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SCIENTIFIC OPINION

Scientific Opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables[1]

EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

This Scientific Opinion, published on 26 May 2015, replaces the earlier versions published on 17 October 2014 and 4 December 2014*.

ABSTRACT

The European Food Safety Authority (EFSA) received a request from the European Commission for a scientific opinion on perchlorate in food, in particular fruits and vegetables. Perchlorate is a contaminant released into the environment from both natural and anthropogenic sources. The use of natural fertilisers and perchlorate contaminated irrigation water may lead to substantial concentrations in leafy vegetables. Water disinfection with chlorinated substances that potentially degrade to perchlorate could be another potential source of contamination. EFSA received analytical results for 11 675 samples submitted by eight Member States, mainly for fruits, vegetables, and fruit and vegetable products. The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) performed estimates of both chronic and 'short-term' exposure considering the available dataset, and data from the literature on the levels of perchlorate in fruit juices, alcoholic beverages, milk, infant formulae and breast milk. The CONTAM Panel established a tolerable daily intake of 0.3 µg/kg body weight per day, based on the inhibition of thyroid iodine uptake in healthy adults. Amongst the vulnerable subpopulations, potential acute effects of perchlorate have been suggested for fetuses and infants. 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. Overall, the

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* In the version published on 4 December 2014, corrections were made to the summary, main body of the text and conclusions on the occurrence levels for 'leafy vegetables', and the median chronic exposure levels in Table 6.
In the version published on 26 May 2015, amendments were made to the abstract, summary, introduction, exposure assessment, risk characterisation, uncertainty analysis, conclusions, recommendations and appendices in order to correct an error in the original occurrence data and to include more recent occurrence data. Further details are available on page 11. The previous versions of the scientific opinion have been removed from the website, but are available on request as are versions showing all the changes made.

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CONTAM Panel concluded that the chronic dietary exposure to perchlorate is of potential concern, in particular for the high consumers in the younger age groups of the population with mild to moderate iodine deficiency. Furthermore, it is possible that exposure to perchlorate is of concern for infants breast-fed by iodine-deficient mothers.

KEY WORDS
perchlorate, human dietary exposure, toxicity, risk assessment, benchmark dose (BMD), tolerable daily intake (TDI)

SUMMARY

Following a request from the European Commission, the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) was asked to deliver a scientific opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables. Perchlorate (ClO_4^-) is a chemical contaminant which is released in the environment from both natural and anthropogenic sources. Biomonitoring studies show the presence of background levels of perchlorate in the general population, suggesting that it is likely a ubiquitous environmental contaminant. Different sources of contamination were identified. These include the use of fertilisers of natural origin in which perchlorate may be present, such as Chilean nitrate; industrial emissions of perchlorate into the environment, in particular resulting from the use of ammonium perchlorate in solid propellants for rocket and missiles; the natural formation of perchlorate in the atmosphere and surface water, and the formation of perchlorate during the degradation of chlorine-based products such as sodium or calcium hypochlorite. While industrial emissions are not expected to represent a main and widespread source of contamination in Europe, the use of natural fertilisers such as Chilean nitrate may lead to substantial concentrations in fruit and vegetables, due to the efficient uptake via the plant roots. Similarly, plant irrigation with perchlorate-contaminated groundwater can contribute to accumulation of perchlorate in fruit and vegetables. Water disinfection with chlorine-based biocidal products, potentially degrading to perchlorate, could be another notable source of contamination for drinking water and food. Additional sources of contamination, such as the use of chlorine-based products in biocidal applications other than water disinfection and plant protection applications and the natural formation of perchlorate in the atmosphere and in surface water, could marginally contribute to the presence of perchlorate in food and drinking water.

Perchlorate has been reported to occur in a wide range of foods, including vegetables, fruit, milk and dairy products, juice, beer, wine and bottled water. In a recent assessment from 2010, the Joint FAO/WHO Committee on Food Additives (JECFA) reviewed the available occurrence data and observed the highest mean concentrations in vegetables (range of means 4.8–110 µg/kg), fruits (range of means 0.5–28 µg/kg), vegetable and fruit juice (26 µg/kg) and infant formulae (10 µg/kg).

EFSA received the analytical results of 11 675 samples submitted by eight Member States, of which about 20 % were considered to be suspect samples. (Suspect sampling is defined as a selection of an individual product or establishment in order to confirm or reject a suspicion of non-conformity. It is not a random sampling, therefore there is no sample extracted from the population.) The majority of the samples belonged to the food groups 'Vegetables and vegetable products' and 'Fruits and fruit products'. Excluding the suspect samples, the highest mean perchlorate concentrations were observed in turnips (350 µg/kg, upper bound (UB)) and in lettuce, excluding Iceberg-type lettuce (120 µg/kg, UB). For all other 'Vegetables and vegetable products' the mean concentration was below 70 µg/kg. For 'Fruits and fruit products' the mean concentration ranged from < limit of detection to 12 µg/kg.

In addition to the data submitted to EFSA, occurrence data from the literature on 'Infant formulae, powder', 'Infant formulae, liquid', 'Milk and dairy products', 'Alcoholic beverages' and 'Fruit juices' and breast milk were used in the exposure assessment.

The CONTAM Panel performed the exposure assessment of perchlorate using a chronic and a 'short-term' exposure scenario. The latter scenario was developed to take into account the possibility of being exposed to relatively high levels of perchlorate for a short period, e.g. two to three weeks, considering that higher levels of thyroid iodine uptake inhibition for short periods could induce adverse effects in vulnerable groups of the population, such as breast-fed infants and young children with low iodine intake. Higher exposure over such periods is plausible for people living in areas where local produce contains higher levels of perchlorate.

The CONTAM Panel concluded that adverse effects following a single-day exposure to perchlorate at levels relevant for dietary exposure are not expected in any group of the population and therefore no acute exposure estimation was carried out.

Only the scenario excluding the suspect samples was considered appropriate to characterise the risk from chronic perchlorate exposure.

The mean chronic dietary exposure ranged from 0.04 to 0.20 µg/kg body weight (b.w.) per day (minimum lower bound (LB)-maximum UB) in adolescents and adult age classes. For 'other children' and 'toddlers', the mean chronic dietary exposure ranged from 0.07 to 0.37 µg/kg b.w. per day and 0.18 to 0.50 µg/kg b.w. per day (minimum LB-maximum UB), respectively. For 'infants', only two consumption surveys were available, resulting in mean chronic dietary exposure of 0.13–0.54 µg/kg b.w. per day (minimum LB-maximum UB). The 95th percentile chronic dietary exposure ranged from 0.10 to 0.51 µg/kg b.w. per day (minimum LB-maximum UB) in 'adolescents' and adult age classes. For 'other children' and 'toddlers' the 95th percentile chronic dietary exposure ranged from 0.19 to 0.72 µg/kg b.w. per day and 0.34 to 0.97 µg/kg b.w. per day (minimum LB-maximum UB), respectively. For infants, the 95th percentile chronic dietary exposure could be calculated for only one consumption survey, resulting in exposure of 0.32–0.61 µg/kg b.w. per day (LB-UB).

'Vegetables and vegetable products' and 'Milk and dairy products' were identified in the chronic exposure assessment as the most important contributors to perchlorate exposure in all age groups.

Based on mean concentrations of perchlorate in breast milk from the USA, the dietary exposure of breast-fed infants with a mean milk consumption ranged from 0.76 to 4.3 µg/kg b.w. per day, and for infants with a high milk consumption ranged from 1.1 to 6.5 µg/kg b.w. per day. The relevance of these data for the European Union is unknown.

For the short-term exposure the CONTAM Panel considered scenarios excluding and including the suspect samples.

For the scenario excluding suspect samples, the estimations of mean 'short-term' dietary exposure to high percentile levels of perchlorate ranged from 0.38 to 1.9 µg/kg b.w. per day in adolescents and adult age classes, and from 1.5 to 2.7 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only two consumption surveys were available resulting in an exposure of 1.2 and 1.5 µg/kg b.w. per day. The highest mean 'short-term' dietary exposure level of 3.0 µg/kg b.w. per day was estimated in the age class 'other children'. The 95th percentile 'short-term' dietary exposure levels ranged from 0.94 to 4.6 µg/kg b.w. per day in adolescents and adult age classes, and from 3.6 to 6.2 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only one consumption survey was available resulting in an exposure of 3.8 µg/kg b.w. per day. The highest 95th percentile 'short-term' dietary exposure level of 7.2 µg/kg b.w. per day was estimated in the age class 'other children'.

For the scenario including suspect samples, the estimations of mean 'short-term' dietary exposure to high percentile levels of perchlorate ranged from 0.54 to 5.0 µg/kg b.w. per day in adolescents and adult age classes, and from 2.2 to 4.4 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only two consumption surveys were available resulting in an exposure of 1.5 and 2.3 µg/kg b.w. per day. The highest mean 'short-term' dietary exposure level of 5.3 µg/kg b.w. per day was estimated in the age class 'other children'. The 95th percentile 'short-term' dietary exposure levels ranged from 1.3 to 14 µg/kg b.w. per day in adolescents and adult age classes, and from 4.5 to 9.4 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only one consumption survey was available resulting in an exposure of 5.7 µg/kg b.w. per day. The highest 95th percentile 'short-term' dietary exposure level of 18 µg/kg b.w. per day was estimated in the age class 'other children'.

For all age groups, the 'short-term' exposure estimates under the scenario in which suspect samples were included were higher compared to the scenario in which suspect samples were excluded. The use of the suspect samples increased the 'short-term' mean exposure estimates in infants and toddlers by up to 64 % and the 95th percentile by up to 53 %. For all other age groups, the inclusion of suspect samples resulted in 'short-term' mean exposure estimates that were from 32 to 163 % higher and the

95th percentile exposure estimates that were from 21 to 227 % higher compared to the scenario excluding the suspect samples.

Perchlorate is readily and extensively absorbed from the gastro-intestinal tract in humans and rats. Following absorption, it is widely distributed in the body with the highest concentrations occurring in the thyroid, and it is rapidly excreted mainly in the urine as unchanged parent compound. Following the repeated exposure of rodents to perchlorate, findings included changes in thyroid hormones and thyroid stimulating hormone (TSH) levels and thyroid weight increases. Histopathological findings were also observed in the thyroid (colloid depletion, follicular cell hypertrophy and hyperplasia) and mammary gland (mild atrophy, atypia of the lobular epithelium, scattered foci of marked hyperplasic activity). Thyroid tumours were observed following chronic exposure in rats and mice.

In the thyroid of humans and rodents, perchlorate competitively inhibits the uptake of iodine via the sodium-iodide symporter (NIS). Iodine uptake in the thyroid is a key step in the synthesis of thyroid hormones, and its inhibition may result in the disruption of thyroid hormone synthesis and consequently disruption of the homeostasis of the hypothalamic-pituitary-thyroid axis, leading eventually to the development of hypothyroid symptoms. In comparison with rats, healthy adult humans have lower thyroid hormone turnover rates and larger reserves of iodinated thyroglobulin, allowing them to compensate for reduced hormone synthesis in the thyroid. Due to these differences in thyroid hormone physiology, the data from toxicological studies in rats are of limited use for extrapolating to humans. Human fetuses, neonates and individuals with low iodine intake or genetically predisposed to develop hypothyroidism are potentially more susceptible to the effects of exposure to perchlorate.

In humans, severe iodine deficiency as a result of insufficient iodine intake or sustained exposure to goitrogenic substances, such as perchlorate, at levels that induce depletion of the thyroid hormone stores can result in hypothyroidism. However, a mild to moderate iodine deficiency can lead to the development of toxic multinodular goitre and can result in hyperthyroidism.

Potassium perchlorate has been used for the medical treatment of hyperthyroidism at doses ranging from 400 mg/day to 2 000 mg/day (corresponding to 4–20 mg perchlorate ion/kg b.w. per day for a 70-kg person) administered for prolonged periods to control thyroid hormone levels. Adverse effects have been reported following application of potassium perchlorate at doses $\geq$ 400 mg/day, with evidence suggesting a direct relationship between the incidence and severity of the effects and the treatment dose and duration. Studies on healthy adult volunteers repeatedly exposed to 0.007–0.5 mg perchlorate ion/kg b.w. per day for two weeks, as well as information from occupational studies, showed no correlation between the exposure to perchlorate and any adverse effects or changes in the thyroid hormone levels, even at exposure levels associated with a substantial inhibition of thyroid iodine uptake. Retrospective epidemiological studies at the general population level, including the most sensitive subjects, showed contradictory results and found no clear association between exposure to perchlorate and an increased incidence of thyroid dysfunction. The CONTAM Panel concluded that these studies were not of use for the risk assessment of perchlorate.

The CONTAM Panel noted that in its evaluation JECFA considered the inhibition of thyroid iodine uptake of 50 % as the benchmark response (BMR), with the justification that both short-term and chronic exposure to perchlorate in healthy adult volunteer studies had shown that such a level of inhibition is not associated with any changes in TSH or thyroid hormone levels.

The CONTAM Panel concluded that the chronic adaptive changes to compensate for a sustained inhibition of thyroid iodine uptake could lead to long term effects such as the development of multinodular toxic goitre, in particular in populations with mild to moderate iodine deficiency. The CONTAM Panel concluded that a prolonged 50 % inhibition of thyroid iodine uptake by exposure to NIS inhibitory chemicals such as perchlorate may lead to goitre and multinodular toxic goitre, even if short-term exposure does not alter thyroid function tests. Although the consequences of thyroid iodine

uptake inhibition below 50 % is unclear, the CONTAM Panel performed benchmark dose (BMD) modelling on the thyroid iodine uptake inhibition using human dose-response data from the Greer et al. (2002) study, applying a benchmark response of 5 %, which is the default value for continuous data. The CONTAM Panel selected the lowest 95 % lower confidence limit for the BMD response of 5 % extra risk ($BMDL_{05}$) of 0.0012 mg/kg b.w. per day as the reference point and established a total daily intake (TDI) of 0.3 µg/kg b.w. per day by applying an uncertainty factor of 4 to allow for inter human differences in toxicokinetics. No additional uncertainty factors were considered necessary to allow for intraspecies differences in toxicodynamics and for the short duration of the human study.

No data are available on the acute toxic effects of perchlorate in humans. In adults, a single treatment with 1 000 mg potassium perchlorate (10 mg perchlorate ion/kg b.w. for a 70-kg person) is used for diagnostic practice without any adverse effect reported. Amongst the vulnerable subpopulations, potential acute effects of perchlorate have been suggested for fetuses and infants, because they lack the reserve capacity that exists in adult humans and because of the key role of thyroid hormones in fetal and neonatal neurological development. The CONTAM Panel noted that a single-day acute exposure to perchlorate at levels found in food and drinking water is unlikely to cause adverse effects on human health, including the more vulnerable groups of the population. The CONTAM Panel concluded that the establishment of an acute reference dose for perchlorate is not warranted.

The CONTAM Panel considered whether it was possible to identify a level of short-term exposure that would not be expected to cause adverse effects. The CONTAM Panel concluded that short-term exposure for two to three weeks to perchlorate, at levels that are high enough to result in a severe depletion of the thyroid iodine depot, would be critical in breast-fed infants and young children. This would be a particular risk in the case of mild to moderate iodine deficiency. However, such a depletion would be associated with compensatory increases in the activity of the thyroid iodide transporter, and no data are available to evaluate in detail how large the doses of perchlorate would be necessary for such depletion. Therefore, the CONTAM Panel could not establish a short-term health-based guidance value for these populations.

The estimated mean chronic dietary exposure levels for adolescents and the adult age groups did not indicate a health concern when compared with the TDI of 0.3 µg/kg b.w. per day. At the estimated 95th percentile chronic dietary exposure there was an exceedance of the TDI for some surveys. In the younger population groups (‘infants’, ‘toddlers’ and ‘other children’), the TDI was exceeded for both mean (in some surveys) and 95th percentile (in the majority of surveys) exposure estimates. In addition, the estimated exposure for breast-fed infants largely exceeded the TDI. However, the relevance to the European Union is unknown since the estimates for human milk are based on limited literature data from the USA.

Overall, the CONTAM Panel concluded that the chronic dietary exposure to perchlorate is of potential concern, in particular for the high consumers in the younger age groups of the population with mild to moderate iodine deficiency. Furthermore, it is possible that exposure to perchlorate is of concern for infants breast-fed by iodine-deficient mothers and in the short-term for young children with low iodine intake.

The CONTAM Panel recommended that more data should be collected on the occurrence of perchlorate in food in Europe, especially for infant formula, and milk and dairy products. The CONTAM Panel identified the need for biomonitoring data for perchlorate and the associated iodine status in Europe, including data on urine and breast milk, and noted that additional data on the level and duration of thyroid iodine uptake inhibition that has an impact on thyroid hormone levels in the vulnerable subpopulation groups would improve the risk assessment. There is a need for a better understanding of the contribution of various dietary factors to the overall thyroid iodine uptake inhibition.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Perchlorate

The perchlorate ion (ClO_4^-) is very stable in water, and its salts are highly soluble in water. Perchlorate occurs naturally in the environment, in deposits of nitrate and potash, and can be formed in the atmosphere and precipitate into soil and groundwater. It also occurs as an environmental contaminant arising from the use of nitrate fertilizers and from the manufacture, use and disposal of ammonium perchlorate used in rocket propellants, explosives, fireworks, flares and air-bag inflators and in other industrial processes. Perchlorate can also be formed during the degradation of sodium hypochlorite used to disinfect water and can contaminate the water supply. Water, soil and fertilizers are considered to be potential sources of perchlorate contamination in food.

Codex and JECFA

The issue of presence of perchlorate in fruits and vegetables was first raised by the US in Codex Committee on Contaminants and Toxins in Food (CCCF) in 2007. It was agreed to collect occurrence data and in 2008 the CCCF agreed to request a risk assessment by JECFA.

The JECFA performed a risk assessment at its 72nd meeting in Rome in February 2010. JECFA established a PMTDI of 0.01 mg/kg b.w. The estimated dietary exposures of 0.7 µg/kg b.w. per day (highest) and 0.1 µg/kg b.w. per day (mean), including both food and drinking-water, were well below the PMTDI. The JECFA considered that these estimated dietary exposures were not of health concern.

Taking into account the outcome of the risk assessment performed by JECFA, the CCCF decided in 2011 that no follow-up was necessary since no health concern was identified at current estimated levels of exposure from food and drinking water.

Findings in the European Union

When JECFA made the risk assessment in 2010, no or very limited data on the presence of perchlorate in food in particular fruits and vegetables of EU production were available.

At the Expert Committee "Industrial and Environmental Contaminants" on 1 February 2013 the German delegation reported the outcome of a survey in which 178 samples of different foods were analysed for the presence of perchlorate. In 16 samples perchlorate was found. The samples were from fruits and vegetables, including potatoes. The German delegations asked the other EU Member States to perform a monitoring on the presence of perchlorate in food, in particular fruits and vegetables, in order to have a more representative view on the presence of perchlorate in fruits and vegetables across the EU.

The continued monitoring indicated that the presence of perchlorate in fruits and vegetables is more widespread than initially expected. From the preliminary investigations it appears that the use of certain fertilizers containing high levels of perchlorate is an important contributor to the presence of perchlorate in fruits and vegetables. However, also other sources may contribute to the presence. Further investigations are needed to have a better view of the different sources of contamination of food, in particular fruits and vegetables with perchlorate and their relative importance.

In April 2013, two findings resulted in a RASFF notification. The risk assessment was performed by making use of the Pesticide Residue Intake Model (PRIMo) for acute effects applying a variability factor for fruits and vegetables with a high unit weight.

The non-harmonised enforcement approach as regards the presence of perchlorate in food, in particular fruits and vegetables have caused some tension in the market. It was therefore appropriate to agree on a common enforcement approach.

Outcome of the discussions at the Standing Committee on the Food Chain and Animal Health on 1 and 16 July 2013

The following was concluded and/or agreed at the Committee

1) EFSA has to be requested by the European Commission to deliver a scientific opinion on the risk for public health as the consequence of the presence of perchlorate in food and in fruits and vegetables in particular.

   The opinion should address the acute and chronic health effects, the need to establish an Acute Reference Dose (ARfD) and assess the risks for specific vulnerable groups of the populations, in particular young children, pregnant woman and iodine-deficient people.

   The scientific opinion should be available by December 2013.

2) There is a need for having more data across the EU on the presence of perchlorate in food. Member States are therefore requested to monitor the presence of perchlorate in food.

3) It is important to continue the investigations on the cause/sources of contamination with increased levels of perchlorate.

4) A provisional harmonised enforcement approach for the intra-Union trade for the period awaiting the availability of the EFSA opinion was agreed.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Art. 29 (1) (a) of Regulation (EC) No 178/2002 the Commission asks EFSA for a scientific opinion on the risks to human health related to the presence of perchlorate in food, in particular fruits and vegetables.

The scientific opinion as regards the presence of perchlorate in food, in particular fruits and vegetables, should, *inter alia,* comprise the:

a) evaluation of the toxicity of perchlorate for humans, considering all relevant adverse acute and chronic health effects, considering the need to establish any health based guidance value such as Acute Reference Dose (ARfD), Tolerable Daily Intake (TDI), etc.

b) estimation of the dietary exposure (chronic and acute dietary exposure) of the EU population to perchlorate, including the consumption patterns of specific (vulnerable) groups of the population (i.e. high consumers of certain fruits and vegetables, (young) children, pregnant women, iodine deficient people).

c) assessment of the acute and chronic human health risks as the consequence of the presence of perchlorate in food, with particular attention to specific (vulnerable) groups of the population (i.e. high consumers of certain fruits and vegetables, (young) children, pregnant women, iodine deficient people).

EVALUATION

Due to a technical error in the occurrence data used for the estimation of dietary exposure to perchlorate, the Scientific Opinion on perchlorate in food adopted by the CONTAM Panel on 30 September 2014 was revised. In particular, a new assessment of dietary exposure was carried out using the corrected occurrence data and occurrence data that became available after the adoption of the Scientific Opinion on 30 September 2014. The revision of the exposure assessment resulted in corrections in the following sections of the Scientific Opinion: abstract, summary, introduction, exposure assessment, risk characterisation, uncertainty analysis, conclusions, recommendations and appendices.

1. Introduction

Perchlorate is a chemical contaminant which is released into the environment from both natural and anthropogenic sources, and therefore it can contaminate food and drinking water. Since 1986, natural perchlorate at unusually high concentrations has been known to occur in the Chilean nitrate deposits from the Atacama Desert (Dasgupta et al., 2005; Rao et al., 2007). Only more recently it was shown that perchlorate can be formed in the atmosphere (Dasgupta et al., 2005), and that natural perchlorate occurs in soil, sediments, groundwater and surface waters in arid and semi-arid regions (Rao et al., 2007; Plummer et al., 2006; Rajagopalan et al., 2006). Industrial perchlorate production in the USA is mainly dedicated to the production of ammonium perchlorate, which is used as an oxidizing agent in solid propellants for rockets and missiles (Trumpolt et al., 2005). Perchlorate is also used in fireworks, military ordnance, flares, airbags and other applications where an energetic oxidant is required (Brown and Gu, 2006). The manufacturing, testing and disposal of rocket fuel and the demilitarization of weaponry are consequently important sources of perchlorate contamination (Urbansky, 1998; Trumpolt et al., 2005) in the regions where these activities take place. In addition, potassium perchlorate has been used as a pharmaceutical agent for the treatment of thyroid disorders, more precisely the overproduction of hormones caused by an overactive thyroid gland (Trumpolt et al., 2005). Perchlorate can also be formed as a by-product during the degradation of disinfectant agents such as sodium and calcium hypochlorite and chlorine dioxide. Perchlorate may have adverse health effects because it can influence thyroid functions of humans and animals.

1.1. Sources of food contamination

The presence of perchlorate in food and drinking water has been attributed to several natural and anthropogenic sources.

High levels of food and water contamination have been associated with the industrial emissions of perchlorate in the environment, in particular in relation to the use of ammonium perchlorate in solid propellants for rocket and missiles. For example, the historical environmental release of ammonium perchlorate from the manufacturing, testing and disposal of rocket fuel and the demilitarization of weaponry is considered the main source of contamination of the Colorado River, which resulted in contamination of drinking water in the South West of the USA with levels as high as 820 µg/L detected in surface water in Arizona and up to 100 µg/L detected in water supplying public water systems in California (Urbansky, 1998; Brandhuber et al., 2009). Similar cases of water contamination related to industrial release of perchlorate are reported in Israel where contamination of groundwater with perchlorate concentrations around 300 µg/L was reported (Amitai et al., 2007).

Another anthropogenic source identified is related to the use of fertilisers of natural origin, in which perchlorate may be present. The well-known example is Chilean nitrate, which may contain up to 1.5 % perchlorate and which has been used in fertilizers throughout the world (Susarla et al., 1999). Despite the fact that the commercial production of synthetic nitrogen fertilizers has led to a decreased use of Chilean nitrate as a major component of fertilisers, research has shown that fertilizers and fertilizer components not derived from Chilean nitrate can also contain traces of perchlorate (Susarla et al., 1999).

The European Food Safety Authority (EFSA) received in the summer of 2013 perchlorate occurrence data from Member States through the European Commission (EC). These included analytical results from 142 soil samples (from Germany and the Netherlands) and 101 fertiliser samples (from Germany). All samples were collected in 2013. Limits of detection (LOD) and quantification (LOQ) ranged in soil from 3.3 to 16.3 µg/kg and from 10 to 50 µg/kg, respectively. The soil samples had a mean concentration of 150 µg/kg (lower bound (LB) = upper bound (UB)). The concentration ranged from < LOD to 2 200 µg/kg and 30 % of the samples were left-censored (below the LOD/LOQ). The LOD and LOQ ranged in fertilizers from 0.003 to 0.33 mg/kg and from 0.01 to 1 mg/kg, respectively. The fertiliser samples had a mean concentration of 100 mg/kg (LB = UB). The concentration ranged from < LOD to 2 300 mg/kg and 61 % of the samples were left-censored. These occurrence data confirm the occurrence of perchlorate in soil and fertilisers used in Europe. The European stakeholder organisation, Fertilizer Europe, reported on 2 December 2013 at a meeting of the Working Group Fertilizers,[4] that after concern about perchlorate concentrations in food were raised following the Rapid Alert System for Food and Feed (RASFF) notifications in spring 2013, all Fertilizer Europe members commercialize only fertilizers containing up to 100 mg/kg of perchlorate (Fertilizer Europe, 2013). In September 2014, a report was issued on the screening of the presence of perchlorate in fertilizers present on the European market. In total, 192 samples were analysed and all samples had perchlorate levels below 100 mg/kg (SGS, 2014).

The knowledge centre for sustainable horticulture (Kenniscentrum voor Duurzame Tuinbouw, KDT) in Belgium conducted preliminary research in about 20 horticultural establishments. Without confirmation by statistical analysis, there appears to be a relationship between the perchlorate level in fertilizers and the perchlorate level in samples of lettuce grown in greenhouses. Additionally, a relationship was observed between the perchlorate level in the soil and the perchlorate level in samples of lettuce grown in greenhouses (De Blaiser R, 2014, personal communication).

The presence of perchlorate in soil and groundwater, as a result of industrial emissions or the use of fertilisers containing perchlorate is a relevant route for the presence of perchlorate in vegetables due to its rapid uptake via plant roots. Plants that grow on contaminated soil or are irrigated with contaminated water can accumulate perchlorate mainly in their leaf tissue. Jackson et al. (2005) studied the uptake of perchlorate via the roots and accumulation in edible crops and observed a high bioconcentration of perchlorate in the transpiration tissue of soybean leaves and pods, tomato leaves, alfalfa, and wheat stems and heads (bioconcentration factor[5] ranged from 40 to 620). Perchlorate was also detected in soybean seeds and tomato, cucumber and cantaloupe fruits but with a lower bioconcentration (bioconcentration factor ranged from 1.6 to 20). The detected concentration of perchlorate in the plant depends on the plant variety, the perchlorate concentration in the soil, the season, the stage of plant maturity and the level of external nutrients (Yu et al., 2004; Yifru and Nzengung, 2007).

In the USA, the results of large biomonitoring studies demonstrated the presence of background levels of perchlorate in urine of a large part of the population, suggesting that perchlorate is likely a ubiquitous environmental contaminant. Although the information for the European population is more limited, recent studies confirm this hypothesis (see Section 5.3.2). Since the ubiquitous presence of perchlorate cannot be directly correlated with the main sources identified, research has been undertaken to identify other potential sources.

Evidence suggests that perchlorate can form naturally as result of environmental processes, including photochemical reactions or oxidation with ozone of chlorinated species in water (Kang et al, 2006, 2008; Rao et al., 2010), or from long term atmospheric deposition in particular in arid and semi-arid regions (Rao et al., 2007). Although the processes leading to atmospheric formation of perchlorate are

[4] The Working Group Fertilizers is composed of representatives of the competent authorities of Member States and is chaired by the European Commission.

[5] Bioconcentration factor is the ratio of the perchlorate concentration in the plant tissue (on a fresh weight basis) to the estimated or measured perchlorate concentration in the groundwater (Jackson et al., 2005).

not known, it has been hypothesised that chloride, transported into the atmosphere from the sea or from chloride-containing compounds, can be converted to perchlorate by means of photochemical reactions with atmospheric ozone or by atmospheric lightning (Dasgupta et al., 2005; Trumpolt et al., 2005). The Federal Office of Consumer Protection and Food Safety (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL) in Germany analysed perchlorate in 15 rain samples and all results were below the LOD of 0.1 µg/L (BVL, 2013). Dasgupta et al. (2005) detected perchlorate in rain (17 out of 24 samples, concentrations ranging from below the LOD of 0.01 µg/L to 1.6 µg/L) and in snow (two out of four samples, concentrations of 0.2 and 0.4 µg/L) collected in Texas (USA). The atmospheric formation of perchlorate could contribute to the overall contamination of vegetables via both surface deposition and uptake from soil and groundwater.

The formation of perchlorate as a by-product during the degradation of chlorine-based disinfectants has also been considered as a potential source of contamination. Sodium and calcium hypochlorite and chlorine dioxide are commonly used for disinfecting purposes, including disinfection of water intended for human consumption. In 2005, the Massachusetts Department of Environmental Protection (MDEP) reported significant levels of perchlorate in commercial solutions of sodium hypochlorite used for water disinfection (levels ranging from 260 to 6 750 µg/L were measured, with concentrations of perchlorate increasing with time of product storage) (MDEP, 2005). MDEP concluded that these levels could result in a concentration of 0.2–0.4 µg/L in drinking water. Further studies were performed to confirm these results. Greiner et al. (2008) analysed chemicals used for water disinfection collected from 102 different manufacturing locations. Perchlorate was detected in more than 91 % of the hypochlorite samples (levels ranging from 0.03 to 29 µg/L) and 19 % of sodium hydroxide samples (0.01–0.12 µg/L). The perchlorate levels increased as the hypochlorite solutions aged. Moreover, Greiner et al. (2008) noted a higher formation of perchlorate in concentrated solutions of hypochlorite than in diluted solutions. Stanford et al. (2011) confirmed these findings and estimated that the formation of perchlorate is reduced by a factor of 7 or a factor of 36, when a 2 M solution of hypochlorite is diluted to 1 or 0.5 M, respectively. In addition, Stanford et al. (2011) noted an increased decomposition of hypochlorite to perchlorate at temperatures > 15 °C and a pH < 11. Although the formation of perchlorate from the degradation of chlorine dioxide is plausible, no evidence of this reaction is available in the literature (Brown and Gu, 2006).

Sodium and calcium hypochlorite can also be applied in the disinfection of surfaces and equipments in food and feed preparation areas, and this use has been listed in the product types[6] under evaluation in the Directive 98/8/EC[7] on biocidal products. During the disinfection of the surfaces in contact with foods such as fruits and vegetables, the disinfectant solution is typically sprayed on the surface or the surface is washed with disinfectant solution (WHO, 1998). Hypochlorite concentrations used in disinfection of food processing equipments are typically in the range 50 to 200 mg/L with a contact time of 1–2 minutes. In the USA, the highest concentration permitted to be used for disinfecting equipment for fruit and vegetable processing is 200 mg/L (WHO, 1998). Hence, the potential presence of perchlorate in sodium and calcium hypochlorite used in disinfection of food production areas could eventually lead to food contamination. However, current practices for disinfection of food and feed production areas include rinsing the surfaces with potable water to remove excess disinfectant after contact (ECHA, personal communication), and this is expected to minimise the amount of perchlorate in contact with food and feed.

Finally, hypochlorite and chlorine dioxide are also used for direct food disinfection outside the European Union (EU). The analysis of leafy vegetables, originally contaminated with perchlorate at levels ranging from 6.2 to 56.7 µg/kg and rinsed or sprayed with solutions of sodium hypochlorite containing from 12 to 120 mg/L perchlorate, showed that the treatment with hypochlorite did not

[6] Product type 4 as defined by Directive 98/8/EC is for biocidal products used for the disinfection of equipment, containers, consumption utensils, surfaces or pipework associated with the production, transport, storage, or consumption of food, feed or drink (including drinking water) for humans and animals.

[7] Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market. OJ L 123, 24.4.98, p. 1–63.

significantly increase the levels of contamination (Sanchez et al., 2009). In the EU, direct disinfection of foods with chlorinated products is prohibited. Only potable water is allowed to be used to decontaminate food as stipulated in Regulation (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004.[8] However, chlorinated products are applied to control the microbiological quality of water used in processing of food of non-animal origin in some EU Member States (EFSA BIOHAZ Panel, 2014).

Sodium hypochlorite has also been approved as an active substance used in plant protection products[9] and its use has been evaluated for mushrooms (currently the default maximum residue level (MRL) is 0.01 mg/kg).[10] In this application sodium hypochlorite is used in the irrigation water from the first appearance of mushrooms until they are pea-sized.

This Scientific Opinion does not deal with the illicit use of chlorine disinfectants in food production.

1.1.1. Conclusions

Perchlorate can enter food and drinking water via the environment, resulting from both anthropogenic and natural sources. Historical industrial emission of perchlorate, in particular in relation to the use of ammonium perchlorate in solid propellants for rocket and missiles, is a well known source of food and water contamination. However, this is not expected to represent a main and widespread source in Europe. The use of natural fertilisers, such as Chilean nitrate, may lead to substantial concentrations in fruits and vegetables, due to the efficient uptake of perchlorate via the plant roots. Similarly the irrigation of the plants with perchlorate-contaminated ground water (well water) can contribute to the perchlorate accumulation in the fruits and vegetables. The natural formation of perchlorate in the atmosphere and in surface water could also contribute to its presence in food and water. The currently available information does not allow conclusions on the contribution of the naturally formed perchlorate in the atmosphere and in surface water to the overall contamination of food and drinking water. However, this is expected to be a minor source. Chlorinated substances used for water potabilisation purposes, particularly sodium and calcium hypochlorite, can degrade to perchlorate. Hence, the wide use of drinking water in food production and preparation can lead to the presence of perchlorate in various foods and beverages. Furthermore, if drinking water is used for irrigation and watering, it could be an additional source of perchlorate contamination in fruits and vegetables. Only minor, if not negligible, contributions are predictable from the application of sodium and calcium hypochlorite in the disinfection of food preparation areas and from other applications such as biocidal or plant protection products.

