospective studies from China and Europe examined the association between urinary perchlorate concentrations in pregnancy with neurodevelopmental outcomes in the offspring.

The study from China recruited 1028 pregnant women who provided urine samples in each trimester (Li, Tu, et al., 2023). The median urinary perchlorate concentrations, averaged over all three trimesters was 14.6 μg/L (25th, 75th percentiles: 9.8, 23.4). Neurodevelopmental outcomes were assessed in the offspring at age 24 months using the Chinese revision of the Bayley Scales of Infant Development (BSID). Overall, no statistically significant association between maternal urinary concentrations of perchlorate and offspring neurodevelopment at 2 years of age was observed.

Based on a sub-set of women ($n = 487$) from the Controlled Antenatal Thyroid Screening (CATS) trial, Taylor et al. (2014) examined the association between maternal urinary concentrations of perchlorate and IQ in the offspring at 3 years of age. The original trial was conducted in the UK and Italy and aimed to establish if a medical treatment for suboptimal thyroid function during pregnancy could improve neurodevelopmental outcomes in the offspring. This study included 487 hypothyroid/hypothyroxinemic[13] women who were recruited before gestation week 16 and whose offspring IQ status was assessed at 3 years using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). The median urinary iodine concentration of the women from the UK and Italy were 95 and 54, μg/L respectively, indicating iodine insufficiency. The median urinary perchlorate concentration was 2.58 μg/L (95% percentile range: 0.08–38.9). Women who had urinary perchlorate concentrations in the first trimester in the upper 10% of the concentration distribution (> 10.9 μg/L) had 2.7 higher odds (95%CI: 1.2, 6.3) of having offspring with IQ in the lowest 10% (< 80 IQ points) of the IQ distribution at age 3 years compared to those with lower perchlorate levels.

Taken together the two studies (Taylor et al., 2014; Li, Tu, et al., 2023) on neurodevelopmental outcomes in children may appear to show conflicting results. However, the study by Li et al. assessed neurodevelopment at 24 months using the Bayley Scales of Infant Development (BSID), which is less precise assessment (a screening tool) compared to measures of full IQ as used in the study by Taylor et al. (WPPSI). The strength of the study by Taylor et al. is that it was conducted in

[12]This study is based on the same cohort as Steinmaus et al. (2015) reported in the thyroid section.

[13]Hypothyroid is a disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormones/hypothyroxinemic is a thyroid disease where the serum levels of thyroxine are lower than expected.

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women who are likely more vulnerable to perchlorate exposure, as they already had suboptimal thyroid function. Their findings may suggest that perchlorate may be adversely associated with neurodevelopment in the offspring. However, limited conclusions can be drawn from a single study and further replication in another setting would add furthermore weight to these findings.

3.1.3.5 | *Exposure in children*

A study of 4447 children aged 6–19 years from the NHANES cycles 2005 to 2016 reported an inverse association between urinary perchlorate concentrations and overweight and obesity (Jiang & Li, 2022). The odds ratio for being overweight or obese when comparing the highest (> 7.6 μg/L) to the lowest (< 2.4 μg/L) quartile of urinary perchlorate concentrations was 0.70 (95% CI: 0.53, 0.93).

Another US study conducted among 940 6–8-year-old girls examined differences in height, waist circumference and body mass index (BMI) among those categorised as having low ($n = 196$), medium ($n = 555$) and high ($n = 189$) combined exposure to perchlorate, thiocyanate and nitrate measured in urine (Mervish et al., 2016). Overall, those in the high exposure group compared to the low exposure group[14] had significantly lower height (~1–3 cm), waist circumference (~1–3 cm) and BMI (~1.0 kg/m^2).

A study from China examined the association between perchlorate in drinking water [mean (SD): 4.3 μg/L (3.2)] with height and weight in 144.655 children and adolescents (Guo, Wu, et al., 2023). After adjusting for average weight data in each county, a 10 μg/L increase in perchlorate in drinking water was associated with 1.0 cm decrease in height and a 1.6 kg decrease in weight.

Overall, the results from these studies suggest that urinary perchlorate exposure may be associated with lower height and weight in children (Jiang & Li, 2022; Mervish et al., 2016). However, it is difficult to draw strong conclusions on childhood growth based on cross-sectional analyses as rate of growth during childhood may differently affect the rate of perchlorate excretion. This potential limitation did not exist in the Chinese study (Guo, Wu, et al., 2023) in which water concentrations were used as indicator of exposure. However, this study adjusted for only mean county income as covariate, which may leave room for residual confounding due to unmeasured factors that vary between counties.

A case–control study from China (Zhu et al., 2023) recruited 355 children with dyslexia and 390 children without dyslexia, aged ~10 years. A positive association between urinary perchlorate concentrations (median: 18.6 μg/L) and risk of dyslexia [OR = 2.7 (95%CI: 1.3, 5.4)] was observed. However, as dyslexia has its origin in early life, the interpretation of this cross-sectional analysis is complicated.

Finally, a study from the NHANES cycles 2011 to 2016 reported a significant inverse association between urinary perchlorate concentrations (median ~ 3.5 μg/L) and testosterone in adolescent males aged 12–19 ($n = 538$). A similar, but non-significant, association was observed for boys aged 6–11 years. No association was observed for adult males (Han et al., 2023). In the absence of replication of these findings in other studies, limited conclusions can be drawn regarding the impact of perchlorate exposure on testosterone levels in adolescents.

3.1.3.6 | *Other health outcomes in adults*

Several studies, most of them based on the NHANES data, addressed different health outcomes or conditions that are briefly reported in this section. In most cases the outcomes were examined in only one study, which makes it difficult to draw conclusions on the robustness and plausibility of their findings.

Another study using a sub-set (462 out of 5560) of adult participants in the NHANES study cycle 2011 to 2012 investigated self-reported hearing difficulties. The study found significantly higher concentrations (6.5 vs. 4.5 μg/L) of urinary perchlorate among those reporting regular 'hearing frustrations' (half-the time to always) compared to those with no hearing issues (Shiue, 2015b).

A study in 16,715 adult participants from the NHANES study cycles 2005 to 2016 reported a lower risk of depression with higher urinary perchlorate concentrations [OR: 0.71 (95% CI: 0.52, 0.97)] (Xue et al., 2023).

Another NHANES study on 4265 adults from the 2005–2006 cycle (Ko et al., 2014) reported significant inverse association between urinary perchlorate and serum parathyroid hormone, with a regression coefficient (β value) of −0.05 (95% CI: −0.08 to −0.02) per 1 mg/L increase in urinary perchlorate concentration.

Several other NHANES studies did not find statistically significant associations between urinary perchlorate and certain health outcomes. For instance, no association was observed with non-fatty alcoholic liver disease in 4325 subjects recruited in the 1999–2014 cycles (Li, Xiao, Wu, et al., 2022); kidney disease in 13,373 subjects from cycles 2005–2016 (Li, Wu, Xu, & Zhang, 2023) or obesity in 16,265 adults recruited in cycles 2001–2014 (Zhu et al., 2019). In addition, two separate NHANES studies found no association between urinary perchlorate and oral health (Yu et al., 2022a, 2022b).

Taken together, there is no consistent evidence for an association between urinary perchlorate concentrations and the various health outcomes discussed in this section.

[14]The median urinary concentrations were 3.6, 626 and 500 mg/g creatinine for perchlorate, thiocyanate and nitrate, respectively in the low exposure group. The corresponding numbers for the high-exposure group were 9.6, 2343 and 955 mg/g creatinine.

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3.1.3.7 | *Variability in iodine status and thyroid hormone economy[15] in humans*

Perchlorate is competing for iodine uptake into the thyroid gland, via the NIS and potentially uptake into other organs. Newly available data provide evidence that iodine deficiency exacerbates thyroidal and neurological effects of developmental perchlorate exposure in rats. Iodine deficiency is one of the main determinants of thyroid disorders, including hypothyroidism and goitre (Zimmermann & Boelaert, 2015). The most common approach to evaluate iodine status on a population basis is to assess the distribution of iodine concentrations using spot urine samples.[16] For a given population (or study sample) the WHO sets the median urinary iodine concentration of < 100 μg/L as a cutoff for deficiency (WHO, 2013a, 2013b). The corresponding value during pregnancy is < 150 μg/L. For non-pregnant subjects WHO defines median values of < 20, 20–49 μg/L and 50–99 μg/L as the cutoff for severe, moderate and mild iodine deficiency, respectively. Due to public health measures including salt iodisation and fortification of cow's fodder, the prevalence of iodine deficiency and goitre decreased substantially in Europe in the 20th century (Kjellevold & Kippler, 2023; Phillips, 1997). Iodine fortification of cow's fodder also largely explains why dairy products are one of the main sources of iodine intake in many European countries (Van der Reijden et al., 2017). Other important dietary sources include seafood and eggs (Nicol et al., 2024). Despite fortification efforts, population-based surveys from Europe suggest that the risk of either severe, moderate or mild iodine deficiency is potentially widespread as reflected by frequent reports of median urinary iodine concentrations below 100 μg/L (Ittermann et al., 2020; Vitti et al., 2003). Ittermann et al. (2020) reports a prevalence of iodine deficiency of 53% in adults.

The reason why iodine requirement for pregnant women is substantially increased is related to both physiological changes in pregnancy, including increased glomerular filtration rate and increased demand to support fetal growth and development (Leung et al., 2011). As a result, the recommended intake for iodine during pregnancy is higher compared to other adults (Kjellevold & Kippler, 2023). Other groups that may be prone to iodine deficiency are infants that have limited iodine storage capacity in the thyroid gland as well as higher requirements (Dold et al., 2016); and those adhering to plant-based diets, particularly vegans who do not use iodine supplements or do not consume fortified salt/foods (Nicol et al., 2024).

In terms of addressing which factors affecting iodine uptake, information from clinical studies in healthy individuals is scarce (Alazraki et al., 1972; Pittman Jr et al., 1969; Wong & Schultz, 1977) and somewhat limited as they have mostly been conducted in selected populations that may not be fully representative of the general population. Based on such data, it is difficult to predict, on a population level, the possible effects of low-dose exogenous iodine inhibitors on iodine deficiency. What is, however, known is that iodine uptake decreases substantially with age (Hansen et al., 1975).

Variations in certain genes coding for proteins (see Figure 2) involved in the action and regulation of the thyroid can contribute to inter-individual differences in susceptibility to thyroid disorders including hypothyroidism (Panicker, 2011). Presence of such genetic variations may therefore contribute substantially to adverse health effects associated with low iodine intake. A review by Kostopoulou et al. (2021) highlights the importance of polygenic variants associated with various genes involved in thyroid dysgenesis or dyshormonogenesis as contributing, predisposing factors in hypothyroidism. There is interplay between such genetic variants and environmental influences such as those leading to iodine deficiency. Thus, genetic factors may exacerbate the thyroid effects of agents such as perchlorate that can lead to iodine deficiency. Regarding perchlorate, genetic variants influencing iodine transport are particularly relevant for potential interplay. Thyroid dyshormonogenesis has been linked to mutations in SLC5A5 (encoding the sodium iodide symporter), SLC26A4 (encoding pendrin), thyroid peroxidase, dual oxidase, thyroglobulin and iodotyrosine deiodinase genes (Targovnik et al., 2017). Specifically, Geysels et al. (2022) reported that defective NIS pre-mRNA splicing leading to lack of sufficient NIS molecules at the basolateral plasma membrane in thyroid follicular cells may explain deficient accumulation of iodide causing dyshormonogenic hypothyroidism.

Concerning consumption of foods high in naturally occurring goitrogens, a recent systematic review concluded that there is limited evidence for any adverse effect due to consumption of such foods among those with adequate iodine intake (Galanty et al., 2024). Another similar review also reached the same conclusion (Felker et al., 2016). On the other hand, there are also numerous other compounds (e.g. lithium, bromide, thiocyanate) which are known to interact with the NIS (Wang et al., 2019; Stoker et al., 2023).

Of public health concern is the link between iodine deficiency during pregnancy and early childhood with impaired offspring neurodevelopment (WHO, 2016; Zimmermann & Boelaert, 2015). That evidence comes mainly from public health interventions such as salt iodisation, which resulted in near elimination of goitre and a marked decrease in the prevalence of low IQ (< 70) in populations where such interventions were well documented (WHO, 2016). Based on such findings a WHO report from 2016 on maternal nutrition stated that '*Iodine deficiency disorders are the greatest cause of preventable brain damage*' (WHO, 2016). Although benefits of sufficient iodine status on neurodevelopment are well-known, the threshold at which such adversity is to be expected is not well-established. Furthermore, the only sufficiently powered randomised controlled trial to date ($n \sim 800$) did not show significant improvement in offspring IQ at 5–6 years following iodine supplementation in pregnancy (Gowachirapant et al., 2017). However, the limitation of this study was the substantial loss to follow-up (> 50%) and the fact that the median urinary iodine concentration (~130 μg/L) among study participants was quite close to the WHO cutoff for adequacy (150 μg/L).

[15]Thyroid hormone economy involves homeostasis, but is extends beyond measurements of TH levels in the serum. It refers to all the checks and balances within the thyroid system that maintain the correct levels of TH at the local level, in the tissue. It is the integrated interaction of all the 'compensatory responses' (e.g. transporter up or down regulation, deiodinase activation/deactivation, stimulation of hormone production). Serum TH is simply a readout that correlates well with production at the level of the gland and catabolism primarily in the liver, but it does not necessarily reflect what is happening in individual tissues.

[16]Given the day to day variation for spot or even 24 h urine, such samples do not accurately reflect iodine status on an individual basis.

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Another indirect line of evidence that suggests that iodine inadequacy affects offspring brain development are reports from well-nourished populations that variation in thyroid function, even within the normal range may be associated with poorer offspring neurodevelopmental outcomes (Abel et al., 2019; Gowachirapant et al., 2017; Jansen et al., 2019). These observations are also backed by findings in experimental animals (Gilbert et al., 2022, Gilbert, O'Shaughnessy, Bell, & Ford, 2023, Gilbert, Hassan, et al., 2024). Furthermore, the CONTAM Panel noted that hearing loss in adult rats has been observed at approximately 50% reduction in T4 during the early developmental period (Crofton, 2004). One of the pivotal studies in this area was a relatively large prospective cohorts study examining the relationship between maternal thyroid function in early pregnancy with later offspring neurological function (Korevaar et al., 2016). The study was based on the Generation R study (Rotterdam, Netherlands) who recruited pregnant women between 2001 and 2006. The women provided blood samples prior to gestation week 18 and their offspring were assessed by non-verbal intelligence test at age ~ 6 years ($n = 3839$) and a sub-sample of those underwent an MRI brain scan at age ~ 8 years ($n = 646$). Maternal FT4 showed a significant inverted U-shape association with offspring IQ, grey matter volume and cortex volume. Based on the dose–response curve the 'optimal' range for FT4 in terms of IQ score was ~12 to 20 pmol/L while at concentrations < 7 or > 33 pmol/L the mean IQ scores were on average ~ 2 and ~ 4 points lower, respectively. Offspring whose mothers were in the optimal range for FT4 had also significantly lower risk of having IQ < 85 points. Same conclusions were reached after excluding women with overt hypothyroidism or hyperthyroidism. However, it is worth noting that variation in thyroid function as observed in these studies may not always be directly linked with iodine insufficiency.

In summary, inadequate iodine intake has historically been prevalent in many EU countries and despite efforts to improve iodine status, existing surveys suggest that a substantial part of the EU population may be at risk of deficiency. Pregnant women, children and those adhering to plant base diets are likely to be at higher risk of iodine deficiency. There is strong evidence linking iodine insufficiency with thyroid function and cognitive development. On the other hand, major data gaps pertain to lack of sufficiently powered studies on iodine supplementation in pregnancy in populations that may benefit from such interventions; and how factors influencing iodine absorption affect iodine deficiency in the general population.

3.1.3.8 | *Clinical use of perchlorate*

The use of the perchlorate in human pharmacology was discussed at length in the 2014 Opinion. Since then, no further studies were identified on the clinical use of perchlorate. The main points are summarised here. Perchlorate was introduced in the 1950s for the treatment of thyrotoxicosis. Subsequently, clinical studies showed perchlorate as an effective treatment of Graves' disease and later of hyperthyroidism with doses up to 6–10 mg perchlorate anion/kg bw per day for adults (Wolff, 1998). Its use has largely been discontinued with the availability of alternative treatments. More recently, perchlorate has been applied in the treatment of thyrotoxicosis caused by large iodine loads, such as those caused by the use of the antiarrhythmic drug amiodarone (Soldin et al., 2001; Wolff, 1998). The typical therapeutic strategy includes treatment with 600–1000 mg/day potassium perchlorate in combination with thionamides for 16–40 days (Martino et al., 2001). A review study, published in 2024 (Lisco et al., 2024), confirmed the potential for perchlorate to be a second line treatment for Graves' disease and specific forms of thyroid disorders.

In 2014, the CONTAM Panel noted that the adverse effects during the clinical use of perchlorate, including skin rash, nausea, lymphadenopathy and blood dyscrasias, were reported following repeated treatment with ≥ 400 mg potassium perchlorate per day (4 mg perchlorate anion/kg bw per day), with evidence suggesting a direct relationship between the incidence and severity of the effects and the treatment dose and duration. The CONTAM Panel also noted that it is unknown whether the modes of action underlying the different side effects are related to the thyroid hormone-lowering effect of perchlorate or to other modes of action that may equally apply in healthy individuals.

A recent study from Rump et al. (2021) discussed the protective effect of perchlorate against accumulation in the thyroid of radioactive iodine following nuclear accidents. Doses of perchlorate of 1000 mg per day were proved efficient in protecting against long-lasting exposure to radioactive iodine.

3.1.3.9 | *Risk of bias assessment*

A risk of bias assessment was carried out for the human studies directly relevant to the risk assessment (i.e. relating to thyroid effects). For these studies the risk of bias was classified as definitely low, probably low, probably high and definitely high separately for selection, confounding, attrition, detection, selective reporting and statistics bias. A tailored OHAT Risk of Bias Tool as included in the NTP-OHAT Approach for Systematic Review (Rooney et al., 2014) was used for the risk of bias assessment. Risk of bias for the studies listed in Tables C.1 and C.2 in Annex C was assessed independently by two experts, the assessments were compared, discussed and consensus was reached on all points.

3.1.4 | Mode of action (MOA)

Perchlorate inhibits the NIS and thereby the transport of iodide into cells. Some studies also suggest perchlorate to inhibit TPO and thyroglobulin (Tg) which are directly involved in the biosynthesis of thyroid hormones. As a background, the mechanisms of iodide transport into thyroid follicular cells including the role of TPO and the NIS is shown in Figure 2 (Pesce & Kopp, 2014).

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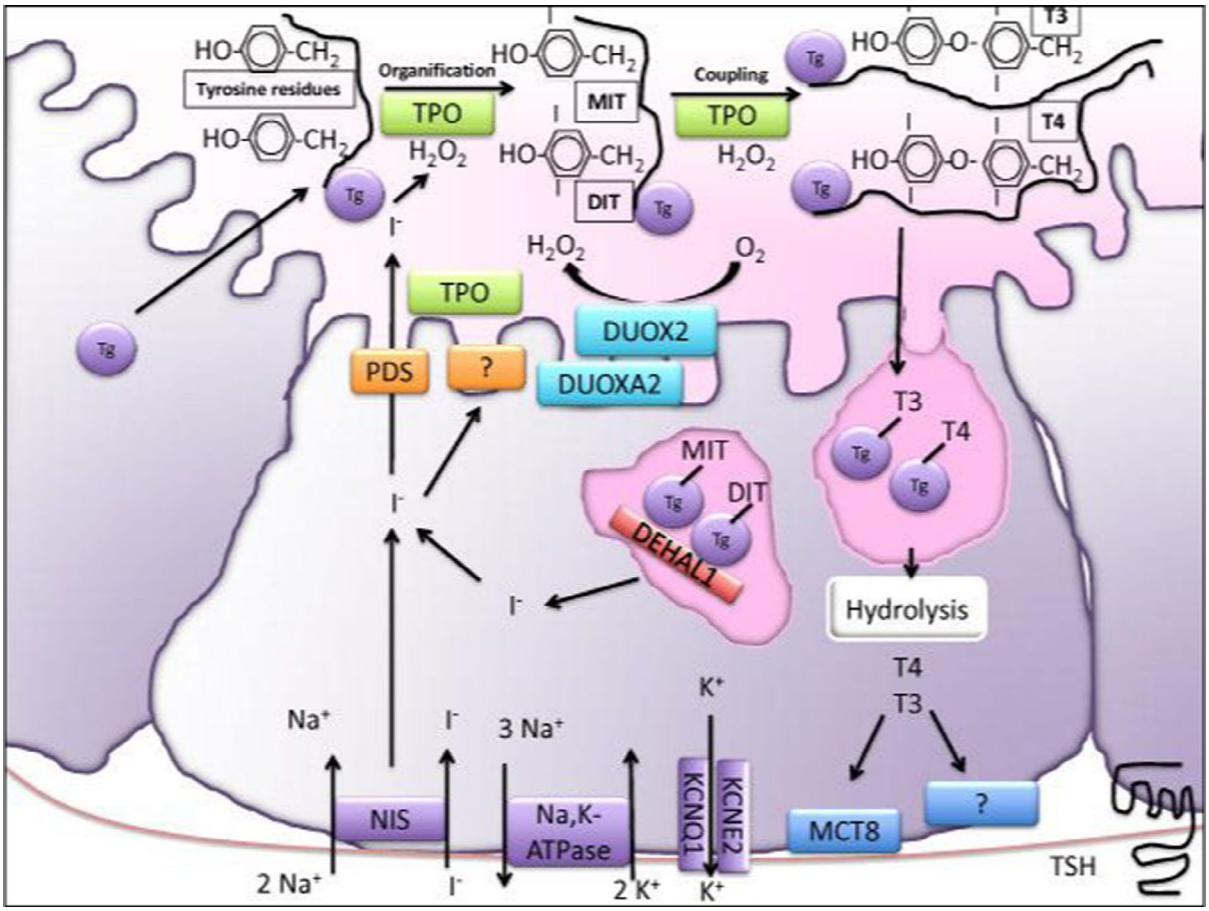

FIGURE 2 Mechanisms of Iodide transport in thyroid follicular cells (Figure reproduced from Figure 1 of Pesce and Kopp (2014): 'Mechanisms of Iodide Transport in Thyroid Follicular Cells'). The first step in iodide uptake is mediated by the sodium iodide symporter NIS, using the sodium gradient generated by the Na, K-ATPase. Active transport of potassium by the KCNE2/KCNQ1 potassium channel is also important, likely for maintaining the membrane potential of thyroid cells. At the apical membrane, pendrin and another yet unidentified transporter mediate iodide efflux. TPO, using H_2O_2 generated by the DUOX2/DUOXA system mediates the oxidation, organification and coupling reaction that result in the synthesis of the iodothyronines T4 and T3. Iodinated thyroglobulin is taken into the cell by micro- and macropinocytosis and digested in lysosomes. T4 and T3 are excreted via MCT8 and other transporters. The iodotyrosines MIT and DIT are dehalogenated by DEHAL1 and the released iodide is recycled. Purple boxes represent steps in basal iodide uptake. Orange boxes represent apical iodide uptake, oxidation, organification and coupling are mediated by TPO, represented in green boxes. The generation of H_2O_2 is represented in aqua. The recycling of iodide after digestion of iodinated thyroglobulin is represented in the red box. The secretion of thyroid hormones at the basolateral membrane is shown in the blue boxes. ATPase, adenosine triphosphatase; DEHAL1, dehalogenase 1; DIT, diiodotyrosine; KCNQ1 or 2, potassium voltage-gated channel subfamily Q member 1 or 2; MCT 8, monocarboxylate transporter 8; MIT, monoiodotyrosine; NIS, sodium iodide symporter; PDS, pendrin; T3, triiodothyronine; T4, thyroxine; Tg, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

3.1.4.1 | *Conclusions of the previous Opinion (EFSA CONTAM Panel, 2014) on mode of action*

In the previous Opinion (EFSA CONTAM Panel, 2014), it was recognised that the mode of action of perchlorate on the thyroid in rats resulted from competitive inhibition of thyroid iodine uptake via interaction with the NIS protein in the basolateral plasma membrane of thymocytes. This results in impairment of the production of thyroid hormones T3 and T4 and increased secretion of TSH by the pituitary gland, hypertrophy and hyperplasia of thyroid follicular cells and thyroid tumours.

In the previous Opinion, it was noted that individuals with heterozygous or homozygous gene mutations which cause a reduction in thyroid hormone synthesis, were considered to be more susceptible to the effects of perchlorate exposure than those who show no genetic variability. These include defects in the NIS and in the thyroid peroxidase mediated oxidation of iodine.

Differences between rats and humans were noted with respect to the binding proteins for T3 and T4, which results in a higher production rate and a markedly shorter half-life of T4 in rats. Differences between rodents and human with respect to both hormone binding proteins and metabolism have been emphasised by EFSA recently in relation to risk assessment of pesticides (EFSA, 2024). Furthermore, the duration of exposure to perchlorate needed to disturb the thyroid hormone status is shorter in rats than in humans. Consequently, in the previous Opinion, humans were considered less sensitive to an increase of TSH than rats.

In humans, severe iodine deficiency either through low iodine intake or exposure to goitrogenic substances such as perchlorate can lead to hypothyroidism. A mild to moderate deficiency of iodine in humans can lead to autonomously functional nodules formation within the thyroid, which have been hypothesised to be a result of potential oxidant-induced mutations. The current CONTAM Panel noted that, although there is evidence for production of ROS with no evidence for

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DNA interaction, it cannot be assumed that mutations arise as a direct consequence. The Panel noted that autonomously functional nodules may arise as a result of sustained follicular cell proliferation.

Individuals with a low iodine status or those with gene mutations causing a reduction of thyroid hormone synthesis may be more susceptible to perchlorate effects in the thyroid (see Section 3.1.3.1). Furthermore, neonates are more susceptible to thyroid perturbation than adults due to a lower serum half-life of T4.

It was noted that decreases in maternal T4 may have adverse effects on rat fetal brain development.

3.1.4.2 | *Newly available evidence on modes of action*

Studies in mammals

Section 3.1.2 herein provides further evidence since the previous Opinion for effects of perchlorate on the thyroid gland and reproductive and developmental toxicity. Various studies have also informed on potential modes of action for these effects as follows.

Chen, Ding, Li, Liu, and Peng (2015) orally administered male Sprague–Dawley rats with perchlorate (0, 130, 260 and 520 mg/kg bw by gavage daily for 13 weeks). In the high-dose group, a significant increase in urinary iodine level was seen at week 6 but no significant difference was found in the urinary iodine level between the exposure groups and controls by week 13. The iodine content of thyroid tissue was significantly reduced at all dose levels and the total protein level in the thyroid glands was significantly reduced at 260 mg/kg bw and above. Oxidative stress was indicated by an increase of superoxide dismutase activity (all dose levels) and catalase activity (520 mg/kg dose). In the study on reproductive toxicity by Yu et al. (2019; see Section 3.1.2) an increase in the expression of testicular *fas* and *c-fos* was suggested by the authors to imply that apoptotic mechanisms were activated but apoptosis was not assessed. Although it has been established that perchlorate does not directly interact with DNA (Section 3.1.2.3), in testicular cells there was an increase in DNA strand breaks induced by perchlorate as measured in the Comet assay. The authors suggested that this may be a consequence of ROS formation based on the finding that testicular glutathione was reduced and malondialdehyde was increased indicating an oxidative stress at rather high-dose levels (1 and 10 mg/kg per day).

When male Wistar rats were given perchlorate orally by gavage (130 mg/kg bw per day) for 45 days, abnormal sperm morphology was observed compared to controls along with a reduction of serum testosterone (Chakraborty, 2021; see Section 3.1.2). There was a reduction of testicular 17β-HSD and 3β-HSD activities and an increase in ROS generation. A moderate deterioration in the sperm head and neckpiece morphology was also seen along with a reduction of epididymal sperm count. Importantly, all of these parameters were more severely affected when potassium iodide (7 mg/kg bw) was co-administered with perchlorate and the authors suggested a synergistic effect between the two. However, the CONTAM Panel noted that no measurements of toxicity were made with iodide alone. There is evidence that excessive iodide can inhibit iodide uptake and it is noted, as an example, that a dose of 37 mg/kg bw per day iodide affected various brain enzymes of rat pups (Scientific Committee on Food, 2006). Consequently, the Panel considers that the available evidence does not support the conclusion of a potential synergistic effect. The epidemiological evidence for an association of iodine deficiency with preeclampsia led De la Peña et al. (2018) to examine gene expression changes by microarray analysis in human placental trophoblasts exposed to perchlorate (1 μM for 24 h). Gene ontology analysis of up- and down-regulated genes indicated disturbance of pathways involved in migration, adhesion and differentiation and there was nuclear translocation of HIF1α protein, and an increase in both Snail and ACE2 proteins as determined by immunoblot. These changes were associated with evidence of an increase in ROS and nitric oxide.

In the study by Gilbert et al. (2023; see Section 3.1.2.2) in which serum and brain thyroid hormone levels were reduced in rat pups at birth, expression of several thyroid hormone-responsive genes was altered in the PN14 pup brain. The exposed pups were also found to have an upregulation of the NIS in the thyroid gland. In the study by Gilbert et al. (2022), T4 and T3 hormones and thyroid hormone-responsive gene expression were reduced in the fetal brain cortex. The study also examined the effects of perchlorate exposure during gestation on gene expression in the thyroid gland of dams and fetuses. In the mothers, there was a significant decrease in the expression of Pax8 and TshR and an upregulation of Nis and Pendrin/Slc26a4. The fetal thyroid glands showed a significant upregulation of NIS and Tpo expression, while Tg expression was reduced. The authors presented a conceptual model encompassing perchlorate dosimetry in the placenta, thyroid gland and serum coupled to a NIS-mediated Adverse Outcome Pathway (AOP) in relation to effects in the fetal brain. The 'molecular-initiating event' of the AOP is the reduction of iodine uptake by perchlorate which leads to the inhibition of the production and release of thyroid hormones to the serum (see Section 3.1.4.2).

When male Wistar rats were treated with 35 mg/kg bw per day of perchlorate administered in drinking water for 60 days, serum TSH levels were increased and serum T4/T3 levels were decreased. The TRH mRNA and protein level was also altered in the hypothalamus (Serrano-Nascimento et al., 2018). Expression of TSH was increased in the pituitary. Pro-inflammatory cytokines were increased in the thyroid and in the serum. These findings point to disruption of the hypothalamus–pituitary–thyroid axis in male rats.

In addition to effects on the thyroid and on reproduction and development, effects on the liver have also been identified. Mice fed a high-fat diet were treated orally with perchlorate (0.1, 1 and 10 mg/kg bw daily for 12 weeks) (Wang, Song et al. 2022). Lipidomic analysis revealed differential metabolites compared to controls at all dose levels indicative of disturbance of the glycerophospholipid pathway.

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Studies in non-mammalian systems

Various additional studies in non-mammalian species shed light on potential modes of action in relation to effects both on the thyroid and on reproduction. These studies are summarised in Table D.1 within Appendix D.

Of particular relevance to the mode of action are the following observations.

Further evidence that perchlorate can produce an oxidative stress comes from studies in liver mitochondria isolated from goldfish (*Carassius auratus*) (Zhao et al., 2014). There was an increase in ROS and malondialdehyde production at a high concentration of perchlorate (1 mM) which the CONTAM Panel considered not relevant to in vivo exposures. Lower concentrations of perchlorate led to inhibition of mitochondrial respiratory complex I (100 μM perchlorate) and IV (10 μM perchlorate). There was also evidence of DNA fragmentation (indicated by a DNA ladder following electophoresis) at 100 μM perchlorate. The authors suggested that perchlorate could cause cytotoxicity resulting from oxidative stress associated with mitochondrial dysfunction.

In the study by Mukhi and Patino (2007) prolonged exposure to perchlorate not only disrupted the thyroid endocrine system of zebrafish but also impaired reproduction and early F1 development.

Lee et al. (2024) exposed zebrafish to sodium perchlorate (0, 3, 30, 300 mg/L, corresponding to 0, 2.44, 24.4, 243.7 mg perchlorate/L) for 21 days. Perchlorate reduced plasma concentrations of thyroid hormones and this effect was observed in both sexes at the lowest concentration of 2.44 mg/L perchlorate, with significant reductions noted at higher concentrations. The decreased TH levels correlated with declining reproductive success assessed using a 21-day short-term reproductive assay with semi-static exposure systems followed by egg counting, odds ration calculation and biomarker analysis post-spawning. Significant reductions in hepatic Vitellogenin mRNA expression were detected in females exposed to 24.4 and 243.7 mg/L perchlorate, indicating a disruption in oocyte maturation. Overall, with increasing concentrations of perchlorate, there was a trend toward decreased reproductive success and hormonal alterations, particularly at the highest concentrations. Moreover, the study revealed increase in cortisol levels in both male and female zebrafish following exposure to all tested concentrations.

The results of a study in adult *Silurana tropicalis* frogs by Campbell et al. (2018) suggest that perchlorate exposure may affect the interaction between the androgen and thyroid hormones, resulting in changes in plasma androgen levels and gonadal thyroid hormone-related transcript levels. These results suggest that perchlorate can potentially disrupt thyroid hormone function, affect androgen-thyroid hormone crosstalk and impair reproductive axes. In the same species, perchlorate exposure led to changes in androgen-related gene expression, particularly in the liver, suggesting altered androgen metabolism under thyroid hormone deficient conditions. These findings highlight the impact of perchlorate on androgen-related gene expression in a stage- and tissue-specific manner, emphasising the complex interplay between thyroid hormone disruption, androgen metabolism and tissue-specific responses in reproductive development of frogs (Flood & Langlois, 2014).

A study by Furin et al. (2015a), in three-spined stickleback embryos suggests that the adverse effects of perchlorate might not be solely attributed to hypothyroidism, as some developmental changes occurred prior to the functional development of thyroid tissue.

Adult sticklebacks were exposed to 100 mg perchlorate/L in water compared to controls and sampled them at 4-hour intervals throughout a 24-h day and weekly throughout the reproductive season (Gardell et al., 2015). Despite the inhibitory effects of perchlorate on the NIS in stickleback fish (Gardell et al., 2015), whole-body T3 and T4 remained stable in response to acute and chronic perchlorate exposure. This suggests the presence of compensatory mechanisms that maintain normal TH levels in the presence of perchlorate. Furthermore, the study suggests that the observed effects of perchlorate in the stickleback may be driven through mechanisms independent of the NIS, such as other SLC5 transporters.

Based on the fact that perchlorate competes with iodine for the NIS for uptake into thyroid follicular cells, Petersen et al. (2022) tested in fish the hypothesis that the symporter might also be expressed in tissues responsible for the development of reproductive organs. Both male and female stickleback were found to express *slc5a5* and its paralogs in gonads. Furthermore, NIS clade-expressing cells in zebrafish included germ cells (*slc5a5, slc5a6a and slc5a6b*) and gonadal soma cells *(slc5a8l)*. These findings indicate the potential for perchlorate to interfere with sexual development directly through interaction with NIS in reproductive tissues. Finally, Zheng et al. (2020) investigated the effects of perchlorate on *Bufo gargarizans* tadpoles' growth, development and the leptin signalling pathway of liver during metamorphosis. Perchlorate caused liver toxicity and might elicit leptin resistance by decreasing the expression of *LepR*, *JAK1*, *JAK2*, *TYK2* and upregulating the level of *SOCS3*. This led to lower energy expenditure, ultimately causing weight gain in the tadpoles.

Adverse Outcome Pathways of relevance to perchlorate

Several AOPs have been proposed supporting the biological plausibility of associations between disruption of the thyroid system and downstream adverse effects such as learning and memory impairment or adverse neurodevelopment outcomes. At present, only a few AOPs have been endorsed by the OECD and address mammalian and/or human effects, including AOP 54 and 42 which are described here after.

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AOP 54: Inhibition of NIS leads to learning and memory impairment

AOP 54[17] describes causative links between inhibition of NIS function during brain development leading to the decreased levels of TH in the blood and consequently in the brain, causing potential learning and memory deficits in children. Such an AOP is relevant to perchlorate and has been peer-reviewed in 2018 and subsequently endorsed by the OECD (Rolaki et al., 2019). The function of the NIS is critical for the physiological production of TH levels in the serum, as it mediates the transport of iodide from the bloodstream into the thyroid cells, which constitutes the initial step for TH synthesis. NIS is a well-studied target of chemicals and its inhibition results in decreased TH synthesis and its secretion into blood leading to subsequent TH insufficiency in the brain. TH regulate the early key brain developmental processes such as neurogenesis, cell migration, proliferation, myelination and neuronal and glial differentiation. TH insufficiency in the brain can lead to detrimental effects in neurocognitive function in children.

Three key events of AOP 54 (i.e. decrease of TH synthesis; T4 in serum and T4 in neuronal tissue) are common to AOP 42[18] describing the inhibition of thyroid peroxidase (TPO) and subsequent adverse neurodevelopmental outcomes in mammals (see below) (Crofton et al., 2019).

AOP 54 refers mainly to humans and rodent species (principally rat). All described key events are applicable to either sex (females and males), in the life-stage 'during brain development', encompassing fetal and perinatal stage, continuing also during childhood and youth. The overall weight of evidence of AOP 54 is strong. The function of NIS and its essentiality for TH synthesis is well-known across species, however, quantitative information on the key-event relationships is limited.

The biological plausibility of AOP 54 is based on the well-established functional relationship between NIS and thyroidal iodide uptake. In humans, NIS mutations are associated with congenital iodide transport defect, a condition characterised by low iodide uptake, hypothyroidism and goitre (Bizhanova & Kopp, 2009; De La Vieja et al., 2000; Pohlenz & Refetoff, 1999). The same is true for the relationship between iodide uptake and serum TH concentration, as it is known that ID is associated with low thyroid hormone levels in the blood (Wolff, 1998; DeLange, 2000). The correlation of serum and brain concentrations of TH are supported by a smaller amount of quantitative data, but the biological plausibility of this connection is mainly based on the number of studies that show that the brain TH is proportional to the serum TH (Broedel et al., 2003).

Multiple events were considered together in only a limited number of studies. The use of potassium or sodium perchlorate has contributed to the identification of a dose–response relationships between NIS inhibition and thyroidal iodide uptake (Cianchetta et al., 2010; Greer et al., 2002; Lecat-Guillet et al., 2007, 2008; Tonacchera et al., 2004; Waltz et al., 2010), but the respective concordance with serum TH was not shown in most of these studies. On the other hand, in the human and animal studies that revealed a strong dose-dependent association between perchlorate exposure and circulating levels of TH (Argus Research Laboratories, 2001; Blount et al., 2006; Cao et al., 2010; Caldwell et al., 1995; Siglin et al., 2000; Steinmaus et al., 2007, 2013; Suh et al., 2014; York et al., 2003, 2004), the decrease of thyroidal iodide was not investigated. In the few cases in which the levels of thyroidal iodide and the serum TH levels were measured in the same study the results are mostly conflicting, mainly due to the well-developed compensatory mechanisms that exist to maintain the TH levels in the body. That means that the effects of NIS inhibitors might not be detectable in short-term experiments or at low doses.

In regard to the downstream events in the pathway, there is a strong correlation between each key event (KE), but the majority of the studies have been performed under severe hypothyroid conditions (high doses of propylthiouracil (PTU) and/or methimazole (MMI), thyroidectomies); therefore, it is difficult to establish the dose–response relationships in each one of them.

TH insufficiency during prenatal and early postnatal periods is linked to deficits in GABAergic neurons, particularly parvalbumin-positive interneurons (Berbel et al., 1996; Gilbert et al., 2007; Westerholz et al., 2013; Westerholz, deLima, & Voigt, 2010), and a decrease in active synapses and synchronised electrical activity in the brain (Hosoda et al., 2003; Westerholz, deLima, & Voigt, 2010). This period is critical for brain development, and TH deficits can result in mental retardation and other neurological impairments in children (Mirabella et al., 2000; Porterfield & Hendrich, 1993). Studies have shown that TH insufficiency during the first two postnatal weeks affects the morphology and function of these neurons and the formation of synaptic connections, with brain-derived neurotrophic factor (BDNF) function also playing a role (Westerholz et al., 2013; Westerholz, De Lima, & Voigt, 2010).

AOP 42: Inhibition of TPO and Subsequent Adverse Neurodevelopmental Outcomes in Mammals

In addition to the perchlorate competitive inhibition of the uptake of iodine via the NIS, some studies suggest that perchlorate can also inhibit TPO. Hosoya (1963) conducted kinetic studies on partially purified preparation of pig thyroid peroxidase using guaiacol as a hydrogen donor, in which the peroxidase enzyme was shown to be inhibited by potassium perchlorate. Price et al. (2020), aiming to develop an assay to screen xenobiotics for their inhibitory effects on rat gland TPO activity, tested nine known TPO inhibitors among which was sodium perchlorate. Sodium perchlorate was the least potent inhibitor, with an IC_{50} value of 13.8 mM. Wu et al. (2012) investigated the effects of ammonium perchlorate on thyroid

[17]AOP 54. Inhibition of Na+/I- symporter (NIS) leads to learning and memory impairment. Alexandra Rolaki A., Pistollato F., Munn S., Bal-Price A. Available at: https://aopwiki.org/aops/54.

[18]AOP 42: Inhibition of Thyroperoxidase and Subsequent Adverse Neurodevelopmental Outcomes in Mammals. Crofton K.M., Gilbert M., Friedman K.P., Demeneix B., Marty M.S., Zoeller R.T., Price A. Available at: https://aopwiki.org/aops/42.

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homeostasis and thyroid-specific gene expression in rat. The study showed a significant decreased gene expression of TPO and of thyroglobulin (Tg) observed at the high-dose treatment of perchlorate (520 mg/kg bw). These findings suggest that perchlorate can suppress gene expression of TPO and Tg which are directly involved in the biosynthesis of thyroid hormones and may therefore aggravate the perturbation of thyroid homeostasis in addition to competitive inhibition of iodide uptake.

AOP 42 describes adverse neurodevelopmental outcomes that may result from the inhibition of TPO during mammalian development, including the implications of developmental TPO inhibition for hippocampal anatomy, function and ultimately neural function controlled by the hippocampus. AOP 42 was originally described and published by Zoeller and Crofton (2005). Chemical inhibition of TPO, the MIE, results in decreased TH synthesis and subsequent reduction in circulating concentrations of THs. As described above, TH insufficiency may result in adverse neurodevelopmental effects in offspring. The adverse consequences of TH insufficiency depend both on severity and developmental timing, indicating that exposure to TPO inhibitors may produce different effects at different developmental windows of exposure.

The taxonomic applicability domain of AOP 42 is mammals, based on the fact that most evidence for this AOP has been gathered from laboratory rodents and humans. However, there are supporting data from amphibians and birds for TPO inhibition leading to altered TH profiles.

The relevant life stages for this AOP are fetal and early postnatal ages during critical windows of nervous system development where thyroid hormones guide normal development of the brain. The influence of maternal thyroid status prior to onset of fetal thyroid function is an important consideration. This AOP does not apply to adult life states.