1.2. Chemistry of perchlorate

The perchlorate ion (ClO_4^-; molecular weight: 99.45) consists of one chlorine atom surrounded by four oxygen atoms in a tetrahedral geometry (Brown and Gu, 2006) (Figure 1). The oxidation state of the chlorine atom is +7, which is the highest oxidation state of this element and perchlorate is consequently a strong oxidizing agent (Brown and Gu, 2006). However, perchlorate reduction is extremely slow and can usually only be observed in concentrated strong acids (Urbansky, 2002). Perchlorate is unreactive as a ligand and its salts are very soluble, even in organic solvents (Urbansky, 1998).

[8] Regulation (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foodstuffs. OJ L 139, 30.4.2004, p. 1–54.

[9] Commission implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 1–186.

[10] EU Pesticides database: http://ec.europa.eu/sanco_pesticides/public/index.cfm?event=homepage&CFID=177582&CFTOKEN=94340452&jsessionid=08a02718bcb7dcb84e27595c596b6f1b7884TR

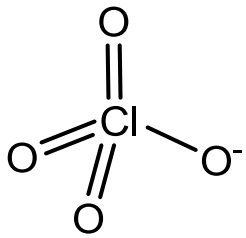


Figure 1: Perchlorate ion

1.3. Previous risk assessments

The United States Environmental Protection Agency (US-EPA) has evaluated the human health risk of perchlorate several times since 1992 and the most recent evaluation is from 2005. This evaluation was based on a review of the health implication of perchlorate ingestion by the National Research Council (NRC) of the National Academies (NRC, 2005), in which an oral reference dose (RfD) of 0.7 µg/kg body weight (b.w.) per day was recommended. The RfD is defined as an estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (US-EPA, 2005). The RfD is based on a no-observed-effect level (NOEL) of 7 µg/kg b.w. per day for perchlorate-induced inhibition of thyroid iodine uptake from a human clinical 14-day study in healthy adult volunteers by Greer et al. (2002). An uncertainty factor of 10 was applied for intra-human variability to protect the most sensitive population groups, namely fetuses of pregnant women who might have hypothyroidism or iodine deficiency. In its review, NRC emphasised that the approach for the RfD derivation differed from the traditional approach, since a non-adverse effect was selected as the point of departure. This choice was considered a conservative, health-protective approach. NRC noted that although the point of departure was selected from a study on a small number of subjects, the NOEL is consistent with other human volunteer studies on thyroid iodine uptake inhibition by perchlorate. NRC estimated that to cause declines in thyroid hormone production that would have adverse health effects in healthy adults, iodine uptake would most likely have to be reduced by at least 75 % for months or longer, and concluded that a sustained exposure to 0.4 mg/kg b.w. per day would most likely be required to cause a sufficient decline in iodine uptake and thyroid hormone synthesis to result in adverse effects in healthy adults. Regarding the applied uncertainty factors, NRC recommended no additional uncertainty factors for the subchronic-to-chronic extrapolation and the adequacy of the database, based on the nature of the selected point of departure. Subsequently, US-EPA adopted the RfD of 0.7 µg/kg b.w. per day (US-EPA, 2005).

In 2004, the Office of Environmental Health Hazard Assessment (OEHHA) from the California Environmental Protection Agency developed a public health goal[11] of 6 µg/L for perchlorate in drinking water. This was based on a lower 95 % confidence limit for a benchmark response of 5 % extra risk ($BMDL_{05}$) of 3.7 µg/kg b.w. day for perchlorate-induced inhibition of thyroid iodine uptake in humans derived from the study of Greer et al. (2002). In 2012, the OEHHA derived an acceptable daily dose (ADD) of 0.37 µg/kg b.w. per day based on the $BMDL_{05}$ of 3.7 µg/kg b.w. day derived from the study of Greer et al. (2002) and an uncertainty factor of 10 for intra-human variability (OEHHA, 2012). The ADD is defined as the estimated maximum daily dose that can be consumed by humans for an entire lifetime without adverse effects. Based on this assessment, a revised public health goal of 1 µg/L was proposed for drinking water.

[11] Public health goals are established by the Californian EPA's Office of Environmental Health Hazard Assessment (OEHHA). They are concentrations of drinking water contaminants that pose no significant health risk if consumed for a lifetime, based on current risk assessment principles, practices, and methods. Available at: http://www.cdph.ca.gov/certlic/drinkingwater/Pages/MCLsandPHGs.aspx

The Agency for Toxic Substances and Disease Registry (ATSDR) from the US Department on Health and Human Services also adopted the RfD of 0.7 µg/kg b.w. per day as recommended by the NRC in 2005 (ATSDR, 2008).

In 2010, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the health risk of perchlorate and established a provisional maximum tolerable daily intake (PMTDI) of 10 µg/kg b.w. (FAO/WHO, 2011). This was based on the inhibition of iodine uptake studied by Greer et al. (2002). A 95 % confidence limit for a benchmark response of 50 % extra risk ($BMDL_{50}$) of 110 µg/kg b.w. per day was used as the point of departure. A response of 50 % was selected, since such a level of inhibition is not associated with any changes in thyroid-stimulating hormone (TSH) or thyroid hormone levels. An uncertainty factor of 10 for intra-human variability was applied, resulting in a PMTDI of 10 µg/kg b.w. This PMTDI was considered protective of potentially vulnerable population groups such as pregnant women, fetuses, neonates and young infants, those with iodine deficient diets and those with clinical or subclinical hypothyroidism. JECFA used the results from the US Food and Drug Administration (US FDA) total diet study (TDS) for comparison with the PMTDI and concluded that the highest estimate of 0.7 µg/kg b.w. per day for 2-year old children and the mean estimate of 0.1 µg/kg b.w. per day for 14-year old and older adolescents were well below the PMTDI and considered that the estimated dietary exposures were not of health concern.

In 2011, l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) evaluated the health risk linked to the presence of perchlorate ions in drinking water. ANSES used the NOEL for thyroid iodine uptake inhibition of 7 µg/kg b.w. per day from the study by Greer et al. (2002) as the point of departure for the hazard characterisation of perchlorate. An uncertainty factor of 10 for intra-human variability was applied, resulting in an oral toxicological reference value[12] of 0.7 µg/kg b.w. per day. ANSES identified several limitations in the pivotal study used for the hazard characterisation (Greer et al., 2002), namely the low number of subjects per treatment dose, the absence of individuals of potential higher sensitivity (neonates and pregnant women) to the perchlorate effects, the fact that the potential contribution to dietary exposure to perchlorate was not considered in the study, and the fact that no information is available on the selection criteria of the study participants, with particular reference to their serum and urinary iodine levels. In addition, ANSES noted that, on the basis of the available data, the application of a benchmark dose (BMD) approach would have not led to any added value in comparison to the no-observed-(adverse)-effect level (NO(A)EL)/lowest-observed-(adverse)-effect level (LO(A)EL) approach. Based on the established toxicological reference value of 0.7 µg/kg b.w. per day, a limit of 15 µg/L of perchlorate in drinking water was proposed to protect the adult consumer (ANSES, 2011). In 2012, ANSES assessed the risk of adults and infants less than six months old consuming drinking water that has a perchlorate concentration above 15 µg/L and 4 µg/L, respectively. This assessment was based on epidemiological studies on the exposure to perchlorate via drinking water and the changes in thyroid hormones and TSH levels in the most sensitive populations (i.e. pregnant women, fetuses and neonates). ANSES concluded that epidemiological data do not allow conclusions to be drawn on whether there is an association between concentrations of perchlorate in drinking water and the level of TSH. The absence of information regarding the iodine status of the studied populations makes the interpretation of the epidemiological data difficult. Cases of hypothyroidism show that the main concern linked to the deficiency of thyroid hormone production by fetuses and children concerns neurobehavioral development, which can be affected if there is dysfunction of the hypothalamus-hypophysis axis. This dysfunction in children with a mother that had severe hypothyroidism during pregnancy, points to extreme situations with subtle changes of the TSH and thyroid hormone levels that might be attributed to an environmental exposure to perchlorate (ANSES, 2012). In order to give advice on the sampling to monitor the occurrence of perchlorate in fruits and vegetables, ANSES assessed the exposure to perchlorate in 2013 (see Section 3.2), without re-evaluating the toxicological reference value (ANSES, 2013).

[12] Valeur toxicologique de référence (VTR) par voie orale.

Recently, the Bundesinstitut für Risikobewertung (BfR) published an opinion on recommendations on how to perform a consumer risk assessment for perchlorate residues in food (BfR, 2013a). BfR recommended the use of the assessment methodology that is applied for the risk assessment of pesticide residues until further information becomes available that would allow an update of this recommendation. For risk characterisation, BfR applied the PMTDI of 10 µg/kg b.w. established by JECFA for the acute risk assessment. This choice was justified considering that the key step for perchlorate toxicity (inhibition of thyroid iodine uptake) is observed following a single exposure episode, and that adverse effects could occur following a single exposure in sensitive subpopulations (population with low iodine dietary intake, late gestation fetuses and infants). For the exposure assessment, BfR recommended the use of the consumption data and variability factors laid down in the Pesticide Residue Intake Model (PRIMo). In addition, BfR was asked by the German Federal Ministry of Food, Agriculture and Consumer Protection to comment from a health assessment perspective on the proposal made by the EC to allow perchlorate residues of up to 500 µg/kg in fruit and vegetables (BfR, 2013b). Based on a general level of 500 µg/kg in fruit and vegetables, both short- and long-term exposure to perchlorate calculated with the German NVS II-model and the PRIMo model, exceeded the PMTDI of 10 µg/kg b.w. For short-term exposure the highest exposure was observed for the consumption of apple juice resulting in an exposure of 271 % of the PMTDI when assuming a uniform distribution of residues (variability factor 1). The PMTDI for perchlorate was also exceeded for the consumption of a large portion of oranges, grapefruit, orange juice, apples, grape juice, pineapples, potatoes, carrot juice, melons, watermelons and spinach (assuming a uniform distribution of residues). Long-term exposure to perchlorate, from the continuous consumption of median portions of fruit and vegetables containing 500 µg/kg perchlorate, was 53 % of the PMTDI for German adults (14–80 years old), but exceeded the PMTDI for children and an exposure up to 181 % was observed in French infants.

1.4. Dietary reference values for iodine intake

Iodine is an essential element for human nutrition, since it is a necessary constituent of thyroid hormones. The Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) (2004) has established dietary reference values for iodine intake, based on the correlation of mean urinary iodine excretion levels with the incidence of thyroid dysfunctions and hypothyroid related diseases observed in different population groups. In particular FAO/WHO established a dietary reference value of 150 µg/day for adults (corresponding to 2 µg/kg b.w. per day), 90 µg/day for infants and children up to 5 years old (corresponding to approximately 15 µg/kg b.w. per day for newborns and infants up to 11 months and 6 µg/kg b.w. per day for children from 1 to 5 years old), 120 µg/day for 6–12-year old children (4 µg/kg b.w. per day), and 200 µg/day for pregnant women (FAO/WHO, 2004). In 2007 WHO revised the values for pregnant and lactating women, indicating 250 µg/day as the recommended nutrient intake for both population groups (Andersson et al., 2007). WHO also gave criteria to assess the iodine status of a given population, based on the data on urinary iodine levels (see Table 1, De Benoist et al., 2008).

Table 1: WHO classification of iodine nutritional status based on median urinary iodine (UI) excretion (De Benoist et al., 2008)

Population	Median UI excretion (µg/L)	Classification
General population	< 100	Insufficient intake
	100–199	Adequate intake
	200–299	More than adequate intake
	> 300	Excessive intake
Pregnant women	< 150	Insufficient intake
	150–249	Adequate intake
	250–499	More than adequate intake
	> 500	No added health benefit expected.

The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) recently published a scientific opinion on the dietary reference values for iodine (EFSA NDA Panel, 2014). The NDA Panel concluded that, although there is insufficient evidence to derive an average requirement and a population reference intake, it was adequate to establish adequate intake (AI) levels from the relationship between iodine intake and urinary iodine excretion in population groups without signs of thyroid dysfunction demonstrated by a minimal prevalence of goitre. The AIs established by the NDA Panel are in line with the values previously established by FAO/WHO for adults, but different levels were proposed for the younger age groups and for pregnant and lactating women (see Table 2).

Table 2: Summary of adequate intakes of iodine for different population groups (from EFSA NDA Panel, 2014)

Age	Adequate intake (µg/day)
7–11 months	70
1–3 years	90
4–6 years	90
7–10 years	90
11–14 years	120
15–17 years	130
≥ 18 years	150
Pregnancy	200
Lactation	200

1.5. Legislation

There are no maximum levels for perchlorate in water intended for human consumption in the EU. However, some countries outside Europe have set maximum levels for perchlorate in drinking water (FAO/WHO, 2011). For example in January 2009, US-EPA established an Interim Drinking Water Health Advisory level of 15 µg/L for perchlorate in drinking water in the USA to give guidance to the state and the local officials (US EPA, 2008).[13] The US-EPA applied the RfD of 0.7 µg/kg b.w. per day as recommended by the National Research Council for perchlorate in 2005 (NRC, 2005).

The Californian Department of Public Health (CDPH) has set a maximum contaminant level (MCL)[14] of 6 µg/L for perchlorate in drinking water based on the public health goal[11] of 6 µg/L developed by OEHHA.[15]

There are no maximum levels for perchlorate in food in the EU. A provisional harmonised enforcement approach was agreed by the EC's Standing Committee on the Food Chain and Animal Health on 16 July 2013[16] to provide sufficient consumer health protection whilst considering what is feasible and achievable and taking into account good practices and regional differences. These levels were revised on 10 March 2015.[17] Table 3 shows the levels of perchlorate as reference for intra-Union trade that are of application as from 16 March 2015.

[13] http://water.epa.gov/drink/contaminants/unregulated/perchlorate.cfm

[14] Maximum contaminant levels (MCLs) are adopted as regulations by the Californian Department of Public Health (CDPH). They are health–protective drinking water standards to be met by public water systems. MCLs take into account not only health risks of chemicals, but also factors such as their detectability and treatability, as well as costs of treatment. Health & Safety Code §116365(a) requires the CDPH to establish a contaminant's MCL at a level as close to its public health goal as is technologically and economically feasible, placing primary emphasis on the protection of public health. Available at: http://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/MCLsandPHGs.shtml

[15] Available at: http://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/MCLsandPHGs.shtml

[16] Available at: http://ec.europa.eu/food/food/chemicalsafety/contaminants/statement–perchlorate_en.pdf

[17] http://ec.europa.eu/food/food/chemicalsafety/contaminants/docs/statement_perchlorate_in_food_en.pdf

Table 3: Levels of perchlorate as reference for intra-Union trade

Food[(a)]	Level (mg/kg)
Fruits and vegetables with the exception of:	0.1
- *Cucurbitaceae* and leafy vegetables with the exception of:	0.2
celery and spinach grown in glasshouse/undercover	0.5
herbs, lettuce and salad plants, including rucola, grown in glasshouse/under cover	1.0
Dried spices (except dried herbs and paprika), dried hops	0.5
Tea (*Camellia sinensis*), dried	0.75
Herbal and fruit infusions, dried	1.0
Foods for infants and young children - ready-to-eat	0.02
Other food	0.05

(a): The levels as reference values for intra-Union trade applies, insofar not specified, to the unprocessed food. For dried, diluted, processed and compound foodstuffs, Article 2 of Regulation (EC) 1881/2006 is of application.

2. Methods of analysis

Several methods for the analysis of perchlorate are available in the scientific literature, but they were not addressed in this scientific opinion, which focussed only on the one selected as method of preference in the European Commission recommendation. To collect more occurrence data on perchlorate in food and in particular in fruits and vegetables, the European Commission recommended to use the multi-residue method for polar pesticides (Quick Polar Pesticides Method, QuPPe) (Anastassiades et al., 2012; Hepperle et al., 2013). In this method, perchlorate is extracted with acidified methanol and extracts are analysed with liquid chromatography-tandem mass spectrometry (LC-MS/MS). This method has an LOQ of 2 µg/kg in cucumber, apple, barley, orange and tomatoes. Recoveries between 70 and 120 % and relative standard deviations (RSDs) below 10 % were observed in apple and barley (Hepperle et al., 2013).

Isotopically labelled internal standards are commercially available (Anastassiades et al., 2012). Proficiency tests are organised and reference materials from proficiency tests are available for perchlorate in tomato and water melon. No certified reference materials are available.

3. Previously reported occurrence data and dietary exposure assessments

3.1. Previously reported occurrence data

In general, perchlorate has been reported to occur in a wide range of foods such as vegetables and fruit, milk and dairy products, rice, infant formula, fish and fish products, juices, beer, wine and bottled water.

In 2010, JECFA reviewed data from China, India, Japan, the Republic of Korea, Canada and the USA on the occurrence of perchlorate in water and different foods analysed between 2004 and 2009. In 98 % of the samples of groundwater and drinking water (35 073 samples in total of which 34 728 were provided by the USA), the concentration was below the LOD or LOQ (0.02–4 µg/L). For food, 1 866 samples (vegetables, fruit, rice, milk, infant formula, fish and fish products, beverages such as juices, beer and wine) were reviewed and the perchlorate concentration was below the LOD or LOQ in 33 % of the samples. The highest weighted mean perchlorate concentrations were reported for vegetables (range of means 4.8–111 µg/kg), fruit (range of means 0.5–28 µg/kg), vegetable and fruit juices (26 µg/kg) and infant formula (10 µg/kg) (Table 4). JECFA noted that general surveys involving a broader range of foods in different countries were lacking; however, in view of the widespread presence of perchlorate in the environment, it is probable that it will be found more widely in drinking-water and food (FAO/WHO, 2011).

Table 4: Occurrence of perchlorate in food samples from different countries (based on FAO/WHO, 2011)

Food item	n	Weighted mean[(a)] (range)[(b)] µg/L or µg/kg	Reporting countries
Vegetables			
Lettuce	372	11.6	Canada, Japan, USA
Spinach	64	111 (< 1–927)	Canada, USA
Potato	90	4.8	Canada, USA
Tomato	95	14	Canada, USA
Carrot	120	10.5	Canada, USA
Eggplant	60	78	USA
Broccoli	115	19	USA
Cauliflower	68	7	USA
Cabbage	31	10	Japan, USA
Fruits			
Apple	33	0.5	Canada, USA
Grape	39	28	Canada, USA
Orange	50	5	Canada, USA
Melon	98	19	Canada, USA
Other			
Vegetable and fruit juice	53	25.8 (0.047–463.5)	Canada
Honeydew	6	0.3 (0.1–0.66)	Canada
Whole wheat flour	38	3.5	USA
Rice	94	1	China, Japan, USA
Milk	221	6.8	China, Japan, USA
Infant formula (powder)	20	10	China, Japan
Fish and fishery products[(c)]	186	n.r. (0.32–1593)	Japan, USA
Wine	104	6 (0.013–56.9)	Canada, Japan
Beer	144	1.04 (0.005–21.1)	Canada

n: number of samples; n.r.: not reported.
(a): Mean of reported concentrations weighted by the number of samples;
(b): Range of occurrence levels, reported only for some food commodities in the JECFA opinion (FAO/WHO, 2011);
(c): Based on 20 samples from Japan: mean = < 0.8 µg/kg (range: 0.32–71.6 µg/kg) and 166 samples from the USA; original reference: Theodorakis et al. (2006). The high value of 1 593 µg/kg was reported in central stoneroller (mean of three samples with a standard deviation of 335). All fish were collected from a contaminated site in Texas.

To date, most of the research on the occurrence of perchlorate in food and drinking water has been performed in the USA. For Europe, only one Italian study on perchlorate in bottled water, one British study on perchlorate in drinking water and one French study on perchlorate in drinking and bottled water were identified. In addition, two studies on food samples from Turkey are reported in this section, due to the lack of occurrence data from EU Member States, and one Canadian study in which European foods and drinking water were analysed. These studies are described in more detail below.

In Italy, 62 commercially available bottled waters were purchased from various local merchants and analysed for their perchlorate content. Perchlorate was quantified in 44 samples LOQ = 0.005 µg/L, with concentrations in the range 0.006–0.075 µg/L (Iannece et al., 2013).

In the UK, 20 water treatment sites (including five control sites chosen from rural areas with no perceived risk factors nearby and 15 perceived higher-risk sites) were monitored four times in one year. Perchlorate was not detected in untreated water samples from two of the five control sites (LOD of 0.039 µg/L for untreated water), and low concentrations (mean ± standard deviation = 0.096 ± 0.053 µg/L; maximum = 0.188 µg/L) were detected in untreated water samples from the other three control sites. Perchlorate was detected in treated drinking water from all higher-risk sites with a mean concentration of 0.747 µg/L (maximum = 2.073 µg/L) (McLaughlin et al., 2011).

ANSES analysed perchlorate levels in drinking water and bottled water during 2011 and 2012 in France. Water from about 300 water treatment sites was analysed and, in 77 % of the samples of untreated and treated drinking water, the perchlorate concentration was below the LOQ of 0.5 µg/L. The highest detected perchlorate concentration was 22 µg/L in untreated water and 13 µg/L in treated drinking water. In addition, untreated water (n = 142) and treated drinking water (n = 55) from sites with a perceived higher risk were analysed. The perchlorate concentration was below the LOQ in 57 % of the samples, and the highest detected perchlorate concentration was 7.3 µg/L in untreated water and 4.1 µg/L in treated drinking water. All samples of bottled water (n = 78) had a perchlorate concentration below 4 µg/L and four samples had a perchlorate concentration equal to or above the LOQ (concentrations not reported) (ANSES, 2014).

Sungur and Sangün (2011) collected vegetable, fruit, cow milk and water samples from eight different regions of Hatay, which is located on the eastern Mediterranean coast of Turkey. For milk samples, the concentration ranged from 0.3 to 0.94 µg/L with a mean concentration of 0.5 µg/L. For fish, it ranged from 0.38 to 0.61 µg/kg. In fruits and vegetables (cabbage, carrot, grapefruit, lemon, lettuce, mandarin, orange, red cabbage, spinach and tomato), the perchlorate concentration ranged from 0.24 to 1.22 µg/kg. In drinking water, the concentration ranged from 0.31 to 0.97 µg/L.

The same research group also looked at perchlorate concentrations in meat, organs, and milk and dairy products from the same region in Turkey and detected perchlorate in cheese from cow's, goat's and ewe's milk at concentrations between 0.11 and 0.42 µg/kg (n = 29). In milk and yoghurt from the same animal species the perchlorate concentration was between 0.11 and 0.26 µg/kg (n = 3) and 0.24 and 0.45 µg/kg (n = 3), respectively. In cow, goat and sheep meat, the concentration ranged from 0.11 to 0.34 µg/kg and in the organs (spleen, liver, lung, heart and kidney) from the same animal species, the concentration ranged from 0.15 to 0.50 µg/kg (Sungur and Atan, 2013).

In a Canadian study by El Aribi et al. (2006), European beer, wine, fruit and vegetables and bottled water were analysed. In bottled water from France, Germany and Portugal (n = 5) the perchlorate concentration ranged from < LOD to 5 µg/L. In fruits and vegetables (n = 8) the concentration ranged from 0.079 µg/L in oranges from Cyprus to 5.67 µg/L in canned mushrooms from Poland. A concentration of 6.195 µg/L was detected in canned grape leaves from Turkey. In wine (n = 30) and beer (n = 52), the concentrations ranged from 0.029 to 50 µg/L and from 0.005 to 21 µg/L, respectively. Overall, the concentrations observed in European beer and wine were comparable to the concentrations observed in non-European beer and wine.

3.1.1. Infant formula

In order to assess the exposure of infants to perchlorate, the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) evaluated the occurrence data for infant formula published in the scientific literature. No literature data were identified for Europe.

Wang et al. (2011) purchased 39 powdered and liquid infant formulae in retail food outlets in Ottawa, Canada in 2008. In the 19 powdered infant formula samples, perchlorate was quantified in 17 samples (LOQ = 0.95 µg/kg) and the concentration was between 1.37 and 64.5 µg/kg, corresponding to 0.21 and 13.5 µg/L as consumed. Perchlorate was quantified in all 20 liquid infant formula samples at concentrations between 0.74 and 7.17 µg/kg, corresponding to 0.37 and 3.56 µg/L as consumed.

Pearce et al. (2007) analysed 17 brands of liquid infant formula from the USA (one sample per brand) and perchlorate was detected in all samples at concentrations between 0.2 and 4.1 µg/L, as consumed.

Schier et al. (2010) tested different types of powdered infant formulae from the USA after reconstitution. The geometric mean concentrations in bovine milk-based formula, soy-based formula, bovine milk-based lactose-free formula and elemental formula were 1.72, 0.21, 0.27, and 0.18 µg/L, respectively.

In Korean infant formula (n = 5), 9.98 µg perchlorate/kg was detected on average, ranging from 5.21 to 22.6 µg/kg (Lee et al., 2012). No indication was given by the authors regarding the concentration in infant formula as consumed. Also Her et al. (2010) analysed milk-based powdered infant formula from Korea and measured a mean perchlorate concentration of 7.83 µg/kg (n = 26; range = 1.49–33.3 µg/kg). The perchlorate concentration in the reconstituted infant formula was not reported.

3.1.2. Breast milk

No data on perchlorate in breast milk samples from Europe were identified. Four studies on perchlorate concentrations in breast milk from the USA were identified and concentrations between 0.01 and 411 µg/L were reported (see Section 5.3.3 and Appendix D). One study from Chile reported mean perchlorate concentrations between 18 and 96 µg/L (Téllez et al., 2005).

3.1.3. Dietary supplements

In the USA, perchlorate was detected in 20 out of 31 dietary supplements at concentrations ranging from < 3.1 µg/kg to 2 400 µg/kg. Of these 31 dietary supplements, eight were specifically marketed for pregnant women and perchlorate was detected in five of them (concentration range: < 3.2–2 400 µg/kg). Based on the recommended dose the authors estimated that exposure could be as high as 18 µg/day (Snyder et al., 2006).

3.2. Previously reported exposure assessments

The FDA's Center for Food Safety and Applied Nutrition (CFSAN) conducted a preliminary human exposure assessment for perchlorate through the consumption of 27 foods and beverages for which FDA had collected occurrence data between October 2003 and September 2005. These data were collected in regions where water sources are known to be contaminated with perchlorate. It was estimated that the mean and 90th percentile exposure of the total population (all persons aged two years and above) was 0.053 and 0.12 µg/kg b.w. per day, respectively. For children (two to five years), the mean and 90th percentile exposure was 0.17 and 0.34 µg/kg b.w. per day, respectively and for females (15–45 years) was 0.037 and 0.074 µg/kg b.w. per day, respectively. Almost half (47 %) of the perchlorate intake of the total population came from milk, but tomatoes (9 %), fruit juices (8 %) and spinach (8 %) were also important contributors to the mean perchlorate exposure. The FDA also indicated that there were uncertainties linked to this exposure assessment (FDA, 2013).

The FDA conducted a TDS between 2005 and 2006 in which the dietary exposure to perchlorate was estimated (Murray et al., 2008). The total estimated daily exposure levels were calculated for 14 different age/sex groups of the population. Perchlorate was detected in 625 out of 1 065 samples (59 %) and was found in a wide range of foods. The mean dietary exposure to perchlorate was the highest for children aged two years (0.35–0.39 µg/kg b.w. per day, LB-UB), and the lowest for adolescents (14–16 years) and the adult age groups (25–70+ years), for whom it ranged from the lowest LB of 0.08 to the highest UB of 0.14 µg/kg b.w. per day. For infants (6–11 months), the food groups that contributed most to the total estimated exposure to perchlorate were baby food (49 %) and dairy products (32 %). For children (2, 6 or 10 years old), dairy products contributed about half of the mean dietary perchlorate exposure (47–51 %) but fruit (9–15 %) and vegetables (12–16 %) were also important contributors. For adolescents, dairy products were still the highest contributor (29–37 %), but also vegetables contributed between 20 and 23 % to the total estimated perchlorate exposure. Vegetables were the most important contributor (26–38 %) to perchlorate exposure in the diet of adult age groups but dairy products also contributed substantially to the total dietary exposure (17–23 %).

JECFA assessed the exposure during its evaluation in 2010. The committee estimated that dietary exposure to perchlorate ranged from 0.03 to 0.22 µg/kg b.w. (excluding exposure from drinking water) and that milk consumption is an important contributor to the perchlorate exposure (between 7 and 42 %). Additional perchlorate exposure from drinking water could be 0.33 µg/kg b.w. per day (FAO/WHO, 2011).

Based on occurrence data from Turkey, Sungur and Sangün (2011) (see Section 3.1) estimated that the perchlorate exposure from foods and beverages for a 70-kg adult would be 0.0174 µg/kg.

ANSES assessed the dietary exposure to perchlorate based on occurrence data in fruits and vegetables from Germany (n = 779) and Spain (n = 159), and occurrence data in milk from the USA (n = 125). The mean dietary exposure was 0.077–0.083 µg/kg b.w. per day (LB-UB) in adults and 0.130–0.136 µg/kg b.w. per day (LB-UB) in children aged 3 to 17 years. However, ANSES indicated that this is an underestimation since the exposure is based on the occurrence only in fruits, vegetables and milk and other foods and water have not been taken into account. The most important contributors (more than 4 % of the exposure) are milk, tomatoes, spinach, courgettes, lettuce, melons, cucumbers, green beans and clementines (ANSES, 2013).

4. Exposure assessment

4.1. Occurrence of perchlorate in food

EFSA received perchlorate occurrence data from Member States and private companies directly and through the EC. Perchlorate occurrence data were available from eight Member States (Belgium, Germany, Denmark, Spain, France, Italy, United Kingdom and the Netherlands), covering 2011, 2012, 2013 and 2014. Most submitted analytical results for the presence of perchlorate in food originated from Germany and were collected in 2013 and 2014. A private company provided results on 22 samples on water (including 'dam' and 'borehole' water) and fruits collected and analysed in South Africa. These data were excluded from the analysis since they were not considered relevant for the European consumers. A total of 341 analytical results on perchlorate were excluded in a preliminary phase, as they did not refer to foods or beverages but mainly to fertilizers and soil.

LODs and LOQs ranged from 0.1 to 20 µg/kg and from 0. 1 to 50 µg/kg, respectively. The CONTAM Panel noted that not all data providers reported both the LOD and LOQ. One analytical result, related to a sample of garlic, was excluded from the analysis due to an excessive LOD (50 µg/kg) and LOQ (100 µg/kg).

Of the 11 675 remaining food samples (Table 5), 147 samples (mainly on vegetables, fruits and grains, herbs and grain-based products) were specifically reported as suspect samples. Suspect food samples are those that have been taken for analysis based on suspicion of high level of perchlorate,[18] such as grown on soil with high perchlorate containing fertilisers. In addition, data from two data providers presented levels of perchlorate substantially higher than the other data providers for a wide range of food items. A clarification request was sent to both asking a confirmation for a number of possible outliers and about the sampling strategy used. One data provider confirmed that the samples analysed by them were not suspect. Another data provider, presenting the highest perchlorate levels by far, stated: '*The data was provided to us in an anonymous way. So it is not directly possible to receive the information if it is a suspect sample or not. But in general, we know that a huge amount of the samples that we received were suspect samples*'. Based on this clarification the CONTAM Panel decided to consider all samples received from this data provider as suspect samples. In total, 2 231 samples were considered to be suspect samples.

[18] Suspect sampling is defined as a selection of an individual product or establishment in order to confirm or reject a suspicion of non–conformity. It is not a random sampling, therefore there is no sample extracted from the population (EFSA, 2013).

Table 5: The number of analytical results on perchlorate in food per country and year of sampling

Country of sampling	Year of sampling				Total number of samples
	2011	2012	2013	2014	
	Number of samples				
Belgium	0	0	66	0	66
Germany	0	314	4 652	4 518	9 484
Denmark	0	0	0	21	21
Spain	0	0	214	0	214
France	119	267	148	0	534
United Kingdom	0	0	60	132	192
Italy	0	0	324	0	324
Netherlands	0	0	758	82	840
Total	119	581	6 222	4 753	11 675

The suspect samples constitute about 20 % of the occurrence data and are expected to be on average higher than the random samples. The impact of the suspect samples was addressed by considering different scenarios, excluding and including the suspect samples.

Foods were grouped according to the FoodEx food classification system (EFSA, 2011b). Drinking water is reported at the first level of FoodEx whereas some of the vegetables and vegetable products (e.g. 'lamb's lettuce', 'lettuce and excluding Iceberg-type lettuce') were reported at the third level of the FoodEx system.The number of submitted analytical results, the left-censored proportion of the total number (i.e. the proportion of results below the LOD/LOQ) and the range for the left-censored limits according to the different FoodEx food categories are shown in Table 6 under the scenario in which suspect samples were excluded. The same information under the scenario including the suspect samples are reported in Appendix A, Table A1.

The majority of samples in the submitted dataset belonged to the food groups 'Vegetables and vegetable products' and 'Fruits and fruit products'.

Previous exposure assessments (see Section 3.2) have shown that dairy products, infant formulae and fruit juices are important contributors to the dietary exposure to perchlorate. However, limited occurrence data for milk, infant formulae, and fruit and vegetable juices were available in the data submitted to EFSA. Therefore, the CONTAM Panel added literature data and data from previous risk assessments on the occurrence of perchlorate in these food groups to estimate the dietary exposure. In addition, analytical results were identified in the literature for the food group 'Alcoholic beverages' that were used in the exposure assessment.

All analytical results available for 'Grains and grain-based products' were below the LOD. Since in previous assessments this food category has never been identified as a relevant contributor to perchlorate exposure, 'Grains and grain-based products' were excluded from the assessment of exposure.

For infant formulae, the CONTAM Panel identified three studies for which the concentrations in the individual samples were reported (see Section 3.1). From the study by Pearce et al. (2007) and Wang et al. (2011) a mean perchlorate concentration of 1.9–2.1 µg/L (LB-UB) in liquid infant formula was calculated (see Section 3.1, Table 4). From the study by Her et al. (2010) and Wang et al. (2011) a mean perchlorate concentration of 10.6 µg/kg (LB = UB) in powdered infant formula was calculated.