AOP 42 applies to both males and females. Disruption of thyroid hormone regulation during fetal and early postnatal development, as well as the subsequent adverse impacts on nervous system development are similar in both sexes. There are no compelling data to suggest sex differences in susceptibility to TH disruption mediated by inhibition of TPO during development.

The overall weight of evidence for AOP 42 is strong although quantitative information at all levels of KERs is limited. Gaps in current understanding include the relationship of TH-dependent gene expression and complexities of brain development. In addition, studies available indicate that perchlorate affects TPO only at high doses (Price et al., 2020; Wu et al., 2012).

3.1.4.3 | *Summary of the modes of action*

Overall, experimental evidence supports the role of perchlorate in competing for iodine uptake into the thyroid gland (via the NIS) and potentially uptake into other organs. Studies demonstrate an indirect, thyroid-mediated effect on reproduction and development with apparent interplay between the thyroid and androgen hormones as well as a potential direct interference of perchlorate with reproduction and development. Oxidative stress and indicators of an apoptotic mechanism of mammalian cell toxicity were evident. Mitochondrial dysfunction associated with oxidative stress may contribute to cytotoxicity as reported only in fish. Some studies also suggest perchlorate to inhibit TPO and Tg which are directly involved in the biosynthesis of thyroid hormones.

AOPs 54 and 42, both endorsed by the OECD, support the biological plausibility of associations between inhibition of NIS function and of TPO during mammalian development, with decreased levels of TH in the blood and in the brain, and consequent potential adverse neurodevelopment outcomes such as learning and memory impairment.

3.1.5 | Consideration of critical effects, dose–response modelling and derivation of HBGV

3.1.5.1 | *Consideration of critical effects*

As concluded in the previous EFSA opinion on perchlorate (EFSA CONTAM Panel, 2014) the results from animal studies clearly show that perchlorate inhibits the uptake of iodine via the sodiumiodide symporter, thereby leading to disruption of thyroid hormone synthesis after chronic exposures. The new animal studies assessed in this Opinion further support that conclusion. In addition, the new results provide a more robust characterisation (or quantification) of the relationship between perchlorate exposure and thyroid disruption in rodents. It should be noted however that significant interspecies differences exist in thyroid function and regulation between rats and humans.

Animal studies provide important mechanistic insights into the toxicity of perchlorate. Although human data should remain the primary basis for evaluating the health effects of perchlorate, animal studies are essential to uncover critical aspects of its toxicity, such as thyroid disruption, developmental and reproductive effects.

Some of the new evidence in rat also demonstrates a direct link between thyroid disruption during pregnancy due to perchlorate exposure and its effect on offspring neurodevelopment (Gilbert et al., 2022; Gilbert, O'Shaughnessy, Bell, & Ford, 2023; Gilbert, Hassan, et al., 2024; Gilbert, Hawks, et al., 2024). Even though it is difficult to extrapolate the rat TH perturbations to humans (because of the lengthy exposure time required to deplete the thyroid gland of iodide in the adult human), it is worth mentioning that the human fetus is reliant on its own production of TH in later stages of pregnancy and that, like the rat, the capacity for iodine storage in humans is much lower in the fetus compared to the maternal thyroid gland.

Since the previous Opinion, no new human intervention studies on perchlorate have been conducted, but several observational studies have been published showing associations between perchlorate concentrations in drinking water or

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urine with thyroid hormones in pregnant and non-pregnant subjects. The overall evidence is in line with findings from animal studies. The results from human observational studies suggest some influence on thyroid hormone synthesis at low environmental exposures to perchlorate (with urinary concentration around 4–6 μg/L). Yet, interpreting these observational findings is somewhat challenging. Modelling the dose–response was not considered optimal because of the likely substantial exposure misclassification (single spot urine samples together with a high within-person variability in perchlorate concentrations). The potential influence of other unknown dietary goitrogens adds to this uncertainty. In addition, the modest magnitude of the observed association with the thyroid hormones, the lack of data on prevalence of an abnormal thyroid hormone profile or risk of hypothyroidism, complicates interpretation of adversity and the establishment of a critical endpoint of relevance for this Opinion.

In terms of establishing a health-based guidance value the use of animal studies to characterise risk is also highly uncertain. These uncertainties are particularly pronounced for thyroid hormones given the lower thyroid hormone turnover rates and larger iodine storage capacity in humans versus rodents.

Based on the above it is concluded that the non-randomised human intervention study by Greer et al. (2002) assessing iodine uptake inhibition at relatively low doses of perchlorate exposure in humans still provides the best evidence for characterising risk to human health. This non-randomised intervention study was designed to examine the short-term effects of perchlorate exposure on thyroidal ^{123}I uptake (RAIU). For this purpose, the investigators recruited 37 male and female healthy volunteers aged 22–56 years (mean 37 years, 57% females). These subjects were assigned to each dose group (four males and four females) and given perchlorate in drinking water at 0.007, 0.02, 0.1 or 0.5 mg/kg bw per day over 14 days. However, only 24 (65%) subjects completed measurements of RAIU at 8- and 24-h on exposure days 2, 14 and at day 15 post exposure, which formed the basis for the main study results.

Inhibition of iodine uptake is a key molecular event in an OECD-endorsed adverse outcome pathway with plausible association with thyroid hormone disruption and downstream neurodevelopmental effects that could lead to learning and memory deficits (see Section 3.1.4). The resulting adverse downstream effects have also been clearly demonstrated in rodent studies.

Despite its strengths, the Greer et al. (2002) study has some limitations as reflected partly by its risk of bias assessment (see Annex C). One of the main limitations is the fact that of the 37 participants recruited only 24 completed the study. However, access to the original study data (Haber et al., 2021) allowed for some assessment of the possible consequences of this 35% dropout. These analyses suggested that this substantial dropout is not likely to be a source of major bias given the similarity of those completing and not completing the trial (see Table 6). Another limitation of the trial is its small sample size which makes the general relationship between perchlorate exposure and iodine uptake somewhat uncertain. As a strong inverse association was reported between age and radioiodine uptake, the age distribution of included participants will influence the dose–response substantially. More importantly the direct extrapolation of the study results to pregnant women whose demand in iodine is increased by ~50% during pregnancy is subject to uncertainty.

Taken together, the CONTAM Panel considered the Greer et al. (2002) study as the key study for the present assessment and selected radioactive iodine uptake in humans as the critical event for dose–response modelling and risk characterisation.

TABLE 6 Comparison of study participants characteristics (Mean (SD) or %) of those completing and not completing the intervention study by (Greer et al., 2002; Haber et al., 2021).

	All recruited (***n*** **= 37)**	**Completed** (***n*** **= 24)**	**Did not complete** (***n*** **= 13)**
Age (year)	37.9 (11.8)	37.8 (12.7)	38.1 (10.3)^{NS}
%males	43%	31%	50%
Weight (kg)	76.4 (14.6)^{NS}	77.3 (13.7)^{NS}	74.7 (16.5)^{NS}
Radioactive iodine uptake			
At 8 h	0.128 (0.046)	0.132 (0.431)	0.122 (0.052)^{NS}
At 24 h	0.196 (0.062)	0.202 (0.058)	0.185 (0.069)^{NS}
148 h post exposure	0.077 (0.036)	0.073 (0.036)	0.086 (0.036)^{NS}
158 h post exposure	0.137 (0.041)	0.137 (0.041)	Not applicable

Abbreviation: NS, non-significant difference between those completing and not completing the study.

3.1.5.2 | *Dose–response analysis*

The dose–response analysis is based on the experimental study by Greer et al. (2002), as discussed above. The RAIU into the thyroid was measured at baseline (1 day prior to administration) and on exposure days 2 and 14, at both 8 and 24 h after the administration of radiolabelled iodine.

The same study by Greer et al. (2002) was adopted for the dose–response analysis in the previous EFSA opinion on perchlorate (EFSA CONTAM Panel, 2014). The study does not include an untreated, independent control group however each individual served as their own control, with repeated measures on the same individuals before, during and after dosing.

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Such an experimental design introduces covariance, requiring separation of the control and the exposed groups during modelling, to not violate the assumption of independence of observations (see Section 'BMD modelling' below).

BMR selection

The CONTAM Panel applied a 4-step approach for determining the BMR value:

Step I: selection of human studies describing the RAIU (%) in euthyroid subjects.
Step II: resampling with Monte Carlo simulation to obtain a new distribution (mean, standard deviation).
Step III: determining the lower bound of the biological reference interval ('cutoff value') based on the following equation:

$$CI_{x\%} = \text{mean} - Z \times \left(\text{standard deviation} / (N)^{1/2}\right)$$

Where CI stands for confidence interval and:

- For $p = 90\%$ CI: $Z = 1.645$
- For $p = 95\%$ CI: $Z = 1.960$
- For $p = 99\%$ CI: $Z = 2.576$

It should be noted that the biological reference interval (also called the reference interval or clinical reference value) is the central interval of the distribution obtained in Step II.

Step IV: transformation of the lower bound of the biological reference interval ('cutoff value') into a BMR (% change compared to control) provided by the following equation:

$$\text{BMR}\,(\%) = ((\text{mean} - \text{lower bound of the CI}) / \text{mean}) \times 100.$$

The details of each step are provided below.

Step I:

In humans, there is no clinical internationally recognised reference value for RAIU. A range between 8% and 25% at 24 h is considered an indication of normal thyroid function (UCLA Health, 2020; ANSES, 2022). It was possible to calculate the distribution of this parameter with its mean and standard deviation (ANSES, 2022) from 4 publications as shown in Table 7 (Culp and Huskison (1978) (men) and Culp and Huskison (1978) (women); Gonzalez et al. (2008); Al-Muqbel and Tashtoush (2010); Ballal et al. (2017)).

TABLE 7 Publications including RAIU measurement.

	Mean RAIU 24 h (%) in euthyroid subjects	Standard deviation (%)	N
Ballal et al. (2017)	12.75	5.51	110
Al-Muqbel and Tashtoush (2010)	15	7	102
Gonzalez et al. (2008)	16.2	4.8	105
Culp and Huskison (1978) (men)	15.9	3.3	25
Culp and Huskison (1978) (women)	20.2	5	28

Abbreviation: RAIU, radioactive iodine uptake.

Step II:

Resampling with Monte Carlo simulation in RStudio:

For each of the above publications, a lognormal distribution of RAIUs is modelled, then N individual values corresponding to N virtual samples are randomly drawn. The N samples obtained for each publication are grouped, giving a set of 370 data (110 + 102 + 105 + 25 + 28). An adjustment is made to this data set to obtain a lognormal distribution from which the mean and standard deviation are extracted.

The mean and standard deviation re-calculated for RAIU were 15.20 and 6.15 respectively, with $N = 370$.

Step III - IV: calculation of lower clinical reference value (cutoff value) and transformation into a BMR (% change compared to the control) (Table 8).

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TABLE 8 Cutoff values (lower confidence intervals (CI) of RAIU 24 h) and corresponding BMRs.

Cutoff value, lower CI of RAIU 24 h (%)		Corresponding BMR (%)
$CI_{90\%}$	14.67	3.5
$CI_{95\%}$	14.57	4.1
$CI_{99\%}$	14.38	5.4

Abbreviations: BMR, benchmark response; $CI_{90/95/99\%}$, lower bound of the 90/95/99% confidence interval; RAIU, radioactive iodine uptake.

In summary, the selected BMR is based on a biological reference interval which reflects normal variation in RAIU at a population level.

Due to heterogeneity in the different populations of the studies listed in Table 7 (India, Jordan, Chile and USA influenced by e.g. different diets and ages) used for estimating the reference range of RAIU, it is assumed that the calculation of RAIU range to some extent takes into account different iodine sources and intake of other goitrogenic compounds.

The lower bound of the 95% confidence interval of RAIU was estimated at 14.6%. The CONTAM Panel considers that a reduction below a RAIU of 14.6% is outside the normal population range and deemed to be a biologically relevant basis for defining the BMR for perchlorate. It was estimated that a 4.1% reduction in RAIU would be outside the biological reference interval on a population basis. This value was rounded up to 5% and was used as the BMR.

BMD modelling

The Reference Point (RP) was derived using the Bayesian Benchmark Dose (BMD) modelling web-tool (version 0.1.5) with RAIU inhibition as the selected endpoint. The BMD analysis was performed in accordance with the latest EFSA BMD guidance (EFSA Scientific Committee, 2022).

Since this guidance addresses the analysis of dose–response data from toxicity studies in experimental animals, an adaptation of the approach for human data was performed taking into consideration more recent guidance on epidemiological studies and how such adaptations could be made (EFSA Scientific Committee, 2024).

The BMD tool is flexible in terms of data and options and offers the possibility to inform the modelling via a Bayesian module. However, the data from Greer et al. (2002) poses some challenges, particularly because a) the RAIU is bounded between 0 and 1, and b) there is covariance among measurements taken at different time points.

a. To address the first issue, the use of a logit transformation of the data was initially appraised. Such a choice, while on one hand allowed to deal with unbounded data, on the other introduced the issue of having to transform the BMR on the same scale, but such a transformation of the BMR was found impractical. Further testing on the data showed that, within the range of RAIU values, the lognormal distribution available in the Bayesian BMD tool did not pose problems at the boundaries. In fact, it behaved similarly to, e.g. a bounded beta distribution that was used by Haber et al. (2021) to model the same Greer et al. (2002) data. A comparison showing similarity of fits to the RAIU data using both beta and lognormal distributions is presented in Appendix C. As a result, it was concluded that the lognormal distribution was appropriate for modelling the Greer et al. (2002) study.
b. The effect of covariance intrinsic to the study design has been addressed by using the control data (baseline measured 24 h after administering radiolabelled iodine) to build a prior distribution and use its minimum, maximum and mode values in the Bayesian module to inform the background parameter. This prior distribution was developed in R and was based on the mean, mode and maximum values derived from a PERT distribution ('Programme evaluation and review technique', a continuous probability distribution) (for details, see Appendix C)) (Clark, 1962; Starkweather, 2010; Vose, 2008). Importantly, this approach ensured that the control data were not used to derive the dose–response curves, thus avoiding any covariance between the control and active doses.

The Bayesian BMD modelling was carried out with the specifications provided above and the settings detailed in the Appendix C. A benchmark response (BMR) of 5% was selected (see Section 'BMR selection' above). Using model averaging, the benchmark dose lower credible interval ($BMDL_5$) was determined to be 0.007 mg/kg body weight per day for a 5% absolute change in RAIU, measured as a continuous variable on day 14, 24 h after radiolabelled iodine administration.

Table 9 provides an overview of the BMD results obtained. A more detailed description of the BMD analysis can be found in Appendix C.

TABLE 9 Benchmark dose (BMD) analysis for the effects of perchlorate in Greer et al. (2002).

Study	Compound	Response	BMR (%)	BMDL (mg/kg bw per day)	BMD (mg/kg bw per day)	BMDU (mg/kg bw per day)	Lowest non-zero dose (mg/kg bw per day)
Greer et al. (2002)	Perchlorate	RAIU inhibition	5	0.007	0.043	0.185	0.007

Abbreviations: BMD, benchmark dose; BMDL, benchmark dose lower credible limit; BMDU, benchmark dose upper credible limit; BMR, benchmark response; bw, body weight.

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In EFSA's previous 2014 opinion on perchlorate in food (EFSA CONTAM Panel, 2014), the BMD modelling was conducted using the software PROAST 38.9 (RIVM) and was based on the EFSA guidance on the use of the BMD for continuous data (EFSA, 2009). Based on this, the following BMDL, BMD and BMDU values were obtained for a 5% excess risk: 0.0012, 0.0036 and 0.0088, respectively. Thus, the BMDL in the previous Opinion was less than one fifth of the BMDL obtained in the current assessment. There are several notable differences between the two opinions that factor in to explain the difference in the estimated BMD parameters between the current and the previous opinion:

- Different statistical paradigms: The previous opinion used a frequentist approach (PROAST), while the current one employs a Bayesian framework (EFSA Bayesian BMD tool). This leads to differences at many levels, including the analytical solver, uncertainty estimation and the use of prior information.
- The previous opinion used summary data, whereas the current assessment utilises individual data (available in Haber et al., 2021).
- The Bayesian platform uses weighted model averaging to estimate the BMD distributions (average of 8 models in the current assessment, see Appendix C, following the recommendations of the EFSA 2022 BMD guidance (EFSA Scientific Committee, 2022). In contrast, the previous opinion included results from the Hill model only.
- As noted earlier, the experimental design of v causes the dose groups to be correlated with the control group. To avoid dependencies and prevent the violation of the assumption of group independence, the current analysis excluded the control group from the modelling and used the data solely to inform the background parameter (see Appendix C). This was not the case in the previous opinion, in which the assumption of group independence was violated.

The study by Greer et al. (2002) has also been utilised by various institutions and researchers for dose–response modelling (see Table 10).

The considerable variability in reported BMDLs reflects different choices of BMR (ranging from 5% to 50%, or using BMR together with a cutoff value), but also the use of single model versus Bayesian averaging. The study by Haber et al. (2021) developed an ad hoc hierarchical model to address the particularities of the data, though the BMDL was estimated using a single model.

3.1.5.3 | *Derivation of a HBGV*

The CONTAM Panel considered limitations associated with the study of Greer et al. (2002) which was used for the derivation of the Reference Point. The study was based on a limited number of subjects (37, 24 of which completed the study) which were all healthy adult volunteers, possibly not reflecting inter-individual variability in TD of the wider population. A default uncertainty factor (UF) of 10 is normally used for variability of TK and TD. Since perchlorate is largely excreted unmetabolised with minimal variability in absorption, distribution and excretion, and given its short half-life, an UF for TK is not considered. However, an uncertainty factor is required for TD due to potential variations in response across individuals and populations.

In addition, the Panel also considered that account needs to be given to the sensitivity of the fetus to maternal thyroid disturbance (see Section 3.1.3.7) and uncertainty around the impact of ID on the perchlorate effects during fetal and early postnatal development (see Section 3.1.4.2). Furthermore, it is noted that there is a higher demand for iodine during pregnancy (approximately 50% increase). The prevalence of ID in the European adult population is high (see Section 3.1.3.7).

Taking into account potential differences in TD, the small sample size of the Greer et al. (2002) study, the uncertainties around the impact of an increased iodine demand during pregnancy and the high prevalence of iodine deficiency in the European population, it was decided that an overall UF of 5 is warranted. This leads to a TDI of 1.4 μg/kg bw per day.

The CONTAM Panel considered that, based on the toxicokinetics (e.g. relative short half-life) and mode of action of perchlorate in relation to iodine uptake, this TDI, derived from a 'short-term' study of 14 days (Greer et al., 2002), is considered to be relevant for chronic exposures. Furthermore, it takes into account the possibility that relatively high levels of thyroid iodine uptake inhibition for short periods could induce adverse effects in vulnerable groups of the population, in particular developing fetuses and neonates.

For comparison, Table 10 summarises the key toxicity reference values established since 2011 by (inter)national organisations and researchers based on the study from Greer et al. (2002).

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TABLE 10 Overview of key dose–response analyses using data from Greer et al. (2002) and derived toxicity reference values by (inter)national organisations and researchers since 2011.

Reference	Endpoint	Time point(s) modelled	Individual/ summary data	Model	Web-tool	BMR (%)	BMDL (μg/kg bw/day)	Uncertainty factor	Toxicity reference value (μg/kg bw per day)
JECFA (2011)	RAIU inhibition	8- and 24-h ^{123}I thyroid uptakes at days 2 and 14	Summary	Exponential model	PROAST (v. 23.2)	50	114	10	10
EFSA CONTAM Panel (2014)	RAIU inhibition	8- and 24-h ^{123}I thyroid uptakes at days 2 and 14 (time as a covariate)	Summary	Hill model	PROAST (v. 38.9)	5	1.2	4	0.3
CalEPA (OEHHA) (2015)	RAIU inhibition	24-h ^{123}I thyroid uptake at day 14	Summary	Hill model	BMDS (v. 2.0.0.33)	5	3.7	10	0.37
Weterings et al. (2016)	RAIU inhibition	8- and 24-h ^{123}I thyroid uptakes at days 2 and 14	Summary	Exponential 5 model	PROAST (v. 38.9)	20	16.6	4	4
Bruce et al. (2018)[a]	RAIU inhibition	24-h ^{123}I thyroid uptake at day 14	Individual	Linear	BMDS (v. 2.6.0.1)	20	21	N.A.	N.A.
Health Canada (2020)	RAIU inhibition	N.R.	Summary	N.R.	BMDS (v. 2.7.0.4)	20	10.9	10	1.09
Haber et al. (2021)	RAIU inhibition: Subjects with an RAIU below 8%	8- and 24-h ^{123}I thyroid uptakes at days 2 and 14	Individual	Hill/Exponential 5 model	ad hoc	Hybrid BMR: 10% excess risk of iodine uptake below 8%	30	4 10	7.5 3
ANSES (2022)	RAIU inhibition: Subjects with an RAIU below 9.1%	24-h ^{123}I thyroid uptake at day 14	Individual[b]	Log-probit model	PROAST (v. 70.1)	Hybrid BMR: 10% excess risk of iodine uptake below 9.1%	15.2	10	1.5
Current assessment	RAIU inhibition	24-h ^{123}I thyroid uptake at day 14	Individual	Model averaged	Bayesian BMD (v. 1.0.5)	5	7	5	1.4

Abbreviations: ANSES, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental, and Occupational Health & Safety); BMDL, benchmark dose lower confidence limit; BMDS, benchmark dose modelling tool, developed by the U.S. Environmental Protection Agency, EPA; BMR, benchmark response; bw, body weight; CalEPA, California Environmental Protection Agency; I, iodine; JECFA, Joint FAO/WHO Expert Committee on Food Additives; N.A., not applicable; N.R., not reported; OEHHA, Office of Environmental Health Hazard Assessment (a division of CalEPA); PROAST, benchmark dose modelling tool, developed by the Dutch National Institute for Public Health and the Environment (RIVM); RAIU, radioactive iodine uptake; v., version.

[a]Pooled data from the clinical studies of Greer et al. (2002), Lawrence et al. (2000) and Lawrence et al., 2001) and Braverman et al. (2006).

[b]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.

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3.2 | Occurrence data

3.2.1 | Occurrence data in food

3.2.1.1 | *Occurrence data in food used for dietary exposure assessment*

An initial number of 40,618 analytical results on perchlorate in food was available in the EFSA database by 4 June 2024 (Annex E). Data were reported by 20 Member States plus Norway, Switzerland and United Kingdom, and sampled between years 2016 and 2022.

The occurrence data were carefully evaluated, and a list of validation steps was applied before being used to estimate dietary exposure.

The description of the food analysed was checked and improved/updated in many instances because of lack of consistency between the reported analytical result value and the values of the limits of detection and quantification. Data providers were contacted to clarify inconsistencies identified during the data check.

Results reported and confirmed by data providers as suspect sampling were excluded from the analysis ($n = 238$).

Where analytical results were reported as not corrected for recovery, the reported result was multiplied by the reported recovery factor. Reported recovery factors ranged from 80% to 100% with a median value of 100%. When no indication was provided on the application of a correction factor it was assumed that the result was reported as corrected. A number of analytical results were reported as not corrected for recovery and no recovery factor was provided ($n = 459$). In this case the recovery was assumed to be 100%.

Analytical result values, LOD and LOQs were checked against the maximum levels set by Commission Regulation (EU) 2023/915 of 25 April 2023. The percentages of quantified analytical results over the total number of samples exceeding the maximum level per FoodEx2 category are displayed in Table 11. These samples were retained in the assessment as considered representative of potential concentrations to which the general population is exposed.

TABLE 11 Percentages of quantified analytical results over the total number of samples per FoodEx2 category, exceeding the maximum level set by Commission Regulation (EU) 2023/915 of 25 April 2023.

FoodEx2	N EX	N TOT	%
Vegetables and vegetable products	77	12,297	0.63%
Fruit and fruit products	12	9568	0.13%
Ingredients for coffee, cocoa, tea and herbal infusions	21	5472	0.38%
Processed cereal-based food for infants and young children	21	519	4.05%
Ready-to-eat meal for infants and young children	3	1171	0.26%
Other food for infants and children	1	138	0.72%
Total	135	29,165	0.46%

Abbreviations: N EX, number of samples exceeding the maximum level; N TOT, total number of samples.

On the other hand, to avoid impacting the UB estimates of perchlorate with measurements of very low reliability, which would introduce very high degree of uncertainty, left-censored analytical results reported with an LOD (result below limit of detection) or an LOQ (results below limit of quantification) greater than the maximum levels set by the legislation were excluded ($n = 24$).

After the described cleaning procedure, 262 analytical results were excluded while 40,356 analytical results were made available to be included in the dietary exposure assessment to perchlorate.

The number of analytical results per year and country in this final dataset is presented in Table 12. Most analytical results were provided by Germany (79.3%) and 79% of samples were sampled between years 2019 and 2022. Although reported by the countries listed in Table 12, 7868 of samples were reported as of non-EU origin (19%) while 9321 samples were of unknown origin (23%).

TABLE 12 Number of analytical results per year and reporting country in the final occurrence dataset used in the dietary exposure assessment.

Country/year	2016	2017	2018	2019	2020	2021	2022	Total	% by country
Austria		104	218	198	178	699	626	2023	5.0%
Belgium						50		50	0.1%
Croatia		15					18	33	0.1%
Cyprus		36				124		160	0.4%
Czechia		12	7	2	3	12	14	50	0.1%
Denmark	40	36			1	2	3	82	0.2%
Estonia						9		9	0.0%

(Continues)

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TABLE 12 (Continued)

Country/year	2016	2017	2018	2019	2020	2021	2022	Total	% by country
Finland	44	31			40	10	3	128	0.3%
France	177	214	232	206	129	193	413	1564	3.9%
Germany	2482	1924	2568	7715	5813	5858	5653	32,013	79.3%
Greece							2	2	0.005%
Hungary	31				74	39		144	0.4%
Ireland	35				21	171	79	306	0.8%
Italy	8	6	24	39	70	66	26	239	0.6%
Luxembourg				15	59	18	76	168	0.4%
Netherlands				328	507	436	130	1401	3.5%
Norway	100							100	0.2%
Poland			1		69	500	104	674	1.7%
Portugal				10	16	291	1	318	0.8%
Spain	7	169	108		70	113	74	541	1.3%
Switzerland					47	27	17	91	0.2%
United Kingdom[a]		15	18	74				107	0.3%
United Kingdom (Northern Ireland)[b]						153		153	0.4%
Total	**2924**	**2562**	**3176**	**8587**	**7097**	**8771**	**7239**	**40,356**	100.0%
% by year	7%	6%	8%	21%	18%	22%	18%	100%	

[a]Occurrence data included in the assessment were submitted to EFSA when the UK was a member of the EU.

[b]Pursuant to Article 5(4) and Section 24 of Annex 2 of the Protocol on Ireland/Northern Ireland, which is an integral part of the Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, the EU requirements on data sampling are also applicable to Northern Ireland and, for the purpose of this assessment, references to Member States are read as including the United Kingdom in respect of Northern Ireland

Left-censored data in the final dataset accounted between 24% and 100% across FoodEx2 Level 1 food categories.

Number of available samples, percentage of left censorship, mean LB and UB occurrence estimates and highest quantified values and LOQs reported per FoodEx2 category are presented in Table 13 (Figure 3).

TABLE 13 Number of available analytical results (*N*), percentage of left censorship (%LC), mean lower bound (LB) and upper bound (UB) occurrence estimates and maximum quantified values and limits of quantification (LOQs) reported per FoodEx2 category (concentrations in μg/kg) in the final perchlorate occurrence dataset used for the dietary exposure assessment.

FOODEX2 CATEGORY	*N*	%LC	Mean LB	Mean UB	Max quantified	Max LOQ
Grains and grain-based products	2048	96%	0.74	10.18	70	50
Vegetables and vegetable products	12,585	77%	10.23	15.15	2600	379
Starchy roots or tubers and products thereof, sugar plants	889	97%	1.26	6.78	160	20
Legumes, nuts, oilseeds and spices	2094	56%	117.23	122.08	13,400	100
Fruit and fruit products	9912	96%	1.05	6.72	540	100
Meat and meat products	342	99%	0.09	7.44	19	30
Fish and seafood	821	96%	1.38	7.01	150	98
Milk and dairy products	528	97%	0.52	7.17	35	300
Eggs and egg products	232	95%	1.46	10.66	63	20
Sugar and similar, confectionery and water-based sweet desserts	128	84%	6.06	13.48	96	30
Animal and vegetable fats and oils and primary derivatives thereof	46	100%	0	16.39	0	33
Fruit and vegetable juices and nectars (including concentrates)	539	98%	11.45	15.79	6100	30
Coffee, cocoa, tea and infusions	5704	24%	111.35	115.14	34,000	750
Alcoholic beverages	550	96%	0.71	6.09	120	50
Products for non-standard diets, food imitates and food supplements	204	95%	19.21	25.13	570	300
Composite dishes	54	65%	9.07	13.01	132	30
Seasoning, sauces and condiments	12	58%	54.33	59.75	230	10

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TABLE 13 (Continued)

FOODEX2 CATEGORY	*N*	%LC	Mean LB	Mean UB	Max quantified	Max LOQ
Major isolated ingredients, additives, flavours, baking and processing aids	629	13%	188.48	191.98	2300	750
Food products for young population	10	100%	0.00	10.00	0	10
Follow-on formulae, powder	385	47%	3.32	6.91	60	30
Infant formulae, powder	643	60%	1.52	5.50	28.4	30
Infant formulae, liquid	42	90%	0.42	3.43	6	10
Follow-on formulae, liquid	73	79%	0.66	2.63	8	10
Follow-on formulae, unspecified	22	95%	0.09	9.64	2	10
Infant formulae, unspecified	12	100%	0.00	10.00	0	10
Processed cereal-based food for infants and young children	519	81%	1.26	5.44	21	30
Ready-to-eat meal for infants and young children	1171	91%	0.57	4.98	260	30
Other food for infants and children	77	84%	0.52	2.49	12.8	25
Drinking water	62	98%	0.03	1.16	1.687	3
Water-based beverages	23	78%	3.12	5.66	44	10
Total	**40,356**					

Abbreviations: LB, lower bound; LC, left-censored; LOQ, limit of quantification; UB, upper bound.

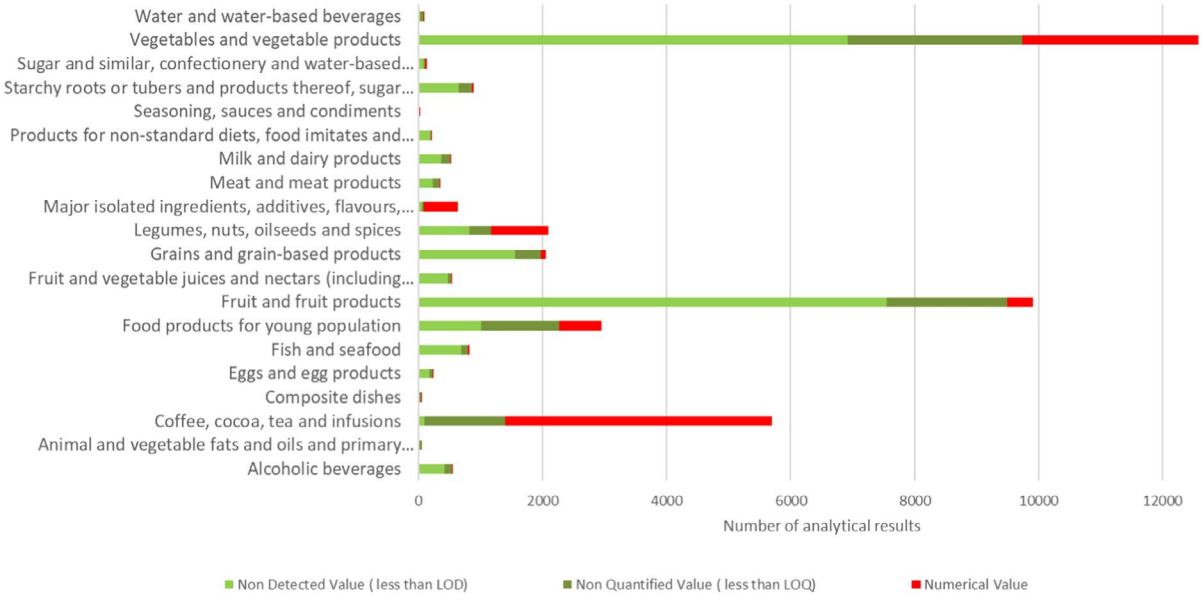

FIGURE 3 Number of available analytical results, proportions of non-detected, non-quantified and quantified analytical results across FoodEx2 Level 1 food categories in the final perchlorate occurrence dataset used for the dietary exposure assessment.

The highest quantified values of perchlorate occurrence in food were found in dried herbs (used for infusions, as spices or flavours) up to 34,000 µg/kg. The highest quantified results different from dried herbs was found in a sample of powder fruit juice (6100 µg/kg) and in samples of unprocessed spinach (up to 1325 µg/kg) and more in general of leafy vegetables. The highest percentage of quantified samples was found in the Foodex2 level 1 category 'Coffee, cocoa, tea and infusions' (76%) and in particular in the subcategory 'Herbal infusion materials from leaves and herbs' where 95% of the 2055 samples had quantified results.

Perchlorate LB and UB mean concentrations and the highest reliable percentile for the different FoodEx2 food categories were calculated as described in Section 2.3.1.

To complement the limited available drinking water occurrence data from the EFSA database. Literature data were used (See Section 3.2.1.2). The contribution of water to the concentration of perchlorate in food was also taken into consideration when calculating concentrations of perchlorate for coffee, tea and herbal beverages from their ingredients, pasta, bread and porridge and food for the young population. The total number of analytical results considered in the calculations and the LB and UB mean and highest reliable percentile (HRP) concentrations calculated for drinking water are displayed in Table 14. It should be noted that for the short-term dietary exposure assessment the mean was used instead of the HRP as the HRP LB value was lower than the mean LB value.

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TABLE 14 Total number of analytical results considered in the calculations and the lower bound (LB) and upper bound (UB) mean and highest reliable percentile (HRP) concentrations calculated for drinking water.

FOODEX2	term_Level	*N*	Mean LB	Mean UB	HRP LB	HRP UB	HRP
Drinking water	2	417	0.06	1.3	0	2	P97.5
Unbottled water	3	305	0.08	1.34	0	1.6	P97.5
Bottled water	3	112	0	1.2	0	2	P97.5

Abbreviations: HRP, highest reliable percentile; LB, lower bound; P97.5, the 97.5th percentile; UB, upper bound.

In addition, for infant and follow-on formula, concentrations for the liquid form were calculated combining the concentrations reported directly for the liquid form ($n = 42$ and $n = 73$ respectively) with those calculated from the concentrations reported for the dry form using a dilution factor of 8 ($n = 643$ and $n = 385$). Concentrations of perchlorate in infant and follow-on formula dry and liquid forms used for the dietary exposure assessment are displayed in Table 15.

TABLE 15 Lower bound (LB) and upper bound (UB) mean and highest reliable percentile (HRP) (99th) concentrations (μg/kg ww) of perchlorate in infant formula (liquid and reconstituted to liquid form) submitted to EFSA.

FOODEX2	*N*	Mean LB	Mean UB	HRP_P99_LB	HRP_P99_UB
Infant formula, liquid	685	0.26	2.08	2.56	6.64
Follow-on formula, liquid	458	0.50	2.24	3.94	8.34

Abbreviations: HRP, highest reliable percentile; LB, lower bound; P99, the 99th percentile; UB, upper bound; ww, wet weight.

For breastfed infants, Table 16 presents the occurrence of perchlorate in human milk samples of the EU lactating women population, derived by the CONTAM Panel using the biomonitoring equivalent equation from chronic dietary exposure data for lactating women, as described in Section 2.6.3. Whilst short-term exposure data were deemed necessary to consider with respect to pregnant women because of the critical stages of neurodevelopment of the fetus including intensive neuronal cell proliferation, it is considered that the chronic dietary exposure was appropriate to use for the breastfed infant scenario when the infant is able to produce thyroid hormones.

Based on daily human milk production of 0.8 L/day, the mean perchlorate concentrations in human milk (LB –UB) ranged from 1.4 to 8.8 μg/L, while the highest reliable percentile (99th) concentrations (LB–UB) range from 4.1 to 15.7 μg/L. With a human milk production of 1.2 L/day, the mean and the highest reliable percentile (99th) concentrations (LB–UB) range from 1.0 to 10.5 μg/L. Of note, assuming a fixed amount of perchlorate exposure via the diet to the mother, the perchlorate concentrations in human milk is larger in smaller volume (0.8 L) and smaller in larger volume (1.2 L). The range of obtained mean concentrations is in line with non-EU literature data presented in Table 18.

TABLE 16 Mean and the highest reliable percentile (99th) concentrations (μg/L) of perchlorate in human milk based on 0.8 L/day and 1.2 L/day human milk production, as estimated by the CONTAM Panel using biomonitoring equivalent equation.

Perchlorate concentration in human milk (μg/L)[a]					
		Mean		Highest reliable percentile 99th	
Human milk production	*N*	LB	UB	LB	UB
0.8 L/day	444[b]	1.4	8.8	4.1	15.7
1.2 L/day	444[b]	1.0	5.9	2.7	10.5

Abbreviations: LB, lower bound; UB, upper bound.

[a]The estimate was calculated using chronic dietary exposure data for lactating women (as calculated for this Opinion), assuming that 54% of perchlorate is excreted in human milk and that daily human milk production is 0.8 L or 1.2 L.

[b]The number of lactating women for whom chronic exposure estimates were used in the calculation, as mentioned in footnote a.

All calculations made as described in Section 2.3.1, to derive perchlorate concentrations in food subcategories for which data were not directly available, are detailed in Annex B (Table B.2).

The concentrations used in the chronic and short-term dietary exposure scenarios for each FoodEx2 code available in the Comprehensive Consumption Database and for which a concentration could be calculated are available in Table B.3 of the Annex B.

3.2.1.2 | *Occurrence data in food from literature*

As part of the comprehensive literature search, potentially relevant studies and reviews relating to occurrence in food were identified. From the articles retrieved from literature, it was noted that for food categories for which data was available, the coverage of occurrence data available in this Opinion for food categories considered in the exposure assessment was in comparison to the previous EFSA statement (EFSA, 2017) much more important in terms of number of analytical results submitted (> 40,000 vs. 18,000) and had a much wider representation of the diet considered for food categories that were

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not covered in the previous 2017 EFSA statement due to a lack of data submitted at that time (e.g. food of animal origin, meat and meat products, fish and seafood and eggs and egg product).

Overall, the CONTAM Panel decided to focus its review for occurrence data from the literature only on food categories for which limited or no information was available from the occurrence data submitted to EFSA (Section 2.3.1) as it was the case for bottled and unbottled water ($n = 62$ samples, see Section 3.2.1.1 vs. 120 in the previous EFSA 2017 scientific report), for human milk ($n = 0$) or for food categories for which available data had shown high concentrations that was needed for checking consistency as it was the case for dry tea leaves/tea beverages data.

Bottled and unbottled water

From the submitted data, sampling from 2016 to 2022 was reported by some Member States for bottled and unbottled water (n = 62 samples). For unbottled water, 46 samples (Hungary, Germany) with 98% LC and applying the lower-middle-upper-bound EFSA approach would result in a mean MB concentration level of perchlorate of 0.54 μg/L (LB of 0.04 and UB of 1.04). For bottled water, 16 samples (Czechia, Germany) with 100% LC would result in a mean MB concentration level of perchlorate of 0.75 μg/L (LB of 0 and UB of 1.5).

For Poland, perchlorate levels in Polish water samples of various origins were published by Nizinski et al. (2021). Samples of bottled ($n = 31$) and unbottled water ($n = 40$) using the IC-CD method with an LOD of 0.43 μg/L and an LOQ of 1.42 μg/L were analysed during the 2020 year. The level of perchlorate was below the LOD in all bottled and unbottled water samples. Applying the lower-middle-upper-bound EFSA approach for the treatment of left-censored data would result in an estimated mean MB concentration level of perchlorate from bottled and unbottled water of 0.22 μg/L (LB of 0 and UB of 0.43).

For Cyprus, Constantinou et al. (2019) published an article on LC–ESI–MS/MS determination of oxyhelides (chlorate, perchlorate and bromate) in food and water samples, and chlorate on household water treatment devices along with perchlorate in plants. In total 284 drinking water samples (219 unbottled water and 65 bottled water) were analysed using the LC–MS/MS with an LOD of 1.5 μg/L and an LOQ of 5 μg/L. The sampling was performed from different sampling points all over Cyprus including tap water from schools, hospitals and houses as well as bottled water, vending machines and mobile water containers originating from springs. A total of 98% of the samples were < LOD, 1.4% below LOQ and 0.7% ($n = 2$) were detected slightly above the LOQ at concentrations of 7 and 8 μg/L. In summary, applying the lower-middle-upper-bound EFSA approach for the treatment of censored data would result in an estimated mean MB concentration level of perchlorate from bottled and unbottled water of 0.15 μg/L (LB of 0.07 and UB of 0.22).

In conclusion, as shown in Table 17, the available data collected within this Opinion and extracted from the EU literature suggest a mean MB concentration level of perchlorate for unbottled water of 0.24 μg/L (range between LB = 0.08 to UB = 1.34 μg/L for 99% LC data) and for bottled water of 0.21 μg/L (range between LB = 0 to UB = 1.2 μg/L for 100% LC data). The highest reliable percentile for the P97.5 MB concentration level of perchlorate for unbottled water would be 0.7 μg/L (range between LB = 0 to UB = 1.6 μg/L) and for bottled water of 1 μg/L (range between LB = 0 to UB = 2 μg/L).

The mean MB concentration level for all drinking water (unbottled and bottled water) would be 0.23 μg/L (range between LB = 0.06 to UB = 1.3 μg/L for 99% LC data). The highest reliable percentile for the P97.5 MB concentration level of perchlorate for all drinking water (unbottled and bottled water) would be 1 μg/L (range between LB = 0 to UB = 2 μg/L).

TABLE 17 Summary of EU occurrence data of perchlorate for unbottled and bottled water collected and retrieved from the literature review published after the 2017 EFSA Scientific Report.

EU Unbottled water (drinking water, tap water)	*N* samples	LOD	LOQ	%LC	% < LOD	Mean LB (μg/L)	Mean MB (μg/L)	Mean UB (μg/L)	HRP P97.5 LB	HRP P97.5 MB	HRP P97.5 UB
Data collected within this Opinion (Hungary, Germany)	46	1	3	98	98	0.04	0.54	1.04			
Poland (Niziński et al., 2021)	40	0.4	1.4	100	100	0.00	0.22	0.43			
Cyprus (Constantinou et al., 2019)	219	1,5	5	99	98	0.11	0.18	1.56			
Total	**305**			**99**		**0.08**	**0.24**	**1.34**	**0.00**	**0.7**	**1.6**

(Continues)

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TABLE 17 (Continued)

EU Bottled water (mineral water and water source)	*N* samples	LOD	LOQ	%LC	% < LOD	Mean LB (μg/L)	Mean MB (μg/L)	Mean UB (μg/L)	HRP P97.5 LB	HRP P97.5 MB	HRP P97.5 UB
Data collected within this Opinion (Czechia, Germany)	16	1	2	100	100	0.00	0.75	1.50			
Poland (Nizinski et al., 2021)	31	0.4	1.4	100	100	0.00	0.22	0.43			
Cyprus (Constantinou et al., 2019)	65	1.5	5	100	100	0.00	0.075	1.5			
Total	**112**			**100**		**0.00**	**0.21**	**1.20**	**0.00**	**1.0**	**2.00**
Total All Water (bottled and unbottled)	**417**			**99.3**		**0.06**	**0.23**	**1.30**	**0.00**	**1.0**	**2.0**

Abbreviations: HRP, highest reliable percentile; LB, lower bound; LC, left-censored; LOD, limit of detection; LOQ, limit of quantification; P97.5, the 97.5th percentile; UB, upper bound.

Human milk

Table 18 presents the occurrence of perchlorate in human milk samples, based on literature data from Türkiye, Canada and China covering sampling years from 2008 to 2020. The reported mean concentrations of perchlorate in human milk range from 1.15 to 36.6 μg/L across these studies. In comparison, this range of mean concentrations was 5.8–33 μg/L in the previous opinion, which was based on U.S. literature data (EFSA CONTAM Panel, 2014).

TABLE 18 Occurrence levels (μg/L) of perchlorate in human milk from the non-EU literature.

			Perchlorate concentrations in human milk (μg/L)			
Country	***N***	**Reference**	**Range**	**Mean**	**Geometric mean**	**Median**
Türkiye	285	Ucal et al. (2018)[a]	N.R.	4.09	N.R.	2.30
Canada	439	Wang et al. (2019)[b]	< 0.27–676	7.62	4.03	4.56
China	52	Li, Xiao, Xiao, et al. (2022)	0.18–7.23	1.15	N.R.	0.65
China	30	Zhang et al. (2016)	< 0.20–204	36.6	14.2	20.0

[a]Data in colostrum milk.

[b]Reported in μg/kg. Converted to μg/L assuming a human milk density of 1 (Neville et al., 1988; Woolridge et al., 1985). N.R.: not reported.

Dry tea leaves

For the current Opinion, 2922 analytical data submitted by several Member States from industry/private monitoring programmes for tea leaves derivatives and tea ingredients from the years 2017–2022 were considered together at the level 3 of the FoodEx2 food classification system. A total of 58% of the samples were below LOQ (2.5–750 μg/kg). Applying the EFSA approach for the treatment of censored data resulted in a mean occurrence MB of perchlorate of 92 μg/kg dw (LB = 89 and UB = 95).

Few literature data were available from EU Member States after the 2017 EFSA Scientific Report. All other relevant publications reviewed from literature for checking consistency with data submitted above to EFSA in this Opinion were from China as described below.

Liao et al. (2022) published an article on the monitoring and risk assessment of perchlorate in tea samples produced in China. A total of 288 samples representing 6 types of tea leaves (white, green, yellow, oolong, dark and black) were obtained from local markets and supermarkets throughout China from 2018 to 2020. The contents of perchlorate were determined both in total concentrations and in 5-minute infusions in boiling water. Analyses were performed using LC–ESI–MS/MS with an LOD of 4 μg/kg and an LOQ of 15 μg/kg. A total of 5.2% of the samples were below the LOD. Applying the middle-bound approach for the treatment of censored data resulted in a mean occurrence MB concentration level of perchlorate of 295 μg/kg dw. The highest concentration was found in dark tea with a maximum of 1274 μg/kg dw. The brewing transfer rate estimated from the 288 infusions of tea leaves was reported between 59% and 89%.

Yao et al. (2022) published an article on perchlorate contamination of tea leaves and a corresponding probabilistic dietary risk assessment using Monte Carlo simulation. A total of 286 samples representing 4 types of tea leaves (white, green, oolong and black) were purchased randomly from six provinces of China during 2020. Analyses were performed using LC–ESI–MS/MS with an LOD of 3 μg/kg and an LOQ of 10 μg/kg. 0.7% of the samples were below the LOD. Applying the middle-bound approach for the treatment of censored data, resulted in a mean occurrence MB concentration level of perchlorate of 152 μg/kg dw. The highest concentration was found in green tea with a maximum of 1650 μg/kg dw.

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Li, Li, Ren (2023) published an article on the occurrence, spatial distribution and risk assessment of perchlorate in tea from typical regions in China. A total of 747 tea samples were randomly collected from the market of 13 major tea producing regions. Analysis were performed using LC–ESI–MS/MS with an LOD of 0.2 μg/kg and an LOQ of 0.6 μg/kg. A total of 100% of the samples were detected. The mean occurrence concentration level of perchlorate was 160 μg/kg dw. The highest concentration was found in yellow tea with a maximum of 3132 μg/kg dw.

Hu et al. (2024) published an article on chlorate and perchlorate in tea leaves from major producing regions in China and related human exposure risk. A total of 216 representative tea samples were collected from the three major tea planting regions (central, eastern and western China). Analyses were performed using LC–ESI–MS/MS with an LOD of 0.1 μg/kg and an LOQ of 0.4 μg/kg. A total of 100% of the samples were detected. The estimated mean occurrence concentration level of perchlorate was 139 μg/kg dw. The highest concentration was found in dark tea with a maximum of 1604 μg/kg dw.

In conclusion, as shown in Table 19, the available data from non-EU data suggest a higher mean concentration level of perchlorate in dry tea leaves approximately two times higher than the EU data. The EU data suggest a mean concentration level of perchlorate for tea leaves of 92 μg/kg dw and of 1.09 μg/L using a brewing transfer rate of 89% (Liao et al., 2022) plus a dilution factor of 75 with water free of perchlorate in tea beverages/infusions.

TABLE 19 Summary of EU/non-EU occurrence data on perchlorate for dry tea leaves, extract from the literature review after the 2017 EFSA statement.

	***N* samples**	**Mean (μg/kg dw)**	**Brewing transfer rate (%)**	**Maximum (μg/kg dw)**
Dry tea leaves				
China (Liao et al., 2022)				
Green	n.a	237.2	62–80	1014
Oolong	n.a	290.6	60–74	1119
Yellow	n.a	276.1	60–73	738
White	n.a	209.7	59–69	655
Dark	n.a	417.2	73–89	1274
Black	n.a	348.9	64–83	876
Total	288	**295**	**59–89**	**1274**
China (Yao et al., 2022)				
Green	39	200	n.a	1650
Oolong	166	170	n.a	1500
White	31	110	n.a	290
Black	50	80	n.a	240
Total	286	**152**	**n.a**	**1650**
China (Li, Tu, et al. 2023)				
Green	189	224	n.a	1364
Oolong	234	67	n.a	1007
Yellow	25	626	n.a	3132
White	56	105	n.a	716
Dark	43	172	n.a	1085
Black	90	168	n.a	1361
Total	637	**160**	**n.a**	**3132**
China (Hu et al., 2024)				
Green	48	135	n.a	934
Oolong	57	166	n.a	1208
White	40	28.6	n.a	232
Dark	40	301	n.a	1604
Black	31	30.8	n.a	268
Total	216	**139**	**n.a**	**1604**
Non-EU data (μg/kg dw)	**1427**	**182**		
EU data, this Opinion (several Member States from industry monitoring)	2922	**92**		
EU data for tea infusion/beverages estimation (89% brewing transfer rate + water free of perchlorate, dilution factor of 75 μg/L)	**2922**	**1.09**	**89%**	

Abbreviations: dw, dry weight; n.a., not available.

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3.2.2 | Food processing

Apart from the identification of brewing transfer for tea infusions, the extensive literature search performed for this Opinion did not identify any other evidence on the effects of food processing on perchlorate occurrence in food. This aspect was also not covered by the previous Opinion.

3.3 | Dietary exposure assessment

The CONTAM Panel assessed the chronic dietary exposure to perchlorate as well as the short-term dietary exposure for pregnant women following the methodology described in Section 2.6. A summary of the perchlorate occurrence data including the number of results and concentrations across the FoodEx2 level food categories used for the dietary exposure assessment is presented in Section 3.2.1.

3.3.1 | Chronic dietary exposure assessment

Table 20 shows the summary statistics of the estimated chronic dietary exposure to perchlorate across surveys for each age group. Detailed mean and 95th percentile dietary exposure estimates for all age groups, population groups and dietary surveys are presented in Annex B (Table B.4).

Mean chronic dietary exposure to perchlorate ranged across surveys and LB and UB estimates, from 0.02 μg/kg bw per day in adults, the elderly and the very elderly to 1.0 μg/kg bw per day in infants.

P95 chronic dietary exposure to perchlorate ranged across surveys and LB and UB estimates, from 0.04 μg/kg bw per day in the elderly and the very elderly to 1.74 μg/kg bw per day in infants.

The special population groups 'Pregnant women', 'Lactating women' resulted in mean and P95 chronic dietary exposure estimates within the range of the adult population group. The highest mean and P95 chronic dietary exposure estimates across the three surveys concerning vegetarians were higher than those of the adult population groups and lower than those of the young population groups (0.35 and 0.55 μg/kg bw per day respectively).

TABLE 20 Lower bound (LB) and upper bound (UB) mean and P95 chronic dietary exposure to perchlorate across surveys for each age group (μg/kg bw per day).

	Mean dietary exposure (μg/kg bw per day)					P95 dietary exposure (μg/kg bw per day)				
		LB		UB			LB		UB	
Age group	***N***	**Min**	**Max**	**Min**	**Max**	***N***	**Min**	**Max**	**Min**	**Max**
Infants[a]	14	0.04	0.13	0.34	1.00	13	0.09	0.68	0.61	1.74
Toddlers	17	0.05	0.15	0.52	0.70	16	0.09	0.54	0.81	1.12
Other children	21	0.05	0.09	0.34	0.50	21	0.09	0.31	0.54	0.77
Adolescents	23	0.03	0.05	0.17	0.30	22	0.06	0.12	0.30	0.44
Adults	23	0.02	0.05	0.13	0.21	23	0.05	0.14	0.22	0.34
Elderly	21	0.02	0.05	0.12	0.19	21	0.04	0.19	0.18	0.31
Very elderly	16	0.02	0.05	0.11	0.21	12	0.04	0.16	0.19	0.30
Pregnant women	**7**	**0.02**	**0.05**	**0.15**	**0.20**	**7**	**0.04**	**0.10**	**0.20**	**0.36**
Lactating women	**2**	**0.03**	**0.03**	**0.16**	**0.21**	**2**	**0.05**	**0.08**	**0.24**	**0.34**
Vegetarians	**3**	**0.03**	**0.06**	**0.16**	**0.35**	**3**	**0.09**	**0.13**	**0.27**	**0.55**

Abbreviations: LB, lower bound; P95, the 95th percentile; UB, upper bound.

[a]The age group of 'Infants' covers subjects from 12 weeks to < 12 months of age (see Section 2.4.1 Food consumption data). An exposure scenario for infants below 16 weeks of age is presented in Section 3.3 Dietary exposure assessment.

Table 21 describes the contribution (%) of each food category to the overall mean LB exposure to perchlorate as the number of surveys in which the contribution was higher than 10% and the percentage contribution range across dietary surveys (minimum and maximum) for all age classes. The percentage contribution of each individual food category at Levels 1 and 3 of the FoodEx2 classification to the total mean LB chronic dietary exposure of perchlorate was estimated across dietary surveys and age groups and is presented in Annex B (Tables B.5 and B.6).

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TABLE 21 Contribution (%) of each food category to the overall mean lower bound (LB) exposure to perchlorate as number of surveys in which contribution was higher than 10% and the percentage contribution range across dietary surveys (minimum and maximum) for all age classes. Only food categories having at least 10 surveys where they contributed more than 10% are shown in the table.

Food	Infants (12)	Toddlers (15)	Other children (19)	Adolescents (21)	Adults (22)	Elderly (19)	Very elderly (14)	*N* survey > 10%
Vegetables and vegetable products	13 (4.1–49)	17 (13–57.1)	20 (9.7–48.8)	23 (16.8–45)	23 (13.7–52.6)	21 (11.9–56.4)	16 (12.9–65.5)	133
Milk and dairy products	13 (9.9–48.5)	12 (5.9–20.6)	10 (5.9–27)	5 (5.2–18.9)	3 (3.6–12.2)	3 (2.5–13.6)	(0–0)	46
Water-based beverages	(0–0)	3 (0–20.4)	10 (1.3–27.3)	16 (3.8–34.1)	10 (3.4–27.9)	(0–0)	(0–0)	39
Grains and grain-based products	(0–0)	2 (2.6–10.7)	6 (3.71–14.4)	10 (3.58–13.2)	1 (4.3–11.7)	1 (3.5–12.8)	2 (3.6–12.8)	22
Food products for young population	13 (4.5–71.6)	3 (1.1–51.8)	1 (0–23.7)	(0–0)	(0–0)	(0–0)	(0–0)	17
Tea beverages	(0–0)	(0–0)	1 (0–10)	2 (0.1–13.3)	4 (0.4–18.1)	3 (0.6–25.7)	4 (0.2–34)	14
Starchy roots or tubers and products thereof, sugar plants	3 (0.8–15.5)	1 (2.1–16.4)	2 (2.2–10.3)	3 (1.9–13.5)	(0–0)	1 (1.5–12)	2 (0.6–11.5)	12

The food category with the highest number of surveys in which the contribution was higher than 10% were 'Vegetables and vegetable products' for all age groups contributing up to 65.5% in the very elderly. 'Milk and dairy products' had the highest number of surveys for infants, toddlers and other children (up to 48.5% in infants), 'Water-based beverages' for other children, adolescent and adults (up to 34.1% in adolescents) and 'Food for the young population' for infants (up to 71.6%).

Within this FoodEx2 Level 1 food categories, the main contributing subcategories were:

- 'Leafy vegetables' for 'Vegetable and vegetable products'.
- 'Milk' and 'Cheese' for 'Milk and dairy products'.
- 'Soft drinks' for 'Water-based beverages' (quantified data referred mainly to beverages containing herbs or fruits).
- 'Infant and follow-on formula' within the 'Food for the young population'.

Drinking water contributed up to 5.9% (toddler survey) while overall contribution of water (including cooking of pasta, coffee and tea beverages and reconstituted foods) is up to 7.7%.

Figures 4 and 5 show the percentage contribution and the contribution in µg/kg bw per day respectively, of food categories to the total exposure to perchlorate for each survey for adults, toddlers and infants.

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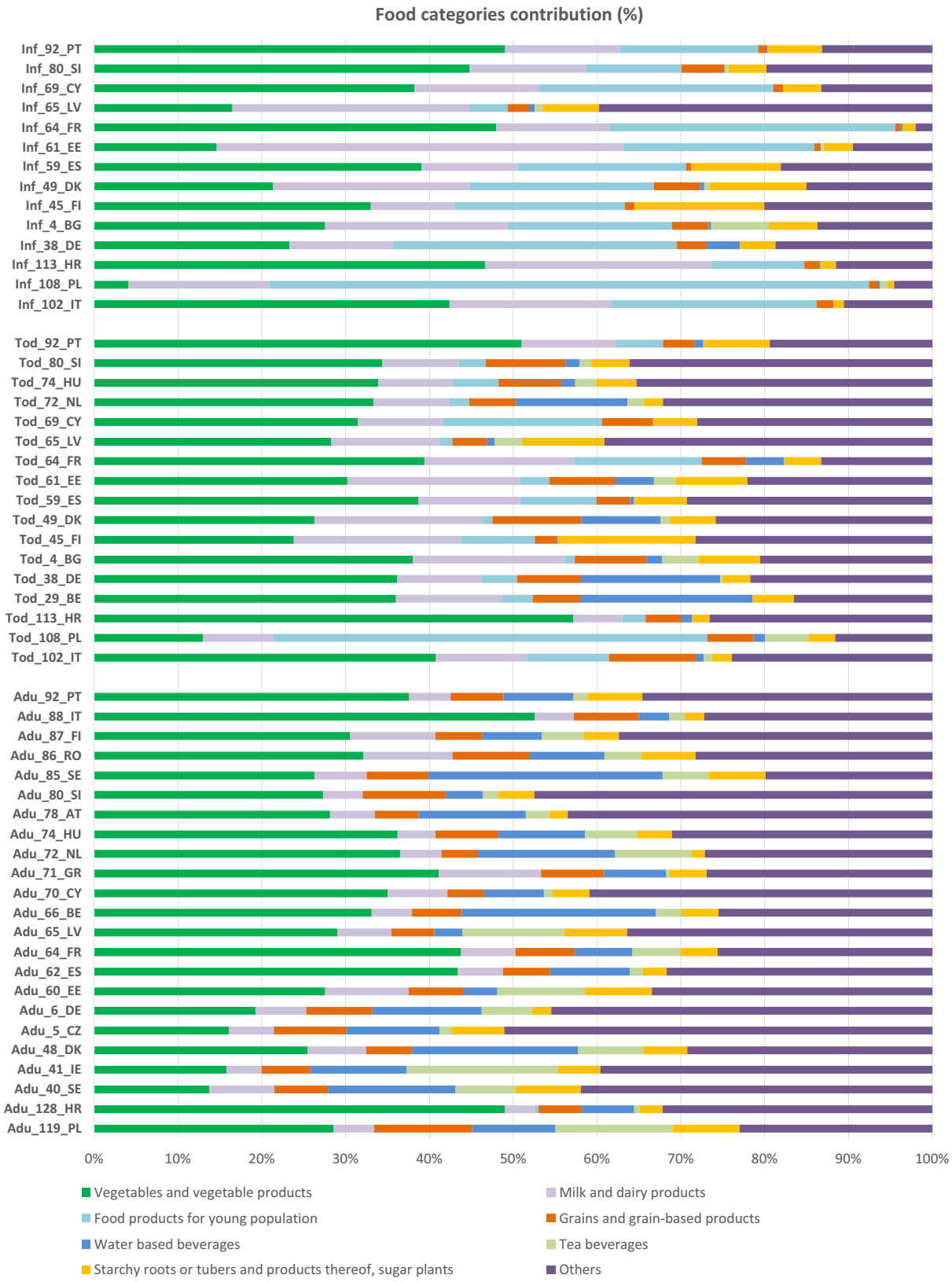

FIGURE 4 Percentage contribution per day of food categories at the level 1 of the FoodEx2 classification, to the total lower bound (LB) chronic dietary exposure to perchlorate for each survey for adults, toddlers and infants.

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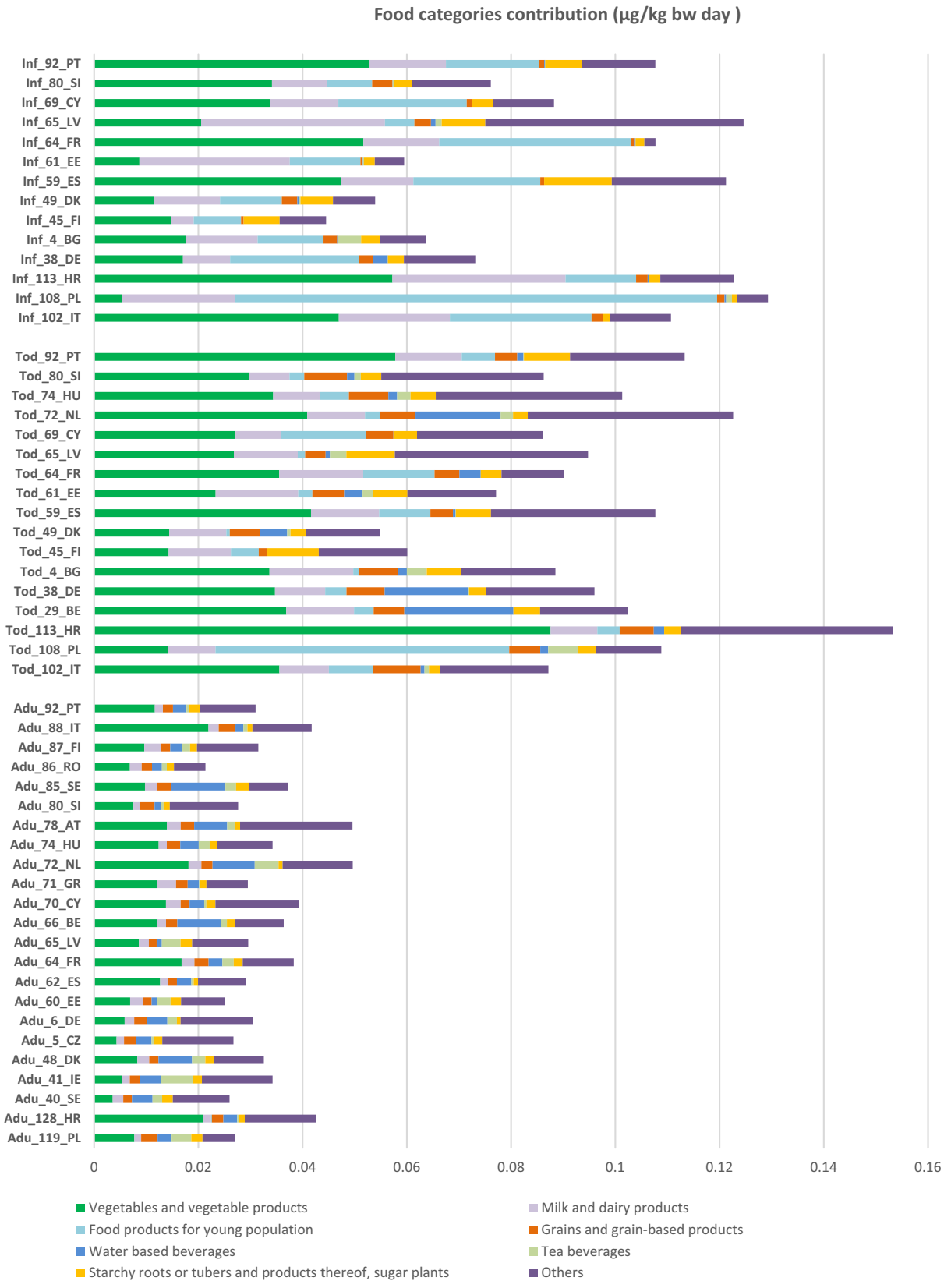

FIGURE 5 Contribution in µg/kg bw per day of food categories at the level 1 of the FoodEx2 classification, to the total lower bound (LB) chronic dietary exposure to perchlorate for each survey for adults, toddlers and infants.

3.3.2 | Short-term dietary exposure assessment for pregnant women

Table 22 shows the summary statistics of the estimated short-term (2 weeks) dietary exposure to perchlorate across surveys for pregnant women. Detailed mean and 95th percentile dietary exposure estimates for each dietary survey are presented in Annex B (Table B.7).

Mean short-term dietary exposure to perchlorate ranged across surveys and LB and UB estimates, from 0.25 µg/kg bw per day to 0.6 µg/kg bw per day.

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P95 short-term dietary exposure to perchlorate ranged across surveys and LB and UB estimates, from 0.47 µg/kg bw per day to 1.29 µg/kg bw per day.

TABLE 22 Lower bound (LB) and upper bound (UB) mean and P95 chronic dietary exposure to perchlorate across surveys for pregnant women (µg/kg bw per day).

	Mean dietary exposure (µg/kg bw per day)					P95 dietary exposure (µg/kg bw per day)				
		LB		UB			LB		UB	
Population group	***N***	**Min**	**Max**	**Min**	**Max**	***N***	**Min**	**Max**	**Min**	**Max**
Pregnant women	7	0.25	0.44	0.38	0.60	7	0.47	1.10	0.66	1.29

Abbreviations: LB, lower bound; P95, the 95th percentile; UB, upper bound.

The percentage contribution of each individual food category at the Levels 1 and 3 of the FoodEx2 classification to the total mean LB chronic dietary exposure of perchlorate was estimated across dietary surveys and is presented in Annex B (Table B.8 and Table B.9).

Main contributors to the short-term exposure to perchlorate for pregnant women were 'Vegetables and vegetable products' (contribution up to 50.3%), 'starchy roots or tubers and products thereof, sugar plants' (up to 26.9%), 'Milk and dairy products' (up to 12.8%).

Figures 6 and 7 show the percentage contribution and the contribution in µg/kg bw per day respectively, of food categories to the total exposure to perchlorate for each survey for pregnant women.

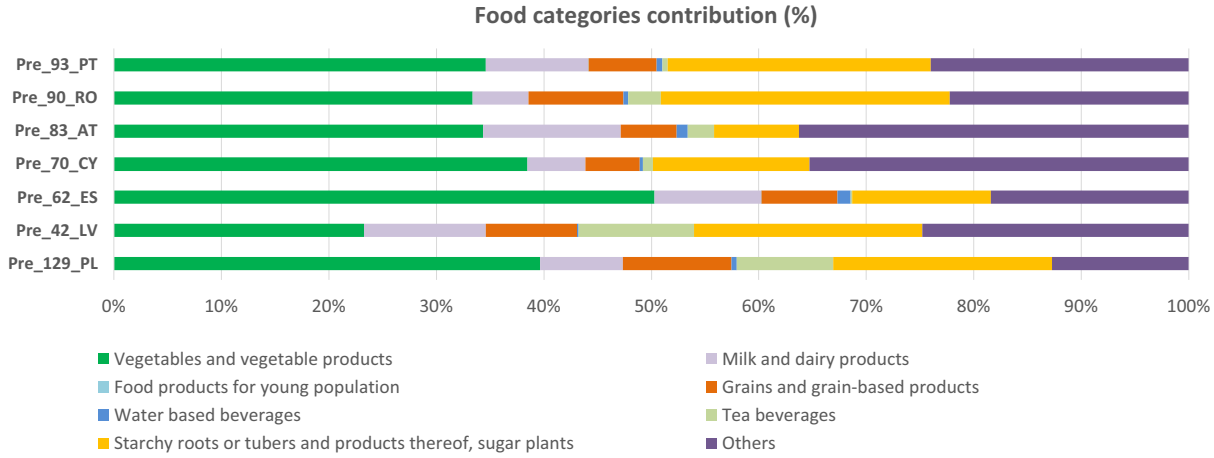

FIGURE 6 Percentage contribution of food categories at the level 1 of the FoodEx2 classification, to the total lower bound (LB) short-term dietary exposure to perchlorate for each survey for pregnant women.

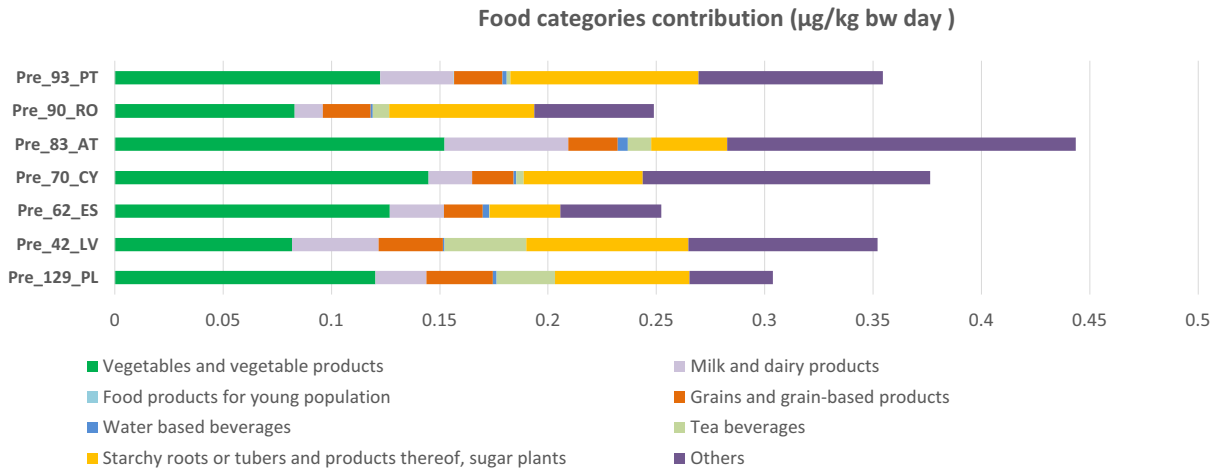

FIGURE 7 Contribution in µg/kg bw per day of food categories at the level 1 of the FoodEx2 classification, to the total lower bound (LB) short-term dietary exposure to perchlorate for each survey for pregnant women.

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3.3.3 | Breastfed infants

A separate dietary exposure scenario was carried out for infants below the age of 16 weeks based on daily human milk consumption. Details on the approach and assumptions used for this exposure scenario are provided in Section 2.6.3, 'Specific exposure scenarios - *Exposure* via *human milk consumption*'.

Table 23 presents the estimated dietary exposure to perchlorate for breastfed infants, calculated using the mean and the highest 99th percentile human milk concentrations from the EU population, calculated via the biomonitoring equivalent equation (see Sections 2.6.3 and 3.2.1.1). For infants with average (mean) milk consumption, the exposure to perchlorate (LB–UB) is estimated to be between 0.2 and 1.2 μg/kg bw per day, based on mean concentrations and between 0.5 and 2.1 μg/kg bw per day, based on the highest reliable percentile concentration (99th) from a daily milk production of 0.8 L/day. For infants with high (P95) milk consumption, the estimated exposure ranges (LB–UB) from 0.2 to 1.2 μg/kg bw per day based on mean concentration and between 0.5 and 2.1 μg/kg bw per day based on the highest reliable percentile concentration (99th) from a daily milk production of 1.2 L/day, as shown in Table 23.

TABLE 23 Exposure (μg/kg bw per day) of breastfed infants to perchlorate based on the mean and highest reliable percentile (99th) concentrations in human milk estimated by the CONTAM Panel using biomonitoring equivalent equation and the mean and high (P95) consumption estimates recommended by the EFSA Scientific Committee (EFSA Scientific Committee, 2017).

Perchlorate exposure (μg/kg bw per day, mean consumption)				
Food commodity	**Mean LB**	**Mean UB**	**Highest reliable percentile (99th) LB**	**Highest reliable percentile (99th) UB**
Human milk	0.2	1.2	0.5	2.1
Perchlorate exposure (μg/kg bw per day, high (P95) consumption)				
Food commodity	**Mean LB**	**Mean UB**	**Highest reliable percentile (99th) LB**	**Highest reliable percentile (99th) UB**
Human milk	0.2	1.2	0.5	2.1

Abbreviations: LB, lower bound; P95, the 95th percentile; UB, upper bound.

The CONTAM Panel noted that the exposure of the breastfed infant depends on the concentration of perchlorate in human milk in relation to the mother's daily milk production.

3.3.4 | Formula-fed infants

A separate dietary exposure scenario was carried out for infants below the age of 16 weeks based on daily infant formula consumption. Details on the approach and assumptions used for this exposure scenario are provided in Section 2.6.3, 'Specific exposure scenarios - *Exposure via infant formula consumption*'.

Table 24 shows the exposure estimates for formula-fed infants based on the recommended consumption levels outlined in the Scientific Committee guidance (EFSA Scientific Committee, 2017) and the mean and the highest reliable percentile (99th) LB, and UB concentrations of perchlorate in infant formula samples submitted to EFSA (see Table 15).

The dietary exposure for infants with average (mean) infant formula consumption is estimated (LB–UB) to be between 0.05 and 0.4 μg/kg bw per day based on mean concentrations, and between 0.5 and 1.3 μg/kg bw per day based on the highest reliable percentile concentrations (99th).

For high (P95) infant formula consumption, dietary exposure estimates range (LB–UB) from 0.07 to 0.5 μg/kg bw per day based on mean concentrations and from 0.7 to 1.7 μg/kg bw per day based on the highest reliable percentile (99th) concentrations.

TABLE 24 Exposure (μg/kg bw per day) of formula-fed infants to perchlorate based on the mean and the highest reliable percentile concentrations (99th) in infant formula (liquid and reconstituted to liquid form) submitted to EFSA and mean and high (P95) consumption estimates recommended by the EFSA Scientific Committee (EFSA Scientific Committee, 2017).

Perchlorate exposure (μg/kg bw per day, mean consumption)					
Food commodity	***N***	**Mean LB**	**Mean UB**	**Highest reliable percentile (99th) LB**	**Highest reliable percentile (99th) UB**
Infant formula	685	0.05	0.4	0.5	1.3
Perchlorate exposure (μg/kg bw per day, high (P95) consumption)					
Food commodity	**N**	**Mean LB**	**Mean UB**	**Highest reliable percentile (99th) LB**	**Highest reliable percentile (99th) UB**
Infant formula	685	0.07	0.5	0.7	1.7

Abbreviations: LB, lower bound; P95, the 95th percentile; UB, upper bound.

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3.3.5 | Previously reported dietary exposure assessment

The Austrian Agency for Health and Food Safety (AGES) conducted a risk assessment of dietary exposure to perchlorate for the Austrian population. This assessment published in 2018 was performed using analytical results on perchlorate occurrence data in food from the Austrian market in the years 2013–2016 and using individual food consumption data for the age classes of adults and children from the Austrian study on nutritional status 2010–2012 (Vejdovszky et al., 2018). It was estimated that the mean and the P95 dietary exposure for all population groups range from 0.036 to 0.078 μg/kg bw per day and from 0.4 to 0.48 μg/kg bw per day, respectively. The most contributing food category was spinach. Pineapples, leaf vegetables and legumes were the next most contributing food categories for adults, children and infants, respectively.

Several studies from China have conducted a risk assessment of dietary exposure assessment from the consumption of tea in different production regions. They all showed that dietary exposure of tea consumers was estimated at up to 0.5 μg/kg bw per day at the P99 (Hu et al., 2024; Li, Wu, Xu, & Zhang, 2023; Yao et al. 2022). Other publications from China in Wuhan and in Fujian have estimated a mean and a P95 dietary exposure for adults populations via diet ranging from 0.32 to 0.44 μg/kg bw per day and from 0.51 to 1.44 μg/kg bw per day, respectively with the most contributing foods groups being vegetables (58%) and drinking water (33%) in the region of Wuhan (Wang et al., 2021) and being cereals (19%), spices (14%) and vegetables (12%) in the region of Fujian (Zhang et al., 2023).

At the request of the European Commission, the European Food Safety Authority conducted in 2017 an update of the dietary exposure assessment to perchlorate in the European population taking into account the occurrence data available in the EFSA database from samples taken after 1 September 2013 (EFSA, 2017). Based on this mandate, 18,217 analytical results corresponding to the requested criteria were extracted from the EFSA database on 6 April 2017 and analysed to determine the occurrence levels in different food groups and consequently estimate the human dietary exposure to perchlorate. The young population groups (infants, toddlers and other children) show higher chronic dietary exposure levels than the other groups: the range across dietary surveys of mean chronic exposure (minimum LB–maximum UB) was overall in these groups 0.04–0.61 μg/kg bw per day, while in the older population groups, the range was 0.04–0.19 μg/kg bw per day. Similarly, in the young population groups, the range of P95 of chronic dietary exposure was 0.09–1.0 μg/kg bw per day, while in the older population groups, it was 0.07–0.34 μg/kg bw per day. 'Vegetable and vegetable products', 'Milk and dairy products' and 'Fruit and fruit products' were important contributors to the exposure across all population groups. Other food groups were more relevant for specific population groups, like 'Food for infants and small children' among infants and toddlers, 'Fruit and vegetable juices' among toddlers, other children and adolescents or 'Teas and herbal infusion (beverage)' among adults. The mean as well as the P95 range (LB–UB) of the short-term dietary exposure in pregnant women was from 0.70 to 0.86 μg/kg bw per day and from 1.4 to 1.6 μg/kg bw per day, respectively.

The CONTAM Panel noted that the dietary exposure assessment performed now is based on a more comprehensive number of dietary surveys than the one available in the previous 2017 EFSA scientific report (i.e. 7 surveys for pregnant women vs. 1 and 14 surveys for infants vs. 6) and also includes a more comprehensive coverage of occurrence data for foods categories considered in the assessment in terms of number of analytical results submitted (> 41,000 vs. 18,000) with a broader representation of the diet that was covered in the previous EFSA scientific report.

Overall, it is observed that the dietary exposure assessment estimated in this Opinion compared to the previous EFSA scientific report of 2017 was similar for all population groups with the exception of pregnant women where it is lower and infants where it is higher due to the availability of new surveys. These new surveys result in higher exposure values.

3.4 | Reported non-dietary sources of exposure

Exposure to perchlorate for the general population is considered to be mainly linked to dietary routes, due to ingestion of contaminated foods and drinking water, nevertheless perchlorate was identified in a number of consumer products (ATSDR, 2008). Perchlorate was found in tobacco products (Ellington et al., 2001), household bleach (MassDEP, 2006) and dietary supplements (Snyder et al., 2006). Gibbs et al. (1998) also pointed out that patients undergoing medical imaging might be exposed to limited amounts of perchlorate.

Occupational exposure to perchlorate is relevant for workers manufacturing perchlorates via inhalation of dust and via dermal contact, nevertheless the dermal absorption of perchlorate is expected to the low (Scheuplein and Bronaugh, 1983).

General populations with potentially high exposure to perchlorate are those living in the vicinity of hazardous waste sites where the groundwater is used for drinking purposes (ATSDR, 2008).

3.5 | Risk characterisation

The CONTAM Panel evaluated the chronic dietary exposure using mean LB and UB levels of perchlorate in various food groups and using the consumption surveys from European countries available in the Comprehensive Food Consumption database (see Section 3.3).

The mean LB and UB exposure estimates are presented in Table 20. Mean dietary exposure to perchlorate ranged across surveys and LB and UB estimates, from 0.02 μg/kg bw per day in pregnant women, Adults, Elderly and Very elderly to 1.00

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µg/kg bw per day in Infants, while P95 dietary exposure ranged from 0.04 µg/kg bw per day in pregnant women, Elderly and Very elderly to 1.74 µg/kg bw per day in Infants.

The exposure estimates are all below the TDI of 1.4 µg/kg bw per day for all age groups at the lower bound and upper bound, with the exception of Infants at the P95 UB dietary exposure.

The mean LB and UB short-term dietary exposure estimates to perchlorate for pregnant women ranged from 0.25 to 0.6 µg/kg bw per day, while P95 dietary exposure ranged from 0.47 to 1.29 µg/kg bw per day. These exposure estimates are below the TDI of 1.4 µg/kg bw per day.

For the breastfed infant scenario, the exposure estimates were obtained using chronic dietary exposure data for lactating women with an excretion value of 54% of perchlorate in milk and a daily human milk production of 0.8 L to 1.2 L (see Section 2.6.3).

Infants of lactating women with mean exposure had perchlorate exposure ranging from 0.2 (LB) to 1.2 (UB) µg/kg bw per day, whereas infants of lactating women at P95 exposure had exposure from 0.5 (LB) to 2.1 (UB) µg/kg bw per day.

These estimates are below the TDI, with the exception of the P95 at the upper bound. Of note, beside the well-known benefits of breastfeeding, human milk is the major source of iodine intake at this stage of life.

For formula-fed infants, the highest exposure estimates were (LB–UB) 0.7–1.7 µg/kg bw per day obtained considering P99 occurrence values and P95 high consumption of infant formula (see Tables 15 and 25 in Section 3.3). These exposure estimates are below the TDI with the exception of the P95 at the upper bound.

3.6 | Uncertainty analysis

Uncertainty analysis

The purpose of the uncertainty analysis is to identify and quantify the specific uncertainties of the risk assessment and combine them to assess the overall certainty of the final conclusion, as recommended in EFSA's guidance on uncertainty analysis (EFSA Scientific Committee, 2018a). The uncertainty assessment was conducted separately for the hazard and exposure assessment. For the hazard assessment, the analysis focused on ensuring that the selected RP (BMDL of the Greer et al., 2002 study) is protective. For the exposure assessment, the analysis estimated the likelihood that the different exposure scenarios are below the RP, which includes the risk characterisation.

This approach aligns with standard risk assessment practices for setting a TDI as a fixed value, derived from the RP and the selected UFs. It describes the certainty, that the TDI is below the dose corresponding to the BMR, and the certainty, and that the exposure is below the proposed TDI.

In a first step, sources of uncertainties related to perchlorate hazard identification and characterisation and to the exposure assessment to perchlorate were listed and discussed (Appendix E). The uncertainty analysis focuses on uncertainties, which are specific to the current assessment. Standard uncertainties as covered by extrapolation factors, the use of contamination data reported to EFSA and food consumption data from national surveys are discussed elsewhere. For the specific uncertainties it was judged, which of these have most impact on the outcome of the hazard identification and characterisation and of the exposure estimations.

These main sources of uncertainty were further discussed individually. Additional evidence was reviewed to quantify its possible impact on the Reference Point used in the current assessment. Semi-formal structured methods of expert knowledge elicitation (semi-formal EKE, Annex B.8 of EFSA Scientific Committee (2018)) were applied to determine a credible range for the ratio between the Reference Point of an assessment without this uncertainty or limitation and the current assessment. Standard uncertainties, which are covered by the default assessment factors used to determine the acceptable TDI, were assumed for both: the assessment without limitations and the current assessment. Their effect is therefore not included in the credible range.

Finally, the combined impact of all main uncertainties, as well as the identified minor uncertainties, was judged by the experts on the hazard assessment giving the distribution of the overall uncertainty of the ratio between the effective dose (BMD) of an assessment without specific uncertainties or limitations and the current assessment, called the uncertainty factor for the hazard. The distribution shows that the selected TDI is sufficiently protective to cover more than 95% of the combined impact of all the uncertainties. This means, that the true BMD (dose corresponding to the BMR) is above the TDI with more than 95% certainty.

The potential impact of the main uncertainties affecting the exposure assessments was explored on two scenarios: the average European toddler and breastfed infants. The toddler age class was used, because it has the highest exposure among all age groups, resulting in highest risk for this age, while the breastfed infants age class was used due to their potential susceptibility to perchlorate exposure and the methodology utilised in the calculation of the exposure. The experts were asked to judge the ratio between the exposure assessment without uncertainties or limitations and the current assessment. The results were used to derive an uncertainty distribution called the 'uncertainty factor' for the exposure. The relative uncertainties for other age groups show similar ratios, which indicates that the 'uncertainty factor' can be assumed similar. Therefore, the same factor was also used for the short-term exposure of pregnant women.

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Assessment objectives

Assessments must indicate what sources of uncertainty have been identified and characterise their overall impact on the assessment conclusion. It is recommended to quantify the overall uncertainty of conclusions using probability to avoid the ambiguity of qualitative approaches. However, the conclusions may subsequently be reported without probabilities if legislation or risk managers require that, providing that the associated probabilities are somewhere defined (EFSA Scientific Committee, 2018a, 2018b). The present uncertainty analysis was conducted with the objective to address the assessment question on the risks for human health related to the presence of perchlorate in food. A TDI approach was applied for the risk characterisation. The TDI is calculated as the ratio of the Reference Point (BMDL) and the appropriate UFs (See Section 3.1.5.3). The risk is characterised by comparing the TDI against the mean and P95 exposure estimate for the EU population in each age group. The uncertainties pertaining to each of these two components (hazard identification and exposure assessment) were identified and quantified separately and combined for the overall uncertainty assessment. The uncertainty analysis, focussed on the hazard identification, chronic P95 exposure for all age groups and short-term (see Section 2.6.2) P95 exposure for breastfed infants. The uncertainty analysis was conducted following the guidance of the EFSA Scientific Committee (2018a). The combined impact of uncertainties on the principal conclusions in each part of the assessment was quantified using % probabilities. These are reported below as % certainty for the more probable outcome for each conclusion, following EFSA's guidance on communication of uncertainty (EFSA, 2019b).