For milk, JECFA collected occurrence results from China, Japan and the USA and used a mean occurrence level of perchlorate in milk of 6.8 µg/kg. The largest dataset of concentrations in

individual samples was the dataset from the USA which contained the analytical results of 125 samples (collected between October 2003 and September 2004) with a mean concentration of 5.8 µg/kg.[19] The CONTAM Panel also used the results from these samples for the exposure assessment.

For 'Fruit and vegetable juices', 14 additional analytical results reported by US FDA with a mean perchlorate concentration of 2.15 µg/L in apple juice and nectar (n = 9) and 2.59 µg/kg in orange juice (n = 5)[19] were included in the dataset used for the exposure assessment.

For 'Alcoholic beverages', analytical results from 77 wine samples originating from 22 different countries (mean concentration 5 µg/L) and 144 beer samples originating from 47 countries (mean concentration 1 µg/L) reported by El Aribi et al. (2006) were added to the occurrence dataset (see Section 3.1, Table 4).

No European occurrence data for breast milk were identified in the literature or submitted to EFSA. Therefore, mean occurrence levels of perchlorate in breast milk reported in the literature (see Section 5.3.1 and Appendix D) were used to assess the exposure of breast-fed infants below six months of age (see Section 4.4).

[19] http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077685.htm

Table 6: Perchlorate occurrence levels under the scenario in which suspect samples were excluded presented according to FoodEx food categories and the proportion of left-censored data (% LC)

FoodEx Level 1	FoodEx Level 2 or 3[(c)]	Number of samples	% LC	Mean perchlorate concentration (µg/kg)		
				Lower Bound	Middle Bound	Upper Bound
Grains and grain-based products[(a)]	Grains for human consumption	87	100	0	1.8	3.6
	Grain milling products	15	100	0	1.1	2.2
	Pasta (Raw)	5	100	0	1	2
	Breakfast cereals	3	100	0	1	2
Vegetables and vegetable products	Vegetables and vegetable products (including fungi)	9	44	15	16	16
	Root vegetables	320	83	3.6	5.8	8.0
	Turnips (*Brassica rapa*)	2	0	350	350	350
	Bulb vegetables	106	97	1.1	3.1	5.1
	Fruiting vegetables	1 745	62	19	21	23
	Brassica vegetables	331	79	8.5	10	12
	Leaf vegetables	675	58	41	43	45
	Lamb's lettuce (*Valerianella locusta*)	166	56	42	43	45
	Lettuce, excluding Iceberg-type lettuce (*Lactuca sativa*)	352	58	120	120	120
	Legume vegetables	42	83	12	14	15
	Stem vegetables (Fresh)	265	93	1.1	3.8	6.6
	Celery (*Apium graveolens* var. dulce)	25	80	12	16	19
	Sugar plants	26	92	1.8	5.8	9.9
	Tea and herbs for infusions (Solid)	17	59	55	56	58
	Peppermint (Mentha × piperita)	4	50	28	29	30
	Vegetable products	4	0	67	67	67
	Fungi, cultivated	141	96	4.3	5.9	7.5
	Fungi, wild, edible	32	94	0.59	1.9	3.1

Table continued overleaf.

Table 6: Perchlorate occurrence levels under the scenario in which suspect samples were excluded presented according to FoodEx food categories and the proportion of left-censored data (% LC) (continued)

FoodEx Level 1	FoodEx Level 2 or 3[c]	Number of samples	% LC	Mean perchlorate concentration (µg/kg)		
				Lower Bound	Middle Bound	Upper Bound
Starchy roots and tubers	Potatoes and potatoes products	191	96	1.8	3.8	5.8
	Other starchy roots and tubers	5	100	0	2.4	4.8
Legumes, nuts and oilseeds	Legumes, beans, green, without pods	134	72	14	15	17
	Legumes, beans, dried	95	89	4.2	5.7	7.1
	Tree nuts	19	100	0	1.1	2.2
	Legumes, beans, green, with pods	8	63	8.4	9.9	12
Fruit and fruit products	Citrus fruits	639	68	8.8	11	12
	Pome fruits	458	100	0.43	2.7	4.9
	Stone fruits	460	97	0.92	3.4	5.9
	Berries and small fruits	1 246	90	2.7	5.0	7.2
	Miscellaneous fruits	624	89	4.8	7.0	9.1
	Dried fruits	107	72	5.7	7.3	9.1
	Jam, marmalade and other fruit spreads	1	100	0	1	2
	Other fruit products (excluding beverages)	24	100	0	1.1	2.2
Milk and dairy products	Milk and dairy products	23	74	4.8	8.5	12
	Liquid milk[b]	148	18	4.9	5.3	5.7
	Concentrated milk	1	100	0	2.5	5
	Cream and cream products	1	100	0	2.5	5
	Fermented milk products	7	100	0	2.5	5
Fruit and vegetable juices	Fruit juice[b]	23	48	1.2	1.7	2.2
	Fruit nectar[b]	13	77	0.47	1.8	3.1
	Mixed fruit juice	1	100	0	1	2
	Vegetable juice	1	100	0	2.5	5

Table continued overleaf.

Table 6: Perchlorate occurrence levels under the scenario in which suspect samples were excluded presented according to FoodEx food categories and the proportion of left-censored data (% LC) (continued)

FoodEx Level 1	FoodEx Level 2 or 3[c]	Number of samples	% LC	Mean perchlorate concentration (µg/kg)		
				Lower Bound	Middle Bound	Upper Bound
Non-alcoholic beverages	Soft drinks	5	80	0.20	0.24	0.28
Alcoholic beverages	Beer and beer-like beverage[b]	144	0	1.0	1.0	1.0
	Wine[b]	114	29	4.0	4.4	4.8
	Alcoholic mixed drinks	1	100	0	5	10
Drinking water	Drinking water	475	82	0.46	0.66	0.86
Herbs, spices and condiments	Herbs	238	34	72	73	74
	Spices	35	51	33	34	35
	Herb and spice mixtures	3	0	75	75	75
Food for infants and small children	Food for infants and small children	90	78	3.5	5.5	7.5
	Infant formulae, powder[b]	75	36	6.6	7.1	7.6
	Follow-on formulae, powder	29	52	2.3	2.8	3.3
	Cereal-based food for infants and young children	20	100	0	1.3	2.6
	Ready-to-eat meal for infants and young children	67	99	0.1	1.8	3.5
	Fruit juice and herbal tea for infants and young children	21	100	0	3	6
	Infant formulae, liquid[b]	56	4	1.9	2.0	2.1
Products for special nutritional use	Dietary supplements	3	100	0	2.5	5
Composite food	Prepared salads	24	88	3.5	5.7	7.9

(a): Excluded from the exposure assessment due to the limited number of samples, to the fact that their results were all left censored, and to the fact that perchlorate is not expected to be present in these foods.
(b): Data from the literature included.
(c): Drinking water is reported at the first level of FoodEx whereas some of the vegetables and vegetable products (e.g. 'lamb's lettuce', 'lettuce and excluding Iceberg-type lettuce') were reported at the third level of the FoodEx system.

4.2. Food consumption

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database) was built in 2010 based on information provided by EU Member States and the food consumption data for children obtained through an EFSA Article 36 project (Huybrechts et al., 2011). The Comprehensive Database version 1 contains results from a total of 32 different dietary surveys (Appendix B, Table B1) carried out in 22 different Member States covering more than 67 000 individuals (EFSA, 2011a). The Comprehensive Database includes individual food consumption data concerning infants (two surveys from two countries), toddlers (eight surveys from eight countries), other children (16 surveys from 14 countries), adolescents (14 surveys from 12 countries), adults (21 surveys from 20 countries), elderly (nine surveys from nine countries) and very elderly (eight surveys from eight countries).

As suggested in the EFSA Guidance on the use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment (EFSA, 2011a), dietary surveys with only one day per subject were not considered to assess chronic intake. Similarly, subjects who participated for only one day in the dietary studies, when the protocol prescribed more reporting days per individual, were also excluded from the exposure assessment. Thus, for the chronic assessment of exposure to perchlorate, food consumption data were available from 26 different dietary surveys carried out in 17 different European countries. Further details on the dietary surveys used for the exposure estimations are given in Appendix B (Table B1).

Within the dietary studies, subjects were classified in different age classes as follows: infants (< 12 months old), toddlers (≥ 12 months to < 36 months old), other children (≥ 36 months to < 10 years old), adolescents (≥ 10 years to < 18 years old), adults (≥ 18 years to < 65 years old), elderly (≥ 65 years to < 75 years old) and very elderly (≥ 75 years old).

Overall, the food consumption data gathered at EFSA in the Comprehensive Database are the most complete and detailed data currently available in the EU. However, it should be pointed out that different methodologies were used in surveys to collect the data and thus direct country-to-country comparisons can be misleading. Similar to what is described for the occurrence data, consumption records are also codified according to the FoodEx classification system. Further details on how the Comprehensive Database is used are published in the Guidance of EFSA (2011a).

4.3. Chronic and 'short-term' exposure estimations in humans

Food consumption data from the Comprehensive Database were combined with perchlorate occurrence levels to assess its dietary exposure in different countries and age groups. All exposure estimates were calculated using SAS software.

Occurrence data are generally related to composite samples, not individual units of a commodity. Therefore, the measured values represent the mean of a number of units and do not reflect the full range of variation occurring in individual units, which needs to be considered for acute assessments. In the hazard identification and characterisation of perchlorate, the CONTAM Panel concluded that acute hazards at doses relevant for dietary exposure are not to be expected in any group of the population, and therefore the establishment of an acute reference dose (ARfD) for perchlorate is not warranted. Hence, no acute exposure assessment was performed.

The exposure assessment of perchlorate was performed for chronic and short-term exposure.

As the suspect samples constitute about 20 % of the occurrence data, the use of these data was considered to unrealistically overestimate the mean perchlorate concentration used to assess chronic exposure. A chronic exposure estimation under the scenario including the suspect samples was only performed to assess the uncertainty related to the different sampling strategies.

For the short-term exposure the CONTAM Panel considered scenarios, excluding and including the suspect samples. The latter was included as a conservative scenario in order to take into account the possibility that a consumer might be exposed during a short-term period to perchlorate levels in the range of those reported for suspect samples.

4.3.1. Chronic exposure

Chronic exposure to perchlorate was assessed by multiplying each individual's mean daily consumption for each food with the corresponding mean contamination for each FoodEx food group as reported in Table 6, summing up the intakes throughout the diet, and finally dividing the results by the individual's body weight. Perchlorate levels in water were used also for tea and coffee beverages for which no occurrence data were available. Only subjects with more than one reporting day were considered appropriate for calculating chronic exposure.

Data from the literature were used for the categories 'Infant formulae, powder', 'Infant formulae, liquid', milk and dairy products, alcoholic beverages and fruit juices.

The mean and the 95th percentile of exposure were derived for each population group (i.e. [survey × age class] combinations).

The contribution of each food group to the total exposure to perchlorate was determined for each population group, as the ratio between the mean perchlorate intake resulting from the consumption of the food group and the total mean exposure to perchlorate.

Left-censored data, i.e. samples with concentrations below LOD or LOQ were handled as recommended in the 'Principles and Methods for the Risk Assessment of Chemicals in Food' (WHO, 2009) and in the EFSA scientific report 'Management of left-censored data in dietary exposure assessment of chemical substances' (EFSA, 2010) through the substitution method. The LB was obtained by assigning a value of zero to all the samples reported as less than the left-censored limit, the middle bound (MB) by assigning half of the left-censored limit and the UB by assigning the left-censored limit as the sample result.

Summary results for chronic exposure are reported in Table 7 under the scenario in which suspect samples were excluded. The 95th percentile of chronic exposure under the UB scenario resulted in values between 6 and 22 % higher than the ones calculated under the LB scenario. In adolescents and the adult age groups, the chronic mean dietary exposure ranged from 0.04 to 0.20 µg/kg b.w. per day (minimum LB to maximum UB across dietary surveys). For other children and toddlers, the mean chronic dietary exposure ranged from 0.07 to 0.37 µg/kg b.w. per day and 0.18 to 0.50 µg/kg b.w. per day (minimum LB to maximum UB across dietary surveys), respectively. For infants, only two consumption surveys were available resulting in an exposure of 0.13–0.30 (LB-UB) and 0.40–0.54 (LB-UB) µg/kg b.w. per day (see Table 7). The 95th percentile chronic dietary exposure ranged from 0.10 to 0.51 µg/kg b.w. per day (minimum LB to maximum UB across dietary surveys) in adolescents and adult age classes. For other children and toddlers the 95th percentile chronic dietary exposure ranged from 0.19 to 0.72 µg/kg b.w. per day and 0.34 to 0.97 µg/kg b.w. per day (minimum LB to maximum UB across dietary surveys), respectively. For infants, 95th percentile chronic dietary exposure could only be calculated for one consumption survey resulting in exposure of 0.32–0.61 µg/kg b.w. per day (LB-UB).

Results per survey and age class and each of the LB, MB and UB considered under the scenario in which suspect samples were excluded are reported in Appendix C, Table C1.

Under the scenario in which suspect samples were excluded, 'vegetables and vegetable products' and 'Milk and dairy products' were identified in the exposure assessment as the most important contributors to perchlorate exposure in all age groups, with contributions above 25 % in several surveys. For infants, 'Food for infants and small children' also contributed more than 10 % to the

perchlorate exposure in one of the two available surveys, and 'Milk and dairy products' exceeded 75 % in the other survey (Appendix C, Table C2). However, the CONTAM Panel noted that the data on milk and dairy products and on food for infants and small children were from outside Europe, with unknown relevance to the EU population. Drinking water contributed between 1 and 10 % to the total perchlorate exposure in all age groups in the majority of surveys and age classes; this category never contributed more than 25 % to the total exposure.

Summary results for chronic exposure under the scenario including the suspect samples are reported in Appendix C, Table C3.

Table 7: Chronic dietary exposure estimates to perchlorate under the scenario in which suspect samples were excluded

Age class	Number of surveys[(a)]	Chronic dietary exposure (µg/kg b.w. per day)											
		Mean						P95					
		Minimum		Median		Maximum		Minimum		Median		Maximum	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Infants	2 (1)	0.13	0.30	–	–	0.40	0.54	–[(b)]	–	–	–	–	–
Toddlers	7 (4)	0.18	0.32	0.24	0.40	0.33	0.50	0.34	0.53	0.45	0.67	0.66	0.97
Other children	15	0.07	0.13	0.15	0.23	0.24	0.37	0.19	0.27	0.30	0.43	0.60	0.72
Adolescents	12	0.05	0.08	0.08	0.12	0.15	0.19	0.13	0.17	0.18	0.23	0.32	0.39
Adults	15	0.04	0.07	0.07	0.11	0.14	0.19	0.10	0.16	0.16	0.21	0.33	0.38
Elderly	7	0.06	0.09	0.08	0.13	0.16	0.20	0.14	0.19	0.17	0.23	0.47	0.51
Very elderly	6	0.06	0.09	0.09	0.13	0.15	0.19	0.13	0.19	0.20	0.25	0.33	0.37

b.w.: body weight; P95: 95th percentile; LB: lower bound; UB: upper bound.
(a): The number in parentheses is the number of surveys presenting more than 60 subjects and for which it was considered possible to calculate the 95th percentile of exposure.
(b): For infants, only one dietary survey included more than 60 subjects, which could be used to calculate a 95th percentile dietary exposure of 0.32–0.61 (LB-UB) µg/kg b.w. per day.

4.3.2. Assessment of 'short-term' exposure to high levels of perchlorate

Although acute effects following a single exposure to perchlorate via the diet are not expected, the CONTAM Panel developed a 'short-term' exposure assessment to take into account the possibility of being exposed to relatively high levels of perchlorate for a short-term period, e.g. two to three weeks. 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, such as breast-fed infants and young children with low iodine intake. The consumption of products containing high levels of perchlorate for short periods is plausible for example, in the case of people consuming, for a limited period of time, leafy vegetables, tomatoes and/or other commodities from the same local producers that have high levels of perchlorate, as a result of e.g. contamination of irrigation water or treatment of fruit and vegetables with natural fertilisers.

For each single FoodEx food group, 'short-term' exposure to high levels of perchlorate was assessed by multiplying each individual's mean daily consumption by the highest reliable percentile of occurrence (see Appendix C, Table C4), summing up the intakes throughout the diet, and finally dividing the results by the individual's body weight. The mean contamination of the corresponding FoodEx level 2 food group was used for food categories presenting fewer than 11 samples and for which the median was considered as sufficiently reliable. Only subjects with more than one reporting consumption day were considered appropriate for calculating 'short-term' exposure, as done for chronic exposure. Results are reported only for the UB scenario since no difference exists with respect to the LB scenario.

Under the scenario in which suspect samples were excluded, the 'short-term' mean dietary exposure ranged from 0.38 to 1.9 µg/kg b.w. per day (across dietary surveys) in adolescents and the adult age groups. In toddlers, the 'short-term' mean dietary exposure ranged from 1.5 to 2.7 µg/kg b.w. per day (across dietary surveys). For infants, only two consumption surveys were available resulting in an exposure of 1.2 and 1.5 µg/kg b.w. per day (see Table 8). The highest mean exposure (3.0 µg/kg b.w. per day) was estimated in the age class 'Other children'. The 95th percentile 'short-term' dietary exposure estimates for adolescents and the adult age groups ranged from a minimum of 0.94 µg/kg b.w. per day to a maximum of 4.6 µg/kg b.w. per day across dietary surveys. In toddlers, the 95th percentile 'short-term' dietary exposure estimates ranged from 3.6 µg/kg b.w. per day to 6.2 µg/kg b.w. per day (across dietary surveys). For infants, only one consumption survey was available resulting in an exposure of 3.8 µg/kg b.w. per day. The highest 95th percentile exposure (7.2 µg/kg b.w. per day) was estimated in the age class 'Other children'.

Under the scenario in which suspect samples were included, the 'short-term' mean dietary exposure ranged from 0.54 to 5.0 µg/kg b.w. per day (across dietary surveys) in adolescents and the adult age groups. In toddlers, the 'short-term' mean dietary exposure ranged from 2.2 to 4.4 µg/kg b.w. per day (across dietary surveys). For infants, only two consumption surveys were available resulting in an exposure of 1.5 and 2.3 µg/kg b.w. per day (see Table 9). The highest mean exposure (5.3 µg/kg b.w. per day) was estimated in the age class 'Other children'. The 95th percentile 'short-term' dietary exposure estimates for adolescents and the adult age groups ranged from a minimum of 1.3 µg/kg b.w. per day to a maximum of 14 µg/kg b.w. per day across dietary surveys. In toddlers, the 95th percentile 'short-term' dietary exposure estimates ranged from 4.5 µg/kg b.w. per day to 9.4 µg/kg b.w. per day (across dietary surveys). For infants, only one consumption survey was available resulting in an exposure of 5.7 µg/kg b.w. per day. The highest 95th percentile exposure (18 µg/kg b.w. per day) was estimated in the age class 'Other children'.

For all age groups, the 'short-term' exposure estimates under the scenario in which suspect samples were included were higher compared to the scenario in which suspect samples were excluded. The use of the suspect samples increased the 'short-term' mean exposure estimates in infants and toddlers by up to 64 % and the 95th percentile by up to 53 %. For all other age groups, the inclusion of suspect samples resulted in 'short-term' mean exposure estimates that were from 32 to 163 % higher and the

95th percentile exposure estimates that were from 21 to 227 % higher compared to the scenario excluding the suspect samples.

Table 8: 'Short-term' dietary exposure estimates to perchlorate under the scenario in which suspect samples were excluded

Age class	Number of surveys[a]	'Short-term' dietary exposure (µg/kg b.w. per day)[b]					
		Mean			P95		
		Minimum	Median	Maximum	Minimum	Median	Maximum
Infants	2 (1)	1.2	–	1.5	–[c]	–	–
Toddlers	7 (4)	1.5	2.0	2.7	3.6	4.8	6.2
Other children	15	0.71	1.4	3.0	1.8	3.3	7.2
Adolescents	12	0.38	0.84	1.8	0.94	2.1	4.2
Adults	15	0.45	0.79	1.9	1.1	2.0	4.6
Elderly	7	0.71	0.87	1.9	1.0	2.0	4.1
Very elderly	6	0.52	0.82	1.8	1.4	2.2	3.9

b.w.: body weight; P95: 95th percentile.
(a): The number in parentheses is the number of surveys presenting more than 60 subjects and for which it was considered possible to calculate the 95th percentile of exposure.
(b): Results are reported only for the upper bound scenario since no difference exists with respect to the lower bound scenario.
(c): For infants, only one dietary survey included more than 60 subjects, which could be used to calculate the 95th percentile dietary exposure of 3.8 µg/kg b.w. per day.

Table 9: 'Short-term' dietary exposure estimates to perchlorate under the scenario in which suspect samples were included

Age class	Number of surveys[a]	'Short-term' dietary exposure (µg/kg b.w. per day)[b]					
		Mean			P95		
		Minimum	Median	Maximum	Minimum	Median	Maximum
Infants	2 (1)	1.5	–	2.3	–[c]	–	–
Toddlers	7 (4)	2.2	3.1	4.4	4.5	6.5	9.4
Other children	15	0.99	2.0	5.3	2.4	4.9	18
Adolescents	12	0.54	1.4	3.6	1.3	4.1	11
Adults	15	0.68	1.5	5.0	1.6	4.6	14
Elderly	7	1.3	1.8	4.0	1.4	4.5	9.5
Very elderly	6	0.93	1.5	3.5	2.0	5.3	8.4

b.w.: body weight; P95: 95th percentile.
(a): The number in parentheses is the number of surveys presenting more than 60 subjects and for which it was considered possible to calculate the 95th percentile of exposure.
(b): Results are reported only for the upper bound scenario since no difference exists with respect to the lower bound scenario.
(c): For infants, only one dietary survey included more than 60 subjects, which could be used to calculate the 95th percentile dietary exposure of 5.7 µg/kg b.w. per day.

4.4. Exposure from breast milk

Perchlorate can be transferred into breast milk and consequently breast-fed infants can be exposed to perchlorate. Section 5.3.1 and Appendix D give overviews of the concentrations in breast milk that have been reported in the literature. No European occurrence data were identified in the literature or submitted to EFSA. Therefore, mean occurrence levels of perchlorate in breast milk reported in the literature (see Section 5.3.1 and Appendix D) were used to assess the exposure of breast-fed infants below six months of age. It has to be noted that the reported mean concentrations reported in Table 10 are from studies with a limited number of subjects and are associated with considerable inter-individual and, when studied, intra-individual variabilities. All the selected studies were from the USA and, overall, are of unknown relevance to the EU. One study from Chile (Téllez et al., 2005) was not used for the exposure assessment due to high exposure via tap water in some regions.

For this exposure assessment of breast-fed infants below six months of age, a value of three months was selected, assuming a body weight of 6.1 kg, with an estimated mean daily consumption of 800 mL and a high consumption of 1 200 mL of breast milk (EFSA CONTAM Panel, 2011). The mean dietary exposure to perchlorate for infants with a mean milk consumption ranged from 0.76 to 4.3 µg/kg b.w. per day (Table 10). For infants with high milk consumption, the dietary exposure ranged from 1.1 to 6.5 µg/kg b.w. per day.

Table 10: Exposure scenario to perchlorate based on mean and high breast milk consumption for infants below six months based on the mean occurrence data reported in literature and estimated mean and high consumption levels of 800 mL and 1 200 mL, respectively (see Section 5.3.1 and Appendix D)

Country	n	Reported mean concentration in breast milk (concentration range) (µg/L)	Dietary exposure to perchlorate (µg/kg b.w. per day)		Reference
			Mean breast milk consumption	High breast milk consumption	
USA	49	33 (1.3–411)	4.3	6.5	Pearce et al. (2007)
USA	36	10.5 (0.6–92.2)	1.4	2.1	Kirk et al. (2005)
USA	13	10.6 (2.2–28.6)	1.4	2.1	Kirk et al. (2012)
USA	10	5.8 (0.5–39.5)	0.76	1.1	Kirk et al. (2007)
USA	13	9.3 (0.01–48)	1.2	1.8	Dasgupta et al. (2008)

b.w.: body weight; n: number of subjects.

5. Hazard identification and characterisation

5.1. Toxicokinetics

The findings from risk assessments carried out by ATSDR (2008) and JECFA (FAO/WHO, 2011) have been summarised below. In addition, further data published after the JECFA assessment have been reviewed and included below.

5.1.1. Absorption

Following oral exposure, perchlorate has been shown to be readily absorbed from the gastro-intestinal (GI) tract, in both human and animal studies (ATSDR, 2008). Human study results 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, by Greer et al. (2002), the serum half-life of perchlorate was calculated as 6.0–9.3 hours (mean 8.1 hours), following oral dosing of perchlorate in drinking water at 0.5 mg/kg b.w. per day. The half-life was later re-calculated by Crump and Gibbs (2005) to be on average 7.5 hours. In rats, peak blood concentrations of orally administered radio-labelled perchlorate were observed at three hours and half-lives range from less than eight hours to approximately 20 hours (Wolff, 1998). In a study by Selivanova et al. (1986) absorption of

ammonium perchlorate was investigated in rats, rabbits and calves following single oral doses of 2, 20, 200 or 600 mg perchlorate/kg b.w. The maximum concentrations of perchlorate in blood occurred at 30–60 minutes in rats and at 5 hours in calves, with 8.5 % of the dose eliminated in faeces and the rest eliminated in urine, suggesting absorption of > 90 % of the dose.

5.1.2. Distribution

Perchlorate is found in human serum, plasma, urine, saliva and breast milk (Kirk et al., 2005, 2007; Téllez et al., 2005; Pearce et al., 2007; Dasgupta et al., 2008; Kannan et al., 2009; Leung et al., 2009; Oldi and Kannan, 2009a,b). In female rhesus monkeys, after 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 GI contents of neonatal rats (Clewell et al., 2003a, b). In the rat, perchlorate is concentrated in the thyroid, GI contents, skin, mammary gland and milk (Clewell et al., 2004). From investigations in rabbits and rats, concentrations of perchlorate in most soft tissues (kidney, liver, skeletal muscle) are similar to serum perchlorate concentrations (Durand, 1938; Yu et al., 2002). Perchlorate binds to bovine and human serum albumin and has high non-specific binding to albumin and prealbumin in rat plasma, with saturation occurring at perchlorate doses of 1.0 and 10.0 mg/kg b.w. per day in the rat (Scatchard and Black, 1949; Carr, 1952; Clewell et al., 2003a; Merrill et al., 2003). Perchlorate uptake and accumulation in the thyroid gland is through a saturable active transport process (peak uptake four to six hours in rats following oral exposure), during which perchlorate 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).

5.1.3. Metabolism

Evidence indicates that very little of the perchlorate ion is metabolised in rats or humans (Wolff, 1998; Fisher et al., 2000; ASTDR, 2008). Potential metabolites of potassium perchlorate (radiolabelled with ^{36}Cl and $^{18}O_4$) were investigated in a study in humans by Anbar et al. (1959) analysing urine sampled three hours after a single oral dose (200 mg/kg b.w.). In the excreted perchlorate, no isotopic exchange of oxygen atoms occurred and the authors concluded that three hours 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 hours following intravenous administration in rats.

5.1.4. Excretion

Oral studies conducted in humans and experimental animals (rabbits, rats and calves) have indicated 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). Breast milk is also indicated as an excretion route for humans and rats (Clewell et al., 2003b; Kirk et al., 2005; Téllez et al., 2005; Pearce et al., 2007).

In conclusion, perchlorate is rapidly absorbed following oral exposure, and evidence indicates that it undergoes very little, if any metabolism; moreover, the main pathway of elimination is via urine.

5.2. Toxicological studies

The available data have been evaluated previously by JECFA (FAO/WHO, 2011), ATSDR (2008) and NRC (2005) and are briefly summarised below. In addition further information from the Registration, Evaluation, Authorisation and Restriction of Chemicals[20] Registration dossier on ammonium perchlorate submitted to the European Chemical Agency (ECHA) (ECHA, 2014) has also been included.

[20] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. OJ L 396, 30.12.2006, p. 1–849.

5.2.1. Acute toxicity

A single dose of ammonium perchlorate was administered to female Sprague-Dawley rats at doses of 300 mg/kg b.w. (n = 3) or 2 000 mg/kg b.w. (n = 6), by oral gavage, followed by a 14-day observation period. No deaths occurred at either dose. Hypoactivity was noted up to 2 hours post dose for all animals dosed at 2 000 mg/kg b.w. Compared with historical control data, a slightly lower body weight gain was noted between days 1 and 8 for one female dosed at 2 000 mg/kg b.w. and between days 8 and 15 for a female dosed at 300 mg/kg and one female dosed at 2 000 mg/kg b.w. (ECHA, 2014).

In conclusion, mild, transient clinical signs (hypoactivity) were evident following a single acute dose of 2 000 mg/kg b.w. in rats. The CONTAM Panel concluded that perchlorate has low acute oral toxicity in rats.

5.2.2. Repeat dose toxicity

In female NMR1 mice exposed for up to 30 days to potassium perchlorate in the diet, a median lethal dose (LD_{50}) dietary concentration of 3.55 % (35 500 mg/kg diet, equivalent to approximately 3 621 mg/kg b.w. per day, as perchlorate) was reported; the first deaths were observed within four days of the start of treatment (Gauss, 1972).

In an eight-week study in female Sprague-Dawley rats, mammary gland tissue was evaluated following exposure to sodium perchlorate in drinking water at perchlorate doses of approximately 600–750 mg/kg b.w. per day. The study found a 52 % reduction in iodine uptake by mammary gland tissue compared with the control, mild atrophy, atypia of the lobular epithelium and scattered foci of marked hyperplastic activity (Eskin et al., 1975). The CONTAM Panel noted that effects on the thyroid and related hormone levels were not investigated in the study.

In a study by Siglin et al. (2000), Sprague-Dawley rats were exposed to ammonium perchlorate via the drinking water at doses of 0, 0.01, 0.05, 0.2, 1.0 and 10.0 mg/kg b.w. per day for 90 days (10 rats/sex/group) followed by a 30-day recovery period for additional rats (10 rats/sex/group) previously dosed at 0, 0.05, 1.0 and 10.0 mg/kg b.w. per day. After 90 days of exposure, significant decreases in serum triiodothyronine (T_3) and thyroxine (T_4) levels were noted for both sexes, at $\geq$ 0.01 mg/kg b.w. per day. Significant increases in serum TSH were observed in males at $\geq$ 0.2 mg/kg b.w. per day and in females at 10.0 mg/kg b.w. per day. Significant increases in thyroid weight and thyroid follicular cell hypertrophy with microfollicle formation and colloid depletion were noted in both sexes at 10 mg/kg b.w. per day. Following the 30-day recovery period, significant decreases in serum T_4 were noted for males at all doses. In females, serum TSH was significantly increased at all doses and serum T_3 was significantly decreased at 10 mg/kg b.w. per day. The authors concluded that the overall NOAEL for this study was 1.0 mg/kg b.w. per day. However, the CONTAM Panel concluded that, as thyroid hormone changes were noted at all treated doses, 0.01 mg/kg b.w. per day could be considered the LOAEL for thyroid hormone changes.

In contrast, ammonium perchlorate had no effect on TSH, T_3 or T_4 levels in a study with Fischer 344 rats (10 rats/group) exposed to ammonium perchlorate in drinking water at doses of 0, 0.024, 0.205 and 1.170 mg/kg b.w. per day for seven days. At 1.170 mg/kg b.w. per day, histological findings were observed in the thyroid gland consisting of colloid depletion, hypertrophy and hyperplasia of follicular epithelial cells (Khan et al., 2005). The CONTAM Panel identified a NOAEL of 0.205 mg/kg b.w. per day for this study.

Exposure to ammonium perchlorate via drinking water for 14 days, at doses of 0, 0.01, 0.1 and 1.0 mg/kg b.w. per day, in male Sprague-Dawley rats (16 rats/group), resulted in significant dose-related increases in serum TSH at 0.1 and 1.0 mg/kg b.w. per day and significant decreases in serum T_4 (free and total) at 1.0 mg/kg b.w. per day (McLanahan et al., 2007). The CONTAM Panel identified a NOAEL of 0.01 mg/kg b.w. per day.

In conclusion, findings resulting from the repeated exposure to perchlorate, included changes in thyroid hormone and TSH levels, thyroid weight increases, and histological findings in the thyroid (colloid depletion, follicular cell hypertrophy and hyperplasia) or mammary gland (mild atrophy, atypia of the lobular epithelium, scattered foci of marked hyperplasic activity) in rats and deaths at high doses in mice (3 621 mg/kg b.w. per day).

No effects other than those related to iodine uptake inhibition in the thyroid and mammary glands were observed in any of the repeat-dose studies.

5.2.3. Genotoxicity

Negative results were observed for magnesium perchlorate in a test for SOS-inducing activity, using a *Salmonella typhimurium* strain TA1535 (Nakamura and Kosaka, 1989) and in a test for production of DNA-protein crosslinks in cultured human lymphocytes (Costa et al., 1996). No evidence of mutagenicity was found for ammonium perchlorate in an Ames test with six different *Salmonella* strains (Zeiger, 1998a) or in the mouse lymphoma assay, with and without metabolic activation (San and Clarke, 1999).

In male and female rats, no changes were noted in bone marrow micronucleus formation following exposure to ammonium perchlorate in the drinking water at 10 mg/kg b.w. per day, after 90 days of treatment (Siglin et al., 2000). No increase was noted in micronucleus formation in bone marrow from mice injected intraperitoneally with ammonium perchlorate for 3 days at 500 mg/kg b.w. per day (Zeiger, 1998b).

Based on the available data, the CONTAM Panel concluded that perchlorate is not of concern with respect to genotoxicity.

5.2.4. Carcinogenicity and long-term toxicity studies

Thyroid tumours (papillary and/or follicular adenomas and/or carcinomas) have been reported to occur upon exposure to perchlorate in various studies (Kessler and Kruskemper, 1966; Gauss, 1972; Florencio Vicente, 1990; Fernandez-Rodriguez et al., 1991; Pajer and Kalisnik, 1991; Toro Guillen, 1991) in rats and mice following exposure to potassium and sodium perchlorate for up to 24 months, through diet or drinking water. The estimated perchlorate doses in these studies ranged from 928 to 2 573 mg/kg b.w. per day, with the tumours noted around 1 000 mg/kg b.w. per day (FAO/WHO, 2011).

In the study by Kessler and Kruskemper (1966), four out of 11 male Wistar rats were noted as having thyroid adenomas, following exposure to potassium perchlorate at an estimated dose of 1 339 mg/kg b.w. per day in drinking water for 24 months (ECHA, 2014). It was noted that the study had limited sensitivity, with only one dose, one sex and one organ investigated for lesions (including tumours). Furthermore, the publication had limited details on the study with unclear pathological diagnoses (NRC, 2005; ECHA, 2014).

Gauss (1972) exposed female NMR1 mice to potassium perchlorate in food at 1 420 mg/kg b.w. per day. Findings in the thyroid consisted of papillomatous hyperplasia and adenomatosis within 60 days of treatment, which developed into thyroid adenomas between day 60 and day 110. Limitations were noted regarding the study design, including unclear methods and results (ECHA, 2014).

Pajer and Kalisnik (1991) exposed female BALB/c mice to sodium perchlorate in drinking water for 46 weeks, at an estimated dose of 2 147 mg/kg b.w. per day. Following histological examination of the thyroids, thyroid follicular cell carcinomas were noted in five out of six treated mice (NRC, 2005).

Exposure of Wistar rats to potassium perchlorate in feed for 19 weeks, corresponding to a perchlorate dose of 64 mg/kg b.w. per day, promoted development of thyroid tumours initiated by *N*-bis (2-hydroxypropyl)-nitrosamine, in all 20 of the treated rats (Hiasa et al., 1987).

Ki-*ras* mutational analysis was performed on thyroid follicular cell carcinomas, from rats exposed to radiolabelled iodine and potassium perchlorate in the drinking water (1 %, or 10 000 mg/L) for 18 months. No mutations were observed that suggested that Ki-*ras* activation via mutations at codons 12 and 13 is not a constant or early event in the development of the carcinomas (Fernández-Santos et al., 2004).

In view of the absence of genotoxicity and considering the mode of action of perchlorate (see Section 5.4), as well as the available data from long term clinical use (see Section 5.3.1) and epidemiological studies (see Section 5.3.3), the CONTAM Panel concluded that the thyroid tumours found in rats and mice following chronic exposure to perchlorate are not relevant for humans.

5.2.5. Reproductive and developmental toxicity

In a two-generation study by York et al. (2001a), Sprague-Dawley rats (30/sex/group) were given ammonium perchlorate at target doses of 0, 0.3, 3.0 and 30 mg/kg b.w. per day in drinking water. Statistically significant increases were noted in the parental (P) generation lactation index at ≥ 3.0 mg/kg b.w. per day, in the F1 adult fertility index at ≥ 0.3 mg/kg b.w. per day and in the number of still born pups born to F1 adults at 30 mg/kg b.w. per day; however, the author did not consider these findings to be treatment-related. Significant increases in thyroid weight were observed in F1 adult males at ≥ 3.0 mg/kg b.w. per day and females ≥ 0.3 mg/kg b.w. per day. Follicular cell hypertrophy and hyperplasia of the thyroid were noted at all doses, which were dose-dependent in severity and incidence and significant at ≥ 3.0 mg/kg b.w. per day for adults (P and F1) and pups (F1 and F2). Significant increases in serum TSH levels were noted in adults (P and F1) at 30 mg/kg b.w. per day. The authors concluded that perchlorate was not a reproductive toxicant at doses of up to 30 mg/kg b.w. per day, although it can affect the thyroid at doses of ≥ 3.0 mg/kg b.w. per day.

In a single-generation study by Mahle et al. (2003), pregnant Sprague-Dawley rats were given perchlorate at either 0 or 1 mg/kg b.w. per day in drinking water, from gestation day (GD) 2 until sacrifice on either GD 20 or on postnatal day (PND) 10. Cross-fostering of some litters was performed on PND 1, resulting in four different groups, comprising eight dams/group with four pups/sex/litter. In dams, serum perchlorate levels were higher on GD 20 than on PND 10. Fetal serum levels were 0.38 µg/mL and for pups killed on PND 10 (exposed *in utero* - lactationally and lactationally alone), serum perchlorate levels were 0.50–0.56 µg/mL. Serum TSH levels were significantly increased in perchlorate exposed dams killed on GD20 and PND 10, in exposed fetuses and in pups exposed *in utero* - lactationally and lactationally alone. Serum T_3 levels were significantly reduced in exposed dams killed on GD 20 and serum T_4 levels were significantly reduced for dams killed on GD 20, in exposed fetuses and in female pups exposed *in utero* – lactationally and lactationally alone. The JECFA review noted that a control for the cross-fostering procedure was not included. This procedure can result in reduced body weights of cross-fostered litters; a finding noted in this study.

The effects of exposure to perchlorate in the diet compared with in drinking water was investigated in a study using prairie voles (64 males and 64 females) and deer mice (39 males and 39 females). The animals were treated continuously from 21 days prior to pairing until PND 21 at doses between 0.32 and 1.120 mg/kg b.w. per day. In both species, perchlorate exposed groups (in diet and water) had lower reproductive success, in terms of number of litters born, than the controls. Minimal or unexpected differences were found in thyroid hormone concentrations resulting from exposure to perchlorate. In mice, plasma T_3 levels were significantly decreased and plasma T_4 levels were significantly increased in unpaired and paired male mice from the food-exposed group, respectively. Plasma T_4 levels were significantly decreased in the food-exposed group and significantly increased in the drinking water exposed group in paired male prairie voles (paired female plasma was not analysed

for thyroid hormones levels during pairing). Significantly increased thyroid epithelial cell heights and smaller colloidal area were noted for prairie voles exposed to perchlorate in water, compared with the food-exposed group and/or the control. The author concluded on the basis of prairie vole thyroid histology, that the trends observed suggested that perchlorate exposure via water may result in slightly greater effects than exposure via food (Smith et al., 2006). The JECFA review noted, however, that the thyroid histology findings were slight and, as no significant differences were noted for any other study endpoints, it is not possible to conclude that the effects of exposure to perchlorate given in water are greater than perchlorate exposure via food. The CONTAM Panel agrees with this conclusion from the JECFA review.

In studies by Thuett et al. (2002a, b), breeding pairs of deer mice (10 pairs/group) were dosed with ammonium perchlorate continuously from cohabitation, until the weaning of the third litter, at concentrations of 117 ng/L, 117 µg/L and 117 mg/L perchlorate in drinking water; as the duration of dosing, water consumption and body weight data were not given, the dose in relation to body weight cannot be calculated. The pups from the second litter, killed on PND 21, were evaluated. There were no significant differences in litter size or in percentage survival between treatment groups. In treated pups, fewer active follicles in the thyroid were noted and T_4 plasma concentrations were higher in the exposure groups 117 ng/L and 117 µg/L than in the control. The authors commented that ammonium perchlorate increases thyroid hormone production in developing deer mice. However, the JECFA review noted that as there was no dose-response relationship for plasma T_4 level changes or thyroid findings, a treatment related effect was not established.

The effects of ammonium perchlorate were investigated in a developmental toxicity study by York et al. (2003) in Sprague-Dawley rats (25 mated rats/group). Doses of 0, 0.01, 0.1, 1.0 and 30 mg/kg b.w. per day were administered in drinking water, from 14 days prior to cohabitation, until GD 21. At 30 mg/kg b.w. per day, small, significant reductions in mean litter size (not considered treatment related by the authors); reduced ossification of fetal sternebrae and phalanges; significant increases in dam thyroid weight; decreased colloid and hypertrophy of the thyroid in dams and decreases in dam serum T_3 and fetal serum T_4 levels, were observed. At ≥ 1.0 mg/kg b.w. per day, decreased colloid in fetal thyroids and significant increases in fetal serum TSH levels were observed. At ≥ 0.01 mg/kg b.w. per day, significant dose-related findings were noted, consisting of decreases in fetal serum T_3 levels and dam serum T_4 levels and increases in dam serum TSH levels. The effect of continuous dosing up to PND 10 using the same study design was further investigated by York et al. (2005a). There were no effects on reproductive or litter parameters. Similar findings were noted in dams compared with the previous study, although an increase in follicular hyperplasia was noted at ≥ 1.0 mg/kg b.w. per day. Significant increases in thyroid weights were noted in male pups at all doses and in female pups at ≥ 1.0 mg/kg b.w. per day and a significant increase in incidence of decreased colloid was noted for both sexes at 1.0 mg/kg b.w. per day. Pup TSH levels were significantly increased at all doses and significant decreases were noted for T_3 at ≥ 1.0 mg/kg b.w. per day and at all doses for T_4. For both studies the CONTAM Panel derived a LOAEL (maternal and developmental) of 0.01 mg/kg b.w. per day, due to the changes in thyroid hormone levels noted from the low-dose group.

In another developmental study by York et al. (2001b), New Zealand White rabbits (25 mated rabbits/group) were given target doses of 0, 0.1, 1.0, 10.0, 30.0 and 100.0 mg/kg b.w. per day from GD 6 to 28, before sacrifice on GD 29. No treatment-related effects on reproductive or fetal parameters were noted at any dose. In does, an increased incidence of thyroid follicular hypertrophy was noted at ≥ 10 mg/kg b.w. per day and significant decreases in serum T_4 levels were noted at ≥ 30 mg/kg b.w. per day. Based on these findings the authors concluded that the maternal NOAEL was 1.0 mg/kg b.w. per day and the developmental NOAEL was 100.0 mg/kg b.w. per day.

In a study investigating pubertal development by Stoker et al. (2006), male Wistar rats were given 62.5, 125, 250 and 500 mg/kg b.w. per day by oral gavage, for 31 days from PND 23 to 53. There were no effects noted on reproductive endpoints. At ≥ 125 mg/kg b.w. per day, significant dose-related increases and decreases were noted for serum TSH and T_4 levels, respectively. At ≥ 62.5 mg/kg b.w. per day, thyroid histology findings consisted of a dose-dependent decrease in

colloid area and an increase in follicular cell height. A NOAEL for effects on the thyroid was not established.

In conclusion, available information on development and reproductive toxicity indicated effects on some reproductive endpoints following exposure to perchlorate. Effects consisted of decreases in the number of litters born and reduced ossification of fetal sternebrae and phalanges. 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 thyroid findings (increased weights and histological changes).

5.2.5.1. Developmental neurotoxicity

In a study by York et al. (2004) investigating developmental neurotoxicity, female Sprague-Dawley rats (24 rats/group) were given ammonium perchlorate in drinking water continuously from GD 0 to PND 10 at 0, 0.1, 1.0, 3.0 and 10.0 mg/kg b.w. per day. No effects were noted on reproductive parameters, litter parameters, or on pup behaviour parameters (passive avoidance, water maze testing, motor activity and auditory startle habituation). An increase in thickness of the corpus callosum was noted in pups at 10 mg/kg b.w. per day group. An increase in incidence of thyroid follicular epithelium hypertrophy and hyperplasia and a reduction in follicle size was noted for female pups at ≥ 3 mg/kg b.w. per day and male pups at 10 mg/kg b.w per day. Decreases in thyroid hormone levels and increases in TSH levels were noted for pups at ≥ 1.0 mg/kg b.w. per day. The authors concluded that the maternal NOAEL was greater than 10 mg/kg b.w. per day and the pup NOAEL was 0.1 mg/kg b.w per day. In a companion paper by York et al. (2005b) additional data on developmental neurotoxicity was generated from rats dosed at 0, 0.1, 1.0, 3.0 and 10.0 mg/kg b.w. per day from two weeks prior to pairing, up to PND 10 (behavioural assessment), or at 0, 0.1, 1.0, 3.0 and 30.0 mg/kg b.w. per day, from GD 0 to PND 10 (neurodevelopmental assessment). Significant increases in the linear dimensions of a number of brain regions in male pups at all doses were noted, although no clear dose-response was observed. However, no effects on male rat brain weights or neuropathology were noted. In contrast, some brain regions were significantly smaller in female pups than in the controls. The CONTAM Panel concluded that a NOAEL or NOEL could not be derived as changes in the dimensions of some brain regions were noted at all doses.

Female Long-Evans rats (30 rats/group) were exposed to ammonium perchlorate at doses of 0, 4.5, 44.2 and 140.3 mg/kg b.w. per day, from GD 6 to PND 30. There were no effects on pup body weight, brain or hippocampal weight, time of eye opening or behavioural tasks. Serum TSH levels were significantly increased at 4.5 and 44.2 mg/kg b.w. per day for pups and at 140.3 mg/kg b.w. per day in dams. Significant decreases in serum T_3 and T_4 were noted at ≥ 44.2 mg/kg b.w. per day in pups and in serum T_4 levels from ≥ 4.5 mg/kg b.w. per day in dams. In adult male offspring (five to nine months old), significant dose-dependent reductions in baseline synaptic transmission were observed in hippocampal field potentials at all three doses (Gilbert and Sui, 2008). A NOAEL was not established. All serum hormone concentrations returned to control levels in adulthood. No behavioural alterations were observed in hippocampal-based learning tasks. However, there was a significant reduction in baseline synaptic transmission in hippocampal field potential that persisted in the adult offspring. This suggests that developmental exposures to perchlorate that perturb the maternal and offspring thyroid hormonal system may result in permanent alteration in brain function.

The NRC (2005) review reiterated the concerns from previous reviews regarding the interpretation of results of developmental neurotoxicity studies with perchlorate. Design and methodological problems were identified in studies where changes in brain region linear measurements (i.e. increased width of corpus callosum) were observed in exposed pups. The methodological problems included the lack of a consistent dose-response relationship and possible systematic differences across the treatment groups regarding the plane of the brain section examined. Issues regarding the study designs included an inappropriate approach (non-blinded) for the collection of linear thickness measurements, and the use of thickness measurements in general, instead of other more accurate and sensitive methods, such as area or volume measurements, or changes in the cellular structure of a brain region. Studies involving

neurobehavioural assessment also received critical attention, as the tests used (screening tests), lacked sensitivity for the detection of subtle changes in motor or cognitive function, resulting from moderate reductions in thyroid hormone levels. Furthermore, in some studies, important functional endpoints were not assessed, i.e. auditory function and balance/coordination. The NRC concluded that these data are not adequate to determine whether or not perchlorate exposure during gestation or lactation can affect behavioural function in rat pups.

Due to the limitations discussed above, the CONTAM Panel concluded that it is not possible to determine an association between exposure to perchlorate and developmental neurotoxicity from the studies in rats.

5.3. Human observations

Most of the data on human exposure to perchlorate have been summarised by NRC (NRC, 2005) and by JECFA (FAO/WHO, 2011) in their risk assessments. The present opinion shortly summarises studies reviewed in these assessments and relies on the conclusions drawn there. Further data published after the assessments have been reviewed and summarised with a higher degree of detail.

5.3.1. Biomarkers of exposure

The monitoring of perchlorate in urine has been consistently used as a biomarker of both occupational and dietary exposure. JECFA reported the data of a large survey carried out in the framework of the US National Health and Nutrition Examination Survey (NHANES) between 2001 and 2002 (Blount et al., 2006). In this study perchlorate was detected in the urine of all 2 820 tested subjects (≥ six year old), with levels ranging from 0.19 to 160 µg/L, with children having a higher median concentration than adults (5.2 and 3.5 µg/L, respectively). Assuming the same urinary excretion rate for creatinine and perchlorate, and applying an equation for the estimation of the creatinine intake from the urinary levels, Blount et al. (2006) estimated a median dietary exposure of 0.066 µg/kg b.w. per day in adults (95th percentile of 0.234 µg/kg b.w. per day). In a follow up study, the observed median levels were in line with, although lower than those observed during the previous survey in 2 522 USA residents screened from 2003 to 2004 (CDC, 2009). Significantly higher urinary concentrations were observed in an epidemiological study in Chile (Téllez et al., 2005), in which pregnant women were selected from three villages with different perchlorate concentrations detected in the municipal water system. Of the subjects studied, 65 were from Antofagasta (mean perchlorate concentration of 0.46 µg/L detected in tap water), 53 were from Chañaral (5.82 µg/L) and 62 were from Taltal (113.9 µg/L). All the subjects were observed during the gestation and post-partum periods. Based on the tap water consumption data provided by the study subjects, the exposure of pregnant women to perchlorate through the consumption of tap water was estimated to be 0.42 µg per day in Antofagasta, 6.1 µg per day in Chañaral and 93.5 µg per day in Taltal. During pregnancy mean urinary perchlorate concentrations were observed to increase consistently with water concentrations, ranging from 16 to 24.5 µg/L in subjects from Antofagasta, from 66.7 to 73.2 µg/L in subjects from Chañaral, and from 128.9 to 132.9 µg/L in subjects from Taltal. The CONTAM Panel noted that a decrease in urinary excretion relative to exposure levels is observed when going from the lowest to the highest contaminated village, possibly indicating a saturation of absorption processes with increasing doses. Decreased urinary concentrations were observed in the post-partum measurements (mean of 22.3, 17.5 and 49.1 µg/L from Antofagasta, Chañaral and Taltal subjects, respectively) possibly due to the contribution of breast milk to the overall excretion. However a high variability was observed in perchlorate levels breast milk, so a clear correlation with the perchlorate urinary levels could not be established (Téllez et al., 2005).

Other studies that considered the presence of perchlorate and iodine in breast milk are reported in the JECFA evaluation.

Kirk et al. (2005) analysed 36 breast milk samples from different states in the USA for the presence of perchlorate and iodine. Perchlorate was detected in all samples, with concentrations ranging from 1.4 to 92.2 µg/L. Overall, no correlation between the levels of perchlorate and iodine was observed,

although an inverse correlation was observed for a limited subset of samples with perchlorate > 10 µg/L. Pearce et al. (2007) evaluated the perchlorate and iodine concentrations in breast milk and urine samples collected from 57 healthy volunteers from the Boston area, at 10–250 days post-partum. Perchlorate was detected in all of the 49 tested breast milk samples (range 1.3–411 µg/L, median of 9.1 µg/L), and the 56 tested urine samples (range 0.37–127 µg/L, median of 3.0 µg/L). Iodine ranged from 2.7 to 1968 µg/L in breast milk (median of 155 µg/L), and from 25 to 920 µg/L in urine (median of 114 µg/L), with no correlation with the perchlorate concentrations. In a follow-up study, perchlorate and iodine concentrations were measured in colostrum (60 hours post partum) from 97 healthy women from the Boston area (Leung et al., 2009).[21] Perchlorate was detected in 43 out of the 46 colostrum samples (range < 0.05 to 188.9 µg/L, median of 2.5 µg/L), and in all the 97 urine samples (range 0.2–160.6 µg/L, median of 2.6 µg/L). Iodine ranged from 21.3 to 304.2 µg/L (median of 51.4 µmol/L) in colostrum, and from 10.3 to 417.1 µg/L (median of 82.2 µg/L) in urine.

Kirk et al. (2007) monitored the levels of perchlorate, thiocyanate and iodine in breast milk. Ten lactating volunteers were recruited from different states in the USA. Subjects provided between six and 18 milk samples for periods ranging from two days to 14 days. For the sample collection subjects were asked to record dates and times and food and drink intakes. A considerable variability was observed in perchlorate, thiocyanate and iodine levels amongst different subjects and different sampling occasions in the same subjects. Iodine ranged from 3.1 to 334 µg/L (mean of 87.9 ± 80.9 µg/L for a total of 108 samples), perchlorate ranged from 0.5 to 39.5 µg/L (mean of 5.8 ± 6.2 µg/L in 147 samples), and thiocyanate ranged from 0.4 to 228.3 µg/L (mean of 35.6 ± 57.9 µg/L in 117 samples). Perchlorate levels were statistically significantly lower in samples collected before consuming any liquid and food in the morning in comparison to samples collected after the evening meal. Milk iodine levels below 50 µg/L, a threshold consistent with iodine deficiency, were recorded in 46 % of the samples.

In another study, breast milk and urine samples were collected for nine consecutive days from 13 lactating women from Texas (Dasgupta et al., 2008). Perchlorate concentrations ranged from 0.01 to 48 µg/L (median concentration of 7.3 µg/L) in breast milk and from 0.6 to 80 µg/L (median of 3.2 µg/L) in urine. Iodine concentrations ranged from 1 to 1 200 µg/L (median of 43 µg/L) in breast milk and from 26 to 630 µg/L (median of 110 µg/L) in urine.

Blount et al. (2009) measured the concentrations of iodine, perchlorate and two other inhibitors of the thyroidal iodine uptake (nitrate and thiocyanate ions) in maternal and fetal fluids collected in 150 women subject to caesarean section. The fluids under examination were maternal blood and urine, amniotic fluid and cord blood. Perchlorate was detected in most of the samples with the higher concentrations detected in maternal urine (detected in 100 % of the 34 subjects tested, median of 2.90 µg/L, 95 % confidence interval (CI) of 0.90–7.71 µg/L). A good correlation was observed between perchlorate levels in urine and in amniotic fluid. The authors concluded that iodine was detected at levels higher than those observed in other studies, possibly due to the wide use of vitamin supplements in the studied group (e.g.urinary iodinemedian of 1 680 µg/L, 95 % CI 309–5 420 µg/L). Perchlorate was detected more frequently and at higher levels in maternal serum than in cord serum for most of the mother/child pairs. No relationship was observed between the perchlorate and iodine levels in cord serum.

Some studies published after the JECFA assessment reported biomarker data in urine and breast milk.

Pearce et al. (2010) studied the effects of perchlorate on thyroid functions in a cross-sectional study in pregnant women (first trimester of pregnancy) from two European cities (Turin, Italy, and Cardiff, Wales). The initial cohort examined included hypothyroid (high serum TSH levels) and/or hypothyroxinaemic (low serum free T_4 levels) women from Cardiff (374 subjects) and Turin (261 subjects). A further cohort of euthyroid women (480 from Cardiff and 526 from Turin) was also

[21] Original data for iodine and perchlorate concentrations were reported as µmol/L in the publication. The levels converted to µg/L and reported in the present Scientific Opinion were confirmed by the study authors by personal communication.

examined. Iodine and perchlorate levels were measured in urine. Perchlorate was detected in all the subjects of the study, at median concentrations of 2.1 and 5.04 µg/L for hypothyroid/hypothyroxinemic subjects in Cardiff and Turin, respectively, and 2.6 and 5.2 µg/L for euthyroid subjects in Cardiff and Turin, respectively. Urinary iodine levels were low in all groups, with median levels of 98 and 55 µg/L for hypothyroid/hypothyroxinemic subjects in Cardiff and Turin, respectively, and levels of 117 and 50 µg/L for euthyroid subjects in Cardiff and Turin, respectively).

Data for 92 infants of 31 different age groups (from < 48 hours up to 12 months of age) were obtained from the original population of 165 infants included in a cross-sectional study performed in Pennsylvania, USA. The study population had a mean age of 122 days and included infants of different sexes, ethnicities and feeding methods (breast milk, cows' milk formula or soy milk formula). Urine samples for the selected population were screened for concentrations of iodine, perchlorate, thiocyanate and nitrate. Median concentration of 1.2 µg/L for perchlorate and 130.3 µg/L for iodine were measured in urine. Perchlorate concentrations were statistically significantly higher in urine from breast-fed infants (geometric mean concentration of 28.0 µg/g creatinine) and cows' milk formulae fed infants (9.5 µg/g creatinine) than from infants fed soya milk formulae (2.5 µg/g creatinine) (Cao et al., 2010).

Leung et al. (2012) studied the infant serum thyroid functions in relation to the environmental contamination with perchlorate and thiocyanate. In this study, 64 breast-fed, one to three-month-old infants and their mothers were recruited from the Boston Medical Center. Iodine, perchlorate and thiocyanate concentrations were measured in breast milk and in maternal and infant urine. Subjects with a history of thyroid disease, or of treatment with thyroid hormones iodine-containing medications or contrast agents were excluded from the study. The samples of breast milk from mothers and samples of urine and serum from the mothers and infants were collected within the same hour, except in one case for which the infant serum was collected 47 hours after the collection of the other samples. Median perchlorate concentrations were 4.4 µg/L in breast milk (range 0.5–29.5 µg/L), 3.1 µg/L in maternal urine (range 0.2–22.4 µg/L), and 4.7 µg/L in infant urine (range 0.3–134.5 µg/L). Median iodine levels of 45.6 µg/L (range 4.3–1 080 µg/L), 101.9 µg/L (27–570 µg/L) and 197.5 µg/L (range 40–785 µg/L) were measured in breast milk, maternal urine and infant urine, respectively. Univariate correlation analyses showed positive correlations for iodine levels in milk with iodine levels in maternal and infant urine, and perchlorate levels in breast milk.

Kirk et al. (2013) analysed the excretion of perchlorate in breast milk from 13 volunteers (between 25 and 34 years old) in Texas, USA. Each lactating woman provided between 27 and 34 breast milk samples (sampled at four different timepoints per day) and a daily sample of urine. Perchlorate and iodine levels were determined in breast milk and urine, and 24-hour excretion was calculated considering the measured concentrations and the daily urine volumes and the predicted daily breast milk volumes. Daily consumption of water and other fluids was recorded for all volunteers. Consumption of local tap water with known concentrations of perchlorate allowed the contribution from water to the overall exposure to be estimated. Mean perchlorate concentration in urine was 3.6 µg/L, corresponding to a daily mean urinary excretion of 5.8 ± 5.3 µg. Perchlorate concentrations in breast milk, reported in a separate publication (Kirk et al., 2012), appeared highly variable, ranging from 2.2 to 28.6 µg/L, with no apparent correlation to iodine levels in breast milk or to supplementation of iodine in the diet. The estimated mean daily amount of perchlorate in breast milk was 12.87 ± 8.99 µg. The maternal mean daily dose, estimated considering the daily excretion via urine and breast milk, was 0.186 µg/kg b.w. per day, the majority of which (0.173 µg/kg b.w. per day) was estimated to be via the consumption of food excluding drinking water (Kirk et al., 2013).

An overview of the perchlorate levels in urine and breast milk reported in the literature is given in Appendix D.

5.3.2. Clinical use of perchlorate

Potassium perchlorate was introduced in human pharmacology in the 1950s for the treatment of thyrotoxicosis.

Preliminary clinical studies on 24 patients showed an effective treatment of Graves' disease (autoimmune disease affecting the thyroid and causing hyperthyroid symptoms). Initially daily doses up to 400 mg potassium perchlorate (equivalent to 4 mg perchlorate ion/kg b.w. per day[22] for a 70-kg person and considering the difference in molecular weights for potassium perchlorate and perchlorate anion), divided in over four to five doses per day, were applied with no major side effects observed (Wolff, 1998). It was noted afterwards that higher dose regimes were necessary to efficiently control the thyroid hormone levels in some patients, and doses in the range of 600–1 000 mg potassium perchlorate per day (equivalent to 6–10 mg perchlorate ion/kg b.w. per day for a 70-kg person) were applied (divided in five dosages per day). With these doses, control of hyperthyroidism was achieved in three to eight weeks (Wolf, 1998) Subsequently doses were increased to 2 000 mg potassium perchlorate per day (20 mg perchlorate ion/kg b.w. per day) to shorten the time needed to obtain the therapeutic effects (Wolff, 1998), but this was associated with a higher incidence of adverse effects (Crooks and Wayne, 1960; Morgans and Trotter, 1960).

Potassium perchlorate has also been administered to children to treat hyperthyroidism. A case study described the effective use of potassium perchlorate at doses ranging from 200–300 mg per day in children of ages 6–13 years (equivalent to approximately 5–6 mg perchlorate ion/kg b.w. per day considering body weights in the range of 23–43 kg (EFSA SC, 2012)), with no significant side effects reported (Smellie, 1957).

The use of potassium perchlorate was virtually discontinued after the occurrence of seven cases of agranulocytosis and fatal aplastic anaemia observed in patients treated for 0.5–6 months with therapeutic doses of 400–1 000 mg potassium perchlorate per day (4–10 mg perchlorate ion/kg b.w. per day for a 70-kg person) (Wolff, 1998; Soldin et al., 2001). However, several studies are available on the treatment of hyperthyroidism with perchlorate during the 1970s and 1980s, with different treatment strategies aimed at minimising the side effects (lower doses and/or shorter treatment periods), which do give information on dose levels that may or may not be linked with adverse effects. For instance, Connell (1981) described the case of a patient suffering from Graves' diseases who was effectively treated for 22 years with 200 mg potassium perchlorate per day (2 mg perchlorate ion/kg b.w. per day) without any apparent complication (Soldin et al., 2001). Wenzel and Lente (1984) reported the case of 18 patients affected by Graves' disease and treated with 900 mg potassium perchlorate per day (9 mg perchlorate ion/kg b.w. per day) in an initial period until the serum thyroid hormone levels declined. After this period, maintenance therapy was continued for 12 months, in which the patients were treated with 40–120 mg potassium perchlorate per day (approximately 0.4–1.2 mg perchlorate ion/kg b.w. per day). During the maintenance therapy periods, the patients showed normal T_3 and T_4 levels and normal TSH-receptor stimulating antibodies (the cause of Graves' disease), and no side effects were reported in the study. The results of the Wenzel and Lente (1984) study, together with the results of the studies in healthy volunteers (see Section 5.3.3) led the NRC (NRC, 2005) to estimate that a sustained exposure to more than 0.4 mg perchlorate/kg b.w. per day is likely necessary to result in hypothyroidism in normal adults, but a lower dose could be sufficient to cause adverse effects in pregnant women, infants, children and people with low iodine intake or pre-existing thyroid dysfunction.

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 (Wolf, 1998; Soldin et al., 2001). The typical therapeutic strategy includes treatment with 600–1 000 mg/day potassium

[22] All the conversions present in the opinion from doses reported in clinical studies (expressed in mg potassium perchlorate/person per day), to doses expressed as mg perchlorate/kg b.w. per day include both the body weight factor (default of 70 kg for adults) and the differences in molecular weight between potassium perchlorate (138.55 g/mol) and perchlorate anion (99.45 g/mol).

perchlorate in combination with thionamides for 16–40 days (Martino et al., 2001). After an initial period, dosages with potassium perchlorate can continue at lower doses for up to six months (Soldin et al., 2001).

Nowadays, perchlorate is also applied for diagnostic purposes in the iodine discharge test to identify defects in iodine organification. In this application, 1000 mg potassium or sodium perchlorate is administered as a single dose (Soldin et al., 2001).

5.3.2.1. Adverse effects

Side effects related to the early use of perchlorate in human medicine included nausea, gastritis, skin rashes, occasional thyroid enlargement and leucopenia that was difficult to differentiate from that caused by thyrotoxicosis (Wolf, 1998).

In the review of 881 clinical cases treated with 400–600 mg potassium perchlorate per day (corresponding to 4–6 mg perchlorate ion/kg b.w. per day for a 70-kg person), the incidence of the adverse effects reported above ranged from 3 to 4 % (27 cases, including one case of leucopenia, 11 cases of cutaneous symptoms[23] and 15 cases of GI disturbances) (Krüskemper, 1960; Wolff, 1998). Crooks and Wayne (1960) and Morgans and Trotter (1960) showed a marked increase in the incidence of side effects when doses were increased above 1 000 mg potassium perchlorate per day (10 mg perchlorate ion/kg b.w. per day), reaching 16–18 % with daily doses of 1 200–2 000 mg potassium perchlorate (12–20 mg perchlorate ion/kg b.w. per day). In particular, Crooks and Wayne (1960) reported one case of skin rash and three cases of nausea in 200 patients treated with 600 or 1 000 mg per day (6–10 mg perchlorate ion/kg b.w. per day), and five cases of skin rash, two cases of nausea and one case of agranulocytosis in 50 patients treated with 1 500 or 2 000 mg per day (15–20 mg perchlorate ion/kg b.w. per day). Morgans and Trotter (1960) noted similar rates, reporting 5 % of side effects in 180 patients treated with 400–1 000 mg potassium perchlorate per day (4–10 mg perchlorate ion/kg b.w. per day) (no details provided), and 18 % of cases in 67 patients treated with 1 200 or 1 600 mg/day (12–16 mg perchlorate ion/kg b.w. per day) (12 cases, of which two cases of skin rash with fever, eight cases of skin rash alone, and two cases of lymphadenopathy). In commenting on the observed side effects, Morgans and Trotter (1960) postulated that they could have resulted from an immunological response to perchlorate.

Crooks and Wayne (1960) reported the therapeutic use of perchlorate in 12 pregnant women affected by hyperthyroidism (doses not reported). At birth, one neonate showed a small and transient goitre, whereas no adverse effects were reported for the others. No follow-up study is available for these children.

Following the report of one case of agranulocytosis reported in a woman treated for three weeks with 1 500 mg potassium perchlorate per day (15 mg perchlorate ion/kg b.w. per day) (Crooks and Wayne, 1960), several cases of blood dyscrasias associated with the use of perchlorate were reported (Soldin et al., 2001). In particular, five cases of aplastic anaemia were reported between 1961 and 1966 in patients treated with 400–1 000 mg potassium perchlorate per day (4–10 mg perchlorate ion/kg b.w. per day) for eight to 33 weeks (Soldin et al., 2001). Wolff (1998) noted that the fact that four cases of aplastic anaemia were reported in a cluster may suggest the presence of a contaminant in the perchlorate used in that period, but that no information was available in this respect. NRC (NRC, 2005) evaluated the possibility that side effects such as skin rash and blood dyscrasias are linked to an immunological reaction to perchlorate rather than to direct toxicity of the substance. NRC noted that the observed dose-dependency of these adverse effects would indicate a direct toxicity of perchlorate and concluded that there is no evidence of immunological abnormalities caused by regular ingestion of perchlorate (NRC, 2005). Wolff (1998) noted that the recent use of potassium perchlorate for shorter periods and at doses ≤ 1 000 mg per day (10 mg perchlorate ion/kg b.w. per day) is considered safe and no additional cases of aplastic anaemia or other serious side effects have been reported in the clinical use of perchlorate for the treatment of thyrotoxicosis induced by amiodarone. On the other

[23] Translated from the original publication (*Haut–sypmtome*).

hand, recently Bogazzi et al. (2008) reported the occurrence of mild leucopenia and of increased creatinine in two different patients, from a group of 10 patients administered 600 mg potassium perchlorate per day (6 mg perchlorate ion/kg b.w. per day) for 15–45 days for the treatment of amiodarone-induced thyrotoxicosis. In both cases, the effects disappeared when the treatment with perchlorate was discontinued.

In conclusion, adverse effects, including skin rash, nausea, lymphadenopathy and blood dyscrasias, have been reported following repeated treatment with ≥ 400 mg potassium perchlorate per day (4 mg perchlorate ion/kg b.w. per day), with evidence suggesting a direct relationship between the incidence and severity of the effects and the treatment dose and duration. The lowest dose at which adverse effects have been reported in patients treated pharmacologically with perchlorate is approximately 10 times higher than the exposure level of 0.4 mg/kg b.w. per day, at which NRC (2005) estimated that normal adults could be exposed to for sustained periods without developing hypothyroidism. 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.

5.3.3. Epidemiological studies and human volunteer studies

5.3.3.1. Healthy, non-pregnant adults

In healthy adults, repeated treatment with large doses of perchlorate was reported to be insufficient to totally deplete the thyroid gland of iodine (Soldin et al., 2001). For instance Brabant et al. (1992) observed incomplete iodine depletion in the thyroid gland in healthy male volunteers following four weeks of treatment with 900 mg potassium perchlorate per day (corresponding to 9 mg perchlorate ion/kg b.w. per day for a 70-kg person), although slightly decreased free T_4 levels and TSH levels were observed.