Hazard identification and characterisation

Possible limitations of the hazard assessment were systematically screened to identify those uncertainties, which may have a high impact on the Reference Point. The following uncertainties were considered of higher priority regarding the estimation of the Reference Point for perchlorate. The magnitude and direction of the impact of these uncertainties on the Reference Point was evaluated by a structured expert elicitation (see Appendix F for further details):

1. Uncertainty in the use of experimental animals for endpoints in humans, due to interspecific differences between rats and humans regarding disruption of thyroid homeostasis;
2. Uncertainties in exposure measurement in human studies, due to the use of spot urine samples to measure perchlorate levels, while exposure is assumed to occur primarily via drinking water, which provides a more stable and steady-state intake;
3. Low sample size in interventional human studies (key study Greer et al. (2002)) for thyroid endpoints: duration is limited;
4. Unclear biological relevance for the BMR (5%) setting (uncertainty of the BMR). BMR developed on general populations, not pregnant or lactating women;
5. Uncertainty on the iodine deficiency in the populations used to derive the BMR.

With respect to the sources of uncertainty described in point 1 above, numerous repeated-dose oral toxicity studies, conducted mostly in rats showed dose-dependent effects of perchlorate, with the thyroid being the most sensitive organ. These animal studies provide valuable dose–response data and important mechanistic insights into the toxicity of perchlorate. Therefore, the CONTAM Panel decided to use them as supportive evidence in the assessment, but not as the primary basis for hazard characterisation for which human data is available (see Section 3.1.2.5 for further details on the use of experimental animals in the current assessment).

The sources of uncertainty described in points 2 to 5 above, were discussed in detail in a quantitative uncertainty analysis of the RP for perchlorate. The review of all lines of evidence and their limitations, along with an EKE analysis, led to an overall uncertainty factor of 1.11 (with 90% certainty range from 0.248 to 3.89). The CONTAM Panel is 90% certain, that the true BMD is within a range that is up to 4-times lower or higher than the selected BMD. The corresponding BMDL of 0.007 mg/kg bw per day from the Greer et al. (2002) study is below this certainty range and is therefore considered protective with more than 95% certainty (meaning that the true BMD will be higher with more than 95% certainty).

Dietary exposure assessment

The EKE analysis was conducted in toddlers and breastfed infants.

Toddlers were chosen as they were, the age class with the highest exposure estimations for perchlorate. The identified uncertainty in toddlers is expected to have a similar impact on the dietary exposure estimated in the other age classes. The discussions on uncertainty concluded that the main uncertainties identified during the EKE analysis refer to:

1. Reporting errors of measurements that may have passed the validation and cleaning (standard uncertainty, see general exposure assessment);
2. Unclear status/form of the food (cooked/uncooked, powder/liquid/reconstituted, etc), which could lead to potential mistakes in the re-calculations;
3. Unknown information on the ingredients of composite food. Assumptions were made to impute measurements that may be incorrect;

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4. Imputations were done for 2000 FoodEx2 codes by assumptions from similar categories/primary ingredients with at least 6 measurements. This may be incorrect. This includes main contributors, like bread, fine bakery wares;
5. 80% of measurements were coming from Germany, which might not be representative of the whole Europe;
6. High LOD or LOQ value (above P95). Calculations of LB/UB show the influence of left-censored data.

The EKE analysis led to an overall uncertainty factor of 1.08 (with 90% certainty range from 0.175 to 2.47) for the average diet of a European toddler. After reviewing all the different exposure scenarios (average/high consumer, age classes, different country surveys and different proportion of left-censored data) this factor was judged to be applicable across all age groups, including high consumers, as the exposure assessment showed similar uncertainties throughout these groups. The age group 'toddler' was used as most exposed age group. Together with the most important uncertainties identified and categorised for the occurrence data by the informal EKE, the CONTAM Panel also noted the uncertainties and limitations related to the use of the EFSA Comprehensive Food Consumption Database (see Appendix F). The main uncertainties have been described by EFSA (2011a) and generally relate to the use of different dietary survey methodologies, standard portion sizes, representativeness of samples included in surveys or to the inclusion of consumption surveys covering only few days to estimate high percentiles of chronic exposure. The Panel noted these uncertainties are common to dietary chronic exposure assessments performed using the Comprehensive Database, and have the potential to cause either an over- or underestimation of the exposure. The uncertainties affecting the food consumption data were not specific for the perchlorate exposure assessment. They are 'standard uncertainties' across all opinions and were considered to have low priority. It is generally accepted that the estimates from the Comprehensive Database are generally considered to be fit for purpose, provided there are no non-standard uncertainties, as it is the case for perchlorate.

A semi-formal EKE was also performed for high consuming (P95) breastfed infants. The discussions on uncertainty concluded that the main uncertainties identified during the EKE analysis refer to:

1. Correct excretion rate of perchlorate via breastmilk/biomonitoring equivalent equation;
2. Interpretation of animal experiments and PBPK models;
3. Amount of left-censored data in the dietary exposure assessment of lactating women.

The EKE analysis led to an overall uncertainty factor of 0.946 (with 90% certainty range from 0.453 to 1.44).

Overall output of the Uncertainty analysis

The likelihood to exceed the TDI of the exposure of toddlers, other age groups, pregnant women and the exposure of breastfed infants is finally calculated by multiplying the current exposure assessment with the corresponding distribution of the uncertainty factor. The replications of the simulation can be interpreted as possible exposures, when the chemical risk assessment would have been done under perfect conditions (assuming only standard uncertainties), without any specific uncertainties. This exercise resulted in the following certainty bands for the final conclusions:

1. It is likely to very likely (no concern with at least 88% certainty) that mean or P95 chronic dietary exposure levels are below the TDI for all age groups.
2. For the short-term scenario, it is likely (no concern with at least 69% certainty) that mean or P95 exposure levels are below the TDI for pregnant women.
3. It is almost certain (no concern with over 99% certainty) that the mean exposure level for breastfed infants is below the TDI. It is as likely as not (no concern with 62% certainty) that the P95 exposure level for breastfed infants does not exceed the TDI. It is likely (no concern with 88% certainty) that the P95 exposure level for formula-fed infants does not exceed the TDI.

4 | CONCLUSIONS

In this Opinion, the CONTAM Panel has re-assessed the risk related to the presence of perchlorate in food and drinking water based on the new scientific developments and information available since the previous EFSA Opinion and dietary exposure assessment of Perchlorate (EFSA, 2017; EFSA CONTAM Panel, 2014).

4.1 | ADME

- Perchlorate is highly water soluble, readily absorbed in the gastrointestinal tract and excreted unmetabolised in urine and human milk.
- The sodium iodide symporter (NIS) actively transports both iodide and perchlorate to thyroid follicular cells and into milk.
- Perchlorate concentrations in urine, serum or human milk represent useful biomarkers of exposure.

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4.2 | Studies in experimental animals

- Perchlorate disrupts thyroid homeostasis in a dose-dependent manner, with reduced levels of T3 and T4 and elevated levels of TSH observed at daily doses as low as 0.01 mg/kg bw in rats. At doses ≥ 10 mg/kg bw per day, changes in thyroid gland weight and histopathological findings in adult male and female rats were also observed.
- Direct oral administration of perchlorate to prenatally exposed rat pups from PND 0 to PND 6 significantly reduced serum and brain T4 levels and led to the development of periventricular heterotopias in the pups. Perchlorate exposure in the prenatal and postnatal period of life can result in neurodevelopmental toxicity that might have long-term consequences.
- Perchlorate exposure during various stages of development exacerbates thyroidal and neurological effects in rats with iodine deficiency.

4.3 | Human studies

- A total of 43 new relevant human observational studies (37 cross-sectional and 6 prospective studies) were retrieved since the previous EFSA opinion (EFSA CONTAM Panel, 2014).
- The human epidemiological evidence suggests that exposure to perchlorate, at levels commonly found in the general population, may affect thyroid function. However, the modest effect size observed in these studies and use of spot urine samples are sources of uncertainty. This makes use of these studies less suitable for hazard characterisation compared to the available evidence on effects of perchlorate on iodine uptake.
- Evidence from three human studies on cancer was inconclusive.
- Results of three studies, despite some limitations, suggest that perchlorate exposure may be associated with lower height and weight in children.
- There was no consistent evidence for an association between urinary perchlorate concentrations and various other health outcomes assessed.
- Population-based surveys from Europe suggest that the risk of either severe, moderate or mild iodine deficiency is potentially widespread as reflected by frequent reports of median urinary iodine concentrations below 100 µg/L. A higher risk can be anticipated from exposure to perchlorate in individuals with iodine deficiency, particularly during critical stages of development.

4.4 | Mode of action

- Experimental evidence supports the role of perchlorate in competing for iodine uptake into the thyroid gland (via the NIS) and potentially uptake into other organs. AOPs 54 and 42, both endorsed by the OECD, support the biological plausibility of associations between inhibition of NIS function and of TPO during mammalian development, with decreased levels of TH in the blood and in the brain and consequent potential adverse neurodevelopment outcomes such as learning and memory impairment.
- Studies in animals demonstrate an indirect, thyroid-mediated effect on reproduction and development with apparent interplay between the thyroid and androgen hormones as well as a potential direct interference of perchlorate with reproduction and development.
- Oxidative stress and indicators of an apoptotic mechanism of mammalian cell toxicity were evident.
- Evidence indicates that perchlorate is not genotoxic.

4.5 | Critical effects and derivation of the TDI

- The non-randomised human intervention study of Greer et al. (2002) was considered the key study for the present assessment and inhibition of radioactive iodine uptake in humans was selected as the critical effect for dose–response modelling and risk characterisation.
- The CONTAM Panel selected a BMR of 5% based on the biological reference interval for radioactive iodine uptake (RAIU) in euthyroid subjects ($n = 370$ from 4 studies) and considered that at a population level a 5% inhibition of RAIU would be adverse. Based on these assumptions, a benchmark dose lower credible limit ($BMDL_5$) of 7 µg/kg bw per day for reduction of RAIU was identified as the Reference Point for perchlorate effects in humans.
- The CONTAM Panel considered limitations associated with the study of Greer et al. (2002). The study was based on a limited number of subjects (37, 24 of which completed the study) which were all healthy adult volunteers, possibly not reflecting inter-individual variability in TD of the wider population. A default uncertainty factor (UF) of 10 is normally used for variability of TK and TD. Since the perchlorate is excreted unmetabolised, an UF for TD is needed but not for TK.
- In addition, the Panel considered the need to account for the sensitivity of the fetus to maternal thyroid disturbances (see Section 3.1.3.7) and the uncertainty around the impact of iodine deficiency on the perchlorate effects during fetal and early postnatal development (see Section 3.1.4.2). Furthermore, it is noted that there is a higher demand for iodine

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during pregnancy (approximately 50% increase). The prevalence of iodine deficiency in the European adult population is high (see Section 3.1.3.7).
- Bearing in mind these limitations the CONTAM Panel decided that an overall UF of 5 is warranted, leading to a TDI of 1.4 μg/kg bw per day.

4.6 | Exposure assessment

- The CONTAM Panel deemed relevant for this Opinion to conduct a chronic dietary exposure assessment for all age groups and a short-term (2 weeks) dietary exposure assessment for pregnant women.
- Mean **chronic dietary exposure** to perchlorate ranged across surveys and lower bound (LB) and upper bound (UB) estimates, from 0.02 μg/kg bw per day in Adults, the Elderly and the Very elderly to 1.0 μg/kg bw per day in Infants. The 95th percentile (P95) chronic dietary exposure to perchlorate ranged across surveys and LB and UB estimates, from 0.04 μg/kg bw per day in the Elderly and the Very elderly to 1.74 μg/kg bw per day in Infants.
- For **pregnant women**, mean **short-term dietary exposure** to perchlorate ranged across surveys and LB and UB estimates, from 0.25 μg/kg bw per day to 0.6 μg/kg bw per day. P95 short-term dietary exposure to perchlorate ranged across pregnant women surveys and LB and UB estimates, from 0.47 μg/kg bw per day to 1.29 μg/kg bw per day.
- For the **breastfed infant scenario**, infants at mean exposure ranged from 0.2 (LB) to 1.2 (UB) μg/kg bw per day, whereas infants at P95 exposure ranged from 0.5 (LB) to 2.1 (UB) μg/kg bw per day.
- For **formula-fed infants**, the dietary exposure for infants with high (P95) infant formula consumption ranged (LB–UB) from 0.07 to 0.5 μg/kg bw per day based on mean concentrations and from 0.7 to 1.7 μg/kg bw per day based on the highest reliable percentile (99th) concentrations.

4.7 | Risk characterisation

The CONTAM Panel concluded that chronic and short-term dietary exposure estimates to perchlorate were below the TDI for all age groups including pregnant women, with the exception at the upper bound of the P95 for infants, breastfed infants and formula-fed infants.

The uncertainty analysis indicated a higher (above 80%) likelihood of 'no concern' for most scenarios. For short-term exposure of high exposed (P95) pregnant women and high exposed (P95) breastfed infants the likelihood of 'no concern' is 69% and 62% respectively.

Of note, beside the well-known benefits of breastfeeding, human milk is the major source of iodine intake at this stage of life.

5 | IMPLICATIONS ON EFSA CONTAM PANEL 2015 CHLORATE OPINION

In 2015, the CONTAM Panel adopted a Scientific Opinion on the risks for public health related to the presence of chlorate in food. A tolerable daily intake (TDI) of 3 μg chlorate/kg bw per day was set by read across from the TDI of 0.3 μg/kg bw per day derived for this effect for perchlorate, multiplied by a factor of 10 to account for the lower inhibitory potency of chlorate at NIS.

In the present Opinion, the CONTAM Panel has derived a TDI for short-term and chronic exposure to perchlorate of 1.4 μg/kg bw per day, based on reduction of radioactive iodine uptake in thyroid of healthy adults. The new TDI for perchlorate was derived using the updated EFSA BMD modelling guidance (EFSA Scientific Committee, 2022). This new TDI differs from the previous TDI (0.3 μg/kg bw per day). As a consequence, in order to assess the risk of public health for the presence of chlorate in food, there is a need to assess in detail the literature relating to the toxicity of chlorate (including its potency for the inhibition of uptake of iodine) and determine the appropriateness of using a revised read across approach, if needed.

6 | RECOMMENDATIONS

- More information is needed on concentrations of perchlorate in human milk in the European population.
- Improvement of the sensitivity of the analytical methods for perchlorate measurement in food is needed to reduce uncertainty in exposure assessments.
- More information on perchlorate exposure to the fetal thyroid gland and its impact on thyroid homeostasis and neurodevelopment is needed.
- A better characterisation of the possible effects of moderate iodine reduction caused by perchlorate (or other goitrogens) in populations with iodine deficiency/insufficiency would reduce uncertainty.

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ABBREVIATIONS

Ab	antibody
ADME	absorption, distribution, metabolism and excretion
AGES	Austrian Agency for Health and Food Safety
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health & Safety)
ALT	alanine transaminase/alanine aminotransferase
AOP	adverse outcome pathway
AP	ammonium perchlorate
ARfD	acute reference dose
ATPase	adenosine triphosphatase
BfR	Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment)
BBDR	biologically-based dose–response
BDNF	brain-derived neurotrophic factor
BMD	Benchmark Dose
BMDL	Benchmark Dose lower confidence/credible limit
BMDU	Benchmark Dose upper confidence/credible limit
BMDS	Benchmark Dose modelling tool
BMI	body mass index
Bmp	human milk perchlorate concentration
BMR	Benchmark Response
BPA	bisphenol A
BPS	bisphenol S
BSID	Bayley Scales of Infant Development
bw	body weight
CalEPA	California Environmental Protection Agency
CATS	Controlled Antenatal Thyroid Screening Study
CDF	cumulative distribution function
CI	confidence interval
C_{max}	maximum concentration
CONTAM	EFSA Panel on Contaminants in the Food Chain
CVD	cardiovascular diseases
DEHAL1	dehalogenase 1
Dio1	type 1 iodothyronine deiodinase
DIT	diiodotyrosine
dSPE	dispersive solid phase extraction
ECHA	European Chemicals Agency
EKE	expert knowledge elicitation
ESI	electrospray ionisation
EURL	European Union Reference Laboratory
FoodEx2	Food Classification and Description System for Exposure Assessment (Version 2)
FR	France
FT3	free triiodothyronine
FT4	free thyroxine
GC–MS	gas chromatography–mass spectrometry
GD	gestational day
GI	gastrointestinal
HBGV	health-based guidance value
HDL	high-density lipoprotein
HDL-c	high-density lipoprotein cholesterol
HPLC	high-performance liquid chromatography
HPT	hypothalamus–pituitary–thyroid
HRP	highest reliable percentile
I	iodine
IC	ion chromatography
IC-DC	ion chromatography conductivity detection
ICR	Institute of Cancer Research
ID	iodine deficiency
IPCS	International Programme on Chemical Safety
IQ	intelligence quotient
IC50	half-maximal inhibitory concentration
JECFA	Joint FAO/WHO Expert Committee on Food Additives

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KE	key event
KCNQ1 or 2	potassium voltage-gated channel subfamily Q member 1 or 2
LB	lower bound
LC	left-censored/liquid chromatography
LCD	liquid crystal display
LCMRL	lowest concentration minimum reporting level
LC–MS	liquid chromatography–mass spectrometry
LC–MS/MS	liquid chromatography–tandem mass spectrometry
LD_{50}	median lethal dose
LDL	low-density lipoprotein
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantification
MB	middle bound
MBP	mono-n-butyl phthalate
MCT 8	monocarboxylate transporter 8
MECPP	mono(2-ethyl-5-carboxypentyl) phthalate
MEHP	mono-2-ethylhexyl phthalate
MEOHP	mono-(2-ethyl-5-oxohexyl) phthalate
MEP	monoethyl phthalate
MIE	molecular-initiating event
MIT	monoiodotyrosine
MMI	methimazole
MoA	mode of action
MoE	margin of exposure
MRL	maximum residue level
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MS/MS	tandem mass spectrometry
N	sample size
N.A.	not applicable/not available
NG	nodular goitre
NHANES	National Health and Nutrition Examination Survey
NIS	sodiumiodide symporter
NO	nitric oxide
NOAEL	no observed adverse effect level
N.R.	not reported
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OEHHA	Office of Environmental Health Hazard Assessment
OHAT	Office of Health Assessment and Translation
P	percentile
PBPK	physiologically based pharmacokinetic
PDS	pendrin
PERT	Program evaluation and review technique
PM	particulate matter
Pme	human excretion fraction of perchlorate
PMTDI	provisional maximum tolerable daily intake
PND	postnatal day
PRIMo	Pesticide Residue Intake Model
PROAST	Benchmark dose modelling tool
PTC	papillary thyroid cancer
PTMC	papillary thyroid microcarcinoma
PTU	propylthiouracil
PVC	polyvinyl chloride
PVH	periventricular heterotopia
QuEChERS	quick easy cheap efficient robust safe
QuPPe	quick polar pesticides
RAIU	radioactive iodine uptake
RBC	red blood cell
ROS	reactive oxygen species
RP	Reference Point

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RPC	raw primary commodity
RSD	relative standard deviation
SAS	Statistical Analysis System
SC	Scientific Committee
SCPAFF	Standing Committee on Plants, Animals, Food and Feed
SD	standard deviation
SOP	Standard Operational Procedure
T3	triiodothyronine
T4	thyroxine
TC	total cholesterol
TD	toxicodynamics
TDI	tolerable daily intake
Tg	thyroglobulin
TG	triglycerides
TH	thyroid hormone
TK	toxicokinetics
TPO	thyroid peroxidase
TRH	thyrotropin-releasing hormone
TRV	toxicity reference value
TSH	thyroid stimulating hormone
TT3	total triiodothyronine
UB	upper bound
UF	uncertainty factor
UI	urinary iodine
US EPA	United States Environmental Protection Agency
v	version
WHO	World Health Organization
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
ww	wet weight

ACKNOWLEDGEMENTS

The CONTAM Panel wishes to thank Diane Benford, Federico Cruciani, Walid El Serry, Mary Gilbert, Marianna Kujawa and Paschalina Papadaki for the inputs and support provided to this scientific output. The Panel wishes to acknowledge all European competent institutions and Member State bodies that provided consumption and occurrence data for this scientific output.

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REFERENCES

Abel, M. H., Brandlistuen, R. E., Caspersen, I. H., Aase, H., Torheim, L. E., Meltzer, H. M., & Brantsaeter, A. L. (2019). Language delay and poorer school performance in children of mothers with inadequate iodine intake in pregnancy: Results from follow-up at 8 years in the Norwegian mother and child cohort study. *European Journal of Nutrition*, *58*(8), 3047–3058.

Alazraki, N. P., Halpern, S. E., & Ashburn, W. L. (1972). A Re-evaluation of 131I thyroid uptakes. *Radiology*, *105*(3), 611–614.

Al-Muqbel, K. M., & Tashtoush, R. M. (2010). Patterns of thyroid radioiodine uptake: Jordanian experience. *Journal of Nuclear Medicine Technology*, *38*(1), 32–36. https://doi.org/10.2967/jnmt.109.069146

Anastassiades, M., Schäfer, A.-K., Kolberg, D. I., Eichhorn, E., Dias, H., Benkenstein, A., Zechmann, S., Mack, D., Wildgrube, C., Barth, A., Sigalov, I., Goerlich, S., Dörk, D., & Cerchia, G. (2021). Quick Method for the Analysis of Highly Polar Pesticides in Food Involving Extraction with Acidified Methanol and LC- or ICMS/MS Measurement - I. Food of Plant Origin (QuPPe-PO-Method) – Version 12 (published on EURL-SRM website on July 23, 2021). https://www.eurlpesticides.eu/docs/public/tmplt_article.asp?CntID=887&LabID=200&Lang=EN

18314732, 2025, 5, Downloaded from https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2025.9393, Wiley Online Library on [20/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Anbar, M., Guttmann, S., & Lewitus, Z. (1959). The mode of action of perchlorate ions on the iodine uptake of the thyroid gland. *International Journal of Applied Radiation and Isotopes*, *7*, 87–96.
ANSES. (2022). Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the "relevance of reassessing the chronic oral TRV for perchlorate". Request No 2019-SA-0116. https://www.anses.fr/en/system/files/VSR2019SA0116EN-1.pdf
Argus Research Laboratories. (2001). Hormone, thyroid and neurohistological effects of oral (drinking water) exposure to ammonium perchlorate in pregnant and lactating rats and in fetuses and nursing pups exposed to ammonium perchlorate during gestation or via material milk. Argus Research Laboratories, Inc. (as cited in U.S. EPA, 2002).
ATSDR (Agency for Toxic Substances and Disease Registry). (2008). *Toxicological profile for perchlorates*. GA, United States Department of Health and Human Services, Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=895&tid=181
Ballal, S., Soundararajan, R., & Bal, C. (2017). Re-establishment of normal radioactive iodine uptake reference range in the era of universal salt iodization in the Indian population. *Indian Journal of Medical Research*, *145*(3), 358–364. https://doi.org/10.4103/ijmr.IJMR_1158_14
Berbel, P., Marco, P., Cerezo, J., & DeFelipe, J. (1996). Distribution of parvalbumin immunoreactivity in the neocortex of hypothyroid adult rats. *Neuroscience Letters*, *204*(1–2), 65–68.
BfR. (2013a). BfR recommendations on how to perform the consumer risk assessment for perchlorate residues in food, BfR Opinion No. 015/2013, 6 June 2013. http://www.bfr.bund.de/cm/349/bfr-recommendations-on-how-to-perform-the-consumer-risk-assessment-for-perchlorate-residues-in-food.pdf
BfR. (2013b). Health assessment of perchlorate residues in foods. BfR Opinion No. 022/2013, 28 June 2013. https://mobil.bfr.bund.de/cm/349/health-assessment-of-perchlorate-residues-in-foods.pdf
BfR. (2018). The entry of perchlorate into the food chain should be reduced. Updated BfR Opinion No 006/2018 of 15 February 2018. https://mobil.bfr.bund.de/cm/349/the-entry-of-perchlorate-into-the-food-chain-should-be-reduced.pdf
Bizhanova, A., & Kopp, P. (2009). The sodium-iodide symporter NIS and pendrin in iodide homeostasis of the thyroid. *Endocrinology*, *150*(3), 1084–1090. https://doi.org/10.1210/en.2008-1437
Bloem, E., & Panten, K. (2021). Transfer of perchlorate into different plant parts - can perchlorate contaminations of soils explain perchlorate findings in vegetables and fruits? *Journal Fur Kulturpflanzen*, *73*(11–12), 353–363.
Blount, B. C., Alwis, K. U., Jain, R. B., Solomon, B. L., Morrow, J. C., & Jackson, W. A. (2010). Perchlorate, nitrate, and iodide intake through tap water. *Environmental Science & Technology*, *44*(24), 9564–9570.
Blount, B. C., Pirkle, J. L., Osterloh, J. D., Valentin-Blasini, L., & Caldwell, K. L. (2006). Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. *Environmental Health Perspectives*, *114*, 1865–1871.
Braverman, L. E., Pearce, E. N., He, X., Pino, S., Seeley, M., Beck, B., Magnani, B., Blount, B. C., & Firek, A. (2006). Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. *Journal of Clinical Endocrinology and Metabolism*, *91*, 2721–2724.
Broedel, O., Eravci, M., Fuxius, S., Smolarz, T., Jeitner, A., Grau, H., Stoltenburg-Didinger, G., Plueckhan, H., Meinhold, H., & Baumgartner, A. (2003). Effects of hyper- and hypothyroidism on thyroid hormone concentrations in regions of the rat brain. *American Journal of Physiology. Endocrinology and Metabolism*, *285*, E470–E480.
Brown, G. M., & Gu, B. (2006). The chemistry of perchlorate in the environment. Chapter 2. In B. Gu & J. D. Coates (Eds.), *Perchlorate. Environmental occurrence, interactions and treatment* (pp. 17–47). Springer Science.
Bruce, G. M., Corey, L. M., Pearce, E. N., Braverman, L. E., & Pleus, R. C. (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. https://doi.org/10.1097/JOM.0000000000001239
Bulaeva, E., Lanctôt, C., Reynolds, L., Trudeau, V. L., & Navarro-Martín, L. (2015). Sodium perchlorate disrupts development and affects metamorphosis- and growth-related gene expression in tadpoles of the wood frog (Lithobates sylvaticus). *General and Comparative Endocrinology*, *222*(1), 33–43. https://doi.org/10.1016/j.ygcen.2015.01.012
Caldwell, D. J., King, J. H., Kinkead, E. R., Wolfe, R. E., Narayanan, L., & Mattie, D. R. (1995). *Results of a fourteen day oral-dosing toxicity study of ammonium perchlorate*. Wright-Patterson Air Force Base, Tri-Service Toxicology Consortium, Armstrong Laboratory.
CalEPA (California Environmental Protection Agency). (2015). Public Health Goal for Perchlorate in Drinking Water Available at: OEHHA. https://oehha.ca.gov/water/public-health-goal-fact-sheet/final-technical-support-document-public-health-goal-perchlorate
Campbell, D. E., Montgomerie, R. D., & Langlois, V. S. (2018). Lifecycle exposure to perchlorate differentially alters morphology, biochemistry, and transcription as well as sperm motility in Silurana tropicalis frogs. *Environmental Pollution*, *237*, 196–204.
Cao, Y., Blount, B. C., Valentin-Blasini, L., Bernbaum, J. C., Phillips, T. M., & Rogan, W. J. (2010). Goitrogenic anions, thyroid-stimulating hormone, and thyroid hormone in infants. *Environmental Health Perspectives*, *118*, 1332–1337.
Carr, C. W. (1952). Studies on the binding of small ions in protein solutions with the use of membraneelectrodes. I. The binding of the chloride ion and other inorganic anions in solutions of serumalbumin. *Archives of Biochemistry and Biophysics*, *40*(2), 286–294. https://doi.org/10.1016/0003-9861(52)90113-6
Chakraborty, A. (2021). Excess iodine supplementation aggravates the toxic effects induced by perchlorate on the male reproductive system in rats. *Asian Pacific Journal of Reproduction*, *10*(5), 215–224.
Chamot, S., Al-Salameh, A., Petit, P., Bonneterre, V., Cancé, C., Decocq, G., Boullier, A., Braun, K., & Desailloud, R. (2023). Does prenatal exposure to multiple airborne and tap-water pollutants increase neonatal thyroid-stimulating hormone concentrations? Data from the Picardy region, France. *Science of the Total Environment*, *905*, 167089. https://doi.org/10.1016/j.scitotenv.2023.167089
Charatcharoenwitthaya, N., Ongphiphadhanakul, B., Pearce, E. N., Somprasit, C., Chanthasenanont, A., He, X., Chailurkit, L., & Braverman, L. E. (2014). The association between perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant Thai women. *The Journal of Clinical Endocrinology & Metabolism*, *99*(7), 2365–2371.
Chen, D., Li, H., Li, J., Liu, Z., Lyu, B., Li, J., Zhao, Y., Zhong, Y., & Wu, Y. (2023). Comprehensive evaluation of perchlorate dietary exposure and health risks for Chinese adult males and breastfed infants. *Science of the Total Environment*, *891*, 164696. https://doi.org/10.1016/j.scitotenv.2023.164696
Chen, H. X., Ding, M. H., Li, Y. G., Liu, Q., & Peng, K. L. (2015). Dose-response relationship between orally administered ammonium perchlorate and urine perchlorate concentrations in rats: Possible biomarker to quantify environmental ammonium perchlorate exposure on thyroid homeostasis. *Archives of Environmental & Occupational Health*, *70*(5), 286–290.
Chen, H. X., Ding, M. H., Liu, Q., & Peng, K. L. (2014). Change of iodine load and thyroid homeostasis induced by ammonium perchlorate in rats. *Journal of Huazhong University of Science and Technology. Medical Sciences*, *34*, 672–678.
Cianchetta, S., di Bernardo, J., Romeo, G., & Rhoden, K. J. (2010). Perchlorate transport and inhibition of the sodium iodide symporter measured with the yellow fluorescent protein variant YFP-H148Q/I152L. *Toxicology and Applied Pharmacology*, *243*, 372–380.
Clark, C. E. (1962). The PERT model for the distribution of an activity time. *Operations Research*, *10*, 405–406.
Clewell, H. J., III, Gentry, P. R., Hack, C. E., Greene, T., & Clewell, R. A. (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. *Regulatory Toxicology and Pharmacology*, *103*(1), 237–252. https://doi.org/10.1016/j.yrtph.2019.01.028

18314732, 2025, 5, Downloaded from https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2025.9393, Wiley Online Library on [20/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Clewell, R. A., Merrill, E. A., Gearhart, J. M., Robinson, P. J., Sterner, T. R., Mattie, D. R., & Clewell, H. J., III. (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. *Journal of Toxicology and Environmental Health, Part A*, *70*(5), 408–428.

Clewell, R. A., Merrill, E. A., Narayanan, L., Gearhart, J. M., & Robinson, P. J. (2004). Evidence for competitive inhibition of iodide uptake by perchlorate and translocation of perchlorate into the thyroid. *International Journal of Toxicology*, *23*, 17–23.

Clewell, R. A., Merrill, E. A., Yu, K. O., Mahle, D. A., Sterner, T. R., Fisher, J. W., & Gearhart, J. M. (2003). Predicting neonatal perchlorate dose and inhibition of iodide uptake in the rat during lactation using physiologically-based pharmacokinetic modeling. *Toxicological Sciences*, *74*, 416–436.

Clewell, R. A., Merrill, E. A., Yu, K. O., Mahle, D. A., Sterner, T. R., Mattie, D. R., Robinson, P. J., Fisher, J. W., & Gearhart, J. M. (2003). Predicting fetal perchlorate dose and inhibition of iodide kinetics during gestation: A physiologically-based pharmacokinetic analysis of perchlorate and iodine kinetics in the rat. *Toxicological Sciences*, *73*, 235–255.

Constantinou, P., Louca-Christodoulou, D., & Agapiou, A. (2019). LC-ESI-MS/MS determination of oxyhalides (chlorate, perchlorate and bromate) in food and water samples, and chlorate on household water treatment devices along with perchlorate in plants. *Chemosphere*, *235*, 757–766. https://doi.org/10.1016/j.chemosphere.2019.06.180

Crofton, K. M. (2004). Developmental disruption of thyroid hormone: Correlations with hearing dysfunction in rats. *Risk Analysis*, *24*, 1665–1671. https://doi.org/10.1111/j.0272-4332.2004.00557.x

Crofton, K. M., Gilbert, M., Friedman, K. P., Demeneix, B., Martyiv, M. S., & Zoellerv, R. T. (2019). *Adverse outcome pathway on inhibition of Thyroperoxidase and subsequent adverse neurodevelopmental outcomes in mammals*. *OECD Series on Adverse Outcome Pathways, No. 13*. OECD Publishing. https://doi.org/10.1787/ea5aa069-en

Crump, K. S., & Gibbs, J. P. (2005). Benchmark calculations for perchlorate from three human cohorts. *Environmental Health Perspectives*, *113*, 1001–1008.

Culp, W. C., & Huskison, W. T. (1978). Changing normal values for thyroid uptake of radioactive iodine. *Southern Medical Journal*, *71*(6), 674–676. https://doi.org/10.1097/00007611-197806000-00021

Dasgupta, P. K., Kirk, A. B., Dyke, J. V., & Ohira, S. (2008). Intake of iodine and perchlorate and excretion in human milk. *Environmental Science & Technology*, *42*(21), 8115–8121. https://doi.org/10.1021/es801549w

Delange, F. (2000). The role of iodine in brain development. *The Proceedings of the Nutrition Society*, *59*(1), 75–79. https://doi.org/10.1017/s0029665100000094

de la Peña, S., Santiago-Roque, I., Olivo-Vidal, Z., Navarro-Meza, M., Xochihua-Rosas, I., & Arroyo-Helguera, O. (2018). Changes in trophoblasts gene expression in response to perchlorate exposition. *Toxicology In Vitro*, *50*, 328–335. https://doi.org/10.1016/j.tiv.2018.04.006

De La Vieja, A., Dohan, O., Levy, O., & Carrasco, N. (2000). Molecular analysis of the sodium/iodide symporter: Impact on thyroid and extrathyroid pathophysiology. *Physiological Reviews*, *80*, 1083–1105.

Dohan, O., Portulano, C., Basquin, C., Reyna-Neyra, A., Amzel, L. M., & Carrasco, N. (2007). The Na^+/I^- symporter (NIS) mediates electroneutral active transport of the environmental pollutant perchlorate. *National Academy of Sciences of the United States of America*, *104*(51), 20250–20255.

Dold, S., Zimmermann, M. B., Baumgartner, J., Davaz, T., Galetti, V., Braegger, C., & Andersson, M. (2016). A dose-response crossover iodine balance study to determine iodine requirements in early infancy. *The American Journal of Clinical Nutrition*, *104*(3), 620–628. https://doi.org/10.3945/ajcn.116.134049

Duncan, P. B., Morrison, R. D., & Vavricka, E. (2005). Forensic Identification of Anthropogenic and Naturally Occurring Sources of Perchlorate. *Environmental Forensics*, *6*(2), 205–215. https://doi.org/10.1080/15275920590952883

Durand, M. J. (1938). Recherches sur l'élimination des perchlorates, sur leur repartition dans les organeset sur leur toxicité. *Bulletin de la Société de Chimie Biologique*, *20*, 428–435.

ECHA (European Chemicals Agency). (2014). Published information on the REACH Registration Dossier on ammonium perchlorate (CAS Number 7790-98-9). European Chemicals Agency. http://echa.europa.eu/information-on-chemicals/registered-substances

EFSA (European Food Safety Authority). (2009). Guidance of the scientific committee on a request from EFSA on the use of the benchmark dose approach in risk assessment. *EFSA Journal*, 1150. https://doi.org/10.2903/j.efsa.2009.1150

EFSA (European Food Safety Authority). (2010a). Standard sample description for food and feed. *EFSA Journal*, *8*(1), 1457. https://doi.org/10.2903/j.efsa.2010.1457

EFSA (European Food Safety Authority). (2010b). Management of left-censored data in dietary exposure assessment of chemical substances. *EFSA Journal*, *8*(3), 1557. https://doi.org/10.2903/j.efsa.2010.1557

EFSA (European Food Safety Authority). (2011a). Report on the development of a food classification and description system for exposure assessment and guidance on its implementation and use. *EFSA Journal*, *9*(12), 2489. https://doi.org/10.2903/j.efsa.2011.2489

EFSA (European Food Safety Authority). (2011b). The food classification and description system FoodEx 2 (draft-revision 1). *EFSA Supporting Publications*, EN-215. https://doi.org/10.2903/sp.efsa.2011.EN-215

EFSA (European Food Safety Authority). (2011c). Use of the EFSA comprehensive European food consumption database in exposure assessment. *EFSA Journal*, *9*(3), 2097. https://doi.org/10.2903/j.efsa.2011.2097

EFSA (European Food Safety Authority). (2013). Standard sample description ver. 2.0. *EFSA Journal*, *11*(10), 3424, 114 pp. https://doi.org/10.2903/j.efsa.2013.3424

EFSA (European Food Safety Authority). (2015). The food classification and description system FoodEx2 (revision 2). *EFSA Supporting Publications*, EN-804. https://doi.org/10.2903/sp.efsa.2015.EN-804

EFSA (European Food Safety Authority). (2018). Internal report on the harmonisation of dilution factors to be used in the assessment of dietary exposure. https://doi.org/10.5281/zenodo.1256085

EFSA (European Food Safety Authority), Dujardin, B., & Kirwan, L. (2019a). Technical report on the raw primary commodity (RPC) model: Strengthening EFSA's capacity to assess dietary exposure at different levels of the food chain, from raw primary commodities to foods as consumed. *EFSA Supporting Publications*, EN-1532. https://doi.org/10.2903/sp.efsa.2019a.EN-1532

EFSA (European Food Safety Authority), Hart, A., Maxim, L., Siegrist, M., Von Goetz, N., da Cruz, C., Merten, C., Mosbach-Schulz, O., Lahaniatis, M., Smith, A., & Hardy, A. (2019b). Guidance on communication of uncertainty in scientific assessments. *EFSA Journal*, *17*(1), 5520. https://doi.org/10.2903/j.efsa.2019.5520

EFSA (European Food Safety Authority), Arcella, D., Cascio, C., Dujardin, B., Gergelová, P., Gómez Ruiz, J. A., Horváth, Z., Ioannidou, S., Medina Pastor, P., & Riolo, F. (2021). Technical report on handling occurrence data for dietary exposure assessments. *EFSA Supporting Publications*, EN-7082. https://doi.org/10.2903/sp.efsa.2021.EN-7082

EFSA (European Food Safety Authority), Crivellente, F., Hernández-Jerez, A. F., Lanzoni, A., Metruccio, F., Mohimont, L., Nikolopoulou, D., & Castoldi, A. F. (2024). Specific effects on the thyroid relevant for performing a dietary cumulative risk assessment of pesticide residues: 2024 update. *EFSA Journal*, *22*(3), e8672. https://doi.org/10.2903/j.efsa.2024.8672

EFSA (European Food Safety Authority), Arcella, D., Binaglia, M., & Vernazza, F. (2017). Scientific Opinion on the dietary exposure assessment to perchlorate in the European population. *EFSA Journal 2017*, *15*(10), 5043, 24 pp. https://doi.org/10.2903/j.efsa.2017.5043

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*, *12*(10), 3869. https://doi.org/10.2903/j.efsa.2014.3869

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EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain). (2015). Scientific opinion on risks for public health related to the presence of chlorate in food. *EFSA Journal*, *13*(6), 4135. https://doi.org/10.2903/j.efsa.2015.4135

EFSA Scientific Committee. (2012). Guidance on selected default values to be used by the EFSA scientific committee, scientific panels and units in the absence of actual measured data. *EFSA Journal*, *10*(3), 2579. https://doi.org/10.2903/j.efsa.2012.2579

EFSA Scientific Committee, Hardy, A., Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., Naegeli, H., Noteborn, H., Ockleford, C., Ricci, A., Rychen, G., Schlatter, J. R., Silano, V., Solecki, R., Turck, D., Bresson, J.-L., Dusemund, B., Gundert-Remy, U., … Mortensen, A. (2017). Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age. *EFSA Journal*, *15*(5), 4849. https://doi.org/10.2903/j.efsa.2017.4849

EFSA Scientific Committee, Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., Naegeli, H., Noteborn, H., Ockleford, C., Ricci, A., Rychen, G., Schlatter, J. R., Silano, V., Solecki, R., Turck, D., Younes, M., Craig, P., Hart, A., Von Goetz, N., … Hardy, A. (2018a). Scientific opinion on the principles and methodsbehind EFSA's guidance on uncertainty analysis in scientific assessment. *EFSA Journal*, *16*(1), 5122. https://doi.org/10.2903/j.efsa.2018.5122

EFSA Scientific Committee, Benford, D., Halldorsson, T., Jeger, M. J., Knutsen, H. K., More, S., Naegeli, H., Noteborn, H., Ockleford, C., Ricci, A., Rychen, G., Schlatter, J. R., Silano, V., Solecki, R., Turck, D., Younes, M., Craig, P., Hart, A., Von Goetz, N., … Hardy, A. (2018b). Guidance on uncertainty analysis in scientific assessments. *EFSA Journal*, *16*(1), 5123. https://doi.org/10.2903/j.efsa.2018.5123

EFSA Scientific Committee, More, S. J., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T. I., Hernandez-Jerez, A. F., Bennekou, S. H., Koutsoumanis, K., Lambre, C., Machera, K., Mennes, W., Mullins, E., Nielsen, S. S., Schrenk, D., Turck, D., Younes, M., Aerts, M., Edler, L., … Schlatter, J. (2022). Guidance on the use of the benchmark dose approach in risk assessment. *EFSA Journal*, *20*(10), 7584. https://doi.org/10.2903/j.efsa.2022.7584

EFSA Scientific Committee, More, S., Bampidis, V., Benford, D., Bragard, C., Hernandez-Jerez, A., Bennekou, S. H., Koutsoumanis, K. P., Lambré, C., Machera, K., Mullins, E., Nielsen, S. S., Schlatter, J., Schrenk, D., Turck, D., Younes, M., Kraft, A., Naegeli, H., Tsaioun, K., … Stancanelli, G. (2023). Guidance on protocol development for EFSA generic scientific assessments. *EFSA Journal*, *21*(10), 8312. https://doi.org/10.2903/j.efsa.2023.8312

EFSA Scientific Committee, More, S., Bampidis, V., Benford, D., Bragard, C., Hernandez-Jerez, A., Bennekou, S. H., Koutsoumanis, K. P., Lambré, C., Machera, K., Mullins, E., Nielsen, S. S., Schlatter, J., Schrenk, D., Turck, D., Younes, M., Fletcher, T., Greiner, M., Ntzani, E., … Halldorsson, T. I. (2024). Guidance on appraising and integrating evidence from epidemiological studies for use in EFSA's scientific assessments. *EFSA Journal*, *22*(7), e8866. https://doi.org/10.2903/j.efsa.2024.8866

Eguchi, A., Kunisue, T., Wu, Q., Trang, P. T., Viet, P. H., Kannan, K., & Tanabe, S. (2014). Occurrence of perchlorate and thiocyanate in human serum from e-waste recycling and reference sites in Vietnam: Association with thyroid hormone and iodide levels. *Archives of Environmental Contamination and Toxicology*, *67*(1), 29–41. https://doi.org/10.1007/s00244-014-0021-y

Eichler, O. (1929). Zur Pharmakologie der Perchloratwirking [the pharmacology of the perchlorate effect]. *Naunyn-Schmiedeberg's Archiv für Experimentelle Pathologie und Pharmakologie*, *144*, 251–260.