Lawrence et al. (2000) investigated the effects of perchlorate exposure in nine healthy male volunteers (22–30 years of age) following a single exposure to 10 mg perchlorate per day for a 14 day period (0.14 mg perchlorate/kg b.w. per day for a 70-kg person). Cumulative daily urinary perchlorate excretion increased from < 0.5 mg/day before the treatment period to approximately 7.5 mg per day at days 7 and 14 of treatment and returned to less than 0.5 mg/day two weeks after the end of the treatment period. No significant changes were observed in thyroid functions (serum TSH, T_4 and T_3) during the 14-day treatment with perchlorate. A mean thyroid iodine uptake inhibition of 38 % was observed at day 14 in comparison with the baseline levels. After the recovery period, the thyroid iodine uptake was statistically significantly higher than the baseline levels (mean of 25 %), suggesting an adaptive change of the iodine uptake in the presence of the perchlorate inhibiting effects. In a follow up study, eight healthy male volunteers were exposed for 14 days to 3 mg/day perchlorate (0.04 mg/kg b.w. per day) and subjected to the experimental protocol performed in the previous study (Lawrence et al., 2001). At this dose, a mean decrease of 10 % in thyroid iodine uptake was observed during the treatment period in comparison with baseline, without reaching statistical significance. Two weeks after the end of the treatment period, iodine uptake rates higher than those observed before treatment with perchlorate were observed, in line with the results of the previous study.

In a study selected by JECFA as key for the hazard characterisation of perchlorate, Greer et al. (2002) studied the effect of perchlorate on the thyroid uptake of radiolabelled iodine in human volunteers. A total of 37 healthy volunteers participated in the experiment (aged between 18 and 57 years). Perchlorate was administered in drinking water (400 mL per day, split into 100 mL every four hours from 8 a.m. until 8 p.m.). In the main study, 12 male and 12 female volunteers were treated orally with a daily dose of 0.02, 0.1 or 0.5 mg perchlorate/kg b.w. per day for 14 consecutive days (four subjects/sex per treatment dose). In a second study six women and one man were treated at a dose of 0.007 mg/kg b.w. per day, and one subject/sex per treatment dose were exposed to the doses used in the main study. Iodine uptake statistically significantly decreased at ≥ 0.02 mg perchlorate/kg b.w. per day during the treatment period, reaching a mean inhibition of 67 % at 0.5 mg/kg b.w. per day,

whereas no statistically significant differences from the baseline were observed on the uptake on day 15 (post-treatment) in all exposure groups. No statistically significant changes were observed in the monitored thyroid functions (total T_4, free T_4, total T_3 and TSH) during the study period in any treatment group in comparison with the baseline levels. Based on the thyroid iodine uptake inhibition, for this study the authors identified a NOEL of 0.007 mg/kg b.w. per day.

Lamm et al. (1999) and Braverman et al. (2005) studied occupational exposure in a perchlorate production plant. In the Lamm et al. (1999) study, 37 workers exposed during 12-hour night shifts in the plant, followed by a 3-day-off period, were selected. A group of 21 workers employed in a different sector in the same production site were included as study controls. The daily exposure by inhalation to perchlorate was estimated to be in the range 0.004–167 mg/person, and workers were divided into four exposure groups (1, 4, 11 or 34 mg/day of mean absorbed perchlorate levels, corresponding to approximately 0.014, 0.057, 0.157, or 0.486 mg/kg b.w. per day, for a 70-kg person). No effects were observed in the monitored thyroid functions (serum total and free T_4, total T_3, thyroglobulin and TSH levels, thyroid hormone binding ratio and thyroid peroxidase antibodies), and no clinical abnormalities were noted in any exposure group. In the Braverman et al. (2005) study, 29 subjects working for at least 1.7 years in the same perchlorate production plant were included. Twelve volunteers not working in the production plant were included as controls. In the production plant, workers were estimated to be exposed to 0.01–3 mg/kg b.w. per shift during the study (three consecutive 12-hour night shifts after a 3-day-off period), with a mean exposure of 0.33 mg/day estimated for the year preceding the study. In the exposed workers, radioactive thyroid iodine uptake was significantly lower during the work shifts (mean uptake of 13.5 % of the administered iodine dose) in comparison with the 3-day-off period (21.5 % mean uptake of the administered iodine dose), but was not statistically different from the control group (14.4 % mean uptake of the administered iodine dose). No differences were observed in TSH and thyroglobulin levels, whereas slight but statistically significant increases in total T_3, total T_4 and free T_4 index were observed in the workers during the work shift in comparison with the 3-day-off period and the control group. No effects on the thyroid were observed in the clinical examinations of the occupationally exposed population.

Braverman et al. (2006) treated 13 healthy volunteers with single oral daily doses of 0 (placebo, four subjects), 0.5 (five subjects) or 3.0 (four subjects) mg perchlorate per day for six months (corresponding approximately to 0, 0.007, or 0.040 mg perchlorate/kg b.w. per day). Urinary and serum perchlorate levels, and thyroid functions (serum total T_3, T_4, TSH and free T_4 index levels) were measured one month before the treatment period, monthly during the six months of treatment, and one month after the end of the treatment. Thyroid radiolabelled iodine uptake was analysed before the treatment period, at month 3 and 6 of treatment and one month after the treatment period. No statistically significant changes in iodine uptake or thyroid functions were observed between the subjects treated with placebo and those treated with 0.5 or 3 mg perchlorate per day. The authors noted that, with respect to the thyroid iodine uptake inhibition, the results differed from those obtained by Greer et al. (2002) following 14-days of exposure. The authors considered that these differences could be attributed to the small number of subjects in their study, to the different dosing regimes (once daily versus the semi-continuous regime of Greer et al., 2002), or to the possible presence of adaptive changes in the longer term exposure in comparison with the two-week study (Braverman et al., 2006).

In the context of the data collected in the 2001–2002 NHANES, Blount et al. (2006) evaluated the potential relationship between the urinary levels of perchlorate and the thyroid functions (serum TSH and total T_4 levels) in 2 299 men and women ≥ 12 years of age. When adjusting for confounding (e.g. age, sex, ethnicity, pregnancy status, or body mass index), a correlation between the perchlorate levels in urine and increased serum TSH levels and an inverse correlation with the serum total T_4 levels was observed in women with low urinary iodine excretion (< 100 μg/L). In subjects with higher urinary iodine excretion, a correlation between perchlorate urinary levels with serum TSH levels, but not with serum T_4 levels, was observed. A following evaluation of the Blount et al. (2006) publication noted that the correlation between serum T_4 levels and urinary perchlorate levels in the group with urinary iodine below 100 μg/L is not observed when iodine levels are adjusted for creatinine levels (Lamm et al., 2007). In the following analysis of the same dataset, Steinmaus et al. (2007) noted that the

correlation between urinary perchlorate levels and decreased T_4 levels in women with low UI levels was stronger for smokers, suggesting an interaction of thiocyanate (present in tobacco smoke) and perchlorate with the changes in thyroid functions.

Two studies were published after the JECFA assessment that evaluated the data from the 2007–2008 NHANES.

In one study, Mendez and Eftim (2012) correlated urinary perchlorate levels with thyroid hormone levels. A subset of the population studied in the 2007–2008 NHANES comprising 970 males and 907 females aged >12 years was selected. Pregnant women, individuals with thyroid diseases or with apparent hyperthyroidism, and subjects taking thyroid disease medications were excluded from the analysis. Urinary excretion data for bisphenol A or phthalate ester metabolites were also included in the analysis as covariates, as they were correlated with thyroid hormone levels in an overlapping subset of subjects from the same dataset. In the studied population, median perchlorate concentrations in urine were 4.3 µg/L (95 % CI 1.0–18.4 µg/L) in males and 3.4 µg/L (95 % CI 0.7–15.6 µg/L) in females. Median urinary iodine levels were 174 µg/L and 145 µg/L in males and females, respectively. urinary iodine excretion below 100 µg/L was reported for 21 % of males and 31 % of females. Statistically significant correlations between the increase in creatinine-adjusted urinary perchlorate levels and the thyroid function parameters (i.e. decrease in total T_4, free T_4 and free T_3 levels) were observed when considering the total population. When data for male and female subjects were analysed separately, a statistically significant association was observed in both sexes between adjusted perchlorate levels and free T_3 and total T_4. While acknowledging the limitations of the study (such as the small population subset and the impossibility of evaluating the temporal relationship between the exposure to perchlorate and the variation in the hormone levels), the authors concluded that exposure to perchlorate is a statistically significant predictor of changes in circulating thyroid hormone levels, although the magnitude of the effects appears to be modest. According to the authors, the study results suggest that the combined exposure to perchlorate and phthalates may lead to physiologically relevant changes in the general population, and noted that these findings increase the level of concern for sensitive populations, such as those presenting mild to moderate hypothyroxinaemia or overt thyroid diseases, and women of reproductive age.

In the other study, Steinmaus et al. (2013) studied the combined effects of perchlorate with thiocyanate and low iodine levels on thyroid hormone levels. Depending on the levels of the biomarkers under analysis, the subjects were categorised into three groups: group A, a low exposure group with both perchlorate and thiocyanate in the lower tertile of the respective distributions and urinary iodine ≥ 100 µg/L A (390 subjects); group B, an intermediate exposure group with both perchlorate and thiocyanate in the middle tertile of the respective distributions and urinary iodine ≥ 100 µg/L (553 subjects), and group C, a high exposure group with both perchlorate and thiocyanate in the upper tertile of the respective distributions and urinary iodine < 100 µg/L (64 subjects). The median urinary perchlorate concentration for the NHANES 2007–2008 was 3.90 µg/L (90 % CI 1.14–12.0 µg/L). When considering the three exposure groups, the median perchlorate levels were in the range 0.36–2.74 µg/L for group A, 2.75–5.80 µg/L for group B and 5.82–47.80 µg/L for group C. Thiocyanate ranges were 47–778 µg/L, 779–1 900 µg/L and 1 970–32 200 µg/L for groups A, B and C, respectively. A decrease in total and free T_4 levels was observed in group B (free T_4 0.793 µg/dl, total T_4 7.84 µg/dL) and group C (free T_4 0.750 µg/dL, total T_4 7.19 µg/dL) in comparison with group A (free T_4 0.822 µg/dL, total T_4 8.31 µg/dL), but no changes in TSH levels were observed. The authors noted that these effects were not dependent on identified confounding factors (such as age, gender or ethnicity).

5.3.3.2. Pregnant adults, fetuses and neonates

Several studies reviewed in the JECFA assessment (FAO/WHO, 2011) focused on the evaluation of the potential effects of environmental perchlorate concentrations on the most sensitive parts of the population.

In a series of studies related to the perchlorate contamination of drinking water (concentration range 4–16 µg/L) in the south west of the USA, populations living in contaminated drinking water areas were studied for the incidence of neonatal congenital hypothyroidism, neonatal thyroid parameters (T_4, TSH), and for potential indications of neurodevelopmental effects (attention deficit hyperactivity disorder, autism and school performances) (Lamm and Doemland, 1999; Li et al., 2000a,b; Chang et al., 2003).

Lamm and Doemland (1999) investigated the incidence of congenital hypothyroidism in 700 000 newborns in 1996–1997 from seven counties of California and Nevada in which perchlorate was detected in drinking water and compared it with the expected incidence for the whole state. No increased incidence was observed when considering the seven counties together (249 cases were identified, compared with the 243 cases expected) or individually.

Two studies considered the comparison of newborns from two cities in Nevada, Las Vegas (affected by perchlorate contamination in drinking water) and Reno (perchlorate below the LOD for the whole study period). In the first study, Li et al. (2000a) examined the blood T_4 levels during the first four days after birth from over 17 000 newborns from Las Vegas and 5 882 newborns from Reno, and observed no differences between the two populations. In the second study Li et al. (2000b) examined the effects on neonatal blood TSH levels in 407 newborns from Las Vegas and 133 newborns from Reno (aged 2 to 30 days). No statistically significant differences in TSH levels were observed between the newborns from the contaminated and non-contaminated areas.

Chang et al. (2003) assessed the school performances and the incidence of attention deficit hyperactivity disorder and autism in approximately 39 000 children from the Clark County with perchlorate-contaminated drinking water, in comparison with 8 471 children from the non-contaminated County Washoe, and with another 7 859 cases from the rest of Nevada. No differences were observed between the exposed population and the two control populations in neurobehavioural diseases or in school performance.

Finally, the general populations from the two Nevada counties were studied for incidence of thyroid diseases, including thyroid cancer in the two-year period of 1997–1998. Data for 122 519 subjects from the Clark county, 29 622 subjects from the Washoe county, and approximately an additional 25 000 subjects from other counties in Nevada were analysed. No increased incidences in overall thyroid diseases or in any specific thyroid disease, including thyroid cancer, were observed (Li et al., 2001).

In a retrospective study, Kelsh et al. (2003) examined the incidence of primary congenital hypothyroidism in a population of 15 090 newborns from 1983 to 1997 in an area in California with an environmental contamination of perchlorate in groundwater (Redlands), associated with the presence of an aerospace facility (data on contamination levels available only from 1997 onwards, ranging from < 4 to 130 µg/L). The findings in the contaminated area were compared with those from a population of 685 161 newborns from neighbouring areas with no groundwater contamination, and with the overall Californian population. In the contaminated area, a lower number of cases were identified than in the non-contaminated areas. No significant differences were observed for the infant serum TSH levels from the contaminated areas, the non-contaminated areas and the whole state. Buffler et al. (2006) analysed the thyroid functions of all Californian newborns in 1989 and compared the data from 24 communities in which perchlorate was detected at more than 5 µg/L with those from 287 communities in which it was detected at 5 µg/L or lower. No association between cases of hypothyroidism and levels of perchlorate in water were observed.

Brechner et al. (2000) compared the neonatal TSH levels recorded between 1994 and 1997 in two communities in Arizona with different levels of perchlorate detected in water. The population unexposed to perchlorate comprised 433 newborns from the city of Flagstaff, whereas 1 099 newborns from the city of Yuma (supplied with water contaminated with 6 µg perchlorate/L or more) were analysed as the exposed population. Following adjustments for age and ethnicity, the mean TSH levels

in the exposed population were significantly higher than those in the unexposed population. Subsequently, Goodman (2001) and Lamm (2003) noted that several confounding factors, including imbalances in ethnicity between the subjects in the two communities and the large difference in the elevations of the two cities, could have influenced the results of the study. In the following comparison between newborns from Yuma and those from two other neighbouring towns not supplied with water contaminated with perchlorate, no differences in TSH levels were observed (Lamm, 2003).

The possible effects of perchlorate were studied in the population from three villages in Chile, characterised by different levels of drinking water contamination with perchlorate (mean concentrations of 112 µg/L in the villages of Taltal, to 6.2 µg/L in the city of Chañaral, and non-detected levels in the city of Antofagasta). In one study, the thyroid functions of newborns and school-aged children were analysed (Crump et al., 2000). Data on TSH and free T_4 levels from 9 784 newborns and 162 children aged six to eight years were analysed. No associations between thyroid functions or the presence of thyroid disease and the levels of perchlorate in water were observed. In a subsequent longitudinal study in populations from the three cities, Téllez et al. (2005) studied the thyroid functions in mothers at early stages of gestation and in neonates at birth, together with signs of growth retardations. Exposure of pregnant women to perchlorate through consumption of tap water was estimated to be 0.42 µg/day in Antofagasta, 6.1 µg/day in Chañaral, and 93.5 µg/day in Taltal. Those estimates were well correlated with the urinary perchlorate excretion measured in the study subjects (see Section 5.3.2). No differences were noted in thyroid functions or neonatal growth parameters among the three populations.

Amitai et al. (2007) assessed the effects of perchlorate in newborn children exposed via mothers drinking tap water during the gestation period. The population target of the study lived in an area subject to a marked perchlorate contamination in groundwater in Israel, due to the presence of a military plant. Perchlorate concentrations in tap water ranged from ≤ 340 µg/L in the area with the most contaminated wells, to 42–94 µg/L in other wells in the proximities of the military plant. The study included 97 newborns from the area with high contaminations (very high exposure group), 216 newborns from the other areas at lower contaminations (high exposure group), and 843 newborns from a neighbouring city with concentration of perchlorate below 3 µg/L detected in groundwater (low exposure group). All the newborns included in the study were examined for the level of T_4 in the blood. In the very high and high exposure groups 31 and 62 mothers regularly drinking tap water during the gestation period were identified, respectively. Serum perchlorate levels measured in serum samples of blood donors from the three areas correlated with the water contamination levels. No statistically significant differences were observed amongst the very high, high and low exposure groups, when newborns from mothers from the very high and high exposure groups drinking tap water during the gestation period were compared with the control group.

Other studies, published after the JECFA review, were identified and are summarised below.

Pearce et al. (2010) studied the effects of perchlorate on thyroid functions in a cross-sectional study in pregnant women (first trimester of pregnancy) from two European cities (Turin, Italy, and Cardiff, Wales). The initial cohort examined included hypothyroid (high serum TSH levels) and/or hypothyroxinaemic (low serum free T_4 levels) women from Cardiff (374) and Turin (261). A further cohort of euthyroid women (480 from Cardiff and 526 from Turin) was also examined. Iodine and perchlorate levels were measured in urine (see Section 5.3.2). No correlation between thyroid functions and urinary perchlorate concentrations was observed in any group, even for subjects with urinary iodine levels below 100 µg/L. The authors concluded that exposure to low levels of perchlorate is ubiquitous, but it is not associated with changes in thyroid functions in iodine deficient women in the first trimester of pregnancy. Similar results were obtained by Pearce et al. (2012) in a cohort of 134 first-trimester pregnant women from Athens, Greece.

In a larger study, data on neonatal blood TSH levels were collected for 497 458 newborns from southern California (Steinmaus et al., 2010). Perchlorate concentrations in the municipal water sources were also collected and the population was divided into an exposed group (mean perchlorate

concentrations higher than 5 µg/L) and an unexposed group (≤ 5 µg/L). Statistical analyses were performed to assess the possible presence of covariates, such as ethnicity, gender, age of newborns and of mothers, and feeding type (breast feeding, infant formula or both). Increased odd ratios for high TSH levels were observed for the exposed group compared to the unexposed group, in particular when blood was taken within the first 24 hours following birth, with little influence of any of the considered covariates. Namely, the odd ratios (not adjusted for any of the considered covariates) between the two exposure groups for TSH > 25 µU/L (the cutoff concentrations at which neonates are screened for primary congenital hypothyroidism) were 1.53 and 0.72 when blood sampling was performed within the first 24 hours or after, respectively. When considering the upper 95th percentile TSH levels for the relative ages (i.e. 15 and 8 µU/L for samples collected within or after the first 24 hours after birth, respectively), odd ratios of 1.23 or 1.27 were calculated. The considered covariates had little influence on the results of the analysis. The authors acknowledged that the study could be biased by the presence of other covariates (such as the variability in iodine levels, or exposure to other goitrogenic agents) or the exposure misclassification. However they concluded that the study provides some evidence that perchlorate exposure is related to increased TSH levels in neonates, although they noted that the possible impact of the observed effects on public health is currently unknown.

Data on urinary and serum TSH and T_4 levels were obtained from a cross-sectional study that enrolled infants from 31 different age groups (from < 48 hours up to 12 months of age). Data for 92 infants were obtained from the original population of 165 infants included in the main cross-sectional study. Urine samples for the selected subgroup were also screened for concentrations of iodine, perchlorate, thiocyanate and nitrate (see Section 4.2.1). The study population had a mean age of 122 days and included infants of different sex, ethnicities and feeding methods (breast milk, cows' milk formula or soy milk formulae). Serum TSH and T_4 levels were available from only 42 out of 92 subjects. Mean concentrations of 1.2 µg/L for perchlorate and 130.3 µg/L for iodine were measured in urine. Perchlorate concentrations were statistically significantly higher in breast-fed and cow's milk formula-fed infants than in soya milk formula-fed infants. No associations between urinary perchlorate levels and serum TSH and T_4 levels were observed (Cao et al., 2010).

Leung et al. (2012) studied the infant serum thyroid functions in relation to the environmental contamination with perchlorate and thiocyanate. In this study, 64 breast-fed, one to three month old infants and their mothers were recruited from the Boston Medical Center. Iodine, perchlorate and thiocyanate concentrations were measured in breast milk and in maternal and infant urine (see Section 5.3.2). Infant serum TSH and free T_4 levels were also measured. Subjects with a history of thyroid disease, or of treatment with thyroid hormones, iodine-containing agents or contrast agents were excluded from the study. The samples of breast milk, urine and serum were collected within the same hour from the mothers and the infants, except in one case for which the infant serum was collected 47 hours after breast feeding. Univariate correlation analyses showed positive correlations for iodine levels in milk with iodine levels in maternal and infant urine, and perchlorate levels in breast milk. No correlations were observed between the thyroid function parameters in infant serum and iodine and perchlorate levels in breast milk, maternal urine and infant urine.

Suh et al. (2013) studied the association of exposure to perchlorate, nitrate and thiocyanate with changes in the thyroid hormone levels in subjects from the 2001–2002 and 2007–2008 NHANES surveys. For the first survey, seven subgroup populations were analysed: all participants (1 875 subjects), men with urinary iodine below 100 µg/L (171 subjects), men with urinary iodine above 100 µg/L (718 subjects), non-pregnant women with urinary iodine below 100 µg/L (307 subjects), non-pregnant women with urinary iodine above 100 µg/L (564 subjects), all pregnant women (92 subjects) and pregnant women with urinary iodine below 150 µg/L (48 subjects). Following the result of the 2001–2002 survey analysis, the study of the 2007–2008 survey focused only on pregnant women (all pregnant women, 49 subjects and pregnant women with urinary iodine below 150 µg/L, 27 subjects). Differences in the creatinine-adjusted geometric mean urinary concentrations of perchlorate, nitrate and thiocyanate were observed among the different populations. Pregnant women with iodine < 150 µg/L from the 2001–2002 survey showed lower free T_4 levels than the other groups. This group of pregnant women also had the lowest creatinine-adjusted geometric

mean concentration of urinary perchlorate, which was statistically significantly lower than that in men with iodine below or above 100 µg/L. Other differences in the urinary concentrations of perchlorate, nitrate and thiocyanate were observed among the different populations. In particular, differences in the thiocyanate urinary concentrations were observed between men and pregnant women, probably indicating exposure via cigarette smoke and smoking cessation during pregnancy. No association was observed between nitrate and thiocyanate levels and changes in thyroid hormones. Perchlorate and nitrate urinary concentrations were found to be significant predictors of free T_4 decreased levels in non-pregnant women only. However the authors pointed out that the collection of single spot samples may be the limiting factor to observe possible correlations during pregnancy, due to the higher variability of free T_4 at different gestation stages, and noted that repeated measurements of urinary perchlorate, nitrate and thiocyanate and serum free T_4 would be needed to study the possible association of the exposure to those chemicals with changes in thyroid status.

Charatcharoenwitthaya et al. (2014) studied the effects of perchlorate and thiocyanate in 200 first-trimester pregnant women in Thailand. The study subjects aged range 18–40 years and in the gestational age less than or equal to 14 weeks. Individuals with a history of thyroid diseases were excluded from the study and healthy subjects were selected based on their medical records and prenatal history. The study participants were analysed for serum TSH, free T_4, free T_3, and urinary perchlorate, thiocyanate and iodine levels. All women were non-smokers but 178 out of 200 reported passive exposure to tobacco smoke. Perchlorate and thiocyanate were detected in the urine of all the study participants (mean perchlorate level 3.0 ± 3.9 µg/L, creatinine-corrected value 0.3 ± 0.4 µg/100 mg creatinine;[24] mean thiocyanate level 624.9 ± 435.9 µg/L, creatinine-corrected value 72 ± 54 µg/100 mg creatinine). Iodine was detected at a mean level of 177.8 µg/L (20 ± 13 µg/100 mg creatinine). The correlations between perchlorate, thiocyanate, and iodine creatinine-normalised levels and the thyroid hormone levels were calculated in all the study subjects. Statistically significant positive correlations were observed between perchlorate and thiocyanate levels and TSH levels. Statistically significant negative correlations were observed between perchlorate and thiocyanate levels and free T_4 levels. A statistically significant positive correlation was also observed when considering the perchlorate/iodine ratio and TSH levels. No differences in correlations of perchlorate and thiocyanate levels with serum thyroid hormone levels were observed when comparing the participants with low iodine urinary levels (< 100 µg/L) with those with high iodine urinary levels (> 100 µg/L). However, statistically significantly higher thiocyanate levels and higher pre-pregnancy body mass index were observed in the low urinary iodine group than in high urinary iodine group. The study authors concluded that the study showed for the first time an association between environmental exposure to perchlorate, increased TSH levels and decreased free T_4 levels in first trimester pregnant women. In comparison with previous similar studies, the authors noted the higher median iodine levels and higher median thiocyanate levels, but also the lower median perchlorate levels of the Thai cohort. Another difference from the previous studies was that the creatinine-normalised urinary levels for iodine, perchlorate and thiocyanate were used for the correlation with the thyroid hormone levels. Finally, the mean gestational age of the Thai cohort was lower than those of the cohorts analysed in the previous studies. The authors noted that, similarly to the other cross sectional studies, it was not possible to establish a clear causality between the levels of environmental contaminants and the changes in thyroid hormone levels. In addition, measurements of urinary perchlorate, thiocyanate and iodine levels were from single spot samples and this hampers the possibility to assess the iodine status and the variability in exposure to the environmental contaminants.

5.3.4. Conclusions

Several observations in humans, including clinical studies and case reports from the medicinal use of potassium perchlorate, volunteer studies and both occupational and ecological epidemiological studies on the effects of exposure to perchlorate are available.

[24] Creatinine-adjusted data reported in the publication were affected by an error in the conversion. Following personal communication with one of the study authors, the corrected data were reported in the present scientific opinion.

Potassium perchlorate was introduced in human pharmacology for the treatment of hyperthyroidism. Clinical doses ranging from 400 mg/day to 2 000 mg/day (administered in four to five dosages per day and corresponding to 4–20 mg perchlorate ion/b.w. per day for a 70 kg person) were applied in order to control the thyroid hormone levels. However, adverse effects, including skin rash, nausea, lymphadenopathy and blood dyscrasias, have been reported following repeated treatment with ≥ 400 mg/day potassium perchlorate (equivalent to 4 mg perchlorate ion/kg b.w. per day for a 70-kg person), with evidence suggesting a direct relationship between the incidence and severity of the effects and the treatment dose and duration. Following the experience from the early use of potassium perchlorate, more careful treatment strategies were developed and several cases of safe use of the substance with lower doses and/or shorter duration are reported in the literature. For instance, thyroid hormone levels in patients suffering from Graves' disease were lowered to normality by an initial daily dose of 900 mg potassium perchlorate (9 mg perchlorate ion/kg b.w. per day for a 70-kg person), and were maintained at a normal level for 12 months with 40–120 mg potassium perchlorate (0.4–1.2 mg perchlorate ion/kg b.w. per day for a 70 kg person), without any adverse effect reported. A case of one patient who was administered a daily dose of 200 mg potassium perchlorate (2 mg/kg b.w. per day) for 22 years without any apparent complication is also reported.

Studies on healthy adult volunteers repeatedly exposed to 0.007–0.5 mg perchlorate/kg b.w. per day for two weeks, as well as information from occupational studies, showed no correlation between the exposure to perchlorate and any adverse effects or significant changes in the thyroid hormone levels, even at exposure levels associated with a substantial inhibition of iodine thyroid uptake. In particular, in one study considered as the pivotal study for hazard characterisation by JECFA (FAO/WHO, 2011), healthy adult volunteers exposed to 0.007–0.5 mg/kg b.w. per day for 14 days showed no changes in thyroid hormones associated with an inhibition of thyroid iodine uptake up to 67 % (Greer et al., 2002).

From the body of evidence available from medicinal use of potassium perchlorate, the studies on adult volunteers and the epidemiological studies in the occupational environment, NRC (2005) and JECFA (FAO/WHO, 2011) concluded that a sustained exposure to more than 0.4 mg perchlorate ion/kg b.w. per day is likely necessary to cause hypothyroidism in normal adults, although a lower dose could be sufficient to cause adverse effects in pregnant women, infants, children and people with low iodine intake or pre-existing thyroid dysfunction.

Retrospective epidemiological studies at the general population level, including sensitive subjects such as pregnant women and infants, showed contradictory results, some of them indicating changes in thyroid hormone levels in populations living in areas with known perchlorate contamination in drinking water (> 5 µg/L). In particular, positive associations were often observed when potential exposure to perchlorate occurred in the presence of other risk factors, such as low dietary iodine intake, or exposure to other goitrogenic agents such as thiocyanate via tobacco smoke. The reported changes were of limited magnitude, were not associated with any disease and were not confirmed in other studies. Moreover, these epidemiological studies are of limited use for the evaluation of risks, because of the limited, or non-existent, information on exposure levels, the general natural high variability of the thyroid hormone levels, and the presence of possible confounding factors that are not taken into account in the analysis (e.g. the potential effect of altitude on changes in thyroid hormone levels observed by Brechner et al., 2000). JECFA noted that in none of the ecological studies a clear relationship between exposure to perchlorate in drinking-water and the incidence of thyroid diseases is shown (FAO/WHO, 2011). The CONTAM Panel agreed with the conclusions drawn by JECFA, and concluded that information published after the JECFA evaluation did not change the previous conclusions on epidemiological studies.

5.4. Mode of action

The toxic effects of perchlorate on the thyroid hormone system result directly from perchlorate's competitive inhibition of thyroidal uptake of iodine into the thyroid follicular cells (ATSDR, 2008). The perchlorate anion interacts with the sodium-iodide symporter protein (NIS), located in the

basolateral membrane of the thyroid follicular cells, competing with iodine. The perchlorate anion is then transported further into the thyroid lumen before it diffuses passively out of the thyroid gland into the blood supply and is subsequently eliminated in urine (FAO/WHO, 2011; Fisher et al., 2012). The NIS is also present in other tissues, including human placenta, breast tissue, salivary gland tissue and gastric mucosa. In breast tissue the NIS is thought to play a role in the transport of iodine into breast milk. In rats, increased expression of NIS was noted to occur during nursing and decreases after weaning (Levy et al., 1997, 1998; Smanik et al., 1997; Clewell et al., 2007; Tran et al., 2008). The NIS has been shown to have a greater affinity for perchlorate (30-fold greater) than for iodine in Chinese hamster ovary cells (Tonacchera et al., 2004). Densities of expression of NIS in thyroid follicular cells are different between humans and rats, with high densities in rats and densities described as 'patchy' in humans (Joseffsson et al., 2002).

Severe and sustained inhibition of iodine uptake in the thyroid following exposure to perchlorate can limit the availability of iodine required for the production of thyroid hormones T_3 and T_4, which could cause depletion of thyroid stores of these hormones and lower hormone serum levels (ASTDR, 2008). Decreases in circulating levels of thyroid hormones, will trigger the hypothalamic-pituitary-thyroid (HPT) feedback pathway, resulting in an increase in secretion of TSH (ATSDR, 2008). TSH binds to a receptor in the basolateral membrane of the thyroid follicle cell and under normal conditions, TSH stimulates thyroid iodine uptake and production and secretion of the thyroid hormones T_3 and T_4, and promotes growth of thyroid follicle cells. Persistent stimulation of the thyroid gland by elevated levels of TSH results in increases in thyroid gland size and weight (goitre), decreased colloid, hypertrophy and hyperplasia of thyroid follicle cells and thyroid tumours in rats (ASTDR, 2008; Fisher et al., 2012).

The pituitary-thyroid system is qualitatively similar in rats and humans in that the HPT feedback pathway maintains homeostasis in both species, however the dynamics of the system in both species differ substantially (NRC, 2005; FAO/WHO, 2011; Fisher et al., 2012).

There are differences in binding proteins for the thyroid hormones T_3 and T_4 between rats and humans. In humans the principal binding protein for T_4 is thyroxine-binding globulin (TBG); however, in rats, T_4 mainly binds to albumin and transthyretin. The rat binding proteins have a 100-times lower binding affinity, than TBG in humans, which contributes to a higher clearance rate of T_4 in rats, causing a higher production of T_4 in order to maintain normal T_4 concentrations. The plasma half-life of T_4 in rats is 12–24 hours compared with 5 to 9 days in humans (NRC, 2005). The higher T_4 production in rats is reflected in a more functionally active histological appearance of the rat thyroid; follicular epithelium in rats is cuboidal, compared with a more flattened appearance in primates (NRC, 2005)

The duration of exposure to perchlorate that is required to cause disturbances in circulating levels of serum thyroid hormones, is shorter in rats compared to humans. This is considered to be due to the rat thyroid gland having a smaller store of iodinated thyroglobulin, compared to humans, that is quickly depleted when iodine is limited (ASTDR, 2008). Close to birth, human fetal stores of iodine are also much greater compared to rat fetal levels, and the weight of the thyroid gland (relative to body weight) is also lower in the rat fetus, indicating the immature nature of the thyroid gland in the rat fetus near birth (Fisher et al., 2012).

The occurrence of thyroid tumours (papillary/follicular adenomas and carcinomas), following exposure to perchlorate, have been noted in rats and mice. There has been no direct evidence of perchlorate causing cancer in humans (ATSDR, 2008). The development of thyroid tumours following exposure to perchlorate is seen as unlikely in humans (NRC, 2005). In rats, thyroid function is easily disrupted and tumours are thought to occur from the constant stimulation by TSH (due to reduced iodine levels) of the thyroid gland to synthesise and secrete T_3 and T_4. However, in humans the thyroid appears to be less sensitive to increased TSH caused by iodine deficiency (Fisher et al., 2012). Studies in humans have shown no increase in serum TSH levels or decreases in T_3 and T_4 levels following exposure to perchlorate for 14 days compared with the same duration of exposure in rats (NRC, 2005).

In humans, severe iodine deficiency as a result of insufficient iodine intake or sustained exposure to goitrogenic substances such as perchlorate to levels that induce depletion of the thyroid hormone stores can result in hypothyroidism. However, a mild to moderate iodine deficiency can lead to the development of toxic multinodular goitre (TMNG) and can result in hyperthyroidism (Laurberg et al., 2010). Adaptation of the thyroid gland in compensating for these less severe iodine deficiencies can cause increased proliferation of thyroid follicular cells, during which mutations can occur, resulting in the development of autonomously functioning nodules within the thyroid (Laurberg et al., 2010). Within the thyroid, both autonomously functioning and non-active areas of inactive tissue co-exist. The autonomously functional nodules within the thyroid secrete thyroid hormones and suppress TSH, which leads to the remaining thyroid tissues becoming quiescent (Sturniolo et al., 2013). The mechanism by which a mild to moderate deficiency in iodine can cause autonomisation may include up-regulation of thyroidal processes resulting in growth of the thyroid gland or the up-regulation of H_20_2 production by the thyroid (Laurberg et al., 2010). Excess levels of H_20_2 may have a role in promoting mutations of thyroid cells which may lead to the formation of autonomously functioning nodules within the thyroid (Laurberg et al., 2010).