Ellington, J. J., Wolfe, N. L., Garrison, A. W., Evans, J. J., Avants, J. K., & Teng, Q. (2001). Determination of perchlorate in tobacco plants and tobacco products. *Environmental Science & Technology*, *35*(15), 3213–3218. https://doi.org/10.1021/es0106321

Evans, K. A., Rich, D. Q., Weinberger, B., Vetrano, A. M., Valentin-Blasini, L., Strickland, P. O., & Blount, B. C. (2015). Association of prenatal perchlorate, thiocyanate, and nitrate exposure with neonatal size and gestational age. *Reproductive Toxicology*, *57*, 183–189.

Felker, P., Bunch, R., & Leung, A. M. (2016). Concentrations of thiocyanate and goitrin in human plasma, their precursor concentrations in brassica vegetables, and associated potential risk for hypothyroidism. *Nutrition Reviews*, *74*(4), 248–258.

Fisher, J., Todd, P., Mattie, D., Godfrey, D., Narayanan, L., & Yu, K. (2000). Preliminary development of a physiological model for perchlorate in the adult male rat: A framework for further studies. *Drug and Chemical Toxicology*, *23*, 243–258.

Fisher, W., Wang, J., George, N. I., Gearhart, J. M., & McLanahan, E. D. (2016). Dietary iodine sufficiency and moderate insufficiency in the lactating mother and nursing infant: A computational perspective. *PLoS One*, *11*(3), e0149300.

Flood, D. E., & Langlois, V. S. (2014). Crosstalk between the thyroid hormone and androgen axes during reproductive development in Silurana tropicalis. *General and Comparative Endocrinology*, *203*, 232–240.

Furin, C. G., von Hippel, F. A., Postlethwait, J., Buck, C. L., Cresko, W. A., & O'Hara, T. M. (2015b). Developmental timing of perchlorate exposure alters threespine stickleback dermal bone. *General and Comparative Endocrinology*, *219*, 36–44. https://doi.org/10.1016/j.ygcen.2015.02.016

Furin, C. G., von Hippel, F. A., Postlethwait, J. H., Buck, C. L., Cresko, W. A., & O'Hara, T. M. (2015a). Developmental timing of sodium perchlorate exposure alters angiogenesis, thyroid follicle proliferation and sexual maturation in stickleback. *General and Comparative Endocrinology*, *219*, 24–35. https://doi.org/10.1016/j.ygcen.2015.04.002

Galanty, A., Grudzińska, M., Paździora, W., Służały, P., & Paśko, P. (2024). Do brassica vegetables affect thyroid function?—A comprehensive systematic review. *International Journal of Molecular Sciences*, *25*(7), 3988.

Gardell, A. M., Dillon, D. M., Smayda, L. C., von Hippel, F. A., Cresko, W. A., Postlethwait, J. H., & Buck, C. L. (2015). Perchlorate exposure does not modulate temporal variation of whole-body thyroid and androgen hormone content in threespine stickleback. *General and Comparative Endocrinology*, *219*, 45–52.

Gardell, A. M., von Hippel, F. A., Adams, E. M., Dillon, D. M., Petersen, A. M., Postlethwait, J. H., Cresko, W. A., & Buck, C. L. (2017). Exogenous iodide ameliorates perchlorate-induced thyroid phenotypes in threespine stickleback. *General and Comparative Endocrinology*, *243*, 60–69. https://doi.org/10.1016/j.ygcen.2016.10.014

Geysels, R. C., Bernal Barquero, C. E., Martín, M., Peyret, V., Nocent, M., Sobrero, G., Muñoz, L., Signorino, M., Testa, G., Castro, R. B., Masini-Repiso, A. M., Miras, M. B., & Nicola, J. P. (2022). Silent but not harmless: A synonymous SLC5A5 gene variant leading to Dyshormonogenic congenital hypothyroidism. *Front Endocrinol (Lausanne)*, *13*, 868891. https://doi.org/10.3389/fendo.2022.868891

Gibbs, J. P., Ahmad, R., Crump, K. S., Houck, D. P., Leveille, T. S., Findley, J. E., & Francis, M. (1998). Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function. *Journal of Occupational and Environmental Medicine*, *40*(12), 1072–1082. https://doi.org/10.1097/00043764-199812000-00007

Gilbert, M. E., Hassan, I., O'Shaughnessy, K. L., Wood, C., Stoker, T. E., Riutta, C., & Ford, J. L. (2024). Ammonium perchlorate: Serum dosimetry, neurotoxicity, and resilience of the neonatal rat thyroid system. *Toxicological Sciences*, *198*(1), 113–127.

Gilbert, M. E., Hassan, I., Wood, C., O'Shaughnessy, K. L., Spring, S., Thomas, S., & Ford, J. (2022). Gestational exposure to perchlorate in the rat: Thyroid hormones in fetal thyroid gland, serum, and brain. *Toxicological Sciences*, *188*(1), 117–130.

Gilbert, M. E., Hawks, M. G., Bell, K. S., Oshiro, W., Wood, C., George, B. J., Thomas, R., & Ford, J. (2024). Iodine deficiency exacerbates thyroidal and neurological effects of developmental perchlorate exposure in the neonatal and adult rat. *Toxics*, *12*(12), 842. https://doi.org/10.3390/toxics12120842

Gilbert, M. E., O'Shaughnessy, K. L., Bell, K. S., & Ford, J. L. (2023). Structural malformations in the neonatal rat brain accompany developmental exposure to ammonium perchlorate. *Toxics*, *11*(12), 1027.

Gilbert, M. E., Sui, L., Walker, M. J., Anderson, W., Thomas, S., Smoller, S. N., Schon, J. P., Phani, S., & Goodman, J. H. (2007). Thyroid hormone insufficiency during brain development reduces parvalbumin immunoreactivity and inhibitory function in the hippocampus. *Endocrinology*, *148*, 92–102.

Gonzalez, E. P., Carmona, C. R., Araya, Q. A. V.. (2008). Normal 131Iodine uptake values at 2 and 24 hours. *Revista médica de Chile*, *136*(10), 1288–1293. https://doi.org/10.4067/S0034-98872008001000008

18314732, 2025, 5, Downloaded from https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2025.9393, Wiley Online Library on [20/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Gowachirapant, S., Jaiswal, N., Melse-Boonstra, A., Galetti, V., Stinca, S., Mackenzie, I., Thomas, S., Thomas, T., Winichagoon, P., Srinivasan, K., & Zimmermann, M. B. (2017). Effect of iodine supplementation in pregnant women on child neurodevelopment: A randomised, double-blind, placebo-controlled trial. *The Lancet Diabetes & Endocrinology*, *5*(11), 853–863.

Greer, M. A., Goodman, G., Pleus, R. C., & Greer, S. E. (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

Greiner, P., McLellan, C., Bennett, D., & Ewing, A. (2008). Occurrence of perchlorate in sodium hypochlorite. *Journal of American Water Works Association*, *100*(11), 68–74.

Gu, B., & Coates, J. D. (2006). *Environmental occurrence, interactions and treatment*. Springer sciences business Media Inc.

Guan, J., Wan, Y., Li, J., Zheng, T., Xia, W., Xu, S., & Li, Y. (2023). Urinary perchlorate, thiocyanate, and nitrate and their associated risk factors among Chinese pregnant women. *Chemosphere*, *345*, 140467. https://doi.org/10.1016/j.chemosphere.2023.140467

Guo, H., Zong, S., Yong, L., Jiang, Y., Qin, L., Zhou, L., Ren, Q., Gao, X., Kang, F., Huang, W., & Chen, J. (2023). The association between perchlorate in drinking water and height and weight of children and adolescents in Southwest China: A retrospective cross-sectional study. *Frontiers in Public Health*, *11*, 1260612. https://doi.org/10.3389/fpubh.2023.1260612

Guo, X., Wu, B., Hu, W., Wang, X., Su, W., Meng, J., Lowe, S., Zhao, D., Huang, C., Liang, M., & Qu, G. (2023). Associations of perchlorate, nitrate, and thiocyanate with metabolic syndrome and its components among US adults: A cross-sectional study from NHANES. *Science of the Total Environment*, *879*, 163083. https://doi.org/10.1016/j.scitotenv.2023.163083

Haber, L., Schoeny, R., & Allen, B. (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

Hakme, E., Herrmann, S. S., & Poulsen, M. E. (2022). Chlorate and perchlorate residues in food products on the Danish market. *Food Additives & Contaminants: Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment*, *39*(3), 551–559. https://doi.org/10.1080/19440049.2021.2017004

Han, Y., Li, D., Zou, C., Li, Y., & Zhao, F. (2023). Effects of perchlorate, nitrate, and thiocyanate exposures on serum total testosterone in children and adolescents. *The Science of the Total Environment*, *861*, 160566.

Hansen, J. M., Skovsted, L., & Siersbaek-Nielsen, K. (1975). Age dependent changes in iodine metabolism and thyroid function. *European Journal of Endocrinology*, *79*(1), 60–65.

Hasselt University. (2022). EFSA Platform for Bayesian Benchmark Dose Analysis. *EFSA Supporting Publications*, *19*(12), EN-7740. https://doi.org/10.2903/sp.efsa.2022.EN-7740

Hays, S. M., Macey, K., Poddalgoda, D., Lu, M., Nong, A., & Aylward, L. L. (2018). Biomonitoring equivalents for interpretation of human biomonitoring data for environmental chemicals. *Environmental Health Perspectives*, *126*(9), 97008. https://doi.org/10.1289/EHP3766

Hedrick, E. J., Behymer, T., Slingsby, R., & Munch, D. (2005). *METHOD 332.0: Determination of perchlorate in drinking water by ion chromatography with suppressed conductivity and electrospray ionization mass spectrometry. EPA Document #: EPA/600/R-05/049*. U.S. Environmental Protection Agency.

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

Hepperle, J., Wolheim, A., Kohlberg, D., Wildgrube, C., & Kaufmann-Horlacher, I. (2013). Analysis of perchlorate in food samples of plant origin applying the QuPPe-method and LC-MS/MS. *Aspects of Food Control and Animal Health*, 1–16.

Horton, M. K., Blount, B. C., Valentin-Blasini, L., Wapner, R., Whyatt, R., Gennings, C., & Factor-Litvak, P. (2015). CO-occurring exposure to perchlorate, nitrate and thiocyanate alters thyroid function in healthy pregnant women. *Environmental Research*, *143*, 1–9.

Hosoda, R., Nakayama, K., Kato-Negishi, M., Kawahara, M., Muramoto, K., & Kuroda, Y. (2003). Thyroid hormone enhances the formation of synapses between cultured neurons of rat cerebral cortex. *Cellular and Molecular Neurobiology*, *23*, 895–906.

Hosoya, T. (1963). Effect of various reagents including antithyroid compounds upon the activity of thyroid peroxidase. *Journal of Biochemistry*, *53*, 381–388. https://doi.org/10.1093/oxfordjournals.jbchem.a127712

Hu, J., Xian, Y., Wu, Y., Chen, R., Dong, H., Hou, X., Liang, M., Wang, B., & Wang, L. (2021). Perchlorate occurrence in foodstuffs and water: Analytical methods and techniques for removal from water–a review. *Food Chemistry*, *360*, 130146.

Hu, W., Li, Z., Jia, X., Feng, X., Zhang, D., Chen, Y., Li, X., Chen, X., Zhu, Z., Ji, J., Luo, D., & Lu, S. (2024). Chlorate and perchlorate in tea leaves from major producing regions in China and related human exposure risk. *Environmental Science and Pollution Research International*, *31*(6), 8510–8518. https://doi.org/10.1007/s11356-023-31742-8

Ismail, R. F., Assem, S. S., Sharaf, H. E. R., Zeitoun, A. A. M., & Srour, T. M. A. (2024). The effect of thyroxine (T4) and goitrogen on growth, liver, thyroid, and gonadal development of red tilapia (O. Mossambicus×O. Urolepis hornorum). *Aquaculture International*, *32*, 1151–1168. https://doi.org/10.1007/s10499-023-01210-8

Ittermann, T., Albrecht, D., Arohonka, P., Bilek, R., De Castro, J. J., Dahl, L., Filipsson Nystrom, H., Gaberscek, S., Garcia-Fuentes, E., Gheorghiu, M. L., & Hubalewska-Dydejczyk, A. (2020). Standardized map of iodine status in Europe. *Thyroid*, *30*(9), 1346–1354.

Jackson, W. A., Böhlke, J. K., Gu, B., Hatzinger, P. B., & Sturchio, N. C. (2010). Isotopic composition and origin of indigenous natural perchlorate and co-occurring nitrate in the southwestern United States. *Environmental Science & Technology*, *44*(13), 4869–4876.

Jaeglé, L., Yung, Y. L., Toon, G. C., Sen, B., & Blavier, J. F. (1996). Balloon observations of organic and inorganic chlorine in the stratosphere: The role of HClO4 production on sulfate aerosols. *Geophysical Research Letters*, *23*(14), 1749–1752.

Jansen, T. A., Korevaar, T. I., Mulder, T. A., White, T., Muetzel, R. L., Peeters, R. P., & Tiemeier, H. (2019). Maternal thyroid function during pregnancy and child brain morphology: A time window-specific analysis of a prospective cohort. *The Lancet Diabetes & Endocrinology*, *7*(8), 629–637.

Javidi, A., Rafiei, N., Amin, M. M., Hovsepian, S., Hashemipour, M., Kelishadi, R., Taghian, Z., Mofateh, S., & Poursafa, P. (2015). The relationship between perchlorate in drinking water and cord blood thyroid hormones: First experience from Iran. *International Journal of Preventive Medicine*, *6*(1), 17.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2011). Safety Evaluation of Certain Contaminants in Food. Perchlorate. WHO Food Additives Series: 63; FAO JECFA Monographs 8. https://apps.who.int/iris/bitstream/handle/10665/44520/9789241660631_eng.pdf;jsessionid=1F13A840E9387F619AC5B059086F9406?sequence=1

Jiang, Q., & Li, Q. (2022). Association of environmental exposure to perchlorate, nitrate, and thiocyanate with overweight/obesity and central obesity among children and adolescents in The United States of America using data from the National Health and nutrition examination survey (NHANES) 2005–2016. *New Directions for Child and Adolescent Development*, *2022*(185–186), 107–122.

Kamm, G., & Drescher, G. (1973). Demonstration of perchlorate in the urine. *Beiträge zur Gerichtlichen Medizin*, *30*, 206–210.

Kannan, K., Praamsma, M. L., Oldi, J. F., Kunisue, T., & Sinha, R. K. (2009). Occurrence of perchlorate in drinking water, groundwater, surface water and human saliva from India. *Chemosphere*, *76*, 22–26.

King, L., Huang, Y., Li, T., Wang, Q., Li, W., Shan, Z., Yin, J., Chen, L., Wang, P., Dun, C., & Zhuang, L. (2022). Associations of urinary perchlorate, nitrate and thiocyanate with central sensitivity to thyroid hormones: A US population-based cross-sectional study. *Environment International*, *164*, 107249.

King, L., Wang, Q., Xia, L., Wang, P., Jiang, G., Li, W., Huang, Y., Liang, X., Peng, X., Li, Y., & Chen, L. (2023). Environmental exposure to perchlorate, nitrate and thiocyanate, and thyroid function in Chinese adults: A community-based cross-sectional study. *Environment International*, *171*, 107713.

Kirk, A. B., Dyke, J. V., Martin, C. F., & Dasgupta, P. K. (2007). Temporal patterns in perchlorate, thiocyanate, and iodide excretion in human Milk. *Environmental Health Perspectives*, *115*, 182–186.

18314732, 2025, 5, Downloaded from https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2025.9393, Wiley Online Library on [20/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Kirk, A. B., Martinelango, P. K., Tian, K., Dutta, A., Smith, E. E., & Dasgupta, P. K. (2005). Perchlorate and iodide in dairy and breast milk. *Environmental Science & Technology*, *39*, 2011–2017.

Kjellevold, M., & Kippler, M. (2023). Fluoride–a scoping review for Nordic nutrition recommendations 2023. *Food & Nutrition Research*, *67*, 1–7.

Knight, B. A., Shields, B. M., He, X., Pearce, E. N., Braverman, L. E., Sturley, R., & Vaidya, B. (2018). Effect of perchlorate and thiocyanate exposure on thyroid function of pregnant women from south-West England: A cohort study. *Thyroid Research*, *11*(1), 1–7. https://doi.org/10.1186/s13044-018-0053-x

Ko, W. C., Liu, C. L., Lee, J. J., Liu, T. P., Yang, P. S., Hsu, Y. C., & Cheng, S. P. (2014). Negative association between serum parathyroid hormone levels and urinary perchlorate, nitrate, and thiocyanate concentrations in US adults: The National Health and nutrition examination survey 2005–2006. *PLoS One*, *9*(12), e115245.

Korevaar, T. I., Muetzel, R., Medici, M., Chaker, L., Jaddoe, V. W., de Rijke, Y. B., Steegers, E. A., Visser, T. J., White, T., Tiemeier, H., & Peeters, R. P. (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 and Endocrinology*, *4*(1), 35–43. https://doi.org/10.1016/S2213-8587(15)00327-7

Kostopoulou, E., Miliordos, K., & Spiliotis, B. (2021). Genetics of primary congenital hypothyroidism—A review. *Hormones*, *20*, 225–236.

Kounaves, S. P., Stroble, S. T., Anderson, R. M., Moore, Q., Catling, D. C., Douglas, S., McKay, C. P., Ming, D. W., Smith, P. H., Tamppari, L. K., & Zent, A. P. (2010). Discovery of natural perchlorate in the Antarctic dry valleys and its global implications. *Environmental Science & Technology*, *44*(7), 2360–2364.

Kumarathilaka, P., Oze, C., Indraratne, S. P., & Vithanage, M. (2016). Perchlorate as an emerging contaminant in soil, water and food. *Chemosphere*, *150*, 667–677.

Lawrence, J. E., Emerson, C. H., Sullaway, S. L., & Braverman, L. E. (2001). The effect of recombinant human TSH on the thyroid 123I uptake in iodide treated normal subjects. *The Journal of Clinical Endocrinology & Metabolism*, *86*(1), 437–440.

Lawrence, J. E., Lamm, S. H., Pino, S., Richman, K., & Braverman, L. E. (2000). The effect of short-term low-dose perchlorate on various aspects of thyroid function. *Thyroid*, *10*, 659–663.

Lecat-Guillet, N., Merer, G., Lopez, R., Pourcher, T., Rousseau, B., & Ambroise, Y. (2007). A 96-well automated radioiodide uptake assay for sodium/iodide symporter inhibitors. *Assay and Drug Development Technologies*, *5*, 535–540.

Lecat-Guillet, N., Merer, G., Lopez, R., Pourcher, T., Rousseau, B., & Ambroise, Y. (2008). Small-molecule inhibitors of sodium iodide symporter function. *Chembiochem*, *9*, 889–895.

Lee, J., Park, J. W., Kim, H. I., Park, C. B., & Cho, S. H. (2024). Thyroid-gonadal hormonal interplay in zebrafish exposed to sodium perchlorate. *Chemosphere*, *346*, 140662.

Lee, S., Ji, K., & Choi, K. (2014). Effects of water temperature on perchlorate toxicity to the thyroid and reproductive system of Oryzias latipes. *Ecotoxicology and Environmental Safety*, *108*, 311–317. https://doi.org/10.1016/j.ecoenv.2014.07.016

Leung, A. M., Pearce, E. N., & Braverman, L. E. (2011). Iodine nutrition in pregnancy and lactation. *Endocrinology and Metabolism Clinics*, *40*(4), 765–777.

Leung, A. M., Pearce, E. N., Hamilton, T., He, X., Pino, S., Merewood, A., & Braverman, L. E. (2009). Colostrum iodine and perchlorate concentrations in Boston-area women: A cross-sectional study. *Clinical Endocrinology*, *70*, 326–330.

Li, D., Huang, W., & Huang, R. (2023). Analysis of environmental pollutants using ion chromatography coupled with mass spectrometry: A review. *Journal of Hazardous Materials*, *458*, 131952. https://doi.org/10.1016/j.jhazmat.2023.131952

Li, J., Tu, F., Wan, Y., Qian, X., Mahai, G., Wang, A., Ma, J., Yang, Z., Xia, W., Xu, S., & Zheng, T. (2023). Associations of trimester-specific exposure to perchlorate, thiocyanate, and nitrate with childhood neurodevelopment: A birth cohort study in China. *Environmental Science & Technology*, *57*(49), 20480–20493. https://doi.org/10.1021/acs.est.3c06013

Li, M., Xiao, M., Xiao, Q., Chen, Y., Guo, Y., Sun, J., Li, R., Li, C., Zhu, Z., Qiu, H., Liu, X., & Lu, S. (2022). Perchlorate and chlorate in breast milk, infant formulas, baby supplementary food and the implications for infant exposure. *Environmental International*, *158*, 106939. https://doi.org/10.1016/j.envint.2021.106939

Li, W., Wu, H., Xu, X., & Zhang, Y. (2023). Environmental exposure to perchlorate, nitrate, and thiocyanate in relation to chronic kidney disease in the general US population, NHANES 2005-2016. *Chinese Medical Journal*, *136*(13), 1573–1582.

Li, W., Xiao, H., Wu, H., Pan, C., Deng, K., Xu, X., & Zhang, Y. (2022). Analysis of environmental chemical mixtures and nonalcoholic fatty liver disease: NHANES 1999–2014. *Environmental Pollution*, *311*, 119915.

Li, X., Li, J., Li, K., Zhang, Z., & Wang, H. (2023). Effects of perchlorate and exogenous T4 exposures on body condition and endochondral ossification of Rana chensinensis tadpoles. *Aquatic Toxicology*, *265*, 106767. https://doi.org/10.1016/j.aquatox.2023.106767

Li, Y., Li, S., Ren, J., Li, J., Zhao, Y., Chen, D., & Wu, Y. (2023). Occurrence, spatial distribution, and risk assessment of perchlorate in tea from typical regions in China. *Current Research in Food Science*, *7*, 100606. https://doi.org/10.1016/j.crfs.2023.100606

Liao, W. R., Wu, K. L., Chiang, K. H., Teng, C. E., & Chen, S. F. (2022). Analysis of highly polar pesticides in foods by LC-MS/MS. *Journal of Food and Drug Analysis*, *30*(4), 538–548. https://doi.org/10.38212/2224-6614.3420

Lisco, G., Accardo, G., Pupilli, C., Malandrino, P., De Geronimo, V., & Triggiani, V. (2024). Perchlorates in the treatment of hyperthyroidism and thyrotoxicosis: A comprehensive review. *Endocrine*, *85*(1), 1–10. https://doi.org/10.1007/s12020-023-03679-y

Liu, G., Zong, G., Dhana, K., Hu, Y., Blount, B. C., Morel-Espinosa, M., & Sun, Q. (2017). Exposure to perchlorate, nitrate and thiocyanate, and prevalence of diabetes mellitus. *International Journal of Epidemiology*, *46*(6), 1913–1923.

Liu, X., Zhang, H., Tian, Y., Fang, M., Xu, L., Wang, Q., Li, J., Shen, H., Wu, Y., & Gong, Z. (2021). Bioavailability evaluation of perchlorate in different foods in vivo: Comparison with in vitro assays and implications for human health risk assessment. *Journal of Agricultural and Food Chemistry*, *69*(17), 5189–5197.

Lumen, A., Mattie, D. R., & Fisher, J. W. (2013). Evaluation of perturbations in serum thyroid hormones during pregnancy due to dietary iodine and perchlorate exposure using a biologically based dose-response model. *Toxicological Sciences*, *133*, 320–341.

Maffini, M. V., Trasande, L., & Neltner, T. G. (2016). Perchlorate and diet: Human exposures, risks, and mitigation strategies. *Current Environmental Health Reports*, *3*, 107–117.

Martino, E., Bartalena, L., Bogazzi, F., & Braverman, L. E. (2001). The effects of amiodarone on the thyroid. *Endocrinology Reviews*, *22*(2), 240–254. https://doi.org/10.1210/edrv.22.2.0427

MassDEP (Massachusetts Department of Environmental Protection). (2006). *Perchlorate concentrations in household bleach. Report on the presence of perchlorate in various consumer products*. Massachusetts Department of Environmental Protection.

McLanahan, E. D., White, P., Flowers, L., & Schlosser, P. M. (2014). The use of PBPK models to inform human health risk assessment: Case study on perchlorate and radioiodide human lifestage models. *Risk Analysis*, *34*(2), 356–366. https://doi.org/10.1111/risa.12101

McMullen, J., Ghassabian, A., Kohn, B., & Trasande, L. (2017). Identifying subpopulations vulnerable to the thyroid-blocking effects of perchlorate and thiocyanate. *The Journal of Clinical Endocrinology & Metabolism*, *102*(7), 2637–2645.

Merrill, E. A., Clewell, R. A., Gearhart, J. M., Robinson, P. J., Sterner, T. R., Yu, K. O., Mattie, D. R., & Fisher, J. W. (2003). PBPK predictions of perchlorate distribution and its effect on thyroid uptake of Radioiodide in the male rat. *Toxicological Sciences*, *73*, 256–269.

Merrill, E. A., Clewell, R. A., Robinson, P. J., Jarabek, A. M., Gearhart, J. M., Sterner, T. R., & Fisher, J. W. (2005). PBPK model for radioactive iodide and perchlorate kinetics and perchlorate-induced inhibition of iodide uptake in humans. *Toxicological Sciences*, *83*(1), 25–43.

18314732, 2025, 5, Downloaded from https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2025.9393, Wiley Online Library on [20/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Mervish, N. A., Pajak, A., Teitelbaum, S. L., Pinney, S. M., Windham, G. C., Kushi, L. H., Biro, F. M., Valentin-Blasini, L., Blount, B. C., Wolff, M. S., & Breast Cancer and Environment Research Project (BCERP). (2016). Thyroid antagonists (perchlorate, thiocyanate, and nitrate) and childhood growth in a longitudinal study of US girls. *Environmental Health Perspectives*, *124*(4), 542–549. https://doi.org/10.1289/ehp.1409309

Mirabella, G., Feig, D., Astzalos, E., Perlman, K., & Rovet, J. F. (2000). The effect of abnormal intrauterine thyroid hormone economies on infant cognitive abilities. *Journal of Pediatric Endocrinology and Metabolism*, *13*(2), 191–194. https://doi.org/10.1515/jpem.2000.13.2.191

Mortensen, M. E., Birch, R., Wong, L. Y., Valentin-Blasini, L., Boyle, E. B., Caldwell, K. L., Merrill, L. S., Moye, J., Jr., & Blount, B. C. (2016). Thyroid antagonists and thyroid indicators in US pregnant women in the vanguard study of the National Children's study. *Environmental Research*, *149*, 179–188.

Mukhi, S., & Patino, R. (2007). Effects of prolonged exposure to perchlorate on thyroid and reproductive function in zebrafish. *Toxicological Sciences*, *96*(2), 246–254.

Murphy, D. M., & Thomson, D. S. (2000). Halogen ions and NO+ in the mass spectra of aerosols in the upper troposphere and lower stratosphere. *Geophysical Research Letters*, *27*(19), 3217–3220.

Murray, C. W., & Bolger, P. M. (2014). Environmental contaminants: perchlorate. In Y. Motarjemi (Ed.), *Encyclopedia of food safety* (pp. 337–341). Academic.

Neville, M. C., Allen, J. C., & Watters, C. (1988). The mechanisms of milk secretion. In B. L. Larson (Ed.), *Lactation* (pp. 49–104). Springer.

Nicol, K., Nugent, A. P., Woodside, J. V., Hart, K. H., & Bath, S. C. (2024). Iodine and plant-based diets–a narrative review and calculation of iodine content. *The British Journal of Nutrition*, *1*, 1–28.

Niziński, P., Wiśniewska, P., Kończyk, J., & Michalski, R. (2021). Perchlorate levels in polish water samples of various origin. *Separations*, *8*(4), 37. https://doi.org/10.3390/separations8040037

Oldi, J. F., & Kannan, K. (2009a). Analysis of perchlorate in human saliva by liquid chromatography-tandem mass spectrometry. *Environmental Science & Technology*, *43*, 142–147.

Oldi, J. F., & Kannan, K. (2009b). Perchlorate in human blood serum and plasma: Relationship to concentrations in saliva. *Chemosphere*, *77*, 43–47.

Opitz, R., Schmidt, F., Braunbeck, T., Wuertz, S., & Kloas, W. (2009). Perchlorate and ethylenethiourea induce different histological and molecular alterations in a non-mammalian vertebrate model of thyroid goitrogenesis. *Molecular and Cellular Endocrinology*, *298*(1–2), 101–114. https://doi.org/10.1016/j.mce.2008.08.020

Orathel, S. P., Thomas, R., Chandramohanakumar, N., Kulavelil, J. J., Kumar, K. G., Menon, V. U., Jayaprakash, P., Krishnan, S., Manju, P. S., Param, S., & Rajamanickam, M. G. (2020). Possible effects of perchlorate contamination of drinking water on thyroid health. *Journal of Thyroid Research*, *2020*(1), 5208656–5208657.

Ozpinar, A., Golub, M. S., Poppenga, R. H., Blount, B. C., & Gillespie, J. R. (2011). Thyroid status of female rhesus monkeys and preliminary information on impact of perchlorate administration. *Laboratory Animals*, *45*, 209–214.

Panicker, V. (2011). Genetics of thyroid function and disease. *The Clinical Biochemist Reviews*, *32*(4), 165–175.

Pearce, E. N., Leung, A. M., Blount, B. C., Bazrafshan, H. R., He, X., Pino, S., Valentin-Blasini, L., & Braverman, L. E. (2007). Breast Milk iodine and perchlorate concentrations in lactating Boston-area women. *Journal of Clinical Endocrinology and Metabolism*, *92*, 1673–1677.

Pesce, L., & Kopp, P. (2014). Iodide transport: Implications for health and disease. *International Journal of Pediatric Endocrinology*, *2014*, 8. https://doi.org/10.1186/1687-9856-2014-8

Petersen, A. M., Small, C. M., Yan, Y. L., Wilson, C., Batzel, P., Bremiller, R. A., Buck, C. L., von Hippel, F. A., Cresko, W. A., & Postlethwait, J. H. (2022). Evolution and developmental expression of the sodium–iodide symporter (NIS, slc5a5) gene family: Implications for perchlorate toxicology. *Evolutionary Applications*, *15*(7), 1079–1098.

Phillips, D. I. (1997). Iodine, milk, and the elimination of endemic goitre in Britain: The story of an accidental public health triumph. *Journal of Epidemiology & Community Health*, *51*(4), 391–393.

Pittman, J. A., Jr., Dailey, G. E., III, & Beschi, R. J. (1969). Changing normal values for thyroidal radioiodine uptake. *New England Journal of Medicine*, *280*(26), 1431–1434.

Poghosyan, A., Sturchio, N. C., Morrison, C. G., Beloso, A. D., Jr., Guan, Y., Eiler, J. M., Jackson, W. A., & Hatzinger, P. B. (2014). Perchlorate in the Great Lakes: Isotopic composition and origin. *Environmental Science & Technology*, *48*(19), 11146–11153.

Pohlenz, J., & Refetoff, S. (1999). Mutations in the sodium/iodide symporter (NIS) gene as a cause for iodide transport defects and congenital hypothyroidism. *Biochimie*, *81*(5), 469–476.

Porterfield, S. P., & Hendrich, C. E. (1993). The role of thyroid hormones in prenatal and neonatal neurological development--current perspectives. *Endocrine Reviews*, *14*(1), 94–106.

Price, R. J., Burch, R., Chatham, L. R., Higgins, L. G., Currie, R. A., & Lake, B. G. (2020). An assay for screening xenobiotics for inhibition of rat thyroid gland peroxidase activity. *Xenobiotica*, *50*, 318–322. https://doi.org/10.1080/00498254.2019.1629044

Przybyla, J., Geldhof, G. J., Smit, E., & Kile, M. L. (2018). A cross sectional study of urinary phthalates, phenols and perchlorate on thyroid hormones in US adults using structural equation models (NHANES 2007–2008). *Environmental Research*, *163*, 26–35.

Rao, B., Anderson, T. A., Orris, G. J., Rainwater, K. A., Rajagopalan, S., Sandvig, R. M., Scanlon, B. R., Stonestrom, D. A., Walvoord, M. A., & Jackson, W. A. (2007). Widespread natural perchlorate in unsaturated zones of the southwest United States. *Environmental Science and Technology*, *41*, 4522–4528.

Reh, B., Wang, X., Feng, Y., & Bhandari, R. K. (2022). Potassium perchlorate effects on primordial germ cells of developing medaka larvae. *Aquatic Toxicology*, *251*, 106283. https://doi.org/10.1016/j.aquatox.2022.106283

Rolaki, A., Pistollato, F., Munn, S., & Bal-Price, A. (2019). *Adverse Outcome Pathway on inhibition of Na+/I- symporter (NIS) leads to learning and memory impairment*. OECD Series on Adverse Outcome Pathways, No. 14, OECD Publishing. https://doi.org/10.1787/7ca86a34-en

Rooney, A. A., Boyles, A. L., Wolfe, M. S., Bucher, J. R., & Thayer, K. A. (2014). Systematic review and evidence integration for literature-based environmental health science assessments. *Environmental Health Perspectives*, *122*(7), 711–718. https://doi.org/10.1289/ehp.1307972

Rubin, R., Pearl, M., Kharrazi, M., Blount, B. C., Miller, M. D., Pearce, E. N., Valentin-Blasini, L., DeLorenze, G., Liaw, J., Hoofnagle, A. N., & Steinmaus, C. (2017). Maternal perchlorate exposure in pregnancy and altered birth outcomes. *Environmental Research*, *158*, 72–81.

Rump, A., Eder, S., Hermann, C., Lamkowski, A., Kinoshita, M., Yamamoto, T., Abend, M., Shinomiya, N., & Port, M. (2021). A comparison of thyroidal protection by iodine and perchlorate against radioiodine exposure in Caucasians and Japanese. *Archives of Toxicology*, *95*(7), 2335–2350.

Sakamaki, Y., Shobudani, M., Ojiro, R., Ozawa, S., Tang, Q., Zou, X., Ebizuka, Y., Karasawa, A., Woo, G.-H., Yoshida, T., & Shibutani, M. (2025). Suppression of hippocampal neurogenesis and oligodendrocyte maturation similar to developmental hypothyroidism by maternal exposure of rats to ammonium perchlorate, a gunpowder raw material and known environmental contaminant. *Environmental Toxicology*, *40*, 30–53.

Scatchard, G., & Black, E. S. (1949). The effect of salts on the isoionic and isoelectric points of proteins. *The Journal of Physical and Colloid Chemistry*, *53*, 88–99.

Scheuplein, R. J., & Bronaugh, R. L. (1983). Percutaneous absorption. In L. A. Goldsmith (Ed.), *Biochemistry and physiology of the skin* (pp. 1255–1295). Oxford University Press.

Schreinemachers, D. M., Ghio, A. J., Sobus, J. R., & Williams, M. A. (2015). Perchlorate exposure is associated with oxidative stress and indicators of serum iron homeostasis among NHANES 2005–2008 subjects. *Biomarker Insights*, *10*, BMI-S20089. https://doi.org/10.4137/BMI.S20089

Selivanova, L. N., Boltromeyuk, L. P., Aref'eva, Z. S.. (1986). Dynamics of the absorption and elimination of perchloric acid salts in laboratory animals and livestock. *Khim Selsk Khoz*, *106*, 43–45.

18314732, 2025, 5, Downloaded from https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2025.9393, Wiley Online Library on [20/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Serrano-Nascimento, C., Calil-Silveira, J., Dalbosco, R., Zorn, T. T., & Nunes, M. T. (2018). Evaluation of hypothalamus-pituitary-thyroid axis function by chronic perchlorate exposure in male rats. *Environmental Toxicology*, *33*(2), 209–219.

Shiue, I. (2015a). Urinary thiocyanate concentrations are associated with adult cancer and lung problems: US NHANES, 2009–2012. *Environmental Science and Pollution Research*, *22*(8), 5952–5960.

Shiue, I. (2015b). Urinary heavy metals, phthalates, perchlorate, nitrate, thiocyanate, hydrocarbons, and polyfluorinated compounds are associated with adult hearing disturbance: USA NHANES, 2011–2012. *Environmental Science and Pollution Research*, *22*(24), 20306–20311. https://doi.org/10.1007/s11356-015-5546-8

Siglin, J. C., Mattie, D. R., Dodd, D. E., Hildebrandt, P. K., & Baker, W. H. (2000). A 90-day drinking water toxicity study in rats of the environmental contaminant ammonium perchlorate. *Toxicological Sciences*, *57*(1), 61–74.

Snyder, S. A., Pleus, R. C., Vanderford, B. J., & Holady, J. C. (2006). Perchlorate and chlorate in dietary supplements and flavor enhancing ingredients. *Analytica Chimica Acta*, *567*(1), 26–32. https://doi.org/10.1016/j.aca.2006.03.029

Soldin, O. P., Braverman, L. E., & Lamm, S. H. (2001). Perchlorate clinical pharmacology and human health: A review. *Therapeutic Drug Monitoring*, *23*(4), 316–331.

Stanford, B. D., Pisarenko, A. N., Snyder, S. A., & Gordon, G. (2011). Perchlorate, bromate, and chlorate in hypochlorite solutions: Guidelines for utilities. *Journal-American Water Works Association*, *103*(6), 71–83. https://doi.org/10.1002/j.1551-8833.2011.tb11474.x

Starkweather, J. (2010). *An introduction to the Beta distribution*. University of North Texas Research and Statistical Support.

Steinmaus, C., Miller, M. D., Cushing, L., Blount, B. C., & Smith, A. H. (2013). Combined effects of perchlorate, thiocyanate, and iodine on thyroid function in the National Health and nutrition examination survey 2007-08. *Environmental Research*, *123*, 17–24.

Steinmaus, C., Miller, M. D., & Howd, R. (2007). Impact of smoking and thiocyanate on perchlorate and thyroid hormone associations in the 2001-2002 national health and nutrition examination survey. *Environmental Health Perspectives*, *115*, 1333–1338.

Steinmaus, C., Pearl, M., Kharrazi, M., Blount, B. C., Miller, M. D., Pearce, E. N., Valentin-Blasini, L., DeLorenze, G., Hoofnagle, A. N., & Liaw, J. (2016). Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in southern California. *Environmental Health Perspectives*, *124*(6), 861–867.

Stoker, T. E., Wang, J., Murr, A. S., Bailey, J. R., & Buckalew, A. R. (2023). High-throughput screening of ToxCast PFAS chemical library for potential inhibitors of the human sodium iodide symporter. *Chemical Research in Toxicology*, *36*(3), 380–389. https://doi.org/10.1021/acs.chemrestox.2c00339

Suarez, M. C., Wilches-Torres, A., Arias Holguín, G., Rojas Camargo, J. A., Millán Reyes, C., & Cipagauta Esquivel, C. (2018). Alteraciones leucocitarias por exposición a perclorato de amonio en ratones de la cepa ICR. *Acta bioquímica clínica Latinoamericana*, *52*(1), 79–87.

Suh, M., Abraham, L., Hixon, J. G., & Proctor, D. M. (2014). The effects of perchlorate, nitrate and thiocyanate on free thyroxine for potentially sensitive subpopulations of the 2001-2002 and 2007-2008 National Health and nutrition examination surveys. *Journal of Exposure Science & Environmental Epidemiology*, *24*(6), 579–587.

Targovnik, H. M., Citterio, C. E., & Rivolta, C. M. (2017). Iodide handling disorders (nis, tpo, tg, iyd). *Best Practice & Research. Clinical Endocrinology & Metabolism*, *31*(2), 195–212.

Taylor, P. N., Okosieme, O. E., Murphy, R., Hales, C., Chiusano, E., Maina, A., Joomun, M., Bestwick, J. P., Smyth, P., Paradice, R., & Channon, S. (2014). Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring: Data from the controlled antenatal thyroid study. *The Journal of Clinical Endocrinology & Metabolism*, *99*(11), 4291–4298.

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

Tian, Y., Xu, H., Liu, S., Fang, M., Wu, Y., & Gong, Z. (2020). Study on the bioaccessibility and bioavailability of perchlorate in different food matrices in vitro. *Food Chemistry*, *333*, 127470.

Tonacchera, M., Pinchera, A., Dimida, A., Ferrarini, E., Agretti, P., Vitti, P., Santini, F., Crump, K., & Gibbs, J. (2004). Relative potencies and additivity of perchlorate, *thiocyanate*, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. *Thyroid*, *14*, 1012–1019.

Trumpolt, C. W., Crain, M., Cullison, G. D., Flanagan, S. J., Siegel, L., & Lathrop, S. (2005). Perchlorate: Sources, uses, and occurrences in the environment. *Remediation Journal: The Journal of Environmental Cleanup Costs, Technologies & Techniques*, *16*(1), 65–89. https://doi.org/10.1002/rem.20071

Ucal, Y., Sahin, O. N., Serdar, M., Blount, B., Kumru, P., Muhcu, M., Eroglu, M., Akin-Levi, C., Keles, Z. Z., Turam, C., & Valentin-Blasini, L. (2018). Exposure to perchlorate in lactating women and its associations with newborn thyroid stimulating hormone. *Frontiers in Endocrinology*, *9*(348), 1–8.

Ucar, D., Cokgor, E. U., Sahinkaya, E., Cetin, U., Bereketoglu, C., Calimlioglu, B., Goncu, B., & Yurtsever, A. (2017). Simultaneous nitrate and perchlorate removal from groundwater by heterotrophic-autotrophic sequential system. *International Biodeterioration and Biodegradation*, *116*, 83–90.

UCLA Health. (2020). Radioactive iodine uptake test. https://www.uclahealth.org/endocrinecenter/radioactive-iodine-uptake-test

Urbansky, E. T. (1998). Perchlorate chemistry: Implications for analysis and remediation. *Bioremediation Journal*, *2*, 81–95.

Urbansky, E. T. (2002). Perchlorate as an environmental contaminant. *Environmental Science and Pollution Research*, *9*, 187–192.

US EPA. (2017). Office of ground water and drinking water. Draft report: proposed approaches to inform the derivation of a maximum contaminant level for perchlorate in drinking water vol. 1.

US EPA. (2019). National Primary Drinking Water Regulations: Proposed Perchlorate Rule. Pre-publication version. https://www.epa.gov/sites/default/files/2019-05/documents/prepub_final_version_npdwr_proposed_perchlorate_rule-508.pdf

Van der Reijden, O. L., Zimmermann, M. B., & Galetti, V. (2017). Iodine in dairy milk: Sources, concentrations and importance to human health. *Best Practice & Research. Clinical Endocrinology & Metabolism*, *31*(4), 385–395.

Van Stempvoort, D. R., Struger, J., & Brown, S. J. (2019). Perchlorate in environmental waters of the Laurentian Great Lakes watershed: Evidence for uneven loading. *Journal of Great Lakes Research*, *45*(2), 240–251.

Vejdovszky, K., Grossgut, R., Unterluggauer, H., Inreiter, N., & Steinwider, J. (2018). Risk assessment of dietary exposure to perchlorate for the Austrian population. *Food Additives & Contaminants. Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment*, *35*(4), 623–631. https://doi.org/10.1080/19440049.2018.1426889

Verlinden, W., Varewyck, M., & Verbeke, T. (2024). Web application for Bayesian benchmark dose modelling. *EFSA Supporting Publications*, *21*(1), EN-8580. https://doi.org/10.2903/sp.efsa.2024.EN-8580

Vitti, P., Delange, F., Pinchera, A., Zimmermann, M., & Dunn, J. T. (2003). Europe is iodine deficient. *The Lancet*, *361*(9364), 1226.

von Oettingen, J. E., Brathwaite, T. D., Carpenter, C., Bonnell, R., He, X., Braverman, L. E., Pearce, E. N., Larco, P., Larco, N. C., Jean-Baptiste, E., & Brown, R. S. (2017). Population survey of iodine deficiency and environmental disruptors of thyroid function in young children in Haiti. *The Journal of Clinical Endocrinology & Metabolism*, *102*(2), 644–651.

Vose, D. (2008). *Risk analysis: A quantitative guide* (3rd ed.). John Wiley & Sons Ltd.

Waltz, F., Pillette, L., & Ambroise, Y. (2010). A nonradioactive iodide uptake assay for sodium iodide symporter function. *Analytical Biochemistry*, *396*, 91–95.

18314732, 2025, 5, Downloaded from https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2025.9393, Wiley Online Library on [20/05/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Wang, H., Jiang, Y., Song, J., Liang, H., Liu, Y., Huang, J., Yin, P., Wu, D., Zhang, H., Liu, X., & Zhou, D. (2022). The risk of perchlorate and iodine on the incidence of thyroid tumors and nodular goiter: A case-control study in southeastern China. *Environmental Health*, *21*(1), 1–2. https://doi.org/10.1186/s12940-021-00818-8

Wang, L., Fu, Z., Zheng, J., Wang, S., Ping, Y., Gao, B., Mo, X., Liang, P., & Huang, J. (2022). Exposure to perchlorate, nitrate and thiocyanate was associated with the prevalence of cardiovascular diseases. *Ecotoxicology and Environmental Safety*, *15*(230), 113161.

Wang, Q., Song, W., Tian, Y., Hu, P., Liu, X., Xu, L., & Gong, Z. (2022). Targeted lipidomics reveal the effect of perchlorate on lipid profiles in liver of high-fat diet mice. *Frontiers in Nutrition*, *14*(9), 837601.

Wang, Y. J., Dong, J. J., Chen, M. Y., Tian, Y., Liu, X., Liu, L., Wu, Y., & Gong, Z. (2021). Dietary exposure and risk assessment of perchlorate in diverse food from Wuhan, China. *Food Chemistry*, *358*, 129881.

Wang, Z., Sparling, M., Wang, K. C., Arbuckle, T. E., & Fraser, W. (2019). Perchlorate in human milk samples from the maternal-infant research on environmental chemicals study (MIREC). *Food Additives & Contaminants: Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment*, *36*(12), 1837–1846. https://doi.org/10.1080/19440049.2019.1668968

Westerholz, S., De Lima, A. D., & Voigt, T. (2010). Regulation of early spontaneous network activity and GABAergic neurons development by thyroid hormone. *Neuroscience*, *168*(2), 573–589.

Westerholz, S., de Lima, A. D., & Voigt, T. (2013). Thyroid hormone-dependent development of early cortical networks: Temporal specificity and the contribution of trkB and mTOR pathways. *Frontiers in Cellular Neuroscience*, *7*(121), 121. https://doi.org/10.3389/fncel.2013.00121

Westerholz, S., deLima, A. D., & Voigt, T. (2010). Regulation of early spontaneous network activity and GABAergic neurons development by thyroid hormone. *Neuroscience*, *168*, 573–589.

Weterings, P. J., Loftus, C., & Lewandowski, T. A. (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.

WHO (World Health Organization). (2009). Environmental Health Criteria 240. Principles and methods for the assessment of chemicals in food.

WHO (World Health Organization). (2013a). *Urinary iodine concentrations for determining iodine status deficiency in populations. Vitamin and Mineral Nutrition Information System*. World Health Organization. http://www.who.int/nutrition/vmnis/indicators/urinaryiodine

WHO (World Health Organization). (2013b). *Vitamin and Mineral Nutrition Information System (VMNIS). Micronutrients database*. World Health Organization. https://www.who.int/vmnis/database/en/

WHO (World Health Organization). (2016). *Good maternal nutrition. The best start in life*. World Health Organzation Regional Office for Europe.

WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (2009). updated in 2020 Principles and Methods for the Risk Assessment of Chemicals in Food, International Programme on Chemical Safety, Environmental Health Criteria 240. https://www.who.int/publications/i/item/9789241572408

WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (2010). *Characterization and application of physiologically based pharmacokinetic models in risk assessment*. World Health Organization, International Programme on Chemical Safety. https://www.who.int/publications/i/item/9789241500906

Wolff, J. (1998). Perchlorate and the thyroid gland. *Pharmacological Reviews*, *50*, 89–105.

Wong, E. T., & Schultz, A. L. (1977). Changing values for the normal thyroid radioactive iodine uptake test. *JAMA*, *238*(16), 1741–1743.

Woolridge, M. W., Baum, J. D., & Drewett, R. F. (1985). Milk flow and sucking rates during breast-feeding. *Developmental Medicine and Child Neurology*, *27*, 626–633.

Wu, F., Zhou, X., Zhang, R., Pan, M., & Peng, K. L. (2012). The effects of ammonium perchlorate on thyroid homeostasis and thyroid-specific gene expression in rat. *Environmental Toxicology*, *27*, 445–452. https://doi.org/10.1002/tox.20655

Wu, Q., Zhang, T., Sun, H., & Kannan, K. (2010). Perchlorate in tap water, groundwater, surface waters, and bottled water from China and its association with other inorganic anions and with disinfection byproducts. *Archives of Environmental Contamination and Toxicology*, *58*, 543–550.

Xu, D., Zhu, X., Xie, X., Huang, C., Fang, X., & Yin, T. (2023). Concurrent dietary intake to nitrate, thiocyanate, and perchlorate is negatively associated with hypertension in adults in the USA. *Environmental Science and Pollution Research*, *30*(7), 17573–17584. https://doi.org/10.1007/s11356-022-23093-7

Xue, B., Lei, R., Tian, X., Zheng, J., Li, Y., Wang, B., & Luo, B. (2023). Perchlorate, nitrate, and thiocyanate and depression: The potential mediating role of sleep. *Environmental Science and Pollution Research*, *30*(6), 16488–16498. https://doi.org/10.1007/s11356-022-23138-x

Yao, Q., Yan, S. A., Liu, W., Huang, M., & Lin, Q. (2022). Perchlorate contamination of tea leaves and a corresponding probabilistic dietary risk assessment using Monte Carlo simulation. *Food Additives & Contaminants. Part A, Chemistry, Analysis, Control, Exposure & Risk Assessment*, *39*(2), 341–350. https://doi.org/10.1080/19440049.2021.2005262.

Ye, L., You, H., Yao, J., Kang, X., & Tang, L. (2013). Seasonal variation and factors influencing perchlorate in water, snow, soil and corns in Northeastern China. *Chemosphere*, *90*(10), 2493–2498.

York, R. G., Barnett, J., Jr., Brown, W. R., Garman, R. H., Mattie, D. R., & Dodd, D. (2004). A rat neurodevelopmental evaluation of offspring, including evaluation of adult and neonatal thyroid, from mothers treated with ammonium perchlorate in drinking water. *International Journal of Toxicology*, *23*(3), 191–214.

York, R. G., Funk, K. A., Girard, M. F., Mattie, D., & Strawson, J. E. (2003). Oral (drinking water) developmental toxicity study of ammonium perchlorate in Sprague-Dawley rats. *International Journal of Toxicology*, *22*(6), 453–464.

Yu, J., Dong, H. W., Shi, L. T., Tang, X. Y., Liu, J. R., & Shi, J. H. (2019). Reproductive toxicity of perchlorate in rats. *Food and Chemical Toxicology*, *128*(1), 212–222. https://doi.org/10.1016/j.fct.2019.04.014

Yu, J., Guo, J., Zhang, H., & Cheng, X. (2022a). Environmental thiocyanate exposure was associated with oral health-related productivity loss among US adults: Results from NHANES. *Environmental Science and Pollution Research*, *29*(39), 58698–58702.

Yu, J., Guo, J., Zhang, H., & Cheng, X. (2022b). The association between environmental perchlorate, nitrate, and thiocyanate exposure and oral pain in NHANES. *Frontiers in Public Health*, *10*, 829466.

Yu, K. O., Narayanan, L., Mattie, D. R., Godfrey, R. J., Todd, P. N., Sterner, T. R., Mahle, D. A., Lumpkin, M. H., & Fisher, J. W. (2002). The pharmacokinetics of perchlorate and its effect on the hypothalamus-pituitary-thyroid axis in the male rat. *Toxicology and Applied Pharmacology*, *182*, 148–159.

Yuan, W., Wang, R., Song, G., Ruan, Z., Zhu, L., & Zhang, W. (2023). Exposure to perchlorate, nitrate, and thiocyanate and the prevalence of abdominal aortic calcification. *Environmental Science and Pollution Research*, *30*(5), 13697–13701. https://doi.org/10.1007/s11356-022-23036-2

Yue, B., Ning, S., Miao, H., Fang, C., Li, J., Zhang, L., Bao, Y., Fan, S., Zhao, Y., & Wu, Y. (2023). Human exposure to a mixture of endocrine disruptors and serum levels of thyroid hormones: A cross-sectional study. *Journal of Environmental Sciences*, *125*, 641–649.

Zhang, L., Fang, C., Liu, L., Liu, X., Fan, S., Li, J., Zhao, Y., Ni, S., Liu, S., & Wu, Y. (2018). A case-control study of urinary levels of iodine, perchlorate and thiocyanate and risk of papillary thyroid cancer. *Environment International*, *120*(1), 388–393. https://doi.org/10.1016/j.envint.2018.08.024

Zhang, L., Jiang, J., Jia, W., Wan, X., Li, Y., Jiao, J., & Zhang, Y. (2023). Physiologically-based toxicokinetic model for the prediction of perchlorate distribution and its application. *Environmental Pollution*, *318*, 120856.

Zhang, T., Ma, Y., Wang, D., Li, R., Chen, X., Mo, W., Qin, X., Sun, H., & Kannan, K. (2016). Placental transfer of and infantile exposure to perchlorate. *Chemosphere*, *144*, 948–954. https://doi.org/10.1016/j.chemosphere.2015.09.073

Zhao, X., Zhou, P., Chen, X., Li, X., & Ding, L. (2014). Perchlorate-induced oxidative stress in isolated liver mitochondria. *Ecotoxicology*, *23*(10), 1846–1853. https://doi.org/10.1007/s10646-014-1312-9

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Zheng, R., Liu, R., Wu, M., Wang, H., & Xie, L. (2020). Effects of sodium perchlorate and exogenous L-thyroxine on growth, development and leptin signaling pathway of Bufo gargarizans tadpoles during metamorphosis. *Ecotoxicology and Environmental Safety*, *206*, 111410.

Zhu, F., Huang, M., Jiao, J., Zhuang, P., Mao, L., & Zhang, Y. (2019). Environmental exposure to perchlorate, nitrate, and thiocyanate in relation to obesity: A population-based study. *Environment International*, *133*, 105191.

Zhu, K., Wan, Y., Zhu, B., Wang, H., Liu, Q., Xie, X., Jiang, Q., Feng, Y., Xiao, P., Xiang, Z., & Song, R. (2023). Association of perchlorate, thiocyanate, and nitrate with dyslexic risk. *Chemosphere*, *325*, 138349.

Zimmermann, M. B., & Boelaert, K. (2015). Iodine deficiency and thyroid disorders. *The Lancet Diabetes & Endocrinology*, *3*(4), 286–295.

Zoeller, R. T., & Crofton, K. M. (2005). Mode of action: Developmental thyroid hormone insufficiency--neurological abnormalities resulting from exposure to propylthiouracil. *Critical Reviews in Toxicology*, *35*(8–9), 771–781.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Knutsen, H. K., Åkesson, A., Bampidis, V., Bignami, M., Bodin, L., Degen, G., Hernández-Jerez, A., Hofer, T., Hogstrand, C., Landi, S., Leblanc, J.-C., Machera, K., Ntzani, E., Rychen, G., Sand, S., Vejdovszky, K., Viviani, B., Djordevic, A. B., … Chipman, J. K. (2025). Update of the Scientific Opinion on the risks for human health related to the presence of perchlorate in food. *EFSA Journal*, *23*(5), e9393. https://doi.org/10.2903/j.efsa.2025.9393

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APPENDIX A

Extensive Literature Search strings

Literature search on perchlorate

Databases

Web of Science (WOS): Web of Science Core Collection[19]
PubMed

Timespan

01/2013 – 01/2024

Key words search

WOS (TS)
PubMed (title/abstract)

Language

No restrictions

Search strategy

Date of the search: 29/1/2024

Set	Query	Results (WOS/ PubMed)	Comments
	#1 AND #2	12K/11K	CHEMISTRY
	#1 AND #2 AND (TS=food*)	212/219	CHEMISTRY in food
	#1 AND #3 AND (concentration OR Occurrence OR presence OR exposure OR intake OR exposure)	4K/1k	OCCURRENCE in food and exposure
	#1 AND #6 AND #7	217/262	TOXICITY in experimental animals
	#1 AND #4 AND #7	186/209	ADME/MOA in experimental animals
	#1 AND #5	1K/618	HUMAN DATA
#1	Perchlorate OR perchlorates OR ClO4 OR 14797-73-0	13.4K 3.8K	**Main search** WOS CORE COLLECTION PUBMED
#2	(chem* OR analy* OR identi* OR charact* OR detect* OR determin* OR method* OR form* OR degrad* OR hydroly* OR reaction* OR "GC-MS*" OR "HPLC" OR "LC-MS" OR "ICP-MS")		**Chemistry**
#3	(food* OR dietar* OR fruit* OR pineapple OR Ananas OR vegetable* OR garlic OR asparagus OR cereal* OR corn* OR mais OR maize OR wheat OR rye OR barley OR oat OR rice OR soybean OR sorghum OR sugar* OR millet OR starch OR flour OR bran OR germ OR dairy OR milk OR egg* OR meat OR liver OR kidney* OR offal OR coffee OR potato* OR onion* OR lettuce OR spinach OR cabbage OR broccoli OR cauliflower OR courgette OR herb* OR spices OR legume* OR bean* OR peas* OR lentil* OR carrot* OR water OR "infant formula" OR formula* OR apple* OR Pear* OR Peach* OR cherries OR cherry OR Plum* OR "stone fruit*" OR Berries OR berry* OR grape* OR lemon* OR orange* OR mandarin* OR lime* OR Grapefruit*OR tomato*)		**Food**

[19]Including the following databases: Science Citation Index Expanded (SCI-EXPANDED) – 1975-present, Social Sciences Citation Index (SSCI) – 1975-present, Arts & Humanities Citation Index (AHCI) – 1975-present, Conference Proceedings Citation Index – Science (CPCI-S) – 1990-present, Conference Proceedings Citation Index – Social Science & Humanities (CPCI-SSH) – 1990-present, Book Citation Index – Science (BKCI-S) – 2005-present, Book Citation Index – Social Sciences & Humanities (BKCI-SSH) – 2005-present, Emerging Sources Citation Index (ESCI) – 2005-present, Current Chemical Reactions (CCR-EXPANDED) – 1985-present, Index Chemicus (IC) – 1993-present.

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(Continued)

Set	Query	Results (WOS/ PubMed)	Comments
#4	("in vivo" OR "in vitro" OR accumulat* OR bioavail* OE bioaccess* OR absor* OR distribut* OR tissue* OR metaboli* OR excret* OR kinetic* OR toxicokinetic* OR pharmacokinetic* OR degrad* OR biotrans* OR eliminat* OR biomark* OR "mode of action" OR MOA)		**Toxicokinetics in vivo and in vitro**
#5	(Aged OR cohort* OR "case study*" OR cross-sectional OR Baby OR Babies OR Boy OR Boys OR Centenarian* OR Child* OR Citizen* OR Client* OR Elder* OR Girl OR Girls OR Human* OR Inpatient* OR Kindergarten* OR Man OR Men OR "middle age" OR Newborn* OR "new born*" OR Nonagenarian* OR Octogenarian* OR Outpatient* OR Participant* OR Patient* OR Pediatric* OR Paediatric* OR Person* OR People OR Preschool* OR Retiree* OR "Research subject" OR "pre school" OR Septuagenarian* OR Schoolchild* OR Seniors OR Sexagenarian* OR Student* OR Teen OR Teenager* OR Teens OR Toddler* OR Volunteer* OR Woman OR Women OR Youngster* OR Youth*)		**Epi data**
#6	(tox* OR poison* OR cancer* OR carcino* OR tumor* OR tumour* OR organ* OR tissue* OR immun* OR neuro* OR developmental OR teratogen* OR repro* OR liver OR kidney* OR brain* OR lung* OR cardiovascular OR health OR clinical OR growth OR weight OR Thyroid*)		**Toxicity**
#7	Cavia OR Cricetinae OR Cricetus OR "guinea pig" OR "guinea pigs" OR Hamster* OR Mice OR Mouse OR Muridae OR Murinae OR Murine OR Mus OR Rat OR Rats OR Rattus OR Rodent* OR Mink OR Minks OR Mustela* OR Monkey OR Monkeys OR Nomascus OR primate*		**Experimental animals**

Literature search on perchlorate up to January 2025

Timespan

29/1/2024 – 16/1/2025

Language

Only English

Strategy

Main search done using string #1 (table above) and restricted to pertinent area of applications: area of engineering, material science, polymers, mathematics, physics and astronomy were excluded from the search.

Other restrictions: only abstracts and meeting documents were excluded.

Results

WOS: 391 entries
PubMed: 376 entries
Combined Without duplicates: 510 entries
The relevant new studies were divided into area as follows:
Toxicity in experimental animals: 7
Humans/EPI: 7
Occurrence: 6
Reviews: 4

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APPENDIX B

PBPK model of perchlorate, iodine and thyroid hormone

Different PBPK models for the simultaneous kinetics of iodine and perchlorate model, have been described, among them Merrill et al. (2005), Clewell et al. (2007) and McLanahan et al. (2014).

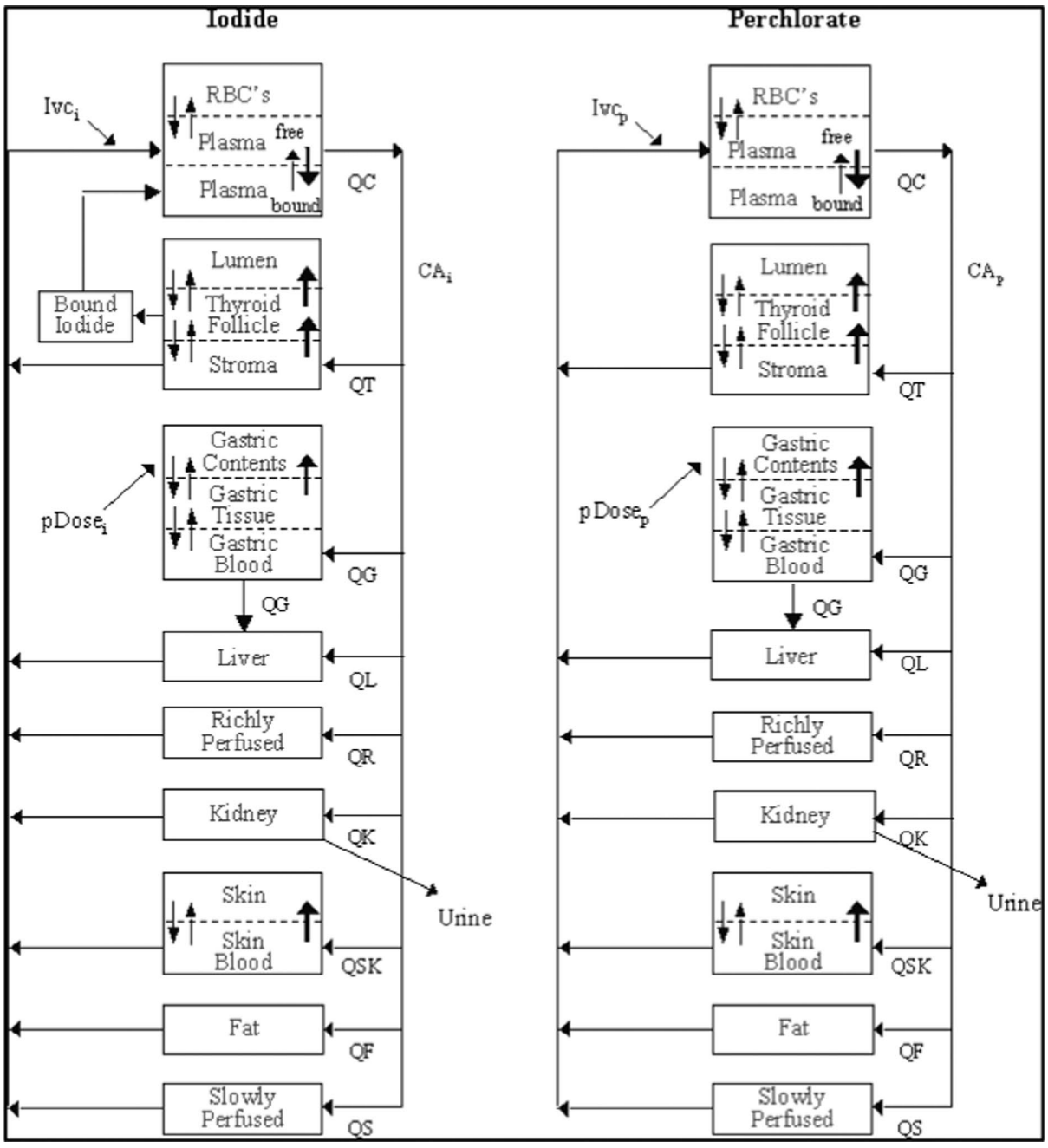

FIGURE B.1 PBPK models structure for perchlorate and iodide (Merrill et al., 2005). CA, arterial concentration; i, iodide; I_{vc}, intravenous; p, perchlorate; QC, cardiac flow; QF, fat blood flow; QG, gastric blood flow; QK, kidney blood flow; QL, liver blood flow; QR, remaining richly perfused; QS, remaining slowly perfused; QSK, skin blood flow; RBC, red blood cell.

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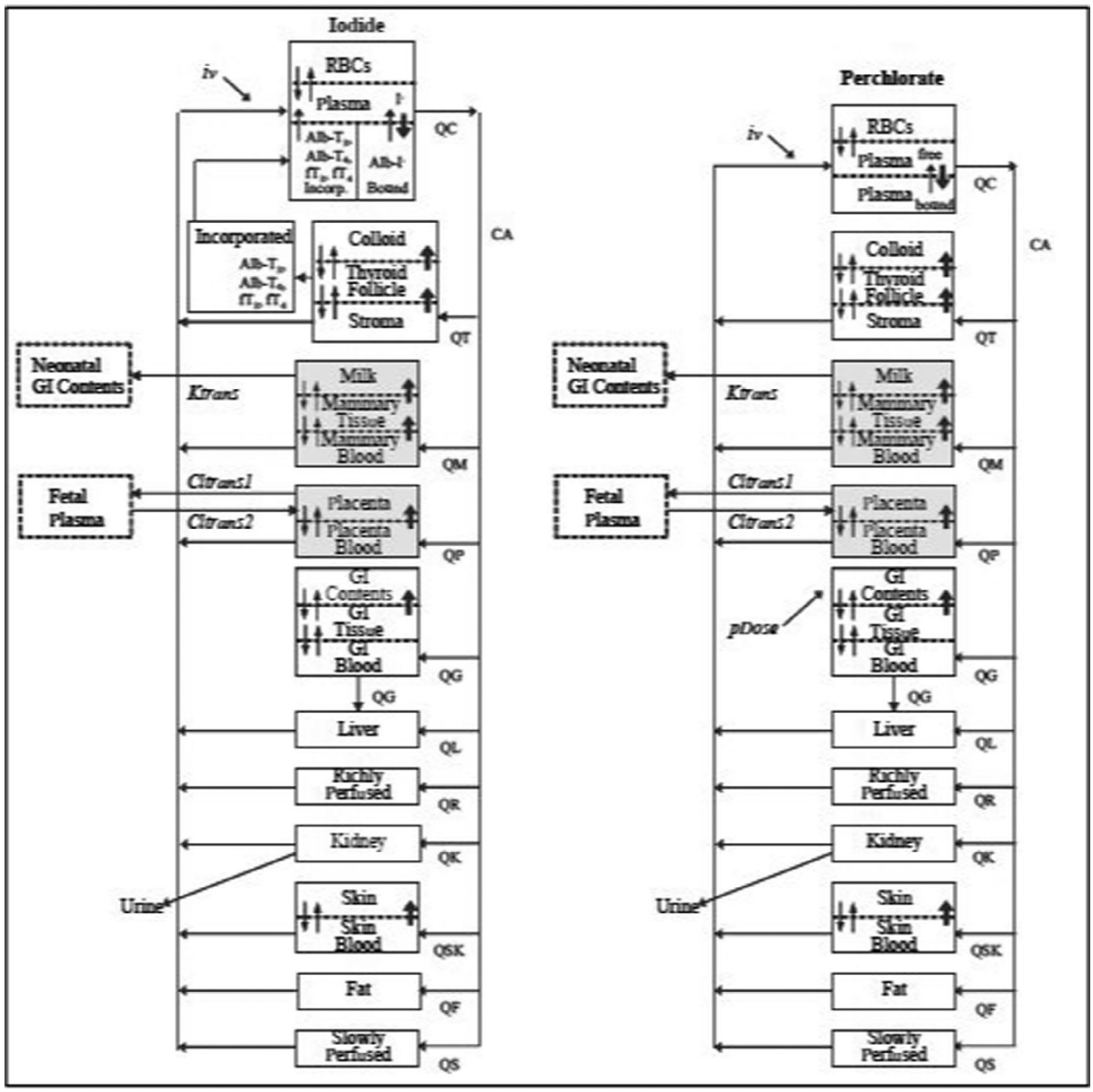

FIGURE B.2 PBPK models structure for perchlorate and iodide (Clewell et al., 2007). Alb, albumin; CA, arterial concentration; Cl_{trans1}, Placenta to fetal blood; Cl_{trans2}, fetal blood to placenta; fT4, free thyroxine; GI, gastrointestinal; i, iodide; iv, intravenous; K_{trans}, transfer constant; QC, cardiac flow; QF, fat blood flow; QG, gastric blood flow; QK, kidney blood flow; QL, liver blood flow; QM, mammary blood flow; QP, placenta blood flow; QR, remaining richly perfused; QS, remaining slowly perfused; QSK, skin blood flow; QT, stroma blood flow; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine.

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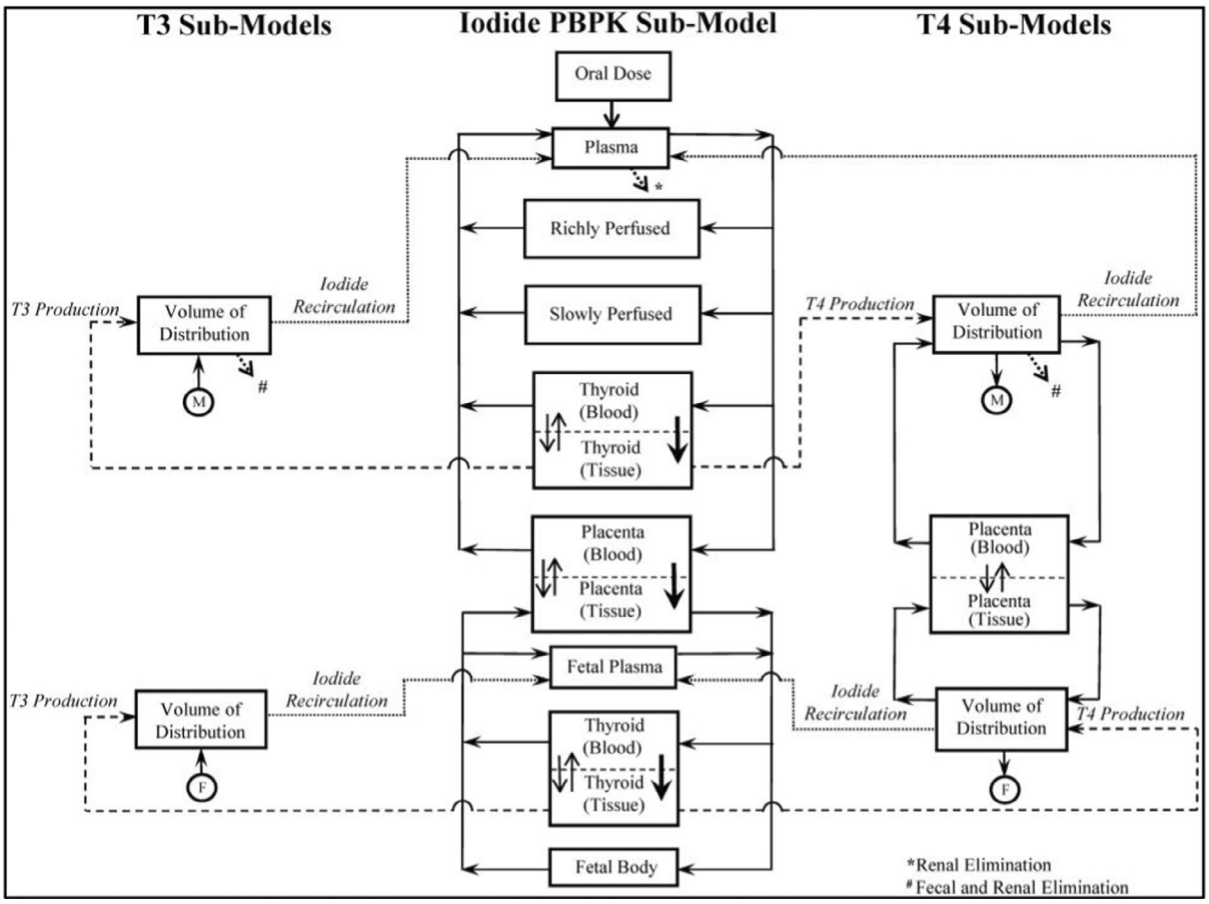

FIGURE B.3 PBPK models structure for perchlorate and iodide (Lumen et al., 2013). F, fetal; M, metabolism; T3, triiodothyronine; T4, thyroxine.

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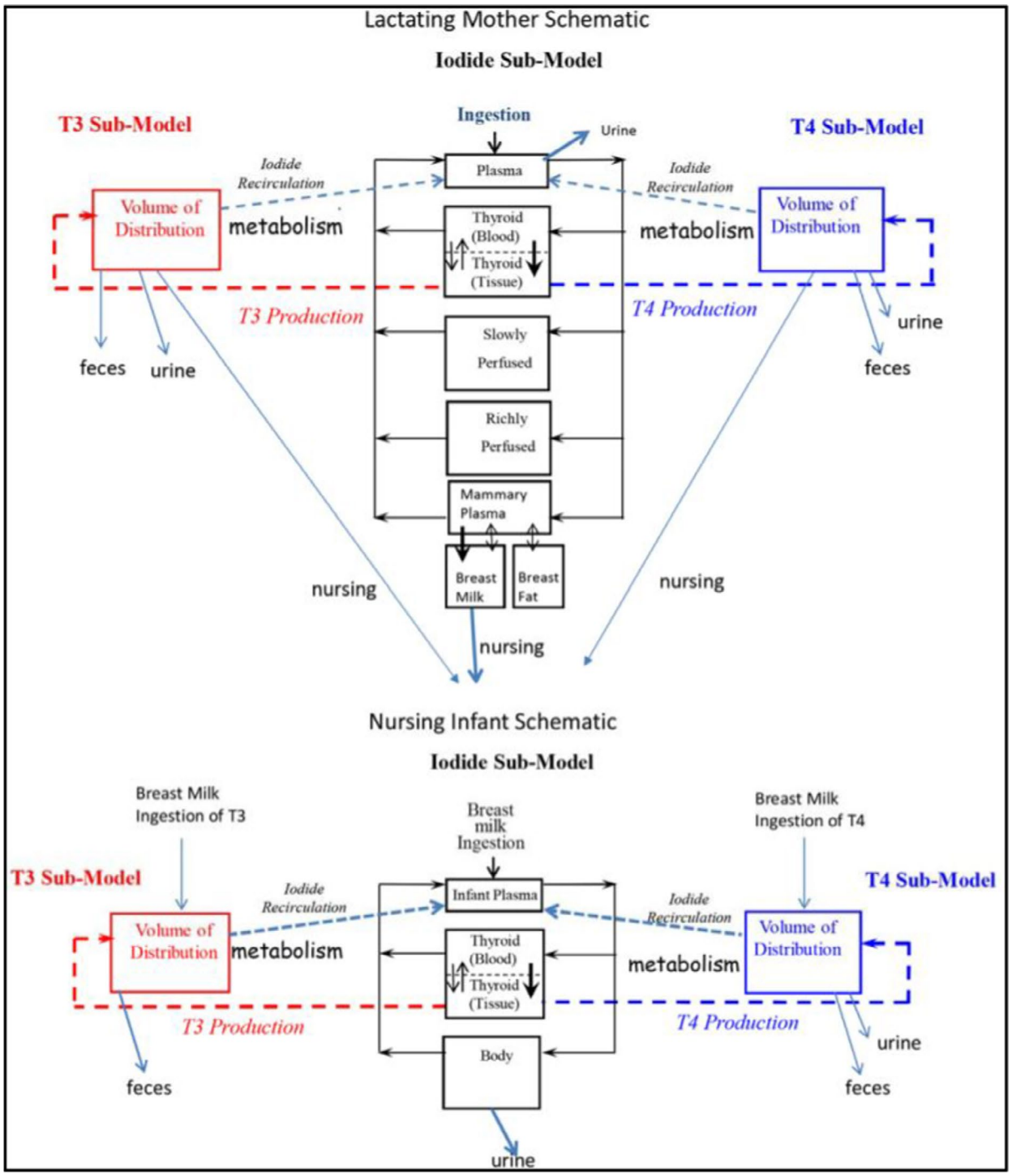

FIGURE B.4 PBPK models structure for iodide (Fisher et al., 2016). T3, triiodothyronine; T4, thyroxine.

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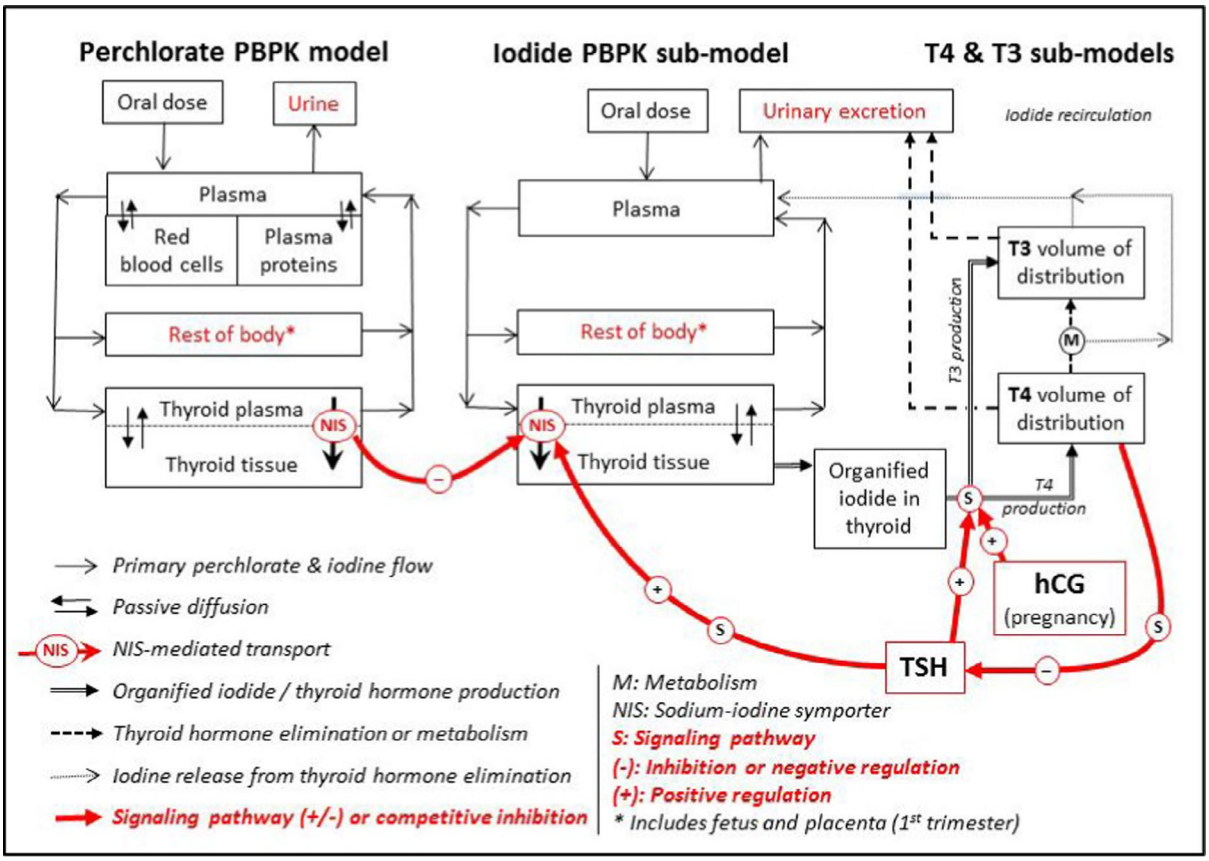

FIGURE B.5 Structure of Biologically-based dose-response (BBDR) (Clewell III et al., 2019; Felker et al., 2016; Lumen et al., 2013; US EPA, 2017). hCG, human chorionic gonadotropin; PBPK, physiologically based pharmacokinetic; M, metabolism; NIS, sodium iodine symporter; S, signalling pathway; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

PBPK models for perchlorate and iodide

The PBPK models for iodide and perchlorate have been extensively developed and revised (Clewell et al., 2007; Merrill et al., 2005) Figures B.1–B.5. The Merrill et al. (2005) PBPK model was extended to pregnant and lactating women, fetuses and infants by Clewell et al. (2007).

In the Merrill et al. (2005) model, the model slightly overpredicted plasma-bound ^{131}I fractions from several euthyroid patients; however, the prediction was acceptable e.g. within in a two-fold compared to the estimated value, which is a criterion of acceptance according to WHO (2009). The predictions of cumulative perchlorate urine after different oral doses were also acceptable.

This model was successfully simulating radio iodide for gestation and lactation, as well as perchlorate from data of the literature.

The major limitation of these models is that these PBPK models were not developed to describe dietary intake of iodide. Moreover, these models were not formulated to predict inhibition of RAIU caused by perchlorate.

Therefore, the same authors developed new PBPK models, called now biologically-based dose-response (BBDR) model (Fisher et al., 2016; Lumen et al., 2013).

The model developed by Lumen et al. (2013) was used to evaluate the influence of dietary iodide intake and exposure to perchlorate on changes in serum thyroid hormones in the near-term mother and fetus.

The prediction of maternal and fetal perchlorate, iodine and thyroid hormone concentration was evaluated from the Tellez et al. (2005) by comparing the observed with the predicted values in Tellez et al. (2005) in the pregnant women at gestational week 33 (Table B.1).

TABLE B.1 Model evaluation from Tellez et al. (2005).

		Tellez et al. (2005), high exposure 'Taltal' group		Model predictions	
Parameters	**Units**	**Mother**	**Fetus**	**Mother**	**Fetus**
Urine iodide	µg/L	217 ± 109	NA	218.1	–
Serum perchlorate	µg/L	13.2 ± 1.7	19.9 ± 5.0	12.4 (6.9–12.4)	19.8 (12.9–19.8)[a]

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TABLE B.1 (Continued)

		Tellez et al. (2005), high exposure 'Taltal' group		Model predictions	
Parameters	**Units**	**Mother**	**Fetus**	**Mother**	**Fetus**
Urine perchlorate	µg/L	128.9 ± 127	NA	176.8	–
Serum fT_4	pmol/L	10.7 ± 1.5	13.3 ± 1.8	13.5	14.4
Serum T_3	nmol/L	2.7 ± 0.6	1.3 ± 0.3	2.5	1.0

Note. NA denotes that data was not available in the study.

[a]Range of serum perchlorate concentrations due to dietary intake patterns.

Fisher et al. (2016) developed a biologically-based model for the lactating woman and nursing infant in order to describe thyroid hormone homeostasis for the euthyroid in infant and lactating. This was used to evaluate dietary iodine insufficiency in the lactating mother and the nursing infant. The serum thyroid hormone concentrations for lactating women from the United States was used to calibrate the model. The serum T4 and fT4 levels, as well T3 levels were adequately predicted (within a factor of two) for lactating women. For infant, serum thyroid hormone levels were also well-predicted.

The last version of BBDR was developed by US EPA (2017) and analysed by Clewell III et al. (2019) and is described below.

Biologically-based dose-response (BBDR)

The biologically-based dose-response model attempts to estimate the internal dose of a chemical associated with a particular exposure scenario and the perturbation this internal dose can have on organisms (thyroid hormone production).

The BBDR model was developed for the uptake and disposition of iodide and perchlorate, and the synthesis and disposition of thyroid hormone parameters in a woman (mother) prior to conception and through early pregnancy (until gestational week 16).

The BBDR model can be described as containing two main components:

1. A pharmacokinetic model for perchlorate and iodide, which describes chemical absorption, distribution, metabolism and excretion of these two anions. This model enables an estimation of perchlorate and iodide internal concentration at the critical target (i.e. thyroidal NIS) in association with a particular exposure scenario (route of exposure, age, dose level).
2. A pharmacodynamic model, which describes the joint effect of varying perchlorate and iodide blood concentrations on thyroidal uptake of iodide and subsequent production of thyroid hormones, most significantly T4.

The structure of the BBDR model was simplified from that of the previously described late-gestation model (reviewed by Clewell III et al., 2019, based on Lumen et al., 2013).

The model structure is adapted from the third-trimester model of Lumen et al. (2013) and the lactation iodide/thyroid hormone model of Fisher et al. (2016). These models were adapted from the life-stage model by Clewell et al. (2007), that was reviewed by US EPA in 2009.