Thyroid hormones are essential for normal fetal growth and differentiation of many organs, especially in pre- and post-natal central nervous system and brain development (Scinicariello et al., 2005). The fetus is dependent on maternal thyroid hormones until it can produce its own at approximately 16–20 weeks of gestation. Brain development in the human fetus occurs prior to this time point, with a major growth spurt due to neuron multiplication, occurring between 12 and 18 weeks of gestation, followed by glial cell multiplication, myelination and formation of dendritic extensions and synapses commencing from approximately 18 weeks of gestation (Oppenheimer and Schwartz, 1997; Boyages, 2000; Fisher and Brown, 2000). At eight weeks of gestation, thyroid hormones have been detected in amniotic fluid and fetal thyroid hormone receptors are present and occupied at this time point, which suggests a fetal response to maternal thyroid hormones (Bernal and Pekonen, 1984; Ferreiro et al., 1988; Thorpe-Beeston et al., 1991; Contempre et al., 1993). The developmental period that is most sensitive to perchlorate exposure is considered to be the first trimester, as the fetal brain is forming and the fetus is dependent on maternal thyroid hormones (Scinicariello et al., 2005; Ginsberg et al., 2007). In addition, the first trimester surge of maternal free T_4 is considered to be a biologically relevant event to ensure that an adequate supply of T_4 is available to the cerebral cortex. Therefore, during early pregnancy women with low T_4 levels could be at risk of producing children with neurological disabilities (Morreale de Escobar et al., 2004). In the rat, maternal thyroid hormones are also important in development; studies have shown that T_3 and T_4 are present in rat fetal tissue prior to the production of these hormones by the fetus itself, which occurs from approximately day 17 of gestation. Decreases in maternal T_4 levels may have adverse consequences on rat fetal brain development (ASTDR, 2008).

Neonates are more vulnerable to thyroid hormone perturbation compared to adults and fetuses. This is because the serum half-life of T_4 is lower in neonates than in adults (approximately three days in neonates), resulting in a higher replacement rate for T_4, which is necessary to maintain T_4 levels at a steady state. In addition, the adult thyroid gland contains a reserve store of thyroid hormone (several months worth), whereas in neonates this reserve would cover less than one day according to the study authors. The neonate must depend on the function of its own thyroid gland for the production of thyroid hormones, as very little is passed from the mother through breast milk. As demands for thyroid hormone are increased in the neonate, due to storage deficiencies and rapid hormone turnover, this population could be more sensitive than individuals of other life stages to the effects of perchlorate exposure. In addition, the ability of perchlorate to limit iodine excretion in to breast milk, together with the potential transfer of perchlorate via breast milk to the neonate, further increases the risk to neonates (Ginsberg et al., 2007).

The effects of perchlorate, in relation to its ability to interfere with iodine uptake, could have a greater impact on individuals with a low iodine dietary intake (FAO/WHO, 2011). In addition, in a review by Scinicariello et al. (2005) genetic factors were identified, which could result in different responses to perchlorate exposure, in order to define a subpopulation more susceptible to perchlorate exposure. The genetic defects identified were those involved in thyroid iodine uptake, which would result in a

reduction in thyroid hormone synthesis i.e., defects in iodine transport from the blood into the thyroid cells and from thyroid cells to the lumen and defects in iodine organification (the thyroid peroxidase mediated oxidation of iodine to facilitate its incorporation into tyrosine residues in thyroglobulin for the production of thyroid hormone). The study concluded that individuals with heterozygous or homozygous genetic 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.

In conclusion, for the quantitative assessment of human health risk and deriving health-based guidance values (HBGVs) for perchlorate, rat study data are of limited use, due to differences in the dynamics of the pituitary-thyroid system between both species. Fetuses, neonates and individuals with low iodine dietary intake or who are genetically predisposed to develop hypothyroidism, are considered to be more susceptible to the effects from perchlorate exposure.

5.5. Physiologically-based kinetic modelling

In a series of studies, Clewell and co-workers developed physiologically-based kinetic (PBK) models for perchlorate and iodine in rats and humans at different life stages.

A PBK model for male adult rats was developed using data from experimental toxicokinetic studies. The model was validated for its ability to predict thyroid iodine uptake at different doses of perchlorate administered by single intravenous injection or by repeated exposure via drinking water (Merrill et al., 2003). The PBK model also successfully predicted perchlorate and iodine concentrations in various tissues determined in different studies. Similarly, rat PBK models were developed for single perchlorate exposure in pregnant females and fetuses (day 20 of gestation) (Clewell et al., 2003a), and for neonates exposed via breast milk (PND 10) (Clewell et al., 2003b). Following a single exposure of the dams to 0.01 mg/kg b.w. via drinking water, the serum area under the curve (AUC) estimates for perchlorate indicated that in late pregnancy the fetus is exposed to relatively higher internal doses than dams, adult rats (male rats, and pregnant and lactating female rats) and neonates. Consistently, at this dose thyroid iodine uptake inhibition was estimated to be higher in the fetus than in the male rat, pregnant rat, lactating rat or neonates. The differences among the life stages progressively disappear as the external dose increases from 0.01 to 10 mg/kg b.w. At 0.01 mg/kg b.w. per day neonate rats showed the lowest inhibition of thyroid iodine uptake in comparison with other life stages, and in particular thyroid iodine uptake inhibition in neonates was 10-times lower than the corresponding inhibition in fetuses.

The human PBK models for the simultaneous kinetics of iodine and perchlorate were developed based on the rat models and took into account some fundamental physiological differences (e.g. iodine and perchlorate binding by plasma proteins was included as a separate compartment in the human models). For adult non-pregnant adults, available human-specific parameters for iodine and perchlorate were used and in general showed to be similar with the male rat-specific data (Merrill et al., 2005). The model developed for adult humans was validated against the available experimental data and showed a good predictability of the cumulative perchlorate urinary excretion and serum perchlorate levels determined in different studies, where subjects were exposed to perchlorate in drinking water at doses ranging from 0.02 to 12 mg/kg b.w. per day. The thyroid iodine uptake inhibition observed in the Greer et al. (2002) study (see Section 5.3.3) was also successfully predicted by the model. The model was considered sufficiently predictive for euthyroid (adult) individuals with adequate iodine intake (Merrill et al., 2005). Similarly to rats, PBK modelling was subsequently extended to pregnant and lactating women, fetuses and infants by Clewell et al. (2007). In this study, most of the chemical specific parameters were not available for the perinatal humans and were estimated from previous data in rats and adult humans applying life-stage and species-specific adjustment factors. The model predictability for iodine kinetics was successfully validated against data available for all the studied life stages. For the model describing iodine and perchlorate kinetics, the number of experimental data available for model validation was much lower, in particular with respect to the thyroid iodine uptake inhibition in fetuses and neonates. The authors assumed that the good predictability for iodine across

human life stages could be extended also to perchlorate, since the almost identical models showed a good predictability for both iodine and perchlorate in adult rats, adults humans and across different rat life stages. A lower perchlorate urinary clearance was considered during gestation and lactation and, using this assumption, the model adequately described the perchlorate levels in maternal serum, cord blood and maternal milk. The epidemiological data from Téllez et al. (2005), Crump et al. (2000) and Gibbs et al. (2004) were used to validate the model predictability for perchlorate kinetics across the different life stages. The models were used to predict the inhibition of iodine thyroid uptake at different single ingested doses of perchlorate in the range 0.001–1 mg/kg b.w. per day and covering different life stages (between gestation week 12 and one year of life) (see Table 11). The model predictions indicated that the fetal dose was consistently higher than the maternal dose (expressed per kg b.w.). A similar trend was observed for neonates exposed via the breast milk at low external doses of perchlorate, whereas the opposite was observed at higher external doses, reflecting the saturation of the NIS in the mammary gland. Predicted serum perchlorate levels were higher in the fetus, pregnant woman, lactating woman and neonate in comparison to the older child and the non-pregnant adult. Maternal and fetal serum AUCs were constant during the gestation period, whereas during lactation maternal and neonate AUCs reached maximum levels in the first postnatal week and at postnatal month three, respectively. Consistently with the predicted differences in the AUC, across the different life stages, the fetus, pregnant woman, lactating woman and neonate showed higher inhibitions of thyroid iodine uptake (e.g. inhibition ranging from 0.9 to 1.1 % is predicted at the exposure level of 0.001 mg/kg b.w. perchlorate in these life stages) than the adult and older child (0.6 % and 0.3 % of inhibition predicted at 0.001 mg/kg b.w. per day perchlorate, respectively), and these differences were less evident with increasing doses (see Table 11).

The human PBK models developed by Clewell and coworkers were evaluated and reviewed by McLanahan et al. (2014). Several errors were reported in the mathematical description of the models, most of them considered to have a little impact on the model output. However, it was noted that iodine uptake inhibition induced by perchlorate in other tissues than thyroid was not taken into account by Clewell and coworkers. This is particularly important for the transfer of iodine into breast milk, which was decreased by about 3 % (for a perchlorate maternal dose of 7 µg/kg b.w.) when the uptake inhibition in the mammary gland tissue was included in the model, resulting in a predicted thyroid iodine uptake inhibition that was nearly doubled in the breast-fed infants. The corrected models were applied to estimate the thyroid iodine uptake inhibition under a steady state perchlorate concentration. The predictions of the corrected models developed by McLanahan et al. (2014) were compared to those of the models developed by Clewell and coworkers, showing a good correlation for all life stages, with the exception of the breast-fed infants and lactating women. For breast-fed infants, the thyroid iodine uptake inhibition almost doubled was predicted by the corrected models in comparison to those developed by Clewell and coworkers (e.g. at a maternal dose of 0.01 mg perchlorate/kg b.w. per day, thyroid iodine uptake inhibitions of 17 % and 8 % were predicted by the revised PBK model and the model from Clewell and coworkers, respectively. See Table 11). A lower thyroid iodine uptake inhibition was predicted for lactating women by the corrected model than the prediction of the model developed by Clewell and coworkers (e.g. 10 % versus 6.0 % inhibitions predicted at 0.01 mg perchlorate/kg b.w. per day; see Table 11). McLanahan et al. (2014) also evaluated uncertainties and limitations associated with the PBK models and identified data that need to be considered for model refinement. Amongst the main limitations identified, it is worth noting that the PBK models were not developed to describe the dietary iodine intake, or to take into account the regulation of the thyroid hormones and thyroid axis. For those reasons, the developed models are not applicable to predict the effects of perchlorate in iodine-deficient individuals or in subjects with thyroid dysfunction (hypothyroid, hyperthyroid and other thyroid disease states).

Table 11: Thyroidal radioactive iodine uptake inhibition percentages estimated from physiologically-based kinetic (PBK) models in different human life stages following exposure to different doses of perchlorate 24 hours after a single dose of iodine (adapted from Clewell et al., 2007 and McLanahan et al., 2014)

Perchlorate (mg/kg b.w. per day)	Pregnant woman[(a)]		Fetus[(a)]		Lactating woman[(b)]		Breast-fed neonate[(c)]		7 years old child		Adult	
	C	ML	C	ML	C	ML	C	ML	C	ML	C	ML[(d)]
0.001	1.0	0.92	1.1	1.3	1.1	0.60	0.9	1.9	0.3	0.3	0.6	–
0.01	9	8.5	10	11	10	6.0	8	17	3	2.7	4	–
0.1	50	49	49	51	54	43	34	68	21	22	31	–
1.0	91	90	84	85	92	89	63	95	72	74	81	–

b.w.: body weight; C: predictions from PBK models developed by Clewell and coworkers; ML: predictions from PBK models developed by McLanahan and coworkers.
(a): Pregnant woman and fetus shown at gestation week 38.
(b): Lactating woman shown at post natal day 7.
(c): Neonate exposed via breast milk shown at post natal day 45. According to Clewell et al. (2007) model predictions, the infant doses via breast milk are higher than the maternal doses in the range 0.001–0.1 mg/kg b.w. per day.
(d): Data not available from McLanahan et al. (2014).

A human PBK model similar to that developed by Clewell and coworkers (2007) was applied by Lumen et al. (2013) for the development of a biologically based dose-response (BBDR) model for the HPT axis in the near-term pregnant mother and fetus. The BBDR model was developed to predict the changes in T_4 and T_3 levels in maternal and fetal serum in association with different perchlorate doses and iodine dietary intakes. Several assumptions were taken in the BBDR model, due to the lack of data, in particular with respect to the thyroid hormone physiology during pregnancy (e.g. no data available for thyroid hormone degradation rates and volumes of distribution during gestation, and thyroid hormone placental transfer to the fetus). The authors also noted that there is a poor understanding of the thyroid functions under conditions of mild-to-moderate iodine deficiency, and that assumptions were made to replicate the non-linear trend in the T_4 levels associated with urinary iodine excretion in the range 60–200 µg/L and that specific assumptions had to be considered to reproduce this trend in the BBDR model. The kinetic parameters of thyroid hormones for the mother and fetus were adapted from those available for non-pregnant adults with some corrections (e.g. increased thyroid hormone synthesis, secretion and metabolism were assumed during gestation in comparison to non-pregnant adults, based on literature data). Published euthyroid maternal and fetal steady-state levels for T_4, free T_4 and T_3 and TSH were used to calibrate the model. Maternal T_4 was estimated to contribute to the fetal serum levels for approximately 20–50 %, with the remaining fraction produced by the fetus thyroid at rates estimated from available literature. T_3 kinetic parameters were not available for the fetus, and were estimated by fitting with the available steady-state levels. The calibration of the BBDR model for varying iodine dietary intake levels was carried out, relying on data from various publications on hormone levels measured in pregnant women with sufficient or deficient intakes of iodine. The calibration of the BBDR model for perchlorate exposure conditions in the mother and fetus relied mainly on the biomonitoring data from Téllez et al. (2005). The BBDR model was applied to estimate maternal and fetal serum free T_4 levels at various exposure levels of perchlorate and under different iodine dietary intakes. For both the mother and the fetus under sufficient maternal iodine intake (100–250 µg per day), no marked changes in serum free T_4 levels were predicted for exposure to perchlorate up to 10 µg/kg b.w. per day, with serum free T_4 levels predicted to always be higher than the threshold associated with hypothyroxinaemia (10 pmol/L). Serum free T_4 levels were predicted to decrease by more than 50 %, falling below the 8.5 pmol/L threshold associated with hypothyroidism, at 100 µg/kg b.w. per day perchlorate in combination with iodine intake levels of 100–250 µg per day. By decreasing the iodine intake levels to 75 µg per day, serum free T_4 levels slightly below the threshold for hypothyroxinaemia (10 pmol/L), but above the threshold associated with hypothyroidism (8.5 pmol/L) were predicted at 10 µg/kg b.w. per day perchlorate. An almost complete depletion of serum free T_4 levels was predicted in both the

mother and the fetus exposed to 1 000 µg/kg b.w. per day perchlorate, independently from the dietary iodine intake (see Table 12) (Lumen et al., 2013). In their conclusion, the authors noted that the developed BBDR model should be considered as a proof of concept for the development of a model using data-informed approaches and identified several requirements for further refinement. The CONTAM Panel concluded that in view of the limited information available on the changes in thyroid hormone levels under conditions of mild to moderate iodine deficiency and on the thyroid hormone kinetic parameters for pregnant women, and the limitations of the PBK model predictability for iodine-deficient individuals identified by Clewell et al. (2007) and McLanahan et al. (2014), the results of the BBDR model at low iodine intake should be interpreted with caution.

Table 12: Biologically-based dose-response model-predicted serum free T_4 levels in the mother and fetus for various exposure levels of perchlorate and iodine dietary intakes. Maternal serum free T_4 levels below 10 pmol/L and 8.5 pmol/L are associated with hypothyroxinaemia and hypothyroidism, respectively (adapted from Lumen et al., 2013).

Iodine intake (µg per day)	Perchlorate exposure levels (µg/kg b.w. per day)						
	0	**0.01**	**0.1**	**1**	**10**	**100**	**1 000**
Serum free T_4 levels in mother (pmol/L)							
250	14.0	14.0	14.0	13.8	12.5	6.5	1.1
200	13.7	13.7	13.7	13.6	12.3	6.4	1.1
150	13.2	13.2	13.2	13.0	11.8	6.2	1.1
100	11.8	11.8	11.8	11.6	10.6	5.7	1.0
75	10.5	10.5	10.5	10.4	9.5	5.1	0.9
Serum free T_4 levels in fetus (pmol/L)							
250	15.0	15.0	15.0	14.7	12.6	5.7	1.0
200	14.8	14.8	14.7	14.5	12.4	5.7	1.0
150	14.2	14.2	14.1	13.9	11.9	5.5	1.0
100	12.7	12.7	12.6	12.4	10.7	4.0	0.9
75	11.3	11.3	11.2	11.0	9.5	4.5	0.8

b.w.: body weight; T_4: thyroxine.

5.6. Iodine status in Europe

In view of the mode of action of perchlorate and of its competitive inhibition on iodine uptake, the conclusions on the risk to human health related to exposure to perchlorate need to take into account the iodine intake levels of the population that are relevant to the assessment.

Iodine deficiency is a known worldwide public health issue (Lazarus, 2014). This is particularly relevant for the European continent where areas with a low presence of iodine were historically characterised by the endemic thyroid diseases typically related to moderate or severe iodine deficiency, i.e. goitre and cretinism (WHO, 2007). In 1993, WHO estimated that in the European region, 97 million people suffered from goitre as a result of iodine deficiency out of a total population of 847 millions (prevalence of 11.4 %) (WHO, 2007). In this context, several efforts have been undertaken in the last 30 years to improve iodine status, in particular through the introduction of salt iodisation programmes and the implementation of national measures to control iodine deficiency, and positive results were obtained globally especially in recent years (Andersson et al., 2012). However, several European countries still suffer from mild iodine deficiency and, although effects related to severe deficiencies are virtually absent, goitre is still endemic in some areas of Italy and Turkey (Trumpff et al., 2013). Although mild iodine deficiency is not expected to cause adverse effects in the adult population, suboptimal iodine intake is correlated to pre- and post-natal alteration in neurodevelopment (Trumpff et al., 2013). A collection of nationally representative surveys in school-aged children was provided in the EFSA NDA opinion to classify the population iodine status in EU Member States (see Appendix B; EFSA NDA Panel, 2014). This limited dataset suggests that several EU countries (including populous countries such as Italy and the UK) could have a mean urinary iodine level below the threshold of 100 µg/L indicating adequate iodine status in a population by the WHO. In general the dataset of the NDA Panel opinion also reported an estimated percentage of the

EU population ranging approximately from 10 to 70 %, with insufficient iodine intake across different Member States. Lazarus (2014) discussed the outcome of a recent investigation on the iodine status in West and Central Europe. Out of 35 countries investigated, 16 performed a survey on iodine status in the last two years, and in six of those surveys mean urinary iodine levels below 100 µg/L were reported. Surveys focusing on iodine status in pregnant women were available from only 21 countries, with only eight of them reporting adequate levels as indicated by WHO (i.e. > 150 µg/L for pregnant women). Overall, the available data indicate that a substantial part of the EU population, including children and pregnant and lactating women, is subject to a mild to moderate deficiency in iodine intake, and therefore is more sensitive to goitrogenic effects of perchlorate in comparison to population groups with an adequate iodine intake.

5.7. Hazard characterisation

5.7.1. Chronic effects

The chronic effects of perchlorate include those mediated by its activity as a competitive inhibitor of iodine uptake via the NIS in the thyroid, and the adverse effects observed in the medicinal use of perchlorate, for which modes of action have not been investigated.

5.7.1.1. Adverse effects reported in medicinal use of perchlorate

Adverse effects have been reported following repeated treatment with ≥ 400 mg/day potassium perchlorate (equivalent to 4 mg perchlorate ion/kg b.w. 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 noted that the lowest dose at which adverse effects have been reported in patients treated pharmacologically with perchlorate is approximately 10 times higher than the dose of 0.4 mg/kg b.w. per day, at which NRC (2005) estimated that healthy adults could be exposed for sustained periods without developing hypothyroidism. 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.

The CONTAM Panel carried out a dose-response analysis for the data on the incidence of cutaneous reactions, combining the observed cases reported by Krüskemper (1960), Crooks and Wayne (1960) and Morgans and Trotter (1960). This combined dataset was considered suitable for BMD modelling and considered indicative of the overall dose-response relationship for effects of perchlorate other than those in the thyroid. BMD analysis for cutaneous effects resulted in $BMDL_{01}$ values in the range of 3.5–4.0 mg/kg b.w. per day and $BMDL_{10}$ values of 11.0–12.2 mg/kg b.w. per day. Details on BMD modelling are given in Appendix E.

5.7.1.2. Effects on thyroid iodine uptake

Regarding the effects on the thyroid, perchlorate acts by competitively inhibiting iodine uptake in the organ. Iodine uptake in the thyroid is a key step in the synthesis of thyroid hormones, such as T_4 and T_3. The inhibition of thyroid iodine uptake may then result in the disruption of thyroid hormone synthesis and consequently disruption of homeostasis of the HPT axis (see Section 5.4), leading eventually to the development of hypothyroid symptoms. As noted in Section 5.4, marked differences exist in the physiology of thyroid hormones between rodents and humans. Those differences do not allow the available information from toxicological studies in the rat to be used for hazard characterisation in humans.

Retrospective epidemiological studies at the general population level, including sensitive subjects such as pregnant women and infants, showed contradictory results, some of them indicating changes in thyroid hormone levels in populations living in areas with known perchlorate contamination in drinking water (> 5 µg/L). In particular, positive associations were often observed when potential exposure to perchlorate occurred in the presence of other risk factors, such as low dietary iodine intake, or exposure to other goitrogenic agents such as thiocyanate via tobacco smoke. The reported

changes were of limited magnitude, not associated to any disease and not confirmed in other studies. Moreover, these epidemiological studies are of limited use for the evaluation of risks because of the limited, if not existent, information on exposure levels, the general natural high variability of the thyroid hormone levels and the presence of possible confounding factors not taken into account in the analysis. The CONTAM Panel concluded that the information from these epidemiological studies cannot be used for risk assessment purposes.

In its evaluation, JECFA based the hazard characterisation of perchlorate on the available human data and selected the human volunteer study from Greer et al. (2002) as the pivotal study for the dose-response assessment (see Section 5.3.3 for the study description) (FAO/WHO, 2011). JECFA considered the inhibition of thyroid iodine uptake as the critical effect for the dose-response assessment by means of the BMD calculation, selecting an inhibition of 50 % as the BMR. The BMR selection was justified by the fact that both short-term and chronic exposure to perchlorate in healthy adult volunteer studies have shown that such a level of inhibition is not associated with any changes in TSH or thyroid hormone levels. In addition, NRC (2005) suggested that in healthy adults with normal iodine intake, a sustained thyroid iodine uptake inhibition of at least 75 % for several months or longer would be necessary in order to cause declines in thyroid hormone production that would have adverse health effects.

Although it is a central issue to keep thyroid hormone production adequate, the approach considering that a prolonged 50 % inhibition of thyroidal iodine transport from perchlorate exposure would do no harm does not take into account the long-term effects that could result from the chronic adaptive changes to compensate the lower thyroid iodine uptake. During prolonged inhibition of NIS, adequate thyroid hormone or TSH production are not the most sensitive indicators of a biological effect. The thyroid gland adapts in several ways to low thyroidal iodine content, whether this is caused by low dietary iodine intake or intake of compounds that inhibit iodine transport and utilization by the thyroid gland. In this way, thyroid hormone production can be kept adequate, which is central for regulation of both development and metabolism. However, the adaptive process may, if longstanding, lead to an increase in the risk of disease.

Thyroid autoregulation to adapt to different levels of iodine is a complex mechanism involving many processes (Gärtner, 2009). One is a stimulation of thyroid growth that leads to an increase in the number of thyroid follicular cells involved in iodine uptake from blood and in thyroid hormone synthesis and secretion. In addition, the various processes involved in iodine utilization are enhanced. This includes an increase in activity of NIS that transports iodine from plasma into the follicular cells against a concentration gradient, and a change of the cellular oxidant-antioxidant system in the thyroid with an increase in the generation of H_2O_2 (Krohn et al., 2007). High H_2O_2 generation may assist in keeping thyroid hormone production adequate, but this highly oxidative product may harm the cells and lead to mutations.

When chronically exposed to low thyroidal iodine content, the adaptation may lead to goitre and the generation of thyroid nodules with autonomously functioning hormone synthesis and secretion even if thyroid function is kept within normal limits for a long period. Thus, people with low iodine intake and/or inhibitors of thyroidal utilization of iodine may become hypothyroid with low T_4 and elevated TSH if the condition is severe. However, the risk to people with mild to moderate iodine deficiency is not the low production of thyroid hormone with hypothyroidism, but is the development of goitre and hyperthyroidism from the so-called TMNG (Laurberg et al., 2010).

This type of disease is very common among elderly people living in areas with mild to moderate iodine deficiency (Denmark (Knudsen et al., 2000), Germany (Völzke et al., 2005), Italy (Aghini-Lombardi et al., 1999)), and prolonged exposure to inhibitors of NIS may worsen the condition as shown in people with an increase in blood concentrations of thiocyanate from smoking (Knudsen et al., 2002a) or industrial exposure (Brauer et al., 2006).

Because the thyroidal NIS is autoregulated by iodine, evaluation of the *in vivo* effect of prolonged exposure to an NIS inhibitor is simpler to perform by measuring iodine excretion in breast milk. Mammary gland NIS is not autoregulated by iodine (Laurberg and Andersen, 2014) and urinary iodine excretion is independent from NIS. Thus a chronic exposure to an NIS inhibitor may lead to a change in the balance between iodine in breast milk and in urine.

In a study performed in mild to moderately iodine deficient Danish breast feeding women, smoking (n = 50) was on average associated with a 50 % decrease in milk iodine content, whereas urinary iodine content was similar to non-smokers (n = 90). The pattern suggests a 50 % inhibition of NIS by the increased thiocyanate level in smokers, which is in accordance with the increase in blood levels of thiocyanate (Laurberg et al., 2004). More recently, a US study of breastfeeding women with sufficient iodine intake corroborated inhibition of milk iodine excretion in a small group of smokers (n = 6) (Pearce et al., 2007).

In a Danish study of populations with mild to moderate iodine deficiency it was estimated that 49 % of goitre was attributable to smoking, with presumably around 50 % inhibition of thyroidal NIS (Knudsen et al., 2002a). Moreover, previous pregnancy was associated with goitre in Denmark (Knudsen, 2002b), presumably because the women had an iodine intake that was too low to meet the increase in demands during pregnancy (Alexander et al., 2004); this association was much more pronounced in the women who smoked (Knudsen et al., 2002b).

As indicated thiocyanate and also nitrate (Tonacchera et al., 2004) are NIS inhibitors present in the environment and intake may often lead to concentrations that will interfere with NIS activity (Laurberg et al., 2009). The NIS inhibitory effects of these various compounds seem to be additive (Tonacchera et al., 2004), and biologically relevant exposure to perchlorate will normally act on top of some NIS inhibition already in action. Thus, the biological importance of perchlorate exposure has to be evaluated within the context of exposure to other NIS inhibitors (De Groef et al., 2006) as well as iodine intake level and any increase in the need for iodine such as that observed during pregnancy.

In conclusion, a prolonged 50 % inhibition of thyroid iodine uptake by exposure to NIS inhibitory chemicals such as perchlorate may lead to goitre and multinodular toxic goitre, even if short-term exposure does not alter thyroid function tests. Multinodular toxic goitre often develop insidiously in elderly people and may be associated with osteoporosis, atrial fibrillation, heart failure and premature death. The risk may be overcome by a high iodine intake, but this may lead to excessive iodine intake in some people in the population, and increased risk of hypothyroidism (Laurberg et al., 2009).

Some European populations still tend to have low iodine intake even in pregnancy. In a study of pregnant women in various clinics in the UK and in Turin, Italy (Pearce et al., 2010), urinary iodine concentrations were borderline low in Cardiff, UK (median 98 µg/L), but clearly insufficient in Turin, Italy (median 50 µg/L) according to EFSA (EFSA NDA Panel, 2014) and FAO/WHO (2004) criteria.

In the absence of clear data on the thyroid iodine uptake inhibition levels lower than 50 % that could be associated to the development of goitre or multinodular toxic goitre, the CONTAM Panel performed BMD modelling on the thyroid iodine uptake inhibition data from the Greer et al. (2002) study. The CONTAM Panel applied a BMR of 5 %, which is the default value for continuous data. This resulted in a $BMDL_{05}$ of 0.0012 mg/kg b.w. per day calculated with the Hill model and selected as reference point (RP) for the effects on thyroid iodine uptake. When applying a BMR of 50 %, the BMD modelling resulted in a $BMDL_{50}$ of 0.11 mg/kg b.w. per day, showing a good agreement with the modelling performed by JECFA (see Table 13 and Appendix E for details).

Table 13: BMD analysis of the thyroid iodine uptake inhibition in human volunteers (Greer et al., 2002), using the BMR of 5 %. BMD values are reported in mg/kg b.w. per day

Model family	Selected model	BMD_{05}	$BMDL_{05}$	$BMDU_{05}$
Exponential	**m4-**	0.0078	**0.0067**	0.0092
Hill	**m5-**	0.0036	**0.0012**	0.0088

5.7.1.3. Establishment of the chronic health-based guidance value (HBGV)

The CONTAM Panel selected the RP of 0.0012 mg/kg b.w. per day, based on a $BMDL_{05}$ for thyroid iodine uptake inhibition, for the establishment of the tolerable daily intake (TDI) for perchlorate. To take vulnerable subpopulation groups into account, including those with relatively low iodine intake, the CONTAM Panel applied the following uncertainty factors:

- An uncertainty factor of 4 to allow for intraspecies differences in toxicokinetics. PBK modelling has shown that the difference in inhibition of iodine uptake is at most four-fold higher (1.9 % instead of 0.6 % and 17 % instead of 4 % at 0.001 and 0.01 mg/kg b.w. perchlorate, respectively) in subgroups including pregnant women, fetuses, lactating women, neonates and children than predicted for non-pregnant adults.

- The CONTAM Panel considered that a 5 % inhibition of iodine uptake would not lead to adverse effects in any subgroup of the population, and therefore no additional uncertainty factor was considered for intraspecies differences in toxicodynamics.

- The CONTAM Panel noted that perchlorate has a short serum half-life (mean of 8.1 hours in humans). The CONTAM Panel noted that in the Greer et al. (2002) study no differences in thyroid iodine uptake inhibition were observed after 2 days of exposure and 14 days of exposure at any tested dose. In addition, thyroid uptake was completely restored the day after the end of the exposure period (day 15) at any tested dose. Overall, the CONTAM Panel considered that a daily exposure to perchlorate resulting in a marginal thyroid iodine uptake inhibition would not lead to long-term adverse adaptive effects and, therefore, that an additional uncertainty factor to account for the short-term exposure duration was not necessary.

The CONTAM Panel applied an overall uncertainty factor of 4 to the RP and established a TDI of 0.3 µg/kg b.w. per day.

5.7.2. Acute effects

Potential acute effects of perchlorate have been suggested by several authors for fetuses in the late gestation period and for infants, although no data are available to support this hypothesis. These life stages are identified as being particularly sensitive to the key effect of perchlorate (inhibition of thyroid iodine uptake), because they do not have the reserve capacity existing in adult humans and the estimated intrathyroidal amount of hormones stored would be less than that required for a day (Zoeller, 2003; Scinicariello et al., 2005; Ginsberg et al., 2007). Moreover, thyroid hormones play a key role in fetal and neonatal neurological development (Zoeller et al., 2002; Morreale de Escobar et al., 2004), and thus a transient fall in the thyroid hormone levels, as result of acute exposure to perchlorate, could result in an adverse neurodevelopmental effect. With regard to the fetus, the limitations in the reserve capacity are mitigated by the maternal supply of thyroidal hormones. On the other hand, neonates can rely only on their hormone synthesis and thus could be considered as the more vulnerable population (Clewell et al., 2003b; Ginsberg et al., 2007).

In rats, ammonium perchlorate caused hypoactivity in all animals administered a single oral dose of 2 000 mg/kg b.w. (equivalent to approximately 1 680 mg/kg b.w. perchlorate), whereas no clinical changes were observed at 300 mg/kg b.w. (corresponding approximately to 250 mg/kg b.w.

perchlorate). The CONTAM Panel concluded that, due to the limited toxicological relevance of the rat model for humans and to the limited design of the study, these data cannot be used for the acute hazard characterisation.

No data are available on the acute effects of perchlorate in humans. In its clinical applications, potassium perchlorate was administered at therapeutic daily doses ranging from 400 to 2 000 mg/kg b.w. per day in adults (corresponding to 4–20 mg perchlorate ion/kg b.w. per day for a 70-kg person), and 200–300 mg /kg b.w. per day in children, with treatment periods ranging from few weeks to several months (see Section 5.3.2). Side effects were reported following repeated treatment at ≥ 400 mg potassium perchlorate per day (≥ 4 mg perchlorate ion/kg b.w. per day for a 70-kg person); in particular, a higher incidence and severity was observed at doses higher than 1 000 mg potassium perchlorate per day (10 mg perchlorate ion/kg b.w. per day). Nowadays, single oral doses of 1 000 mg potassium perchlorate are used for diagnostic purposes without reported evidence of adverse effects.

5.7.2.1. Consequences of a single exposure to perchlorate

The main effect of a single large perchlorate exposure (e.g. the doses used for medical and diagnostic purposes) would be a near total NIS inhibition. NIS transports iodine into the thyroid gland and also into the mammary gland during lactation. Iodine intake with diet may be highly variable from day to day, and the thyroid system has developed to have a high capacity to adapt to such large changes in the supply of the key substrate for thyroid hormone synthesis.

5.7.2.2. Healthy non-pregnant and non-breast feeding adult with adequate iodine intake

In theory, the effects of a one-day block of active iodine transport in an adult person with adequate iodine intake will be minimal. The iodine content of the thyroid gland is 10–20 mg (Fisher and Oddie, 1969), most of which is present as organically bound iodine in thyroglobulin, the major part having been built into thyroid hormone precursors. The daily release of iodine as part of thyroid hormone is around 0.065 mg (Bianco et al., 2002). Thus, a depot of 1 mg of iodine alone would be sufficient for around two weeks of thyroid hormone secretion. In the thyroid gland, NIS is autoregulated by thyroidal iodine content (Gärtner, 2009), and a transient small decrease in iodine content would easily be replaced by a subsequent small transient increase in NIS activity.