The six compartments used for perchlorate and iodide in the third-trimester BBDR model of Lumen et al. (2013) were condensed to essentially three compartments: plasma, thyroid, rest of body (ROB) including the placenta and the fetus. Condensation of other maternal compartments into one compartment is not expected to significantly affect the estimated concentrations of the key anions and hormones given that they are described for long-term, continuous ingestion of iodine and perchlorate.

This model is based on the following assumptions for ADME:

Absorption: Exposure to iodine and perchlorate are treated as being delivered directly to the central plasma compartment. Neither is metabolised or otherwise transformed in the GI tract or liver and 100% absorption is assumed for both. Therefore, at steady-state the rate of delivery to the plasma must equal the (average) rate of ingestion. While this simplification in model structure would affect simulations of short-term kinetics, it does not alter the longer-term model predictions.

Distribution: The perchlorate sub-model includes binding of perchlorate to plasma binding proteins and distribution of perchlorate between blood plasma and red blood cells (RBCs). This distribution of perchlorate to multiple subcompartments of the blood was not incorporated into the BBDR model of 2013. The perchlorate binding affects the short-term kinetics of perchlorate, but not the long-term average free concentration in the blood plasma which determines its effect on iodide uptake and TH levels. Active transport of iodide and perchlorate by the NIS protein in the thyroid was described. Perchlorate and iodide function as mutual competitive inhibitors for NIS-mediated anion uptake and the enzyme-substrate-inhibitor interactions were described using Michaelis-Menten kinetics.

Metabolism

No metabolism

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Elimination

Urinary excretion was calibrated with human studies (short half-life and approximately 60% to 70% excretion of perchlorate per day).

Model calibration

The parameters values were set from the previous PBPK models. Four parameters were estimated from the Greer et al. (2002) dataset using MCMC methods (Bayesian theory):

- urinary perchlorate clearance,
- urinary iodide clearance,
- the Michaelis-Menten saturation concentration (Km) for perchlorate uptake and inhibition of iodine uptake by the sodium iodide symporter (NIS) in the thyroid,
- the Michaelis-Menten maximum rate (Vmax) for iodide uptake by the thyroid (in nmol/h).

Model validation (perchlorate model)

The perchlorate pharmacokinetic data in adult humans (i.e. measurements of perchlorate concentrations in human blood and/or urine for defined or known exposures) are quite limited and no suitable data have been identified for pregnant women. Human biomonitoring data were excluded.

The data sets available for evaluation of **the perchlorate sub-model** are those of:

- Greer et al. (2002) (also used for calibration)
- Merrill et al. (2005)
- Durand (1938)
- Eichler (1929)
- Kamm and Drescher (1973)

The comparison between predicted values and reported values for serum concentrations of perchlorate (data from Greer et al., 2002 and Merrill et al., 2005) were included in a two-fold error interval (acceptance criteria) (Figures B.6 and B.7)

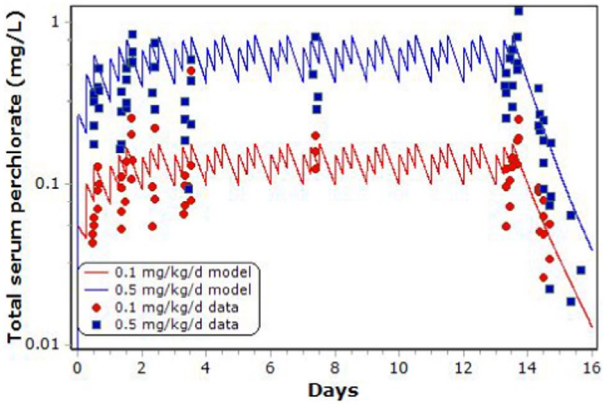

FIGURE B.6 Comparison between predicted values and reported values for serum concentrations from Greer et al. (2002) study (from US EPA, 2019).

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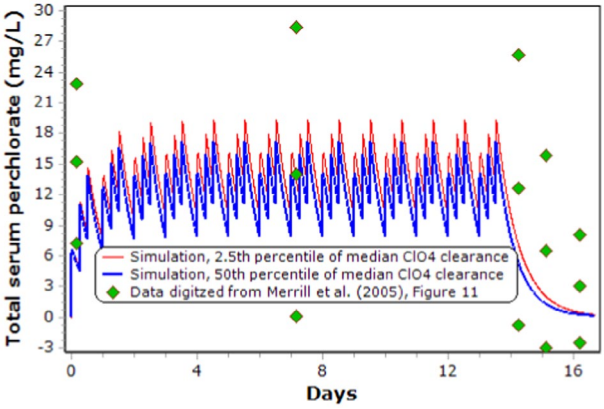

FIGURE B.7 Comparison between predicted values and reported values for serum concentrations from Merrill et al. (2005) study (from US EPA, 2019).

The total amount of perchlorate excreted was also well-predicted (Figure B.8)

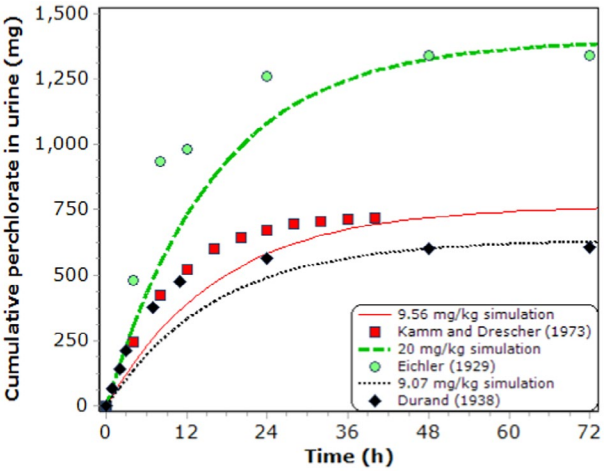

FIGURE B.8 Comparison between predicted values and reported values for urinary excretion from Durand (1938), Eichler (1929), Kamm and Drescher (1973) (from US EPA, 2019)

Model validation (toxicodynamic model)

The model evaluation was performed with the Steinmaus et al. (2016), Greer et al. (2002), Braverman et al. (2006) and Tellez et al. (2005).

The Figure B.9 shows the comparison between the predicted and measured value in the Steinmaus et al. (2016) study. This comparison shows a large underestimation by the BBDR model of fT4 concentrations.

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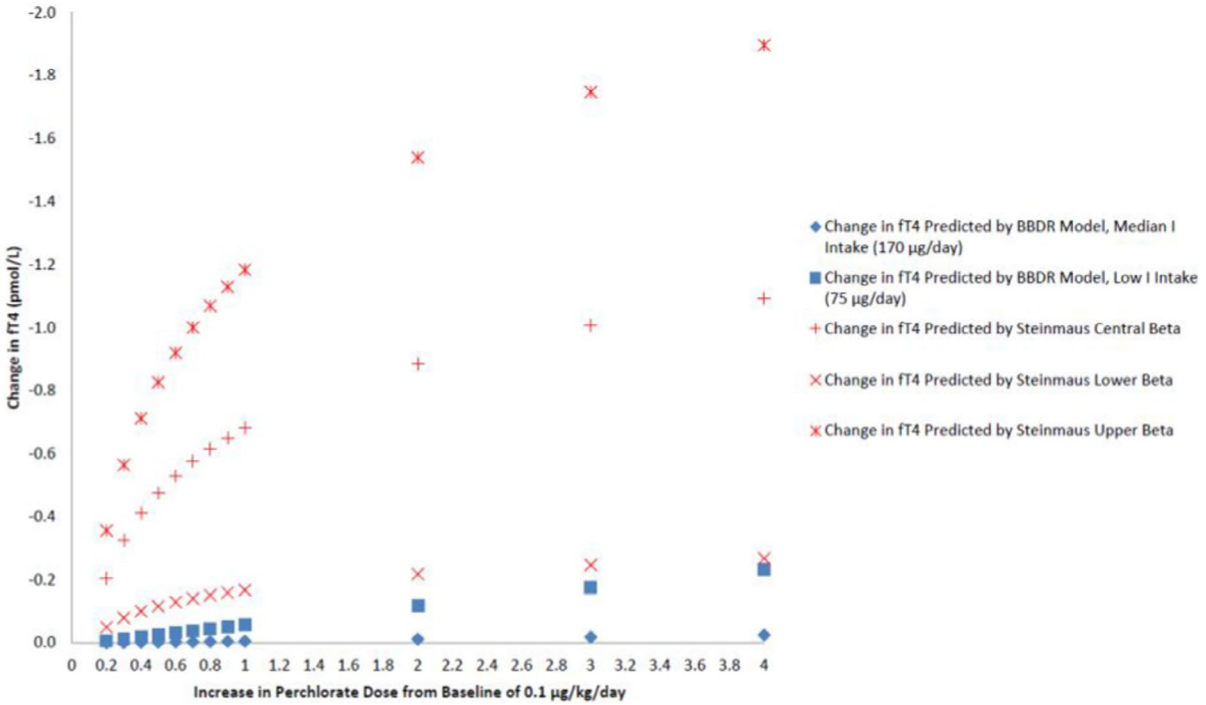

FIGURE B.9 Comparison between the predicted and measured value of fT4 and perchlorate exposure in the Steinmaus et al. (2016) study (from US EPA, 2017; Clewell III et al., 2019).

The comparison to Greer et al. (2002), Tellez et al. (2005) and Braverman et al. (2006) are shown below (Tables B.2–B.4).

TABLE B.2 Comparison between the predicted and measured value of fT4, RAIU and perchlorate exposure in the Greer et al. (2002) study (from US EPA, 2017; Clewell III et al., 2019).

	RAIU (%)		fT_4 (pM)	
Dose (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

Abbreviations: fT4, free thyroxine; RAIU, radioactive iodine uptake.

TABLE B.3 Comparison between the predicted and measured value of T3, TSH and perchlorate exposure in the Braverman et al. (2006) study (from US EPA, 2017; Clewell III et al., 2019).

	T_3 (nM)		TSH (mIU/L)	
Dose (µg/kg per day)	Simulated	Measured	Simulated	Measured
0	2.63	2.49	1.51	1.20
7	2.63	2.51	1.52	1.60
43	2.62	1.77	1.53	2.60

Abbreviations: T3, triiodothyronine; TSH, thyroid stimulating hormone.

TABLE B.4 Comparison between the predicted and measured value of fT4 and perchlorate exposure in the Tellez et al. (2005) study (from US EPA, 2017; Clewell III et al., 2019).

	fT4 (pM)	
Dose (µg/kg per day)	Simulated	Measured
0.01	9.74	12.5
0.08	9.73	12.2
2	9.69	12.7

Abbreviation: fT4, free thyroxine.

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Conclusion on PBPK models for perchlorate

By comparing the observed with the predicted values from the different data available in the literature, i.e. the changes in plasma concentration and cumulative urinary excretion in adults, it can be concluded that the PBPK model of perchlorate is valid since the model fulfils the IPCS (WHO/IPCS, 2010) requirements for use in health risk assessment.

Conclusion on PBPK models for iodide

The pharmacokinetic models for iodide are suitable to be used in risk assessment according to WHO guidance.

Conclusion on the Biologically-based dose-response (BBDR)

The **pharmacokinetic models** for perchlorate and iodide included in the BBDR model are suitable to be used in risk assessment according to WHO guidance.

For the **toxicodynamic 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, it should be noted that the studies from Greer et al. (2002), Tellez et al. (2005) and Braverman et al. (2006) do not show a statistically significant impact of perchlorate exposure on fT4 concentration. Thus, the comparison with Greer et al. (2002), Tellez et al. (2005) and Braverman et al. (2006) to evaluate the model do not show any impact of perchlorate exposure on the free fT4 concentration.

In conclusion, due to the lack of data available to perform a robust validation, **the BBDR model is not able to describe the relationship between exposure to perchlorate and the decrease in maternal of fT4**.

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APPENDIX C

BMD analysis

This Appendix details the BMD modelling of the thyroid iodine inhibition in human adult volunteers, using the data published by Greer et al. (2002) and subsequently elaborated by Haber et al. (2021). It includes:

- Introductory sub-section outlining the modelling approach (Section C.1).
- BMD modelling report (Section C.2).
- Details of the construction of an informative background prior (Section C.3).
- Comparison of fits to the RAIU data using beta and lognormal distributions (Section C.4).

C.1 | INTRODUCTION

C.1.1 | Selection of the BMR

The benchmark dose (BMD) is defined as the estimated dose that corresponds with a predefined change in response compared with the background response. The benchmark response (BMR) is the response corresponding with the estimated BMD of interest.

The EFSA guidance on BMD (EFSA Scientific Committee, 2022) recommends defining the BMR for continuous outcomes as a percentage change in response relative to the control group (background exposure). The BMR should represent the dose at which an effect becomes adverse. Ideally, the change specified by the BMR should fall within the observed experimental range to avoid extrapolation. For selecting a BMR for continuous data, the EFSA BMD guidance (EFSA Scientific Committee, 2022) suggests a tiered approach.

The BMR was selected as described in Section 3.1.5.2. Regarding the resampling with Monte Carlo simulation was performed as detailed in the R script provided below.

```
# Load necessary libraries
library(MASS)
library(boot)

# Define the data for each study
study_data <- data.frame(
  study = c("Ballal", "Al-Muqbel", "Gonzalez", "Culp_men", "Culp_women"),
  mean_RAIU = c(12.75, 15, 16.2, 15.9, 20.2),
  sd_RAIU = c(5.51, 7, 4.8, 3.3, 5),
  N = c(110, 102, 105, 25, 28)
)

# Function to simulate a lognormal distribution for a given mean, SD, and N
simulate_lognormal <- function(mean, sd, N) {
# Estimate the lognormal parameters based on the given mean and SD
mu <- log((mean^2)/sqrt(sd^2 + mean^2))
sigma <- sqrt(log(1 + (sd^2/mean^2)))

# Generate N random samples from the lognormal distribution
rlnorm(N, meanlog = mu, sdlog = sigma)
}

# Generate Monte Carlo samples for each study and combine them
set.seed(123)

# For reproducibility
combined_samples <- unlist(lapply(1:nrow(study_data), function(i) {simulate_lognormal(study_data$mean_RAIU[i],
 study_data$sd_RAIU[i], study_data$N[i])
}))

# Calculate the mean and standard deviation for the combined dataset
combined_mean <- mean(combined_samples)
combined_sd <- sd(combined_samples)
combined_N <- length(combined_samples)
```

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```
# Output the results
combined_mean
combined_sd
combined_N
```

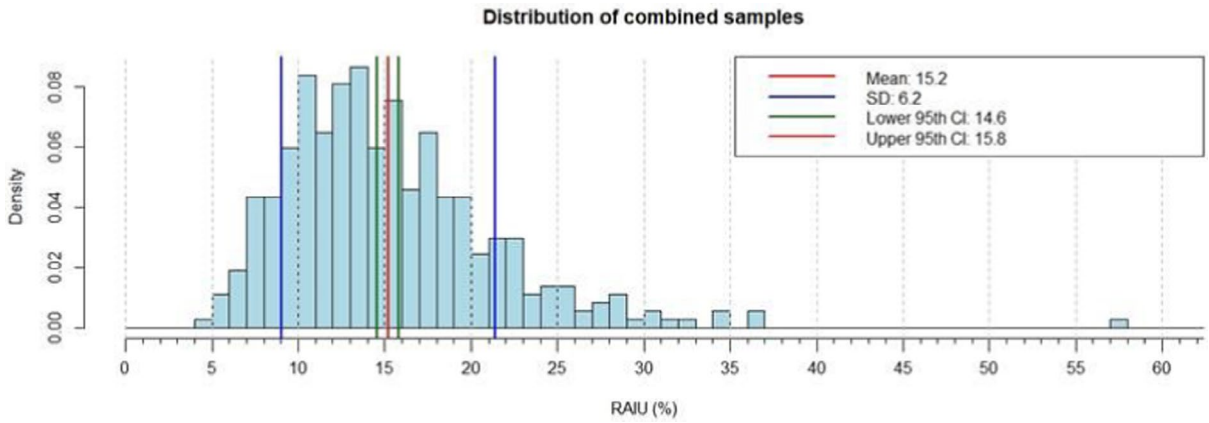

FIGURE C.1 Distribution of RAIU 24 h (%) in euthyroid subjects based on Monte Carlo simulation.

C.1.2 | Software used

Results are obtained using the EFSA web-tool for Bayesian BMD analysis, which uses the R-package [BMABMDR] version 0.1.5 for the underlying calculations.

C.1.3 | Specification of deviations from default assumptions

The EFSA web-tool for Bayesian BMD analysis provides a set of default assumptions and parameter choices to facilitate the analysis (EFSA Scientific Committee, 2022; Hasselt University, 2022). For the current analysis, the following settings were adopted:

1. The 'Prior Specification' is set to 'Informative' allowing the incorporation of baseline 24-h ^{123}I thyroid uptake data from the study of Greer et al. (2002) as an informative background prior. Refer to Section C.3 for details.
2. The selected 'Distribution' is set to 'Lognormal' because the Shapiro-Wilk normality test showed evidence against normality across dose levels at level 0.05 (p-value 0.0012). See Section C.2, 'Results,' for further information.

All other assumptions remain at their default settings (Figure C.2).

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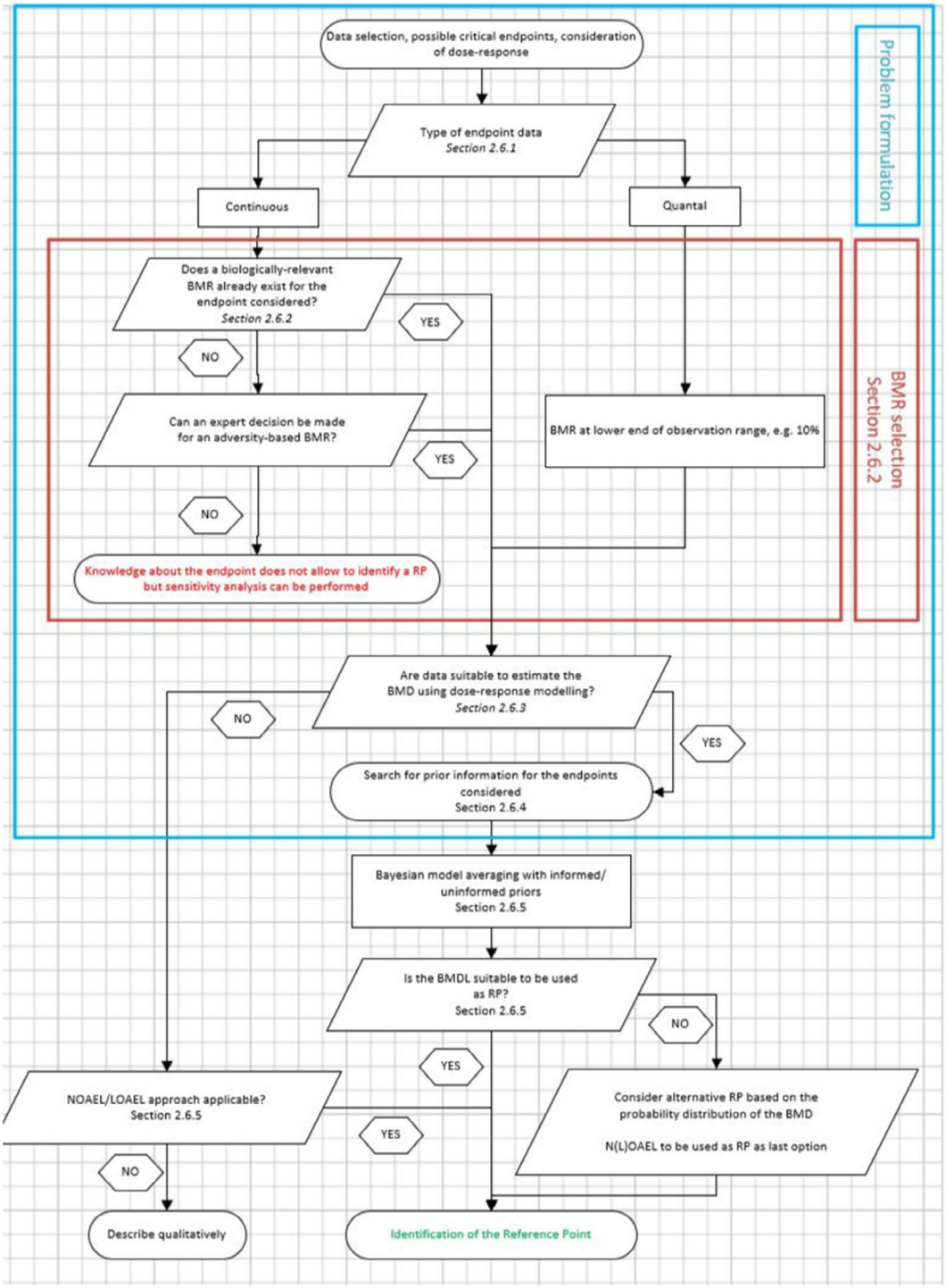

FIGURE C.2 Flowchart to derive a Reference Point (RP) from a dose-response dataset of a specified endpoint, using BMD analysis (Figure from EFSA Scientific Committee, 2022). BMD, benchmark dose; BMDL, benchmark dose lower credible limit; BMR, benchmark response; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; RP, Reference Point.

C.2 | BMD MODELLING REPORT: GREER ET AL. (2002)

C.2.1 | Data description and parameter selection

The endpoint to be analysed: Inhibition in Radioactive Iodine Uptake (RAIU)

Informative background prior: Minimum = 0.0898; Most likely = 0.1591; Maximum = 0.4435 (with selected shape parameter), detailed in Section C.3.2.

Distribution: Lognormal

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C.2.2 | Data used for analysis

Response variable: RAIU

Subject	Dose	RAIU
1	0.500	0.072
2	0.500	0.034
3	0.500	0.123
4	0.500	0.058
5	0.500	0.088
6	0.500	0.037
7	0.500	0.099
8	0.500	0.074
9	0.500	0.052
10	0.500	0.053
11	0.100	0.091
12	0.100	0.104
13	0.100	0.067
14	0.100	0.113
15	0.100	0.078
16	0.100	0.236
17	0.100	0.066
18	0.100	0.141
19	0.100	0.117
20	0.100	0.084
21	0.020	0.183
22	0.020	0.206
23	0.020	0.133
24	0.020	0.154
25	0.020	0.168
26	0.020	0.190
27	0.020	0.114
28	0.020	0.127
29	0.020	0.111
30	0.020	0.136
31	0.007	0.132
32	0.007	0.187
33	0.007	0.139
34	0.007	0.135
35	0.007	0.178
36	0.007	0.247
37	0.007	0.134

Note that the control group (baseline) is not included in the input data, as it is used as prior to inform the modelling, thus avoiding covariance effects.

Selection of the BMR

The BMR (benchmark response) used is a 5% change in mean response compared to the controls. The BMD (benchmark dose) is the dose corresponding with the BMR of interest. Details on the BMR selection are provided in the main body of the Opinion (see Section 3.1.5.2 'Dose–response analysis - BMR selection').

A 90% credible interval around the BMD will be estimated, the lower bound is reported by BMDL and the upper bound by BMDU.

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C.2.3 | Results

Shapiro-Wilk normality test

There is evidence against normality across dose levels at level 0.05 (*p*-value 0.0012).
There is no evidence against log-normality across dose levels at level 0.05 (*p*-value 0.5922).

Goodness of Fit

Best fitting model fits sufficiently well (Bayes factor is 1.35e+00).

Model Averaged BMD

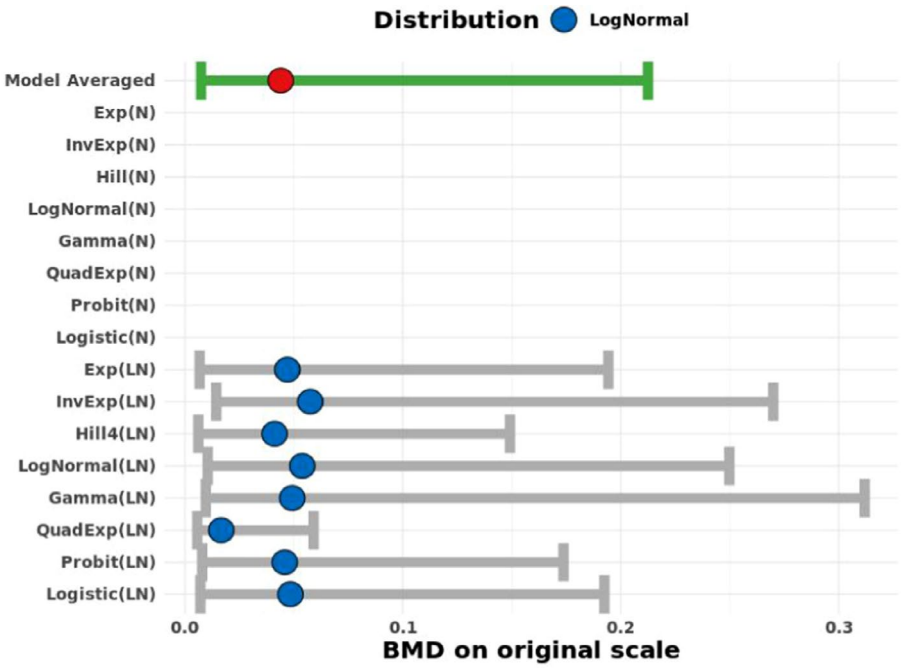
Model	Type	BMDL	BMD	BMDU
Model Averaged	BS	0.007	0.043	0.185

Estimated BMDs per model

Model	BMDL	BMD	BMDU	Model weights	Converged
E4_LN	0.007	0.047	0.194	0.102	1
IE4_LN	0.014	0.058	0.270	0.165	1
H4_LN	0.006	0.041	0.149	0.127	1
LN4_LN	0.011	0.054	0.250	0.135	1
G4_LN	0.010	0.049	0.312	0.141	0
QE4_LN	0.006	0.017	0.059	0.141	1
P4_LN	0.008	0.046	0.174	0.093	1
L4_LN	0.007	0.048	0.193	0.096	1

Note that the gamma model (G4_LN) did not converge and hence, although it is included in the plots below, it is not part of the model averaging.

BMD estimates and their credible intervals



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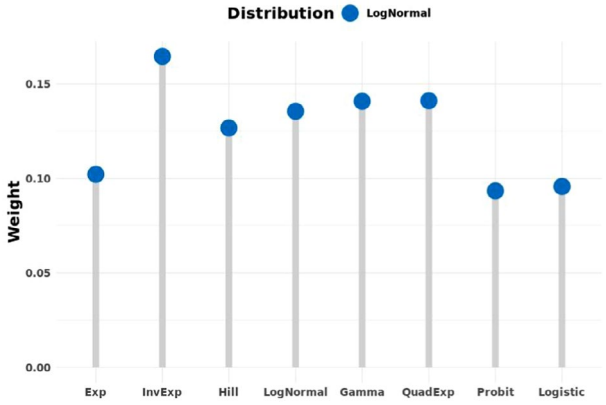
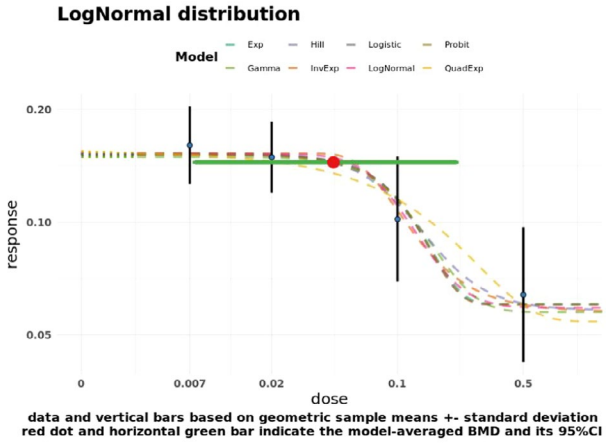
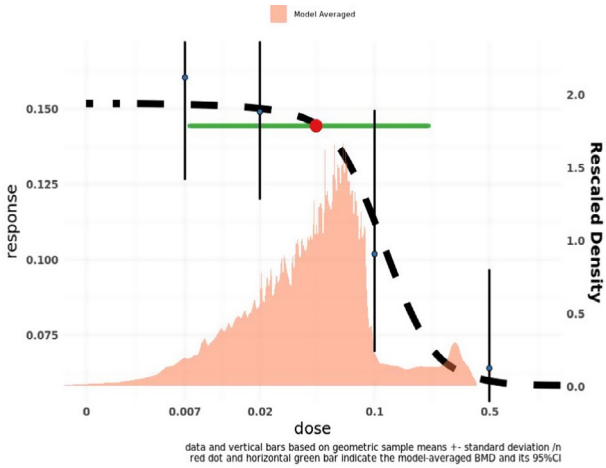
Model weights for individual models in model averaging



Fitted dose-response curves for each individual lognormal model



Fitted dose-response averaged model and its posterior distribution



C.3 | CONSTRUCTION OF AN INFORMATIVE BACKGROUND PRIOR

C.3.1 | Description of the approach

An informative background prior for the BMD analysis of the Greer et al. (2002) study was constructed using baseline 24-h ^{123}I thyroid uptake data fitted to a PERT distribution in R, utilising the R script provided in Section C.3.2. The script extracts the minimum, mode and maximum values from this distribution that were used as the minimum, most likely and maximum values in the prior specification of the Bayesian BMD tool. The input dataset used is also provided in Section C.3.3.

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C.3.2 | R script used to construct an informative background prior

```
### Using the data of the baseline measures to identify ###
### background priors for the Bayesian BMD modelling ###

### loading libraries ###
library(dplyr)
library(tidyr)
library(ggplot2)
library(fitdistrplus)
library(rriskDistributions)
library(mc2d)

## set working directory to wherever all input and executables are
setwd("Path to working directory")

# Read Subject Data
In_data <- read.csv("data_input.csv", header=TRUE)
# filtering the data to keep only relevant individual data for baseline #
background <- In_data %>% filter(dose==0 & t==0 & post==0)

# Define the function
plot_pert_density <- function(data, var_name,min,mode,max) {

# creating functions for fitting pert distribution #
dpert<-mc2d::dpert
ppert<-mc2d::ppert
qpert<-mc2d::qpert

# Extract the variable from the dataframe
var <- data[[var_name]]

# Fit PERT distribution to individual data
fitPert <- fitdist(var, distr="pert", start = list(min = min, mode = mode, max = max))
temp1<-summary(fitPert)

# Extract parameters
min_val <- fitPert$estimate[1]
mode_val <- fitPert$estimate[2]
max_val <- fitPert$estimate[3]

# Fit other distributions to compare the fit based on AIC values
fitD<-useFitdist(var,show.output = F)
temp2<-fitD$res.matrix[,2]

# Plot the results
p<-ggplot(data, aes_string(x = var_name)) +
geom_histogram(aes(y = ..density..), binwidth = diff(range(var))/nclass.FD(var), color = "black", fill = "blue") +
labs(x = toupper(var_name), y = "Density") +
geom_density(aes_string(x = var_name, y = "..density.."), color = "red", linewidth = 1.5)+
stat_function(fun = dpert, args = list(min = min_val, mode = mode_val, max = max_val), color = "red", size = 1)
return(list(temp1,temp2,p))
}

outResraiu<-plot_pert_density(data=background, var_name="raiu", min=0, mode=0.1, max=1)

outResraiu[[1]]$estimate
```

Output of the command SessionInfo()