5.7.2.3. Healthy pregnant woman with adequate iodine intake

A higher iodine demand is present during pregnancy, because thyroid hormone production is around 50 % higher in pregnant women (Alexander et al., 2004). However, as indicated above, a one-day block of iodine uptake into the thyroid gland would not lead to deficient thyroid hormone secretion.

NIS is present in the placenta, and whether NIS is also the main transporter of iodine across the placenta has been discussed. Recent studies suggest that transport of iodine across the placenta is unaltered when NIS activity is inhibited from maternal smoking (Andersen et al., 2013). Thus, either additional transporters are in action in the placenta or placenta NIS is up-regulated to compensate (autoregulation).

Current knowledge is not adequate to precisely describe the effects on fetal thyroid hormone production from a one-day block of placenta transport of iodine, if this could happen (which is speculative), and the possible effect of perchlorate in the fetus would also be speculative. However, during the majority of pregnancy, considerable parts of the thyroid hormones present in the fetus are of maternal origin, and short-term iodine transport inhibition in the placenta and fetal thyroid would, with all likelihood, not do any harm.

5.7.2.4. Breastfeeding woman with adequate iodine intake

Maternal thyroid hormone secretion will not be affected because the situation is similar to above. NIS in the mammary gland will be blocked by a high dose of perchlorate, and breast milk will have very low iodine content for one day. Moreover, some perchlorate will be transported into milk and there

may be a block of thyroidal NIS in the breast-fed neonate/infant. Data on iodine content in the neonatal thyroid are limited

5.7.2.5. Young children with adequate iodine intake

A single large exposure to perchlorate will block thyroid transport of iodine for one day, as described above. During the first year of life the capacity of the thyroid to store iodine will rapidly increase, and the risk will be gradually lower than what is described above for the breast-fed neonate.

5.7.2.6. People with iodine deficiency

In people with severe iodine deficiency, the thyroid depot of iodine and thyroid hormone can be much lower (Dumont et al., 1995). Most of these people will have some degree of enlarged thyroid gland (goitre). Severe iodine deficiency has not been identified in Europe for many years. In mild and moderate iodine deficiency the stores of iodine will also be lower than in adequate iodine intake. However, the thyroidal iodine stores are considered to be sufficient to cover a one-day need, as described above.

5.7.2.7. Conclusions

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. Although potential acute effects of perchlorate on pregnant women and infants with low iodine intake have been speculated, there is no clear evidence of the presence of those effects and of the related dose/response relationship. The CONTAM Panel noted that, according to limited data, even a one-day complete thyroid iodine uptake inhibition would not deplete the thyroid iodine content in infants with mild to moderate iodine deficiency, and concluded that the establishment of an ARfD is not warranted.

5.7.3. Short-term effects

The CONTAM Panel considered whether it was possible to identify a level of short-term exposure higher than the TDI that would not be expected to cause adverse effects.

A study from Belgium (van den Hove et al., 1999), the population of which had mild (to moderate) iodine deficiency at the time of the study (Ciardelli et al., 2002), found thyroidal iodine content values in newborns to be around 0.3 mg. The infant thyroid uses around 0.020 mg iodine per day for hormone synthesis (Laurberg and Andersen, 2014). Thus, a one-day iodine supply inhibition will do no harm but, if the inhibition continues, the situation could become critical within a week or two.

There are no data that allow a firm conclusion to be drawn on the perchlorate dose and duration of exposure that would induce a severe depletion of iodine in newborns. There has been insufficient iodine content of the diet in large parts of the world for thousands of years. The thyroid gland, the HPT feedback system and the peripheral metabolism of thyroid hormones are able to compensate for low iodine intake in many ways. Iodine depletion will lead to up-regulation of practically all processes involved in thyroid utilization of iodine, and excess TSH will be secreted from the pituitary gland to increase thyroid activity. Studies in which perchlorate was used to treat patients with hyperthyroidism that caused by the Graves' disease (Wolff, 1998) give an indication of the amount of perchlorate necessary to effectively block iodine accumulation in the hyperactive adult thyroid. In Graves' disease, the thyroid is excessively stimulated by TSH-receptor autoantibodies. The dose used for therapy in adults was in the range 250–1 000 mg potassium perchlorate per day, and it is likely that rather high doses would also be necessary to induce overt hypothyroidism in otherwise healthy newborns. On the other hand, even minor abnormalities in neonatal thyroid function should be avoided.

The CONTAM Panel concluded that short-term exposure for two to three weeks to perchlorate, at levels that are sufficiently high to result in a severe depletion of the thyroid iodine depot would be

critical in breast-fed infants and young children. This would be a particular risk in the case of mild to moderate iodine deficiency. However, such a depletion would be associated with compensatory increases in the activity of the thyroid iodide transporter, and no data are available to evaluate in detail how large the doses of perchlorate would be necessary for such depletion. Therefore, the CONTAM Panel could not establish a short-term HBGV for these populations.

6. Risk characterisation

The mean and high chronic and short-term dietary exposure levels to perchlorate were based on the occurrence dataset and from data available from the literature for perchlorate occurrence in fruit juices, alcoholic beverages, milk and infant formulae. The exposure of breast-fed infants was calculated based on mean occurrence data from the USA available from the literature.

As indicated in Section 4.3, only the scenario excluding the suspect samples was considered appropriate to characterise the risk from chronic perchlorate exposure. In 'toddlers', the age group with the highest exposure estimates, the levels for mean and 95th percentile chronic dietary exposure ranged from 0.18 to 0.50 µg/kg b.w. per day, and from 0.34 to 0.97 µg/kg b.w. per day (minimum LB-maximum UB across different dietary surveys), respectively. In the age group 'Other children', mean exposure levels in the range 0.07–0.37 µg/kg b.w. per day and 95th percentile exposure levels in the range 0.19–0.72 µg/kg b.w. per day (minimum LB-maximum UB across different dietary surveys), were estimated. In the adolescents and adult age groups, the estimated mean and 95th percentile chronic dietary exposure levels ranged from 0.04 to 0.20 µg/kg b.w. per day, and from 0.10 to 0.51 µg/kg b.w. per day (minimum LB-maximum UB) across different dietary surveys, respectively. Based on mean concentrations of perchlorate in breast milk available in the literature, the estimated dietary exposure of breast-fed infants with mean milk consumption ranged from 0.76 to 4.3 µg/kg b.w. per day, and for infants with high milk consumption ranged from 1.1 to 6.5 µg/kg b.w. per day.

The chronic effects of perchlorate are mediated by its activity as a competitive inhibitor of iodine uptake via the NIS in the thyroid. Hence, the adverse effects of perchlorate have to be considered in conjunction with the iodine status of the exposed population. The CONTAM Panel noted that a sustained and marked inhibition of thyroid iodine uptake could lead to the development of TMNG as a result of thyroid autoregulation to overcome the lower iodine bioavailability. This chronic effect is particularly relevant for populations with mild to moderate iodine intake. For this chronic effect of perchlorate, the CONTAM Panel established a TDI of 0.3 µg/kg b.w. per day derived from a $BMDL_{05}$ of 0.0012 mg/kg b.w. per day, calculated from a two-week human volunteer study on thyroid iodine uptake inhibition following oral exposure to perchlorate (Greer et al., 2002).

The mean chronic exposure estimates for adolescents and the adult age groups are all below the TDI of 0.3 µg/kg b.w. per day, while an exceedance of the TDI is observed for the 95th percentile chronic exposure estimates in some surveys. On the other hand, in the younger population groups ('infants', 'toddlers' and 'other children'), the TDI was exceeded for both mean (in some surveys) and 95th percentile (in the majority of surveys) exposure estimates. In addition, the estimates of exposure for breast-fed infants largely exceed the TDI for both mean and high breast milk consumption. The CONTAM Panel noted that the breast milk data selected for the exposure estimation were literature data from USA with unknown relevance to EU. In addition, the identified studies included limited numbers of subjects and often only one sample of breast milk per subject was collected. In addition measurements were associated with considerable inter-individual variability and, in those studies where several breast milk samples were collected from the same subject, intra-individual variability.

For the short-term exposure assessment, the CONTAM Panel considered two scenarios, one excluding and one including the suspect samples. For the scenario excluding suspect samples, the short-term mean exposure estimates ranged from 0.38 to 1.9 µg/kg b.w. per day in adolescents and the adult age classes, and from 1.5 to 2.7 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only two consumption surveys were available resulting in an exposure of 1.2 and 1.5 µg/kg b.w. per day. The highest mean 'short-term' dietary exposure level of 3.0 µg/kg b.w. per day was estimated in the age

class 'other children'. The 95th percentile 'short-term' dietary exposure levels ranged from 0.94 to 4.6 µg/kg b.w. per day in adolescents and the adult age classes, and from 3.6 to 6.2 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only one consumption survey was available resulting in an exposure of 3.8 µg/kg b.w. per day. The highest 95th percentile 'short-term' dietary exposure level of 7.2 µg/kg b.w. per day was estimated in the age class 'other children'.

For the scenario including suspect samples, the short-term mean exposure estimates ranged from 0.54 to 5.0 µg/kg b.w. per day in adolescents and the adult age classes, and from 2.2 to 4.4 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only two consumption surveys were available resulting in an exposure of 1.5 and 2.3 µg/kg b.w. per day. The highest mean 'short-term' dietary exposure level of 5.3 µg/kg b.w. per day was estimated in the age class 'other children'. The 95th percentile 'short-term' dietary exposure levels ranged from 1.3 to 14 µg/kg b.w. per day in adolescents and the adult age classes, and from 4.5 to 9.4 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only one consumption survey was available resulting in an exposure of 5.7 µg/kg b.w. per day. The highest 95th percentile 'short-term' dietary exposure level of 18 µg/kg b.w. per day was estimated in the age class 'other children'.

For the scenario excluding the suspect samples, short-term exposure estimates were below 10 µg/kg b.w. per day. According to the PBK models reported in Section 5.5, these levels would correspond to thyroid iodine uptake inhibition lower than 20 % in all the age groups. For the scenario including the suspect samples short-term exposure estimates were below 10 µg/kg b.w. per day for infants, toddlers, elderly and very elderly. For other children, adolescents and adults, the 95th percentile exposure estimates were between 10 and 20 µg/kg b.w. per day in some surveys. According to the PBK models, these levels would correspond to thyroid iodine uptake inhibition lower than 20 % in these age groups.

Due to the existing uncertainties highlighted in Section 5.7, the CONTAM Panel could not conclude on the potential risks of short-term exposure to levels of perchlorate higher than the TDI.

Overall the CONTAM Panel concluded that the chronic dietary exposure to perchlorate is of potential concern in particular for the high consumers in the younger age groups of the population with mild to moderate iodine deficiency. Furthermore, it is possible that short-term exposure to perchlorate is also of concern for breast-fed infants and young children with low iodine intake.

7. Uncertainty analysis

The evaluation of the inherent uncertainties in the assessment of exposure to perchlorate has been performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2006). In addition, the report on 'Characterizing and Communicating Uncertainty in Exposure Assessment' has been considered (WHO/IPCS, 2008). According to the guidance provided by the EFSA opinion (2006) the following sources of uncertainties have been considered: Assessment objectives, the exposure scenario and the exposure model.

7.1. Assessment objectives

The objectives of the assessment were clearly specified in the terms of reference.

7.2. Exposure model/exposure scenario

EFSA received the analytical results of 11 675 samples submitted by eight countries (Belgium, Germany, Denmark, Spain, France, Italy, the United Kingdom and the Netherlands). The majority of the samples belonged to the food groups 'Vegetables and vegetable products' and 'Fruits and fruit products'. 'Grains and grain-based products' were excluded from the dietary exposure assessment considering that this food category has never been identified as a relevant contributor to perchlorate exposure and all available analytical results were below the LOD. In addition, no or a limited number of perchlorate concentrations in milk and dairy products, infant formulae, alcohol beverages, and fruit and vegetables juices were submitted to EFSA or were identified in the scientific literature for Europe.

Therefore, literature data on the occurrence of perchlorate in these foods were used. Limited data indicating the presence of perchlorate in fish and fishery products were also identified but were considered not sufficiently robust by the CONTAM Panel for their inclusion in the dataset for the exposure estimates. In addition, there is an uncertainty in possible regional differences in perchlorate contamination of food commodities and it is evident that the dataset is not fully representative for food on the EU market.

From the 11 675 samples, 2231 were considered to be suspect samples. As the suspect samples constitute about 20 % of the occurrence data and are expected to be on average higher than the random samples, these data were excluded from the chronic exposure assessment in order not to unrealistically overestimate the mean perchlorate concentration used to assess chronic exposure. In order to assess the magnitude of this uncertainty, the CONTAM Panel compared the chronic exposures under the scenarios in which suspect samples were included and excluded (Table 7 and Appendix C, Table C3). The use of the suspect samples would have increased the chronic mean exposure estimates in infants and toddlers by up to 74 % and the 95th percentile by up to 87 %. For all other age groups, the inclusion of suspect samples would have resulted in chronic mean exposure estimates that were from 21 to 165 % higher and the 95th percentile exposure estimates that were from 19 to 263 % higher compared to the scenario excluding the suspect samples.

For infants only two consumption surveys with a low number of participants were available and this introduces some uncertainties in the estimated exposure of infants. In addition the potential exposure of infants via breast milk was estimated considering literature data from the USA with unknown relevance to the EU. In addition, the identified studies included a limited number of subjects and often only one sample of breast milk per subject was collected. In addition, measurements were associated with considerable inter-individual variability and, in those studies where several breast milk samples were collected from the same subject, intra-individual variability.

Perchlorate can contaminate food and drinking water via different sources. The use of natural fertilisers and the irrigation of plants with perchlorate-contaminated water may lead to substantial concentrations in fruits and vegetables, due to the efficient uptake of perchlorate via plant roots. Water disinfection with chlorinated substances that potentially degrade to perchlorate could be another notable source of contamination for drinking water, foods and beverages. Overall, there is considerable uncertainty regarding the dietary exposure to perchlorate.

7.3. Other uncertainties

The CONTAM Panel established a TDI of 0.3 µg/kg b.w. per day, based on the lowest $BMDL_{05}$ calculated for the thyroid iodine uptake inhibition measured in a human volunteer study, which is considered to be a conservative Reference Point. The CONTAM Panel noted that there is uncertainty on the level of thyroid iodine uptake inhibition that could be tolerated for long term periods without the development of adverse effects.

Although acute effects in human sensitive life stages (fetuses and infants) have been suggested, the CONTAM Panel concluded that even a complete inhibition of thyroid iodine uptake for a single day would not cause adverse effects in any groups within the population.

The CONTAM Panel noted that short-term exposure to perchlorate at doses higher than the TDI could be critical in breast-fed infants and in young children with mild to low iodine deficiency. However, no dose-response data are available to derive a short-term HBGV for these populations.

The effects of perchlorate could be exacerbated by concurrent exposure to other substances that also act as antithyroid substances (e.g. thiocyanate and nitrate, among others).

7.4. Summary of uncertainties

In Table 14, a summary of the uncertainty evaluation is presented for perchlorate highlighting the main sources of uncertainty and indicating an estimate of whether the respective source of uncertainty might have led to an over- or underestimation of the exposure or the resulting risk.

Table 14: Summary of qualitative evaluation of the impact of uncertainties on the risk assessment of the dietary exposure of perchlorate

Sources of uncertainty	Direction[(a)]
Uncertainty on analytical results	+/–
Extrapolation of occurrence data from eight Member States to whole Europe	+/–
Occurrence data available for a limited number of food commodities	–
Limited consumption data for infants	+/–
Use of literature data on occurrence from outside the European Union	+/–
Lack of occurrence data in breast milk for Europe	+/–
Exclusion of suspect samples for the assessment of chronic exposure	–
Selection of the benchmark response of 5 % for the derivation of the chronic Tolerable Daily Intake	+
Lack of dose response data on short–term effects in infants and young children with mild to moderate iodine deficiency	+/–
Concurrent exposure to other antithyroid substances	–

(a): + = uncertainty with potential to cause over-estimation of exposure/risk; – = uncertainty with potential to cause under-estimation of exposure/risk.

The CONTAM Panel considered that the impact of the uncertainties on the risk assessment of human chronic exposure to perchlorate is moderate, and is greater for the short-term exposure.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

General

- Perchlorate (ClO_4^-) is released into the environment from both natural and anthropogenic sources resulting in its presence in food and drinking water.

- The use of natural fertilisers and perchlorate contaminated irrigation water may lead to substantial concentrations in vegetables and some fruits, due to the efficient uptake of perchlorate via the plant roots.

- Water disinfection with chlorinated substances that potentially degrade to perchlorate, particularly sodium and calcium hypochlorite, could be another notable source of contamination for drinking water and consequently various foods and beverages.

- The Panel on Contaminants in the Food Chain (CONTAM Panel) noted that additional sources of contamination, such as the use of chlorine-based products that potentially degrade to perchlorate in biocidal applications (for purposes other than water disinfection) and plant protection applications, and the natural formation of perchlorate in the atmosphere and in surface water could marginally contribute to the presence of perchlorate in food and drinking water.

Occurrence/Exposure

- Perchlorate has been reported to occur in a wide range of foods such as vegetables and fruits, milk and dairy products, rice, infant formula, fish and fish products, juices, beer, wine and bottled water.

- The Joint FAO/WHO Expert Committee on Food Additives (JECFA) reviewed occurrence data on perchlorate in 2010 and observed the highest weighted mean concentrations for vegetables (range of means 4.8–110 µg/kg), fruits (range of means 0.5–28 µg/kg), vegetable and fruit juices (26 µg/kg), and infant formula (10 µg/kg).

- Previous exposure assessments carried out by JECFA and the US Food and Drug Administration FDA have shown that milk and dairy products, baby foods, fruits and vegetables and fruit juices are important contributors to the perchlorate exposure.

- EFSA received the analytical results of 11 675 samples submitted by eight Member States, of which about 20 % were considered to be suspect samples. The majority of the samples belonged to the food groups 'Vegetables and vegetable products' and 'Fruits and fruit products'.

- Excluding the suspect samples, the highest mean perchlorate concentrations were observed in turnips (350 µg/kg, upper bound (UB)) and in lettuce, excluding Iceberg-type lettuce (120 µg/kg, UB). For all other 'Vegetables and vegetable products' the mean concentration was below 70 µg/kg. For 'Fruits and fruit products' the mean concentration ranged from < limit of detection to 12 µg/kg.

- In addition to the data submitted to EFSA, occurrence data from the literature on 'Infant formulae, powder', 'Infant formulae, liquid', 'Milk and dairy products', 'Alcoholic beverages' and 'Fruit juices' and breast milk were used in the exposure assessment.

- The CONTAM Panel performed the exposure assessment of perchlorate using a chronic and a 'short-term' exposure scenario. The latter scenario was developed to take into account the possibility of being exposed to relatively high levels of perchlorate for a short-term period, e.g. two to three weeks, considering that higher levels of thyroid iodine uptake inhibition for short periods could induce adverse effects in vulnerable groups of the population, such as breast-fed infants and young children with low iodine intake. Higher exposure over such periods is plausible for people living in areas where local produce contains higher levels of perchlorate.

- The CONTAM Panel concluded that adverse effects following a single day exposure to perchlorate at levels relevant for dietary exposure are not expected in any group of the population and therefore no acute exposure estimation was carried out.

- Only the scenario excluding the suspect samples was considered appropriate to characterise the risk from chronic perchlorate exposure.

- The mean chronic dietary exposure ranged from 0.04 to 0.20 µg/kg body weight (b.w.) per day (minimum lower bound (LB)-maximum UB) in adolescents and adult age classes. For other children and toddlers the mean chronic dietary exposure ranged from 0.07 to 0.37 µg/kg b.w. per day and 0.18 to 0.50 µg/kg b.w. per day (minimum LB-maximum UB), respectively. For infants, only two consumption surveys were available resulting in mean chronic dietary exposure of 0.13–0.54 µg/kg b.w. per day (minimum LB-maximum UB).

- The 95th percentile chronic dietary exposure ranged from 0.10 to 0.51 µg/kg b.w. per day (minimum LB-maximum UB) in adolescents and adult age classes. For other children and

toddlers the 95th percentile chronic dietary exposure ranged from 0.19 to 0.72 µg/kg b.w. per day and 0.34 to 0.97 µg/kg b.w. per day (minimum LB-maximum UB), respectively. For infants, 95th percentile chronic dietary exposure could only be calculated for one consumption survey resulting in exposure of 0.32–0.61 µg/kg b.w. per day (LB-UB).

- 'Vegetables and vegetable products' and 'Milk and dairy products' were identified in the chronic exposure assessment as the most important contributors to perchlorate exposure in all age groups.

- Based on mean concentrations of perchlorate in breast milk from the USA, the dietary exposure of breast-fed infants with a mean milk consumption ranged from 0.76 to 4.3 µg/kg b.w. per day and from 1.1 to 6.5 µg/kg b.w. per day for infants with a high milk consumption. The relevance of these data for the European Union is unknown.

- For the short-term exposure the CONTAM Panel considered scenarios excluding and including the suspect samples.

- For the scenario excluding suspect samples, the estimations of mean 'short-term' dietary exposure to high percentile levels of perchlorate ranged from 0.38 to 1.9 µg/kg b.w. per day in adolescents and adult age classes, and from 1.5 to 2.7 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only two consumption surveys were available resulting in an exposure of 1.2 and 1.5 µg/kg b.w. per day. The highest mean 'short-term' dietary exposure level of 3.0 µg/kg b.w. per day was estimated in the age class 'other children'. The 95th percentile 'short-term' dietary exposure levels ranged from 0.94 to 4.6 µg/kg b.w. per day in adolescents and adult age classes, and from 3.6 to 6.2 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only one consumption survey was available resulting in an exposure of 3.8 µg/kg b.w. per day. The highest 95th percentile 'short-term' dietary exposure level of 7.2 µg/kg b.w. per day was estimated in the age class 'other children'.

- For the scenario including suspect samples, the estimations of mean 'short-term' dietary exposure to high percentile levels of perchlorate ranged from 0.54 to 5.0 µg/kg b.w. per day in adolescents and adult age classes, and from 2.2 to 4.4 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only two consumption surveys were available resulting in an exposure of 1.5 and 2.3 µg/kg b.w. per day. The highest mean 'short-term' dietary exposure level of 5.3 µg/kg b.w. per day was estimated in the age class 'other children'. The 95th percentile 'short-term' dietary exposure levels ranged from 1.3 to 14 µg/kg b.w. per day in adolescents and adult age classes, and from 4.5 to 9.4 µg/kg b.w. per day in toddlers across dietary surveys. For infants, only one consumption survey was available resulting in an exposure of 5.7 µg/kg b.w. per day. The highest 95th percentile 'short-term' dietary exposure level of 18 µg/kg b.w. per day was estimated in the age class 'other children'.

Toxicokinetics

- Perchlorate is rapidly and extensively absorbed from the gastrointestinal tract following oral exposure. Half-lives range from 6.0 to 9.3 hours in humans and approximately from 8 to 20 hours in rats.

- Following absorption, perchlorate widely distributes in the body both for humans and rats, with the highest concentration observed in thyroid tissue in rats.

- In rats and humans, perchlorate is rapidly excreted, predominantly in the urine as unchanged parent compound.

Toxicity in experimental studies

- Perchlorate has low acute oral toxicity in laboratory animals.

- Following repeated exposure to perchlorate in rodents, findings included changes in levels of thyroid hormones and thyroid-stimulating hormone (TSH), thyroid weight increases, and histological findings in the thyroid (colloid depletion, follicular cell hypertrophy and hyperplasia) and mammary gland (mild atrophy, atypia of the lobular epithelium, scattered foci of marked hyperplasic activity).

- Based on the available data, perchlorate is of no concern with respect to genotoxicity.

- Increased thyroid tumour incidence was observed in rats and mice following chronic exposure to perchlorate.

- Data on developmental and reproductive toxicity indicate lower number of litters and reduced ossification of rat fetuses. Changes in thyroid hormone levels, TSH levels, thyroid weights and thyroid histology in rat fetuses and pups were also noted. Findings from developmental neurotoxicity studies were considered to be inconclusive due to limitations in the study designs and methodologies used.

- Due to a number of limitations, the CONTAM Panel concluded that it is not possible to determine an association between exposure to perchlorate and developmental neurotoxicity from the studies in rats.

Human data

- Potassium perchlorate has been used for the medical treatment of hyperthyroidism at doses ranging from 400 mg/day to 2 000 mg/day (corresponding to 4–20 mg perchlorate ion/b.w. per day for a 70-kg person) administered for prolonged periods to control the thyroid hormone levels.

- Adverse effects, including skin rash, nausea, lymphoadenopathy and blood dyscrasias, have been reported following repeated application of potassium perchlorate at doses ≥ 400 mg/day potassium perchlorate, with evidence suggesting a direct relationship between the incidence and severity of the effects and the treatment dose and duration. No adverse effects were reported with administered doses of 200 mg/day or lower for prolonged periods.

- Studies on healthy adult volunteers repeatedly exposed to 0.007–0.5 mg perchlorate/kg b.w. per day for two weeks, as well as information from occupational studies, showed no correlation between the exposure to perchlorate and any adverse effects or changes in the thyroid hormone levels, even at exposure levels associated with a substantial inhibition of thyroid iodine uptake.

- Retrospective epidemiological studies at the general population level, including the most sensitive subjects, showed contradictory results and no clear association between exposure to perchlorate and an increased incidence of thyroid dysfunction. The CONTAM Panel concluded that these studies were not of use for the risk assessment on perchlorate.

Mode of action

- The toxic effects of perchlorate result from its ability to competitively inhibit iodine uptake via the sodium-iodide symporter protein (NIS), causing hypothyroidism and, in rats and mice, the development of thyroid tumours.

- In humans, severe iodine deficiency, as a result of insufficient iodine intake or sustained exposure to goitrogenic substances such as perchlorate to levels that induce depletion of the thyroid hormone stores, can result in hypothyroidism. However, a mild to moderate iodine

deficiency can lead to the development of toxic multinodular goitre and can result in hyperthyroidism.

- In comparison with rodents, healthy adult humans have lower thyroid hormone turnover rates and larger reserves of iodinated thyroglobulin, allowing them to compensate for reduced hormone synthesis in the thyroid. Due to these differences in thyroid hormone physiology, the data from toxicological studies in rats are of limited use for extrapolating to humans.

- In the absence of genotoxicity and on the basis of the species differences in the physiology of thyroid hormones, it can be concluded that the neoplastic changes observed in rodents are not relevant for humans and therefore that perchlorate is not of carcinogenic concern to humans.

- Fetuses, neonates, and individuals with low iodine intake or genetically predisposed to develop hypothyroidism are likely to be more sensitive to the effects of exposure to perchlorate.

Hazard characterisation

- The chronic effects of perchlorate include those mediated by its activity as competitive inhibitor of iodine uptake via the NIS in the thyroid, and the adverse effects observed in the medicinal use of perchlorate, for which modes of action have not been investigated.

- The CONTAM Panel noted that in its evaluation JECFA considered the inhibition of thyroid iodine uptake of 50 % as the benchmark response (BMR), with the justification that both short-term and chronic exposure to perchlorate in healthy adult volunteer studies had shown that such a level of inhibition is not associated with any changes in thyroid stimulating hormone (TSH) or thyroid hormone levels.

- The CONTAM Panel concluded that the chronic adaptive changes to compensate to a sustained inhibition of thyroid iodine uptake could lead to long term effects such as the development of toxic multinodular goitre, in particular in populations with mild to moderate iodine deficiency.

- The CONTAM Panel concluded that a prolonged 50 % inhibition of thyroid iodine uptake by exposure to NIS inhibitory chemicals such as perchlorate may lead to goitre and multinodular toxic goitre, even if short-term exposure does not alter thyroid function tests. Although the consequences of thyroid iodine uptake inhibition below 50% is unclear, the CONTAM Panel performed benchmark dose (BMD) modelling on the thyroid iodine uptake inhibition data from the Greer et al. (2002) study, using a benchmark response (BMR) of 5 %, which is the default value for continuous data. This resulted in $BMDL_{05}$ values ranging from 0.0012 to 0.0067 mg/kg b.w. per day.

- The CONTAM Panel selected the lowest $BMDL_{05}$ value of 0.0012 mg/kg b.w. per day as reference point and established a tolerable daily intake (TDI) of 0.3 µg/kg b.w. per day by applying an uncertainty factor of 4 to allow for inter human differences in toxicokinetics. No additional uncertainty factors were considered necessary to allow for intraspecies differences in toxicodynamics and for the short duration of the human study.

- No data are available on the acute effects of perchlorate in humans. In adults, a single treatment with 1 000 mg potassium perchlorate (10 mg perchlorate ion/kg b.w. for a 70-kg person) is used for diagnostic practice without any adverse effect reported.

- Amongst the vulnerable subpopulations, potential acute effects of perchlorate have been suggested for fetuses and infants, because they lack the reserve capacity that exists in adult humans and because of the key role of thyroid hormones in fetal and neonatal neurological

development 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. The CONTAM Panel concluded that the establishment of an acute reference dose for perchlorate is not warranted.

- The CONTAM Panel concluded that short-term exposure for two to three weeks to perchlorate at levels that are sufficiently high to result in a severe depletion of the thyroid iodine depot would be critical in breast-fed infants and young children. This would be a particular risk in the case of mild to moderate iodine deficiency. However, such a depletion would be associated with compensatory increases in the activity of the thyroid iodide transporter, and no data are available to evaluate in detail how large the doses of perchlorate would be necessary for such depletion. Therefore, the CONTAM Panel could not establish a short-term health-based guidance value for these populations.

Risk characterisation

- The estimated mean chronic dietary exposure levels for adolescents and the adult age groups did not indicate a health concern when compared with the TDI of 0.3 µg/kg b.w. per day. At the estimated 95th percentile chronic dietary exposure there was an exceedance of the TDI for some surveys.

- In the younger population groups ('infants', 'toddlers' and 'other children'), the TDI was exceeded for both mean (in some surveys) and 95th percentile (in the majority of surveys) exposure estimates. In addition, the estimated exposure levels for breast-fed infants largely exceeded the TDI. However, the relevance to the European Union is unknown since these estimates are based on limited literature data from the USA.

- The chronic dietary exposure to perchlorate is of potential concern in particular for the high consumers in the younger age groups of the population with mild to moderate iodine deficiency.

- It is possible that exposure to perchlorate is of concern for breast-fed infants of mothers with low iodine intake.

- Furthermore, it is possible that short-term exposure to perchlorate is of concern for young children with low iodine intake.

RECOMMENDATIONS

- To further reduce the uncertainty in the risk assessment, there is a need for more data on the occurrence of perchlorate in food in Europe, especially for infant formula, and milk and dairy products.

- There is a need for biomonitoring data for perchlorate and the associated iodine status in Europe, including data on urine and breast milk.

- Additional data on the level and duration of thyroid iodine uptake inhibition that has an impact on thyroid hormone levels in the vulnerable subpopulation groups would improve the risk assessment.

- There is a need for a better understanding of the contribution of various dietary factors to the overall thyroid iodine uptake inhibition.

DOCUMENTATION PROVIDED TO EFSA

Documentation submitted to EFSA through the European Commission:

1. BVL (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit), 2013. Report of the German Federal Environment Agency (20 November 2013) Background perchlorate-contamination levels of various environmental samples. Submitted in December 2013.

2. Fertilizer Europe, 2013. Presentation given at the Fertilizer Working Group of DG Enterprise on 2 December 2013. Submitted in April 2015.

3. SGS, 2014. Report fertilizer screening project on perchlorate levels in Europe. Test report AN14-22424. Submitted in April 2015.

REFERENCES

Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, Rago T, Grasso L, Valeriano R, Balestrieri A and Pinchera A, 1999. The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. Journal of Clinical Endocrinology and Metabolism, 84, 561–566.

Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA and Larsen PR, 2004. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. New England Journal of Medicine, 351, 241–249.

Amitai Y, Winston G, Sack J, Wasser J, Lewis M, Blount BC, Valentin-Blasini L, Fisher N, Israeli A and Leventhal A, 2007. Gestational exposure to high perchlorate concentrations in drinking water and neonatal thyroxine levels. Thyroid, 17, 843–850.

Anastassiades M, Kolberg DI, Mack D, Wildgrube C, Sigalova I, Roux D and Fugel D, 2012. Quick method for the analysis of residues of numerous high polar pesticides in foods of plant origin involving simultaneous extraction with methanol and LC-MS/MS determination. EU reference laboratory for pesticides requiring single residue methods (EURL-SRM), 1–43.

Anbar M, Guttmann S and 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.

Andersen SL, Nøhr SB, Wu CS, Olsen J, Pedersen KM and Laurberg P, 2013. Thyroglobulin in smoking mothers and their newborns at delivery suggests autoregulation of placental iodine transport overcoming thiocyanate inhibition. European Journal of Endocrinology, 168, 723–731.

Andersson M, de Benoist B, Delange F and Zupan J, 2007. Prevention and control of iodide deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutrition, 10, 1606–1611.

Andersson M, Karumbunathan V and Zimmermann MB, 2012. Global iodine status in 2011 and trends over the past decade. The Journal of Nutrition, 142, 744–750.

ANSES (l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail), 2011. AVIS de l' Agence nationale de sécurité sanitaires lié à la présence d'ions perchlorate dans les eaux destinées à la consommation humaine. ANSES-Request No.2011-SA-0024, 21 pp.

ANSES (l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail), 2012. AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif aux études épidémiologiques portant sur les associations entre une exposition aux ions perchlorate dans l'eau de boisson et la fonction thyroïdienne dans des populations spécifiques. Saisine 2012-SA-0119, 16 pp.

ANSES (l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail), 2013. AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif à « la contamination des denrées alimentaires par les ions perchlorate». Saisine n. 2013-SA-0120, 12 pp.

ANSES (l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail), 2014. Opinion of the French Agency for Food, Environmental and Occupational Health and Safety on the presence of perchlorate in infant formula and in drinking water in France. Request Nos. 2011-SA-0208 and 2011-SA-0336, 52 pp.

ATSDR (Agency for Toxic Substances and Disease Registry), 2008. Toxicological profile for perchlorates. Atlanta, GA, United States Department of Health and Human Services, Public Health Service. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=895&tid=181.

Bernal J and Pekonen F, 1984. Ontogenesis of the nuclear 3,5,3'-triiodothyronine receptor in the human fetal brain. Endocrinology, 114, 677–679.

BfR (Federal Institute for Risk Assessment), 2013a. BfR recommendations on how to perform the consumer risk assessment for perchlorate in food. BfR opinion No.015/2013, 6.6.2013, 6 pp.

BfR (Federal Institute for Risk Assessment), 2013b. EU proposal for maximum percholorate concentrations in foods is inadequate. Updated BfR Opinion No. 027/2013, 9.7.2013, 11 pp.