```
R version 4.3.2 (2023-10-31 ucrt)
Platform: x86_64-w64-mingw32/x64 (64-bit)
```

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Running under: Windows 10 x64 (build 19045)

attached base packages:
stats graphics grDevices utils datasets methods base

other attached packages:

mc2d_0.2.0	mvtnorm_1.2-3	rriskDistributions_2.1.2
fitdistrplus_1.2-1 s	urvival_3.5-7	MASS_7.3-60
ggplot2_3.4.4	tidyr_1.3.0	dplyr_1.1.4

loaded via a namespace (and not attached):

utf8_1.2.4	generics_0.1.3	nortest_1.0-4	rstatix_0.7.2	stringi_1.8.1
lattice_0.21-9	magrittr_2.0.3	grid_4.3.2	Matrix_1.6-1.1	zip_2.3.0
backports_1.4.1	purrr_1.0.2	fansi_1.0.5	scales_1.2.1	eha_2.11.4
abind_1.4-5	cli_3.6.1	rlang_1.1.2	expm_0.999-7	munsell_0.5.0
splines_4.3.2	withr_2.5.2	tools_4.3.2	ggsignif_0.6.4	colorspace_2.1-0
ggpubr_0.6.0	broom_1.0.5	vctrs_0.6.4	R6_2.5.1	lifecycle_1.0.4
car_3.1-2	pkgconfig_2.0.3	pillar_1.9.0	openxlsx_4.2.5.2	gtable_0.3.4
glue_1.6.2	Rcpp_1.0.11	xfun_0.41	tibble_3.2.1	tidyselect_1.2.1
rstudioapi_0.15.0	knitr_1.45	msm_1.7.1	carData_3.0-5	compiler_4.3.2

C.3.3 | Input data used for the R script

Subj	Dose	t	Post	Raiu	Group
1	0	1	0	0.133	1
1	0	0	0	0.215	1
1	0.5	1	0	0.049	2
1	0.5	0	0	0.079	2
1	0.5	1	0	0.045	3
1	0.5	0	0	0.072	3
1	0	1	1	0.101	4
1	0	0	1	0.178	4
2	0	1	0	0.111	1
2	0	0	0	0.204	1
2	0.5	1	0	0.032	2
2	0.5	0	0	0.052	2
2	0.5	1	0	0.025	3
2	0.5	0	0	0.034	3
2	0	1	1	0.125	4
2	0	0	1	0.208	4
3	0	1	0	0.176	1
3	0	0	0	0.278	1
3	0.5	1	0	0.048	2
3	0.5	0	0	0.068	2
3	0.5	1	0	0.078	3
3	0.5	0	0	0.123	3
3	0	1	1	0.204	4
3	0	0	1	0.322	4
4	0	1	0	0.168	1
4	0	0	0	0.25	1
4	0.5	1	0	0.034	2
4	0.5	0	0	0.056	2
4	0.5	1	0	0.04	3
4	0.5	0	0	0.058	3
4	0	1	1	0.145	4
4	0	0	1	0.208	4

(Continues)

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(Continued)

Subj	Dose	t	Post	Raiu	Group
5	0	1	0	0.236	1
5	0	0	0	0.328	1
5	0.5	1	0	0.055	2
5	0.5	0	0	0.084	2
5	0.5	1	0	0.053	3
5	0.5	0	0	0.088	3
5	0	1	1	0.146	4
5	0	0	1	0.216	4
6	0	1	0	0.089	1
6	0	0	0	0.137	1
6	0.5	1	0	0.03	2
6	0.5	0	0	0.042	2
6	0.5	1	0	0.025	3
6	0.5	0	0	0.037	3
6	0	1	1	0.13	4
6	0	0	1	0.207	4
7	0	1	0	0.138	1
7	0	0	0	0.194	1
7	0.5	1	0	0.063	2
7	0.5	0	0	0.084	2
7	0.5	1	0	0.063	3
7	0.5	0	0	0.099	3
7	0	1	1	0.21	4
7	0	0	1	0.302	4
8	0	1	0	0.106	1
8	0	0	0	0.152	1
8	0.5	1	0	0.039	2
8	0.5	0	0	0.055	2
8	0.5	1	0	0.048	3
8	0.5	0	0	0.074	3
8	0	1	1	0.117	4
8	0	0	1	0.165	4
9	0	1	0	0.161	1
9	0	0	0	0.257	1
9	0.5	1	0	0.033	3
9	0.5	0	0	0.052	3
9	0	0	1	0.253	4
10	0	1	0	0.096	1
10	0	0	0	0.14	1
10	0.5	1	0	0.038	3
10	0.5	0	0	0.053	3
10	0	0	1	0.115	4
11	0	1	0	0.123	1
11	0	0	0	0.194	1
11	0.1	1	0	0.07	5
11	0.1	0	0	0.103	5
11	0.1	1	0	0.06	6
11	0.1	0	0	0.091	6
11	0	1	1	0.124	7
11	0	0	1	0.187	7

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(Continued)

Subj	Dose	t	Post	Raiu	Group
12	0	1	0	0.156	1
12	0	0	0	0.207	1
12	0.1	1	0	0.102	5
12	0.1	0	0	0.169	5
12	0.1	1	0	0.067	6
12	0.1	0	0	0.104	6
12	0	1	1	0.163	7
12	0	0	1	0.247	7
13	0	1	0	0.073	1
13	0	0	0	0.112	1
13	0.1	1	0	0.037	5
13	0.1	0	0	0.057	5
13	0.1	1	0	0.045	6
13	0.1	0	0	0.067	6
13	0	1	1	0.07	7
13	0	0	1	0.108	7
14	0	1	0	0.156	1
14	0	0	0	0.241	1
14	0.1	1	0	0.093	5
14	0.1	0	0	0.138	5
14	0.1	1	0	0.075	6
14	0.1	0	0	0.113	6
14	0	1	1	0.171	7
14	0	0	1	0.247	7
15	0	1	0	0.13	1
15	0	0	0	0.2	1
15	0.1	1	0	0.08	5
15	0.1	0	0	0.119	5
15	0.1	1	0	0.045	6
15	0.1	0	0	0.078	6
15	0	1	1	0.078	7
15	0	0	1	0.139	7
16	0	1	0	0.22	1
16	0	0	0	0.329	1
16	0.1	1	0	0.127	5
16	0.1	0	0	0.187	5
16	0.1	1	0	0.17	6
16	0.1	0	0	0.236	6
16	0	1	1	0.21	7
16	0	0	1	0.296	7
17	0	1	0	0.056	1
17	0	0	0	0.098	1
17	0.1	1	0	0.031	5
17	0.1	0	0	0.051	5
17	0.1	1	0	0.04	6
17	0.1	0	0	0.066	6
17	0	1	1	0.075	7
17	0	0	1	0.102	7
18	0	1	0	0.112	1
18	0	0	0	0.188	1

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(Continued)

Subj	Dose	t	Post	Raiu	Group
18	0.1	1	0	0.076	5
18	0.1	0	0	0.117	5
18	0.1	1	0	0.086	6
18	0.1	0	0	0.141	6
18	0	1	1	0.143	7
18	0	0	1	0.237	7
19	0	1	0	0.152	1
19	0	0	0	0.252	1
19	0.1	1	0	0.074	6
19	0.1	0	0	0.117	6
19	0	0	1	0.226	7
20	0	1	0	0.099	1
20	0	0	0	0.169	1
20	0.1	0	0	0.084	6
20	0	0	1	0.29	7
21	0	1	0	0.127	1
21	0	0	0	0.23	1
21	0.02	1	0	0.146	8
21	0.02	0	0	0.226	8
21	0.02	1	0	0.086	9
21	0.02	0	0	0.183	9
21	0	1	1	0.139	10
21	0	0	1	0.241	10
22	0	1	0	0.152	1
22	0	0	0	0.201	1
22	0.02	1	0	0.116	8
22	0.02	0	0	0.16	8
22	0.02	1	0	0.142	9
22	0.02	0	0	0.206	9
22	0	1	1	0.146	10
22	0	0	1	0.201	10
23	0	1	0	0.09	1
23	0	0	0	0.135	1
23	0.02	1	0	0.098	8
23	0.02	0	0	0.142	8
23	0.02	1	0	0.089	9
23	0.02	0	0	0.133	9
23	0	1	1	0.138	10
23	0	0	1	0.187	10
24	0	1	0	0.136	1
24	0	0	0	0.185	1
24	0.02	1	0	0.106	8
24	0.02	0	0	0.182	8
24	0.02	1	0	0.104	9
24	0.02	0	0	0.154	9
24	0	1	1	0.108	10
24	0	0	1	0.185	10
25	0	1	0	0.143	1
25	0	0	0	0.208	1
25	0.02	1	0	0.1	8

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(Continued)

Subj	Dose	t	Post	Raiu	Group
25	0.02	0	0	0.128	8
25	0.02	1	0	0.102	9
25	0.02	0	0	0.168	9
25	0	1	1	0.162	10
25	0	0	1	0.223	10
26	0	1	0	0.16	1
26	0	0	0	0.233	1
26	0.02	1	0	0.122	8
26	0.02	0	0	0.185	8
26	0.02	1	0	0.115	9
26	0.02	0	0	0.19	9
26	0	1	1	0.192	10
26	0	0	1	0.264	10
27	0	1	0	0.086	1
27	0	0	0	0.187	1
27	0.02	1	0	0.059	8
27	0.02	0	0	0.13	8
27	0.02	1	0	0.068	9
27	0.02	0	0	0.114	9
27	0	1	1	0.081	10
27	0	0	1	0.138	10
28	0	1	0	0.09	1
28	0	0	0	0.143	1
28	0.02	1	0	0.07	8
28	0.02	0	0	0.101	8
28	0.02	1	0	0.09	9
28	0.02	0	0	0.127	9
28	0	1	1	0.115	10
28	0	0	1	0.162	10
29	0	1	0	0.068	1
29	0	0	0	0.12	1
29	0.02	1	0	0.064	9
29	0.02	0	0	0.111	9
29	0	0	1	0.137	10
30	0	1	0	0.125	1
30	0	0	0	0.201	1
30	0.02	1	0	0.082	9
30	0.02	0	0	0.136	9
30	0	0	1	0.176	10
31	0	1	0	0.082	1
31	0	0	0	0.122	1
31	0.007	1	0	0.087	11
31	0.007	0	0	0.132	11
31	0	0	1	0.139	12
32	0	1	0	0.13	1
32	0	0	0	0.215	1
32	0.007	1	0	0.128	11
32	0.007	0	0	0.187	11
32	0	0	1	0.207	12
33	0	1	0	0.068	1

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(Continued)

Subj	Dose	t	Post	Raiu	Group
33	0	0	0	0.1	1
33	0.007	1	0	0.087	11
33	0.007	0	0	0.139	11
33	0	0	1	0.145	12
34	0	1	0	0.076	1
34	0	0	0	0.127	1
34	0.007	1	0	0.08	11
34	0.007	0	0	0.135	11
34	0	0	1	0.114	12
35	0	1	0	0.166	1
35	0	0	0	0.22	1
35	0.007	1	0	0.102	11
35	0.007	0	0	0.178	11
35	0	0	1	0.195	12
36	0	1	0	0.254	1
36	0	0	0	0.337	1
36	0.007	1	0	0.163	11
36	0.007	0	0	0.247	11
36	0	0	1	0.296	12
37	0	1	0	0.105	1
37	0	0	0	0.145	1
37	0.007	1	0	0.098	11
37	0.007	0	0	0.134	11
37	0	0	1	0.117	12

C.4 | COMPARISON OF FITS TO THE RAIU DATA USING BETA AND LOGNORMAL DISTRIBUTIONS

As discussed in the main text of the current opinion (Section 3.1.5.2 'Dose-response analysis'), a lognormal distribution was found suitable for the RAIU data of the Greer et al. (2002) study. Figure C.3 below compares the fitting of lognormal and beta distributions on the RAIU data (by dose):

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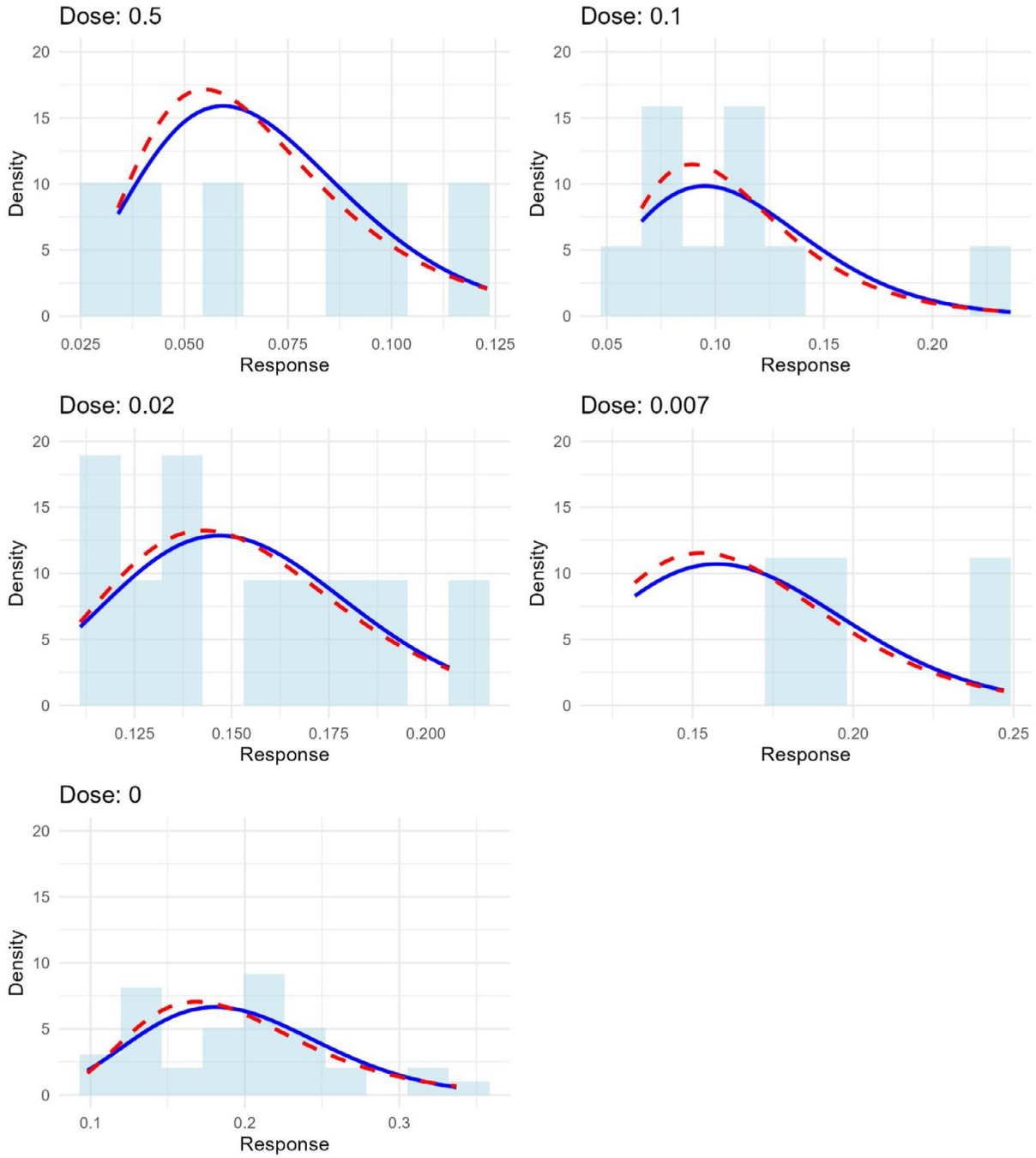

FIGURE C.3 Comparison of lognormal and beta distributions for RAIU at doses of 0, 0.007, 0.02, 0.1 and 0.5 mg/kg bw per day from Greer et al. (2002), showing the beta distribution in blue and the lognormal distribution in red.

Table C.4 below summarises the skill scores of the two distributions, showing that they are comparable across all doses.

TABLE C.4 Scores of the fit of the two distributions by doses.

	Beta distribution				Lognormal distribution			
Dose	**AIC**	**BIC**	**MAE**	**RMSE**	**AIC**	**BIC**	**MAE**	**RMSE**
0.5	−41.23	−40.63	0.03	0.04	−41.30	−40.70	0.03	0.04
0.1	−31.77	−31.17	0.05	0.06	−33.49	−32.89	0.04	0.06
0.02	−37.13	−36.53	0.05	0.05	−37.24	−36.63	0.05	0.05
0.007	−22.78	−22.76	0.03	0.04	−22.90	−23.01	0.03	0.04
0	−100.09	−96.87	0.07	0.09	−99.85	−96.63	0.07	0.09

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian Information Criterion; MAE, mean absolute error; RMSE, root mean square error.

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APPENDIX D

Studies on non-mammalian species

TABLE D.1 Studies on non-mammalian species.

Authors	Animal species	Substance	Exposure (doses)	Duration	Way of dosing	Critical endpoint	Association signal	Results
Mukhi and Patino (2007)	*Danio rerio*, zebrafish	Sodium perchlorate	0, 10 and 100 mg/L	Phase 1: 10 weeks Phase 2: 6 weeks	Directly to system water	Thyroid toxicity	Perchlorate-treated females: T3: – ↓ T4 Embryos: T3: – ↓ T4	Sodium perchlorate at both concentrations caused thyroidal hypertrophy and colloid depletion. Prolonged exposure resulted in disruption of thyroid endocrine system, impaired reproduction and Influenced early F1 development.
Zhao et al. (2014)	*Carassius auratus*, goldfish	Perchlorate	0, 0.1, 1, 10, 100, 1,000 μM	30 min	In vitro assay (isolated mitochondria were added into a 96-well microplate and incubated with ClO4-)	Liver toxicity	Perchlorate-treated mitochondria: ↑ mitochondrial swelling	Incubation of mitochondria with ClO4- caused a concentration-dependent manner in mitochondrial swelling. In addition, treatment of mitochondria with 1,000 μM ClO4- elevated the production of ROS.
Campbell et al. (2018)	*Silurana tropicalis*	Potassium perchlorate	0, 20, 53 and 107 mg/L	1 year	Directly to system water	Thyroid toxicity	↓ expression of dio1 (testis; males) ↑ expression of srd5a2 and cyp19 (ovary; females)	Prolonged exposure to KClO4 resulted in distinct thyroid hormone- and sex steroid-related gene expression patterns in the reproductive tissues of male and female frogs. In addition, prolonged exposure caused changes to reproductive indices (i.e. plasma androgen levels, gonadal thyroid hormone- and sex steroid-related transcript levels and sperm motility
Flood and Langlois (2014)	*Silurana tropicalis*	Potassium perchlorate	0, 20, 53 and 107 mg/L	12 weeks	Directly to system water	Thyroid & develop-mental toxicity	↓ expression of dio2	Sodium perchlorate exposure led to changes in androgen-related gene expression
Furin et al. (2015b)	*Gastero-steus aculeatus*	Sodium perchlorate	30 and 100 mg/L	1 year	Exposure to contaminated water at varying times	Develop-mental toxicity	↑ abnormal skeletal development	Exposure to sodium perchlorate caused abnormal development of the stickleback dermal skeleton

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TABLE D.1 (Continued)

Authors	Animal species	Substance	Exposure (doses)	Duration	Way of dosing	Critical endpoint	Association signal	Results
Gardell et al. (2015)	*Gastero-steus aculeatus*	Sodium perchlorate	100 mg/L	7 weeks	Directly to system water	Thyroid & develop-mental toxicity	T3: – T4: –	Exposure to 100 mg/L perchlorate whole-body thyroid hormone contents (T3 and T4) remained stable in response to acute and chronic perchlorate exposure. This suggests the presence of compensatory mechanisms that maintain normal TH levels in the presence of perchlorate.
Opitz et al. (2009)	*Xenopus laevis* tadpoles	Sodium perchlorate	20 mg/L	12 days	Directly to system water	Thyroid toxicity	↓ expression of TH-regulated genes ↑ expression of negative growth regulators	Sodium perchlorate-treated tadpoles, caused colloid resorption, follicular cell hypertrophy, thyroid hyperplasia and goitre formation
Zheng et al. (2020)	*Bufo gargarizans* tadpoles	Sodium perchlorate	250 µg/L	Exposure ended when 60% of tadpoles in control groups reached metamorphic climax Gs42	Directly to system water	Develop-mental toxicity	↓ expression of LepR, JAK1, JAK2, TYK2 ↑ levels of SOCS3	Exposure to perchlorate had inhibitory effects on amphibians' metamorphosis, however, resulted in a larger body size. Perchlorate caused liver toxicity and might elicit leptin resistance by decreasing the expression of LepR, JAK1, JAK2, TYK2 and upregulating the level of SOCS3.
Bulaeva et al. (2015)	*Lithobates sylvaticus*	Sodium perchlorate	14 mg/L	2 weeks	Directly to system water	Developmental toxicity	↓ levels of trβ mRNA levels ↑ expression of igf1	Sodium perchlorate exposure resulted in long-lasting effects on body weight and size during later development.
Furin et al. (2015a)	*Gastero-steus aculeatus*	Sodium perchlorate	30 and 100 mg/L	1 year	Exposure to contaminated water at varying times	Thyroid & develop-mental toxicity	T3: – T4: –	Exposure to sodium perchlorate increased angiogenesis and follicle proliferation in thyroid tissue, delayed gonadal maturity, and skewed sex ratios toward males
Gardell et al. (2017)	*Gastero-steus aculeatus*	Sodium perchlorate (with/-out Iodine or T4)	10, 30 and 100 mg/L	1 year	Directly to system water	Thyroid toxicity	T3: – T4: –	Perchlorate-induced alterations in thyroid tissue were formed. Those effects were significantly improved by exogenous iodide
Ismail et al. (2024)	*O.mossambicus* × *O. urolepis hornorum* red tilapia fish	Sodium perchlorate	30 mg/L	30 days	Directly to system water	Develop-mental toxicity	↑ T3 T4: –	Sodium perchlorate exposure disrupted thyroid hormone levels and altered thyroid follicle morphology. Perchlorate twisted sex ratios toward males

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TABLE D.1 (Continued)

Authors	Animal species	Substance	Exposure (doses)	Duration	Way of dosing	Critical endpoint	Association signal	Results
Lee et al. (2014)	*Oryzias latipes*	Sodium perchlorate	100 mg/L	7 days	Directly to system water	Thyroid & develop-mental toxicity	T3: – ↑ T4 ↓ THR-α; THR-β ↑ expression of dio2	The decrease of T4 concentration was the most evident in the perchlorate exposure group at 33°C.
Li, Li, Li, Zhang et al. (2023)	*Rana chensinensis* tadpoles	Sodium perchlorate	250 μg/L	Exposure ended when tadpoles reached metamorphic climax Gs42	Directly to system water	Develop-mental toxicity	↓ Sox5 & Sox9	Sodium perchlorate exposure caused histological damage to the femur and tibia-fibula and inhibited the hindlimb length of R. *chensinensis* tadpoles.
Reh et al. (2022)	*Oryzias latipes* larvae	Potassium perchlorate	0, 10, 100 and 1000 μg/L	Exposure lasted until the 15 days post fertilisation (dpf) stage	Directly to system water	Develop-mental toxicity	↓cyp7a1	Potassium perchlorate exposure caused developmental abnormalities in embryos and disruption in the migration of PGCs. Ingenuity Pathway Analysis of PGC transcriptomes revealed thyroid hormone signalling to be affected by all concentrations of perchlorate.
Lee et al. (2024)	Zebrafish	Sodium perchlorate	0, 2.44, 24.4, 243.7 mg/L	21 days	Directly to system water	Thyroid toxicity	↓TH ↓reproductive success	Sodium perchlorate increased cortisol levels while decreasing thyroid hormone production.

Abbreviations: Dio1, type 1 iodothyronine deiodinase; JAK1, Janus kinase 1; JAK2, Janus kinase 2; mRNA, messenger ribonucleic acid; ROS, reactive oxygen species; SOCS3, suppressor of cytokine signalling-3; T3, triiodothyronine; T4, thyroxine; TC, total cholesterol; TYK2, Tyrosine kinase 2.

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APPENDIX E

Sources of uncertainty

TABLE E.1 Hazard identification and characterisation.

Main group	Sub-group	Overarching questions	Examples of sources of uncertainty in CONTAM opinions	Sources of uncertainty in the opinion	Impact ranking of the uncertainty
Chemical composition and analytical methods	**Chemical composition**	**Is there uncertainty associated with the dose in the critical studies used in the risk assessment?**	Uncertainty in the applied dose (e.g. evaporation, feed or drinking water) for (e.g. dead volumes in syringe, calibration of the equipment used, feed or drinking water) The exact composition of the tested items (e.g. congener pattern of technical mixtures used in toxicological studies do not resemble the profiles found in food or presence of impurities is based on limited information) and its characteristics (e.g. storage, processing etc) are based on limited information.	**Purity not reported**.	1[20]
	Analytical methods		Lack of certified reference materials, proficiency tests and method validation	**Established analytical methods. Certified materials existing and accessible**.	**0**
Hazard identification and characterisation	**ADME**	**Is there uncertainty in any aspect of ADME?**	Insufficient information on absorption when ingesting different foods	**Uncertainty relating to the food ingested**	**1**
			Accumulation potential (e.g. duration of studies, sample size, sex, number of studies, direct measurements, biomarkers, metabolites)	No accumulation.	**0**
			Confounders (e.g. effects of other chemicals that may affect the ADME of the tested compounds)	**N/A**	
			Elimination	**Fast elim. (N/A)**	**0**
			Little information on transfer rate to animal products	**Present in dairy milk, not in others (e.g. meat, etc.). Mainly from vegetables and water**.	**1**
			Insufficient information on the extent of metabolism of the parent compounds (degradation/hydrolysis/reduction/other reactions).	**N/A**	**0**
			Relevance in humans, genetic background/ susceptibility/sensitive populations	**Iodine nutritional status (influence on uptake/ milk excretion)**	**1**

(Continues)

[20] **0 – U with negligible impact; 1 – U with low impact; 2 – U with medium impact; 3 – U with high impact**.

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TABLE E.1 (Continued)

Main group	Sub-group	Overarching questions	Examples of sources of uncertainty in CONTAM opinions	Sources of uncertainty in the opinion	Impact ranking of the uncertainty
	Toxicity studies in experimental animals: critical endpoints and critical study design	**Are there sources of uncertainties in the design of the studies in experimental animals?**	Studies carried out only in one gender or certain age groups, duration of studies, sample size, direct measurements, biomarkers, dosing regimen.	**Studies are carried in animals of both sexes, in animals of different age groups. Duration covers subacute to subchronic exposure**.	**1**
		Are there uncertainties in the use of the animal model?	Relevance for humans of the adverse effect/ biomarkers of adversity (e.g. combined incidences, validated biomarkers), species/ strain, target site, metabolic pathway, etc	**Different susceptibility of the thyroid gland in rats and humans**	**2**
			Limited information on other effects that could be considered as critical.	**Majority of studies deals with thyroid and reproductive effects**	**1**
			Dietary studies, default factors used for conversion	**Possible uncertainty as perchlorate administration is through drinking water**	**2**
	Genotoxicity	**Is there uncertainty on the genotoxicity of the substance?**	Insufficient/inconclusive data or inconsistent results	**Slight concern might be secondary DNA damage from ROS but this would still not classify perchlorate as genotoxic**	**1**
	Co-exposure	**Is there uncertainty on the extent and profile of effects due to co-exposure (e.g. metabolites, interaction of chemicals, combined effects)?**	Combined affects for co-exposure with other compounds	**Studies with various compounds being assessed (other NIS inhibitors) but not used as critical studies for the assessment**	**1**
	Observations in humans	Is there uncertainty in the study design, sample size, exposure assessment (in the method used), outcome assessment (e.g. histology versus self-report), statistical analysis including control of confounding factors, missing data, dose response	Variations in human studies regarding exposure (study design)	**Most studies used spot urine which does not reflect long-term exposure. However, it may reasonably reflect exposure if people are exposed to varying levels of perchlorate in drinking water**	**3**
			Inconsistency in human studies (study results)	**The results for the human studies, taking different design and conduct into considerations were relatively consistent (at least for thyroid hormones). For both observational and intervention studies**	**1**
			Low number of studies per outcome and limited cumulative sample size	**Main outcome (thyroid) had several studies so no concern. For both observational and intervention studies**	**1**
			Small sample size of the individual studies	**Intervention studies were very limited in sample size and are unlikely to reflect the variation that exist in the general population**	**3**
				The observational studies were generally of sufficient sample size	**1**

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TABLE E.1 (Continued)

Main group	Sub-group	Overarching questions	Examples of sources of uncertainty in CONTAM opinions	Sources of uncertainty in the opinion	Impact ranking of the uncertainty
			Limitations in epidemiological study at the individual study level: e.g. co-exposure, confounding, bias in the study, exposure and outcome assessment	**For the observational studies confounding is always an issue although the use of spot urine samples would not be a source of confounding** **Insufficient duration is of concern for the intervention studies. For both observational and intervention studies**	**2**
			Limitations in the epidemiological data at the study group level: e.g. research question (correct outcome assessed), detection, reporting and publication bias	**No major concerns. Measurements of thyroid hormones are quite standard and research questions addressed were quite clear. For both observational and intervention studies**	**1**
			Geographical representativeness and consistency	**No major concern. Population from EU and North America were generally quite representative, for both observational and intervention studies**	**1**
			Consumption patterns, stratification in terms of geographical location and diet	**No concern. For both observational and intervention studies**	**0**
	Mode of action	**Are there uncertainties on the MoA of the substance that could affect the conclusions of the risk assessment?** **Is there uncertainty on the human relevance of the MoA identified in experimental animals?**	Uncertainties in the strength, consistency and specificity of the association of the key events and the critical effect in humans	**Possible uncertainty regarding reproductive effects being a direct effect rather than via thyroid effects. Relating to animal data, used as supportive information (not as critical study)**	**2**
	Selection of reference point	**Is there uncertainty on the biological relevance of the selected BMR?**	Sufficient information to justify the selection of the BMR (including the uncertainty on the iodine status of the EU population)	**BMR selected based on human data from various studies**	**2**
		Are there uncertainties in the selection of the RP that are not covered by the BMD confidence interval e.g. is model uncertainty covered?	Uncertainty in the confidence intervals of the selected BMR	**BMD confidence interval and BMR based on studies in non-pregnant adults**	**3**
	Dose–response analysis of critical endpoints	**Is there uncertainty regarding the dose–response analysis e.g. trend occurrence, large data variation, possible covariants?**	Lack of raw data points	**Raw data is available. Covariants were taken into account. Intermediate measurements could not be taken into account.**	**1**
			No dose-response relationship/not well defined	N/a	

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TABLE E.2 Elements of the CONTAM road map and relevance for the uncertainty analysis of the perchlorate in food draft Opinion – **OCCURRENCE AND EXPOSURE**.

Main group	Sub-group	Overarching questions	Description of uncertainty	Sources of uncertainty in the opinion	Impact ranking of the Uncertainty[1]
Occurrence data	**Analytical measurements**	Is there uncertainty due to the performance of the analytical method? This may include identification, sensitivity and recovery	Performance (e.g. specificity for the target compounds) of the analytical method (GC–ECD, GC–MS, etc)	It seems that there are no issues with analytical methods for perchlorate	0
			Analytical capability of the method - sensitivity (e.g. LOQ, LOD)	It seems that there are no issues with analytical methods for perchlorate	0
			Coeluting congeners	It seems that there are no issues with analytical methods for perchlorate	0
			Consideration of recovery (e.g. correction carried out or not)	It seems that there are no issues with analytical methods for perchlorate	0
			Lack of certified reference materials and proficiency tests	It seems that there are no issues with analytical methods for perchlorate	0
		Is there uncertainty in the information on processing, e.g. processing prior to the analysis of the samples	Unclear whether and what kind of the treatment/processing has been applied prior to the analysis of the sample	No impact was identified linked to treatment/processing of the sample	0
	Data reporting	Is there uncertainty on whether there are errors in the reported occurrence data or linked to missing information?	Potential errors in reporting the occurrence data (e.g. in the classification of the food category, of the compound, unit of measurement, parameter, fat vs whole weight, etc.) – unidentified errors (not apparent from the data provided)	Data went through a thorough validation and cleaning, but it is possible that some reporting errors went undetected	2
			Missing information in reporting the occurrence data (e.g. analytical method)		
		Is there uncertainty in the information on sampling strategy	Sampling strategy not fully random (e.g. risk based or based on screening methods)	Samples reported as suspect sampling were confirmed by the data providers (DPs) and excluded from the analysis. Not specified sampling strategy was linked to industry reporting as in this case sampling is based on industry practices.	0
		Is there uncertainty in the form of the food reported	Unclear status/form of the food (cooked/uncooked, powder/liquid/reconstituted etc)	Yes, uncertainty is present in the form reported. Identified issue were solved during data validation and cleaning checking consistency among the filed used to report the matrix. In some cases, concentration in the dry form was calculated from the liquid form and vice versa depending on data availability	2

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TABLE E.2 (Continued)

Main group	Sub-group	Overarching questions	Description of uncertainty	Sources of uncertainty in the opinion	Impact ranking of the Uncertainty[1]
	Representativeness and completeness of the data	Is there uncertainty in the occurrence data due to limited data availability	Use of food categories at high (often not enough specified) FoodEx/FoodEx2 level	Almost 90% of results were reported at a level higher than 3 of the FoddEx2 classification	0
			Composite foods with no clear information about ingredients and their proportion	Uncertainty is present in deriving perchlorate concentration for composite foods or complex foods such as fine bakery wares. Calculations were performed using the main ingredients (e.g. flour and water for bread)	2
			Low number of samples per food category	This uncertainty is present for some food categories	2
			Low number of reporting countries	80% of data were reported by Germany but assuming a single market this uncertainty should have a low to moderate impact	1-2
			Not optimal distribution of year of samplings (e.g. too many old data)	Seasonality should not play a role in perchlorate concentration	0
			Extrapolation of data from one food category to others	Data were available for calculating mean concentration for about 723 Foodex2 codes (minimum number of samples=6). 2000 Foodex2 codes were included in the dietary exposure assessment for which the value was extrapolated from similar foods or calculated from concentration in primary commodities or ingredients	2
			Limited number of analytical results per variables that could explain higher/lower levels, such as production method (e.g. wild vs farmed), processing (e.g. peeled vs raw), etc.	Additional variables were considered as having a negligible impact	0
		Is there uncertainty in the occurrence data due to lack of data for potentially relevant major food categories?	Lack of data for potentially relevant major food categories	Data for major food categories such as bread, fine bakery wares were lacking and were calculated from ingredients (see above)	2
	Multiple chemicals and metabolites	Is there uncertainty in the occurrence data due to that not **all relevant substances** are reported.	Lack of data for some potentially relevant compounds	This opinion concerns only one compound	0
			Limited data on the **co-occurrence** for the chemicals belonging to the group of interest	This opinion concerns only one compound	0
			Missing information on metabolites or degradation products	This opinion concerns only one compound and no metabolites or degradation products	0

(Continues)

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TABLE E.2 (Continued)

Main group	Sub-group	Overarching questions	Description of uncertainty	Sources of uncertainty in the opinion	Impact ranking of the Uncertainty[1]
	Left censorship	Is there uncertainty in the occurrence data due to extrapolation or use of models?	High LOQ and LOD		1
		Is there uncertainty in the occurrence data due to left censorship and the substitution method	High percentage of left-censored data	The presence of LC data generates uncertainty. This is handled using the LB and UB approach.	2
Consumption data	**Data reporting**	Is there uncertainty in the consumption data due to errors e.g. in classification, body weight, age, memory errors etc?	Unidentified errors in reporting consumption data (e.g. in the classification of the food, portion size, etc.) Body weight estimation (measured, self-reported or estimated) Memory errors and capacity to report details in dietary surveys, possible under and over reporting	**1 – Low impact**. Uncertainties and limitations related to the use of the EFSA Comprehensive Food Consumption Database have been described by EFSA (EFSA, 2011a). These uncertainties are common to dietary exposure assessments performed using the Comprehensive Database, and have the potential to cause either an over- or underestimation of the exposure. No specific uncertainties in the methodology of the collection of consumption data were identified for this assessment	1
		Is there uncertainty in consumption data, e.g. due to methodology of the dietary survey, weekdays, national recipes?	Dietary survey methodology (dietary record vs. 24-h recall), dietary software, interview options (place, face to face vs telephone and background of the interviewers) and use of portion-size measurement aids for the estimation of portion sizes) Long-term (chronic) exposure assessed based on few days of consumption per individual Representativeness over different weekdays and seasons within dietary surveys Sample size and response rate of the dietary surveys		

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TABLE E.2 (Continued)

Main group	Sub-group	Overarching questions	Description of uncertainty	Sources of uncertainty in the opinion	Impact ranking of the Uncertainty[1]
			Use of national standard recipes and ingredients factors for composite dishes (e.g. underestimation of minor ingredients, overestimation of standard ingredients, etc) Sampling frame, method and design of the dietary surveys		
			Use of national standard recipes and ingredients factors for composite dishes (e.g. underestimation of minor ingredients, overestimation of standard ingredients, etc). Sampling frame, method and design of the dietary surveys		
		Is there uncertainty in the form of the food reported (powder/ liquid/reconstituted etc)	Data submitted to EFSA is indicated as uncooked but consumption data refers to cooked food.		
	Representativeness of the data	Is there uncertainty in the representativeness of the consumption data (e.g. of the countries, special population groups, sample size and response rates.)	Lack of food consumption data for special population groups, including consumers only of specific foods of special interest, or following special diets, countries etc		
Dietary Exposure estimates methodology		Is there uncertainty linked to the methodology used for calculating the exposure?	No specific uncertainty for this Opinion was identified concerning the chronic dietary exposure assessment methodology		0
Non-dietary exposure		Is there uncertainty in the exposure due to other sources than dietary are not included?			1

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APPENDIX F

Overview of the results of the Expert Knowledge Elicitation

Overview of the results of the Expert Knowledge Elicitation

Parameter	Relative uncertainty of the hazard assessment to perchlorate via food														
Stratification	None														
Question	Assuming the ideal situation: (i) that all necessary studies to assess the potential hazards are performed, (ii) that all studies are done with highest quality (e.g. representative study population, sufficient size, no risk of bias, perfect measurement of exposure and outcome). What would be the BMD of the 'ideal situation'?														
Unit	[mg/(kg BW day)]														
Results	P1%	P2.5%	**P5%**	P10%	P16.7%	P25%	P33.3%	**P50%**	P66.7%	P75%	P83.3%	P90%	**P95%**	P97.5%	P99%
Elicited values	0.01					0.03		0.04		0.10					0.20
EKE results	0.0100	0.0102	**0.0107**	0.0123	0.0155	0.0211	0.0283	**0.0478**	0.0759	0.0945	0.118	0.142	**0.167**	0.185	0.201
Ratio 'ideal'/current	0.233	0.237	**0.248**	0.286	0.361	0.490	0.658	**1.11**	1.77	2.20	2.74	3.31	**3.89**	4.31	4.67
Fitted distribution	BetaGeneral(0.59763,1.7995,0.00995,0.225)														

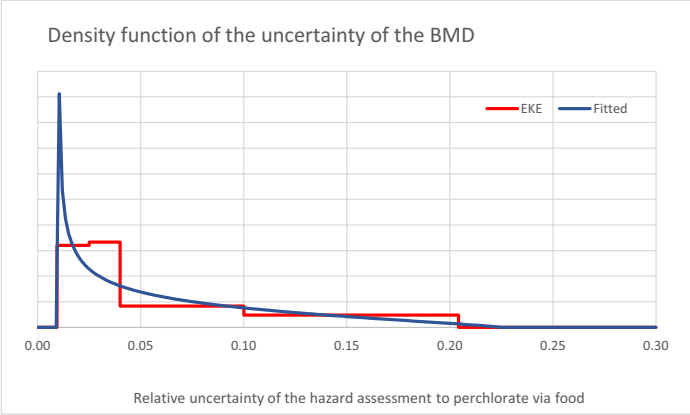

Figure (a): Comparison of elicited and fitted values/density function to describe the remaining uncertainties of the parameter

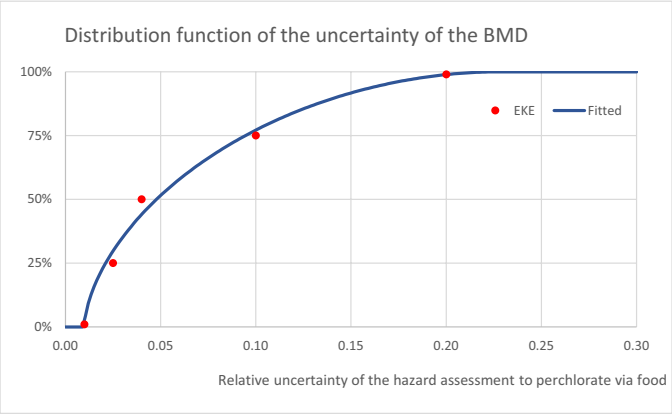

Figure (b): Cumulative distribution function (CDF) of the likelihood of the parameter

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Summary of the evidence used for the evaluation

- The hazard assessment uses the results of the human interventional study of Greer et al. (2002).
- The current hazard assessment sets a BMR of 5% and concludes to a BMD of 0.043 mg/(kg BW day) with a 95% confidence interval of [0.007–0.185 mg/(kg BW day)] calculated with the BMD modelling.
- Results of human observational studies and animal experiments are supporting the assessment.
- The list of identified uncertainties of the hazard assessment.

Main uncertainties

- Limitations of the study population, study duration and size of the study of Greer et al. (2002) (human interventional).
- Limitations of the observational studies related to the exposure assessment via spot urine.
- Limitations of the animal experiments related to the different susceptibility of the thyroid gland in rats compared to humans.
- Limitations in the setting of the BMR on iodine deficiency related to unknown relation to adverse human effects, esp. reproductive effects.
- Limitations in the knowledge of the iodine status of (European) populations to set a cutoff point, in the current assessment 5%.

Reasoning for a scenario which would lead to a reasonable high BMD	The judgement on the upper limit considers that • The confidence intervals of the BMD modelling are wide due to small sample sizes in the Greer et al. (2002) study. • The human observational studies may overestimate the risk due to imprecise exposure assessment. • The BMR setting maybe conservative, due to the use of data from countries with assumed iodine deficiency. • Changes in the iodine status may not indicate adverse effects of human health.
Reasoning for a scenario which would lead to a reasonable low BMD	The judgement on the lower limit considers that • The confidence intervals of the BMD modelling are wide due to small sample sizes in the Greer et al. (2002) study. • Sensitive population groups (pregnant women) were not part of the study population. • Study duration was not sufficient to capture chronic effects, e.g. on the thyroid. • The human observational studies may underestimate the risk due to imprecise exposure assessment, but showing some effects on the thyroid.
Fair estimate as judgement on the weighted evidence	The judgement on the median considers that • The median is close to the geometric mean of the lower/upper limit, this mean has a similar factor of 4. • The uncertainties point both in direction of over- and underestimating with no preference. • The key study of Greer et al. (2002) is not biased to over- or underestimation.
Precision of the judgement as description of remaining uncertainties	The judgement on the interquartile range considers that • The confidence interval of the BMD model is wide enough to cover all uncertainties, due to the small sample size.
Experts	Laurent BODIN, Kevin J CHIPMAN, Gisela DEGEN, Aleksandra Buha DJORDJEVIC, Thorhallur I HALLDORSSON
Facilitator/Reporter	Olaf MOSBACH-SCHULZ, Elena ROVESTI
Observers	Mary GILBERT, Tuuli TAURIAINEN (adviser), Jean-Charles LEBLANC, Walid EL SERRY, Chantra ESKES (observer)
Date and place of the EKE	Virtual TEAMS meeting, 11 October 2024

Overview of the results of the Expert Knowledge Elicitation

Parameter	Relative uncertainty of the exposure assessment to perchlorate via food of toddlers
Stratification	Toddlers
Question	Assuming the ideal situation: (i) that a representative diet study for the average European toddler is given; (ii) that all concentrations of perchlorate are measured with sufficient quality for quantification of the mean contamination of the (eaten) products. How much would the exposure assessment derived from this evidence base differ from the current assessment (of the European average toddler = median survey), expressed as ratio 'ideal/current'?
Unit	[–]/> 1 increased exposure/< 1 decreased exposure

Results	P1%	P2.5%	**P5%**	P10%	P16.7%	P25%	P33.3%	**P50%**	P66.7%	P75%	P83.3%	P90%	**P95%**	P97.5%	P99%
Elicited values	0.13					0.30		1.00		1.70					2.65

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EKE results	0.130	0.145	0.175	0.247	0.36	0.52	0.69	1.08	1.53	1.77	2.04	2.28	2.47	2.58	2.65
Fitted distribution	BetaGeneral (0.8012, 1.1711, 0.123, 2.715) was adopted after review of the best fit. After applying the maximum uncertainty assumption (1st & 3rd quartiles set to the midpoints) the fitted distribution was accepted as representing the judgements of the experts														

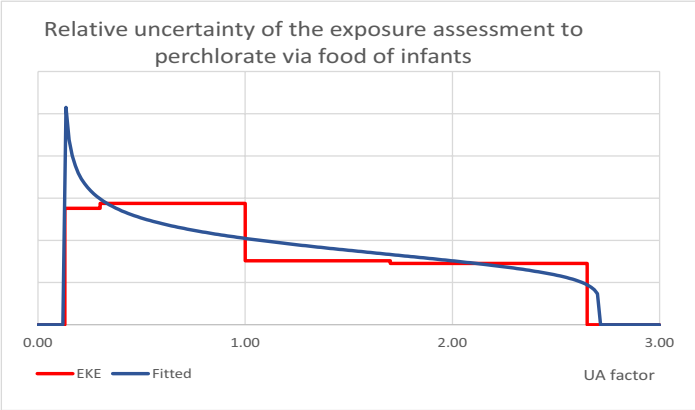

Figure (a): Comparison of elicited and fitted values/density function to describe the remaining uncertainties of the parameter

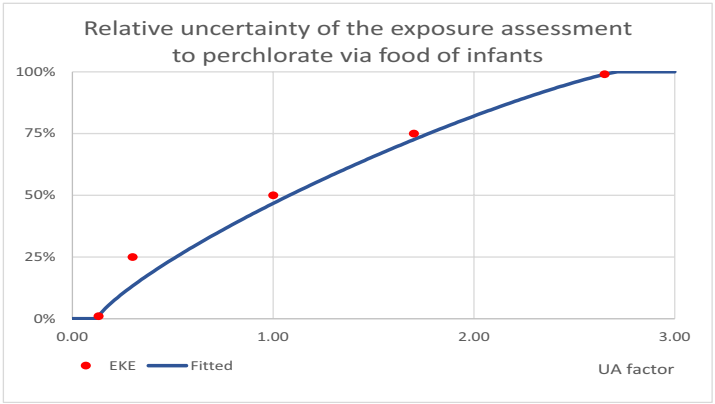

Figure (b): Cumulative distribution function (CDF) of the likelihood of the parameter

Summary of the evidence used for the evaluation

- Exposure calculations using the EFSA concise food consumption database and reported measurements of perchlorate. Broad coverage of measurements along the diet of infants, toddlers and other age classes.
- Different scenarios to estimate the effect of the uncertainties, e.g. LB–UB for left-censored data, differences in national consumption habits, handling of food categories with high proportion of left-censored data.

Main uncertainties

- Assumptions made to extrapolate contaminations of composite food from main ingredients may be incorrect.
- High proportion of left-censored data in some food categories.

Reasoning for a scenario which would lead to a reasonable high proportion	The judgement on the upper limit considers • The calculations done to estimate the worst-case scenario.
Reasoning for a scenario which would lead to a reasonable low proportion	The judgement on the lower limit considers • The calculations done to estimate the best-case scenario.
Fair estimate as judgement on the weighted evidence	The judgement on the median considers that • The data available don't indicate a (major) bias.
Precision of the judgement as description of remaining uncertainties	The judgement on the interquartile range considers that • The standard LB–UB approach is a valid estimator of the interquartile range/high uncertainties to both sides.
Experts	Kevin J CHIPMAN, Jean-Charles LEBLANC, Francesca RIOLO
Facilitator/Reporter	Olaf MOSBACH-SCHULZ, Elena ROVESTI, Chantra ESKES
Observers	Walid EL SERRY (ANSES), Thorhallur I HALLDORSSON, Tuuli TAURIAINEN
Date and place of the EKE	Virtual, 17 October 2024

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Overview of the results of the Expert Knowledge Elicitation

Parameter	Uncertainty of the exposure assessment to perchlorate via food of the 95th percentile breastfed infants														
Stratification	P95 breastfed infants														
Question	Assuming the ideal situation: (i) that a representative study on European breastfeeding habits is given; (ii) that all concentrations of perchlorate are measured with sufficient quality for quantification of the mean contamination in human milk. How much would the exposure assessment derived from this evidence base differ from the current assessment of the European 95% percentile breastfed infant, expressed in µg/(kg BW*day)?														
Unit	[µg/(kg BW*day)]														
Results	P1%	P2.5%	**P5%**	P10%	P16.7%	P25%	P33.3%	**P50%**	P66.7%	P75%	P83.3%	P90%	**P95%**	P97.5%	P99%
Elicited values	3					5		7		9					11
EKE results	3.00	3.13	**3.35**	3.77	4.32	5.00	5.67	**7.00**	8.33	9.00	9.68	10.2	**10.6**	10.9	11.0
Expressed as factor	0.405	0.423	**0.453**	0.510	0.584	0.676	0.766	**0.946**	1.13	1.22	1.31	1.38	**1.44**	1.47	1.49
Fitted distribution	BetaGeneral (1.049, 1.049, 2.9, 11.1)														

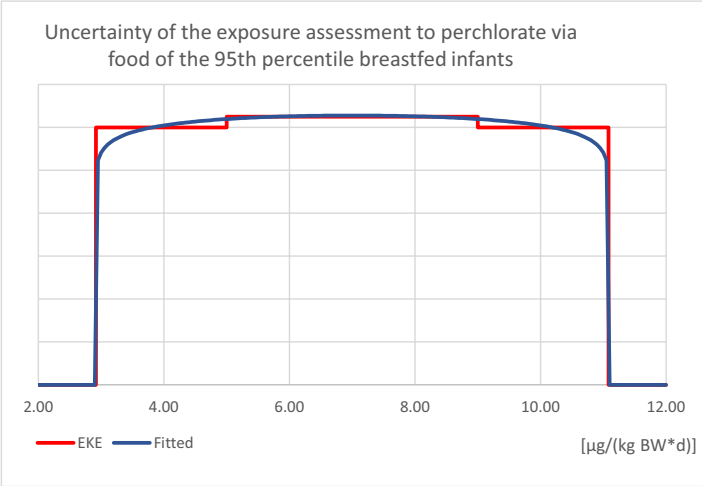

Figure (a): Comparison of elicited and fitted values/density function to describe the remaining uncertainties of the parameter

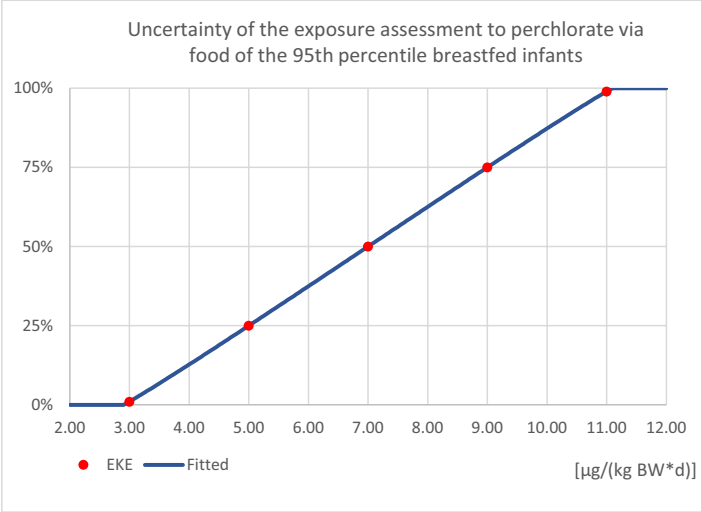

Figure (b): Cumulative distribution function (CDF) of the likelihood of the parameter

Summary of the evidence used for the evaluation

- Exposure (µg/kg bw per day) of breastfed infants to perchlorate based on the mean and highest reliable percentile (99%) concentrations in human milk estimated by the CONTAM Panel using biomonitoring equivalent equation and the mean and high (P95) consumption estimates recommended by the EFSA Scientific Committee (2017).

Main uncertainties

- Correct excretion rate of perchlorate via breastmilk/biomonitoring equivalent equation.
- Interpretation of animal experiments and PBPK models.
- Amount of left-censored data in the dietary exposure assessment of pregnant women.
- Possible difference between the intake of pregnant and lactating women.

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Reasoning for a scenario which would lead to a reasonable high proportion	The judgement on the upper limit considers • High level of excretion via breastmilk (upper limit of the CI). • High intake of perchlorate of pregnant women (Upper bound). • Lactating women may have a higher intake of perchlorate than pregnant women (less importance).
Reasoning for a scenario which would lead to a reasonable low proportion	The judgement on the lower limit considers • Low level of excretion via breastmilk (lower limit of the CI). • Lower values are confirmed by animal experiments and PBPK calculation. • Low intake of perchlorate of pregnant women Lower bound). • Lactating women may have a lower intake of perchlorate than pregnant women (less importance).
Fair estimate as judgement on the weighted evidence	The judgement on the median considers that • No tendency for lower or higher values in the credible interval.
Precision of the judgement as description of remaining uncertainties	The judgement on the interquartile range considers that • High uncertainty above and below the median.
Experts	Laurent BODIN, Kevin J CHIPMAN, Gisela DEGEN, Aleksandra Buha DJORDJEVIC, Jean-Charles LEBLANC, Tuuli TAURIAINEN
Facilitator/Reporter	Olaf MOSBACH-SCHULZ, Elena ROVESTI, Chantra ESKES
Observers	Mary GILBERT, Walid EL SERRY, Paschalina PAPADAKI, Francesca RIOLO
Date and place of the EKE	Virtual, 22 November 2024

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ANNEX A

Protocol for the development of the opinion

The protocol undertaken for the scientific development of this Opinion is available under the Supporting Information section on the online version of the scientific output.

ANNEX B

Occurrence data and exposure results

The occurrence data after data cleaning and exposure assessment results are available on EFSA's Knowledge Junction Community on Zenodo at: https://doi.org/10.5281/zenodo.15324284

ANNEX C

Risk of Bias analysis

Results of the risk of bias analysis are available under the Supporting Information section on the online version of the scientific output.

ANNEX D

Output of the Public Consultation

The output of the public consultation on the draft update of the Scientific Opinion on the risks for human health related to the presence of perchlorate in food is available under the Supporting Information section on the online version of the scientific output.

ANNEX E

Raw occurrence data

The raw occurrence data on perchlorate in food extracted from EFSA Data Warehouse on the 4th of June 2024 and sampled between years 2016 and 2022 are available on EFSA's Knowledge Junction Community on Zenodo at: https://doi.org/10.5281/zenodo.15324284

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