Bianco AC, Salvatore D, Gereben B, Berry MJ and Larsen PR, 2002. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocrine Reviews, 23, 38–89.

Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L and Caldwell KL, 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.

Blount BC, Rich DQ, Valentin-Blasini L, Lashley S, Ananth CV, Murphy E, Smulian JC, Spain BJ, Barr DB, Ledoux T, Hore P and Robson M, 2009. Perinatal exposure to perchlorate. thiocyanate, and nitrate in New Jersey mothers and newborns. Environmental Science & Technology, 43, 7543–7549.

Bogazzi F, Bartalena L, Tomisti L, Dell'Unto E, Cosci C, Sardella C, Tanda ML, Lai A, Gasperi M, Aghini-Lombardi F and Martino E, 2008. Potassium perchlorate only temporarily restores euthyroidism in patients with amiodarone-induced hypothyroidism who continue amiodarone therapy. Journal of Endocrinological Investigation, 31, 515–519.

Boyages SC, 2000. The neuromuscular system and brain in hypothyroidism. In: Werner and Ingbar's the thyroid: A fundamental and clinical text. Eds Braverman LE and Utiger RD. Lippincott Williams & Wilkins, Philadelphia, USA, 803–810.

Brabant G, Bergmann P, Kirsch CM, Köhrle J, Hesch RD and von zur Mühlen A, 1992. Early adaptation of thyrotropin and thyroglobulin secretion to experimentally decreased iodine supply in man. Metabolism, 41, 1093–1096.

Brauer VF, Below H, Kramer A, Führer D and Paschke R, 2006. The role of thiocyanate in the etiology of goiter in an industrial metropolitan area. European Journal of Endocrinology, 154, 229–235.

Brandhuber P, Clark S and Morley K, 2009. A review of perchlorate occurrence in public water systems. Journal of American Water Works Association, 101, 63–73.

Brauer VF, Below H, Kramer A, Führer D and Paschke R, 2006. The role of thiocyanate in the etiology of goiter in an industrial metropolitan area. European Journal of Endocrinology, 154, 229–235.

Braverman LE, He X, Pino S, Cross M, Magnani B, Lamm SH, Kruse MB, Engel A, Crump KS and Gibbs JP, 2005. The Effect of Perchlorate, Thiocyanate, and Nitrate on Thyroid Function in

Workers Exposed to Perchlorate Long-Term. Journal of Clinical Endocrinology and Metabolism, 90, 700–706.

Braverman LE, Pearce EN, He X, Pino S, Seeley M, Beck B, Magnani B, Blount BC and 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.

Brechner RJ, Parkhurst GD, Humble WO, Brown MB and Herman WH, 2000. Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. Journal of Occupational and Environmental Medicine, 42, 777–782.

Brown GM and Gu B, 2006. The Chemistry of Perchlorate in the Environment. In: Perchlorate. Environmental Occurrence, Interactions and Treatment. Chapter 2. Eds Gu B and Coates JD, Springer Science, New York, Philadelphia, USA, 17–47.

Buffler PA, Kelsh MA, Lau EC, Edinboro CH, Barnard JC, Rutherford GW, Daaboul JJ, Palmer L and Lorey FW, 2006. Thyroid function and perchlorate in drinking water: an evaluation among California newborns, 1998. Environmental Health Perspectives, 114, 798–804.

Cao Y, Blount BC, Valentin-Blasini L, Bernbaum JC, Phillips TM and Rogan WJ, 2010. Goitrogenic anions, thyroid-stimulating hormone, and thyroid hormone in infants. Environmental Health Perspectives, 118, 1332–1337. Erratum in: Environmental Health Perspectives, 118, A470.

Carr CW, 1952. Studies on the binding of small ions in protein solutions with the use of membrane electrodes. I. The binding of the chloride ion and other inorganic anions in solutions of serum albumin. Archives of Biochemistry and Biophysics, 40, 286–294.

CDC (Centers for Disease Control and Prevention), 2009. Perchlorate. In: Fourth national report on human exposure to environmental chemicals. United States Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA, USA, 243–246.

Chang S, Crothers C, Lai S and Lamm S, 2003. Pediatric neurobehavioral diseases in Nevada counties with respect to perchlorate in drinking water: an ecological inquiry. Birth Defects Research A, 67, 886–892.

Charatcharoenwitthaya N, Ongphiphadhanakul B, Pearce EN, Somprasit C, Chanthasenanont A, He X, Chailurkit L and Braverman LE, 2014. The association between perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant Thai women. Journal of Clinical Endocrinology and Metabolism, 99, 2365–2371.

Ciardelli R, Haumont D, Gnat D, Vertongen F and Delange F, 2002. The nutritional iodine supply of Belgian neonates is still insufficient. European Journal of Pediatrics, 161, 519–523.

Clewell RA, Merrill EA , Gearhart JM , Robinson PJ , Sterner TR , Mattie DR and Clewell HJ 3rd, 2007. Perchlorate and Radioiodide Kinetics Across Life Stages in the Human: Using PBPK Models to Predict Dosimetry and Thyroid Inhibition and Sensitive Subpopulations Based on Developmental Stage. Journal of Toxicology and Environmental Health Part A, 70, 408–428.

Clewell RA, Merrill EA, Narayanan L, Gearhart JM and Robinson PJ, 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 RA, Merrill EA, Yu KO, Mahle DA, Sterner TR, Fisher JW and Gearhart JM, 2003b. 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 RA, Merrill EA, Yu KO, Mahle DA, Sterner TR, Mattie DR, Robinson PJ, Fisher JW and Gearhart JM, 2003a. 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.

Connell JM, 1981. Long-term use of potassium perchlorate. Postgraduate Medical Journal, 57, 516–517.

Contempre B, Jauniaux E, Calvo R, Jurkovic D, Campbell S and de Escobar GM, 1993. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. Journal of Clinical Endocrinology and Metabolism, 77, 1719–1722.

Costa M, Zhitkovich A, Gargas M, Paustenbach D, Finley B, Kuykendall J, Billings R, Carlson TJ, Wetterhahn K, Xu J, Patierno S and Bogdanffy M, 1996. Interlaboratory validation of a new assay for DNA-protein crosslinks. Mutation Research, 369, 13–21.

Crooks J and Wayne EJ, 1960. A comparison of potassium perchlorate, methylthiouracil, and carbimazole in the treatment of thyrotoxicosis. Lancet, 1, 401–404.

Crump C, Michaud P, Tellez R, Reyes C, Gonzalez G, Montgomery EL, Crump KS, Lobo G, Becerra C and Gibbs JP, 2000. Does perchlorate in drinking water affect thyroid function in newborns or school-age children? Journal of Occupational and Environmental Medicine, 42, 603–612.

Crump KS and Gibbs JP, 2005. Benchmark calculations for perchlorate from three human cohorts. Environmental Health Perspectives, 113, 1001–1008.

Dasgupta PK, Kirk AB, Dyke JV and Ohira S, 2008. Intake of iodine and perchlorate and excretion in human milk. Environmental Science & Technology, 42, 8115–8121.

Dasgupta PK, Martinelango PK, Jackson WA, Anderson TA, Tian K, Tock RW and Rajagopalan S, 2005. The origin of naturally occurring perchlorate: the role of atmospheric processes. Environmental Science &Technology, 39, 1569–1575.

De Benoist B, McLean E, Andersson M and Rogers L, 2008. Iodine deficiency in 2007: global progress since 2003. Food Nutrition Bulletin, 29, 195–202.

De Groef B, Decallonne BR, Van der Geyten S, Darras VM and Bouillon R, 2006. Perchlorate versus other environmental sodium/iodide symporter inhibitors: potential thyroid-related health effects. European Journal of Endocrinology, 155, 17–25.

Dumont JE, Ermans AM, Maenhaut C, Coppée F and Stanbury JB, 1995. Large goitre as a maladaptation to iodine deficiency. Clinical Endocrinology, 43, 1–10.

Durand MJ, 1938. Recherches sur l'élimination des perchlorates, sur leur repartition dans les organes et 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. Available at: http://echa.europa.eu/information-on-chemicals/registered-substances

EFSA (European Food Safety Authority), 2006. Guidance of the Scientific Committee on a request from EFSA related to Uncertainties in Dietary Exposure Assessment. The EFSA Journal 2006, 438, 1–54.

EFSA (European Food Safety Authority), 2007. Reasoned opinion on the potential chronic and acute risk to consumers' health arising from proposed temporary EU MRLs. Available at: www.efsa.europa.eu

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. The EFSA Journal 2009, 1150, 1–72.

EFSA (European Food Safety Authority), 2010. Management of left-censored data in dietary exposure assessment of chemical substances. EFSA Journal 2010;8(3):1557, 96 pp. doi:10.2903/j.efsa.2010.1557

EFSA (European Food Safety Authority), 2011a. Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment. EFSA Journal 2011;9(3):2097, 34 pp. doi:10.2903/j.efsa.2011.2097

EFSA (European Food Safety Authority), 2011b. Evaluation of the FoodEx, the food classification system applied to the development of the EFSA Comprehensive European Food Consumption Database. EFSA Journal 2011;9(3):1970, 27 pp. doi:10.2903/j.efsa.2011.1970

EFSA BIOHAZ Panel (EFSA Panel on Biological Hazards), 2014. Scientific Opinion on the risk posed by pathogens in food of non-animal origin. Part 2 (*Salmonella* and Norovirus in leafy greens eaten raw as salads). EFSA Journal 2014;12(3):3600, 118 pp. doi:10.2903/j.efsa.2014.3600

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2011. Scientific Opinion on Tetrabromobisphenol A (TBBPA) and its derivatives in food. EFSA Journal 2011;9(12):2477, 67 pp. doi:10.2903/j.efsa.2011.2477

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on Dietary Reference Values for iodine. EFSA Journal 2014;12(5):3660, 57 pp. doi:10.2903/j.efsa.2014.3660

EFSA SC (EFSA Scientific Committee), 2012. Scientific Committee; Guidance on selected defaultvalues to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence ofactual measured data. EFSA Journal 2012;10(3):2579, 32 pp. doi:10.2903/j.efsa.2012.2579

El Aribi H, Le Blanc YJ, Antonsen S and Sakuma T, 2006. Analysis of perchlorate in foods and beverages by ion chromatography coupled with tandem mass spectrometry (IC-ESI-MS/MS). Analytica Chimica Acta, 567, 39–47.

English P, Blount B, Wong M, Copan L, Olmedo L, Patton S, Haas R, Atencio R, Xu J and Valentin-Blasini L. 2011. Direct measurement of perchlorate exposure biomarkers in a highly exposed population: a pilot study. PloS One 6 (3):e17015.

Eskin BA, Shuman R, Krouse T and Merion JA, 1975. Rat mammary gland atypia produced by iodine blockade with perchlorate. Cancer Research, 35, 2332–2339.

FAO/WHO (Food and Agriculture Organisation/World Health Organization), 2004. Vitamin and mineral requirements in human nutrition: Joint FAO/WHO Expert Consultation on human vitamin and mineral requirements. 2nd edition. World Health Organization and Food and Agriculture Organization of the United Nations, Switzerland, Geneva, 341 pp. Available at: http://whqlibdoc.who.int/publications/2004/9241546123.pdf

FAO/WHO (Food and Agriculture Organisation/World Health Organization), 2011. Safety evaluation of certain contaminants in food prepared by the Seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series 63, 685–762. Available at: http://www.inchem.org/documents/jecfa/jecmono/v63je01.pdf

FDA (US Food and Drug Administration), 2013. Preliminary estimation of perchlorate dietary exposure based on FDA 2004/2005 exploratory data. Available at: http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm077653.htm

Fernandez Rodriguez A, Galera Davidson H, Salguero Villadiego M, Moreno Fernandez A, Martin Lacave I and Fernandez Sanz J, 1991. Induction of thyroid proliferative changes in rats treated with antithyroid compound. Anatomia Histologia Embryologia, 20, 289–298.

Fernández-Santos JM, De-Miguel M, Gonzalez-Campora R, Salguero-Viladiego M, Cabrera JJ and Galera-Davidson H, 2004. Ki-*ras* mutational analysis in rat follicular-cell proliferative lesions of the thyroid gland induced by radioactive iodine and potassium perchlorate. Journal of Endocrinological Investigation, 27, 12–17.

Ferreiro B, Bernal J, Goodyer CG and Branchard, CL, 1988. Estimation of nuclear thyroid hormone receptor saturation in human fetal brain and lung during early gestation. Journal of Clinical Endocrinology & Metabolism, 67, 853–856.

Fisher DA and Brown RS, 2000. Thyroid physiology in the perinatal period and during childhood. In: Werner and Ingbar's the thyroid: A fundamental and clinical text. Eds Braverman LE and Utiger RD. Lippincott Williams & Wilkins, Philadelphia, USA, 959–972.

Fisher DA and Oddie TH, 1969. Thyroid iodine content and turnover in euthyroid subjects: validity of estimation of thyroid iodine accumulation from short-term clearance studies. Journal of Clinical Endocrinology and Metabolism, 29, 721–727.

Fisher J, Lumen A, Latendresse J and Mattie D, 2012. Extrapolation of hypothalamic-pituitary-thyroid axis perturbations and associated toxicity in rodents to humans: case study with perchlorate. Journal of Environmental Science and Health Part C, 30, 81–105.

Fisher J, Todd P, Mattie D, Godfrey D, Narayanan L and 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.

Florencio Vicente MDR, 1990. Proliferative thyroid lesions: An experimental study. Dissertations Abstracts International C, 54, 176.

Gärtner R, 2009. Autoregulation of thyroid growth and function by iodine: independent regulation of the thyroid gland by iodocompounds. In: Comprehensive handbook of iodine: nutritional, biochemical and therapeutic aspects. Eds Preedy VR, Burrow GN and Watson RW. Elsevier, 243–247.

Gauss W, 1972. Physiological and histological criteria of thyroid gland function following a single or long-term administration of potassium perchlorate in adult mice (*Mus musculus* L.). I. Long-term experiments. Zeitschrift fur Mikroskopisch-Anatomische Forschung, 85, 469–500.

Gibbs JP, Narayanan L and Mattie DR, 2004. Crump et al. study among school children in Chile: subsequent urine and serum perchlorate levels are consistent with perchlorate in water in Taltal. Journal of Occupational and Environmental Medicine, 46, 516–517.

Gilbert ME and Sui L 2008. Developmental exposure to perchlorate alters synaptic transmission in hippocampus of the adult rat. Environmental Health Perspectives, 116, 752–760.

Ginsberg GL, Hattis DB, Zoeller RT and Rice DC, 2007. Evaluation of the U.S. EPA/OSWER preliminary remediation goal for perchlorate in groundwater: focus on exposure to nursing infants. Environmental Health Perspectives, 115, 361–369.

Goodman G, 2001. The conclusions of the Arizona perchlorate study require reexamination. Journal of Occupational and Environmental Medicine, 43, 305–309.

Greer MA, Goodman G, Pleus RC and Greer SE, 2002. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environmental Health Perspectives, 110, 927–937. Erratum in: Environmental Health Perspectives, 2005, 113, A732.

Greiner P, Mc Lellean C, Bennet D and Ewing A, 2008. Occurrence of perchlorate in sodium hypochlorite. Journal of Water Works Association, 100, 68–74.

Hepperle J, Wolheim A, Kohlberg D, Wildgrube C and 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, 2013, 1–16.

Her N, Kim J and Yoon Y, 2010. Perchlorate in dairy milk and milk-based powdered infant formula in South Korea. Chemosphere, 81, 732–737.

Hiasa Y, Kitahori Y, Kato Y, Ohshima M, Konishi N, Shimoyama T, Sakaguchi Y, Hashimoto H, Minami S and Murata Y, 1987. Potassium perchlorate, potassium iodide, and propylthiouracil: promoting effect on the development of thyroid tumors in rats treated with N-bis(2-hydroxypropyl)-nitrosamine. Japanese Journal of Cancer Research, 78, 1335–1340.

Huybrechts I, Sioen I, Boon PE, Ruprich J, Lafay L, Turrini A, Amiano P, Hirvonen T, De Neve M, Arcella D, Moschandreas J, Westerlund A, Ribas-Barba L, Hilbig A, Papoutsou S, Christensen T, Oltarzewski M, Virtanen S, Rehurkova I, Azpiri M, Sette S, Kersting M, Walkiewicz A, Serra-Majem L, Volatier J-L, Trolle E, Tornaritis M, Busk L, Kafatos A, Fabiansson S, De Henauw S and Van Klaveren J, 2011. Dietary Exposure Assessments for Children in Europe (the EXPOCHI project): rationale, methods and design. Archives of Public Health, 69, 1–12.

Iannece P, Motta O, Tedesco R, Carotenuto M and Proto A, 2013. Determination of Perchlorate in Bottled Water from Italy. Water, 5, 767–779.

Jackson WA, Joseph P, Laxman P, Tan K, Smith PN, Yu L and Anderson TA, 2005. Perchlorate accumulation in forage and edible vegetation. Journal of Agricultural and Food Chemistry, 53, 369–373.

Jain RB, 2013. Impact of pregnancy and other factors on the levels of urinary perchlorate, thiocyanate, and nitrate among females aged 15-44 years: data from National Health and Nutrition Examination Survey: 2003-2008. Chemosphere, 91, 882–887.

Josefsson M, Grunditz T, Ohlsson T and Ekblad E, 2002. Sodium/iodide-symporter: distribution in different mammals and role in entero-thyroid circulation of iodide. Acta Physiologica Scandinavica, 175, 129–137.

Kang N, Anderson TA and JacksonWA, 2006. Photochemical formation of perchlorate from aqueous oxychlorine anions. Analytica Chimica Acta, 567, 48–56.

Kang N, Jackson WA, Dasgupta PK and Anderson TA, 2008. Perchlorate production by ozone oxidation of chloride in aqueous and dry systems. The Science of the Total Environment, 405, 301–309.

Kannan K, Praamsma ML, Oldi JF, Kunisue T and Sinha RK, 2009. Occurrence of perchlorate in drinking water, groundwater, surface water and human saliva from India. Chemosphere, 76, 22–26.

Kelsh MA, Buffler PA, Daaboul JJ, Rutherford GW, Lau EC, Barnard JC, Exuzides AK, Madl AK, Palmer LG and Lorey FW, 2003. Primary congenital hypothyroidism, newborn thyroid function, and environmental perchlorate exposure among residents of a Southern California community. Journal of Occupational and Environmental Medicine, 45, 1116–1127.

Kessler FJ and Krüskemper HL, 1966. Experimental thyroid tumors caused by many years of potassium perchlorate administration. Klinische Wochenschrift, 44, 1154–1156.

Khan MA, Fenton SE, Swank AE, Hester SD, Williams A and Wolf DC, 2005. A mixture of ammonium perchlorate and sodium chlorate enhances alterations of the pituitary-thyroid axis caused by the individual chemicals in adult male F344 rats. Toxicologic Pathology, 33, 776–783.

Kirk AB, Dyke JV, Martin CF, and Dasgupta PK, 2007. Temporal Patterns in Perchlorate, Thiocyanate, and Iodide Excretion in Human Milk. Environmental Health Perspectives, 115, 182–186.

Kirk AB, Dyke JV, Ohira S and Dasgupta PK, 2013. Relative source contributions for perchlorate exposures in a lactating human cohort. The Science of the Total Environment, 15, 939–943.

Kirk AB, Kroll M Dyke JV, Shin-Ichi O, Dias RA and Dasgupta PK, 2012. Perchlorate, iodine supplements, iodized salt and breast milk iodine content. The Science of the Total Environment, 420, 73–78.

Kirk AB, Martinelango PK, Tian K, Dutta A, Smith EE and Dasgupta PK, 2005. Perchlorate and iodide in dairy and breast milk. Environmental Science & Technology, 39, 2011–2017.

Knudsen N, Bülow I, Jørgensen T, Laurberg P, Ovesen L and Perrild H, 2000. Goitre prevalence and thyroid abnormalities at ultrasonography: a comparative epidemiological study in two regions with slightly different iodine status. Clinical Endocrinology, 53, 479–485.

Knudsen N, Bülow I, Laurberg P, Ovesen L, Perrild H and Jørgensen T, 2002b. Association of tobacco smoking with goiter in a low-iodine-intake area. Archives of Internal Medicine, 162, 439–443.

Knudsen N, Bülow I, Laurberg P, Ovesen L, Perrild H and Jørgensen T, 2002a. Parity is associated with increased thyroid volume solely among smokers in an area with moderate to mild iodine deficiency. European Journal of Endocrinology, 146, 39–43.

Krohn K, Maier J and Paschke R, 2007. Mechanisms of disease: hydrogen peroxide, DNA damage and mutagenesis in the development of thyroid tumors. Nature Clinical Practice Endocrinology & Metabolism, 3, 713–720.

Krüskemper HL, 1960. Theoretische grundlagen und klinische ergebnisse der behandlung von hyperthyreosen mit perchlorat. Arzneimittel Forschung, 10, 13–17.

Lamm SH, 2003. Perchlorate exposure does not explain differences in neonatal thyroid function between Yuma and Flagstaff. Journal of Occupational and Environmental Medicine, 45, 1131–1132.

Lamm SH, Braverman LE, Li FX, Richman K, Pino S and Howearth G, 1999. Thyroid health status of ammonium perchlorate workers: a cross-sectional occupational health study. Journal of Occupational and Environmental Medicine, 41, 248–260.

Lamm SH and Doemland M, 1999. Has perchlorate in drinking water increased the rate of congenital hypothyroidism? Journal of Occupational and Environmental Medicine, 41, 409–411.

Lamm SH, Hollowell JG, Engel A and Chen R, 2007. Perchlorate, thiocyanate and low iodine association not seen with low creatinine-adjusted urine iodine among women of childbearing age. Thyroid, 17, S51.

Laurberg P and Andersen SL, 2014. Nutrition: Breast milk - a gateway to iodine-dependent brain development. Nature Reviews Endocrinology, 10, 134–135.

Laurberg P, Cerqueira C, Ovesen L, Rasmussen LB, Perrild H, Andersen S, Pedersen IB and Carlé A, 2010. Iodine intake as a determinant of thyroid disorders in populations. Best Practice and Research Clinical Endocrinology & Metabolism, 24, 13–27.

Laurberg P, Nøhr SB, Pedersen KM and Fuglsang E, 2004. Iodine nutrition in breast-fed infants is impaired by maternal smoking. Journal of Clinical Endocrinology and Metabolism, 89, 181–187.

Laurberg P, Pedersen IB, Carlé A, Andersen S, Knudsen N and Karmisholt J, 2009. The Relationship between Thiocyanate and Iodine. In: Comprehensive handbook of iodine: nutritional, biochemical and therapeutic aspects. Eds Preedy VR, Burrow GN and Watson RW, Elsevier Science, New York, Philadelphia, PA, USA, 275–281.

Lawrence J, Lamm S and Braverman LE, 2001. Low dose perchlorate (3 mg daily) and thyroid function. Thyroid, 11, 295.

Lawrence JE, Lamm SH, Pino S, Richman K and Braverman LE, 2000. The effect of short-term low-dose perchlorate on various aspects of thyroid function. Thyroid, 10, 659–663.

Lazarus JH, 2014. Iodine status in Europe in 2014. European Thyroid Journal, 3, 3–6.

Lee JW, Oh SH and Oh JE, 2012. Monitoring of perchlorate in diverse foods and its estimated dietary exposure for Korea populations. Journal of Hazardous Materials, 243, 52–58.

Leung AM, Braverman LE, He X, Schuller KE, Roussilhes A, Jahreis KA and Pearce EN, 2012. Environmental Perchlorate and Thiocyanate Exposures and Infant Serum Thyroid Function. Thyroid, 22, 938–943.

Leung AM, Pearce EN, Hamilton T, He X, Pino S, Merewood A and Braverman LE, 2009. Colostrum iodine and perchlorate concentrations in Boston-area women: a cross-sectional study. Clinical Endocrinology, 70, 326–330.

Levy O, Dai G, Riedel C, Ginter CS, Paul EM, Lebowitz AN and Carrasco N, 1997. Characterization of the thyroid Na+/I- symporter with an anti-COOH terminus antibody. Proceedings of the National Academy of Sciences of the United States of America, 94, 5568–5573.

Levy O, De la Vieja A and Carrasco N, 1998. The Na+/I- symporter (NIS): recent advances. Journal of Bioenergetics and Biomembranes, 30, 195–206.

Li FX, Byrd DM, Deyhle GM, Sesser DE, Skeels MR, Katkowsky SR and Lamm SH, 2000b. Neonatal thyroid-stimulating hormone level and perchlorate in drinking water. Teratology, 62, 429–431.

Li FX, Squartsoff L and Lamm SH, 2001. Prevalence of thyroid diseases in Nevada counties with respect to perchlorate in drinking water. Journal of Occupational and Environmental Medicine, 43, 630–634.

Li Z, Li FX, Byrd D, Deyhle GM, Sesser DE, Skeels MR and Lamm SH, 2000a. Neonatal thyroxine level and perchlorate in drinking water. Journal of Occupational and Environmental Medicine, 42, 200–205.

Lumen A, Mattie DR, Fisher JW, 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.

Mahle DA, Yu KO, Narayanan L, Mattie DR and Fisher JW, 2003. Changes in cross-fostered Sprague-Dawley rat litters exposed to perchlorate. International Journal of Toxicology, 22, 87–94.

Martino E, Bartalena L, Bogazzi F and Braverman LE, 2001. The effects of amiodarone on the thyroid. Endocrinology Reviews, 22, 240–254.

McLanahan ED, Campbell JL, Jr., Ferguson DC, Harmon B, Hedge JM, Crofton KM, Mattie DR, Braverman L, Keys DA, Mumtaz M and Fisher JW, 2007. Low-dose effects of ammonium perchlorate on the hypothalamic-pituitary-thyroid axis of adult male rats pretreated with PCB126. Toxicological Sciences, 97, 308–317.

McLanahan ED, White P, Flowers L and Schlosser PM, 2014. The use of PBPK models to inform human health risk assessment: case study on perchlorate and radioiodide human lifestage models. Risk Analysis, 34, 356–66.

McLaughlin CL, Blake S, Hall T, Harman M, Kanda R, Hunt J and Rumsby PC, 2011. Perchlorate in raw and drinking water sources in England and Wales. Water and Environment Journal, 25, 456–465.

MDEP (Massachusetts Department of Environmental Protection), 2005. Draft Report - The Occurrence and sources of perchlorate in Massachusetts. Massachusetts Department of Environmental Protection, Boston, MA, USA, 48 pp. Available at: http://www.mass.gov/eea/docs/dep/cleanup/sites/percsour.pdf

Mendez W Jr. and Eftim SE, 2012. Biomarkers of perchlorate exposure are correlated with circulating thyroid hormone levels in the 2007–2008 NHANES. Environmental Research, 118, 137–144.

Merrill EA, Clewell RA, Gearhart JM, Robinson PJ, Sterner TR, Yu KO, Mattie DR and Fisher JW, 2003. PBPK Predictions of Perchlorate Distribution and Its Effect on Thyroid Uptake of Radioiodide in the Male Rat. Toxicological Sciences, 73, 256–269.

Merrill EA, Clewell RA, Robinson PJ, Jarabek AM, Gearhart JM, Sterner TR and Fisher JW, 2005. PBPK model for radioactive iodide and perchlorate kinetics and perchlorate-induced inhibition of iodide uptake in humans. Toxicological Sciences, 83, 25–43.

Morgans ME and Trotter WR, 1960. Potassium Perchlorate in Thyrotoxicosis. British Medical Journal, 2, 1086–1087.

Morreale de Escobar G, Obregon MJ and Escobar del Rey F, 2004. Role of thyroid hormone during early brain development. European Journal of Endocrinology, 151, U25–37.

Murray CW, Egan SK, Kim H, Beru N and Bolger PM, 2008. US Food and Drug Administration's Total Diet Study: Dietary intake of perchlorate and iodine. Journal of Exposure Analysis and Environmental Epidemiology, 18, 571–580.

Nakamura S and Kosaka H, 1989. Genotoxicity of inorganic metal compounds with umu test. Japanese Journal of Industrial Health, 31, 430–431.

NRC (National Research Council), 2005. Health implications of perchlorate ingestion. National Academics Press, Washington DC, 2005. Available at: http://www.nap.edu/openbook.php?isbn=0309095689

OEHHA (Office of Environmental Health Hazard Assessment), 2012. Public Health Goal for perchlorate in drinking water (draft). Public Health Goal (PHG) Technical Support Document, 165 pp. Available at: http://www.oehha.ca.gov/water/phg/pdf/120612Perchloratedraft.pdf

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

Oldi JF and Kannan K, 2009b. Perchlorate in human blood serum and plasma: Relationship to concentrations in saliva. Chemosphere, 77, 43–47.

Oppenheimer JH and Schwartz HL, 1997. Molecular basis of thyroid hormone-dependent brain development. Endocrine Reviews, 18, 462–475.

Ozpinar A, Golub MS, Poppenga RH, Blount BC and Gillespie JR, 2011. Thyroid status of female rhesus monkeys and preliminary information on impact of perchlorate administration. Laboratory Animals, 45, 209–214.

Pajer Z and Kalisnik M. 1991. The effect of sodium perchlorate and ionizing irradiation on the thyroid parenchymal and pituitary thyrotropic cells. Oncology, 48, 317–320.

Pearce EN, Alexiou M, Koukkou E, Braverman LE, He X, Ilias I, Alevizaki M and Markou KB, 2012. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women from Greece. Clinical Endocrinology, 77, 471–474.

Pearce EN, Lazarus JH, Smyth PP, He X, Dall'amico D, Parkes AB, Burns R, Smith DF, Maina A, Bestwick JP, Jooman M, Leung AM and Braverman LE, 2010. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women. Journal of Clinical Endocrinology and Metabolism, 95, 3207–3215.

Pearce EN, Leung AM, Blount BC, Bazrafshan HR, He X, Pino S, Valentin-Blasini L and Braverman LE, 2007. Breast Milk Iodine and Perchlorate Concentrations in Lactating Boston-Area Women. Journal of Clinical Endocrinology and Metabolism, 92, 1673–1677.

Pearce EN, Spencer CA, Mestman JH, Lee RH, Bergoglio LM, Mereshian P, He X, Leung AM and Braverman LE, 2011. Effect of environmental perchlorate on thyroid function in pregnant women from Còrdoba, Argentina, and Los Angeles, California. Endocrinology Practices, 17, 412–427.

Plummer LN, Böhlke JK and Doughten MW, 2006. Perchlorate in pleistocene and holocene groundwater in north-central New Mexico. Environmental Science and Technology, 40, 1757–1763.

Rajagopalan S, Anderson TA, Fahlquist L, Rainwater KA, Ridley M and Jackson WA, 2006. Widespread presence of naturally occurring perchlorate in high plains of Texas and New Mexico. Environmental Science and Technology, 40, 3156–3162.

Rao B, Anderson TA, Orris GJ, Rainwater KA, Rajagopalan S, Sandvig RM, Scanlon BR, Stonestrom DA, Walvoord MA and Jackson WA, 2007. Widespread natural perchlorate in unsaturated zones of the southwest United States. Environmental Science and Technology, 41, 4522–4528.

Rao B, Anderson TA, Redder A and Jackson WA, 2010. Perchlorate formation by ozone oxidation of aqueous chlorine/oxy-chlorine species: role of ClxOy radicals. Environmental Science & Technology, 44, 2961–2967.

San RHC and Clarke JJ, 1999. *In vitro* mammalian cell gene mutation test (L5178Y/TK$^{+/-}$ mouse lymphoma assay). BioReliance study number G98BAO6.702. Perchlorate Study Group, Rockville, MD, USA, 9 pp. Available at: http://www.tera.org/ART/Perchlorate/2nd%20study%20protocol.pdf

Sanchez CA, Fonseca JM, Blount BC and Krieger RI, 2009. Hypochlorite treatments are not a significant source of perchlorate exposure in lettuce. Journal of Agriculture and food Chemistry, 57, 2320–2323.

Scatchard G and Black ES, 1949. The effect of salts on the isoionic and isoelectric points of proteins. The Journal of Physical and Colloid Chemistry, 53, 88–99.

Schier JG, Wolkin AF, Valentin-Blasini L, Belson MG, Kieszak SM, Rubin CS and Blount BC, 2010. Perchlorate exposure from infant formula and comparisons with the perchlorate reference dose. Journal of Exposure Analysis and Environmental Epidemiology, 20, 281–287.

Schreinemachers DM, 2011. Association between Perchlorate and Indirect Indicators of Thyroid Dysfunction in NHANES 2001–2002, a Cross-Sectional, Hypothesis-Generating Study. Biomarker Insights, 6, 135–146.

Scinicariello F, Murray HE, Smith L, Wilbur S and Fowler BA, 2005. Genetic factors that might lead to different responses in individuals exposed to perchlorate. Environmental Health Perspectives, 113, 1479–1484.

Selivanova LN, Boltromeyuk LP, Aref'eva ZS et al., 1986. Dynamics of the absorption and elimination of perchloric acid salts in laboratory animals and livestock. Khim Selsk Khoz 106, 43–45 (as cited by ATSDR, 2008).

Siglin JC, Mattie DR, Dodd DE, Hildebrandt PK and Baker WH, 2000. A 90-day drinking water toxicity study in rats of the environmental contaminant ammonium perchlorate. Toxicological Sciences, 57, 61–74.

Smanik PA, Ryu KY, Theil KS, Mazzaferri EL and Jhiang SM, 1997. Expression, exon-intron organization, and chromosome mapping of the human sodium iodide symporter. Endocrinology, 138, 3555–3558.

Smellie JM, 1957. The Treatment of Juvenile Thyrotoxicosis with Potassium Perchlorate. Proceedings of the Royal Society of Medicine, 50, 1026.

Smith PN, Severt SA, Jackson JW and Anderson TA, 2006. Thyroid function and reproductive success in rodents exposed to perchlorate via food and water. Environmental Toxicology and Chemistry, 25, 1050–1059.

Snyder SA, Pleus RC, Vanderford BJ and Holady JC, 2006. Perchlorate and chlorate in dietary supplements and flavor enhancing ingredients. Analytica Chimica Acta, 567, 26–32.

Soldin OP, Braverman LE and Lamm SH, 2001. Perchlorate clinical pharmacology and human health: a review. Therapeutic Drug Monitoring, 23, 316–331.

Stanford BD, Pisarenko AN and Snyder SA, 2011. Perchlorate, broate and chlorate in hypochlorite solutions: guidelines for utilities. Journal of Water Works Association, 100, 1–13.

Steinmaus C, Miller MD, Cushing L, Blount BC and Smith AH, 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 MD and 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, Miller MD and Smith AH, 2010. Perchlorate in drinking water during pregnancy and neonatal thyroid hormone levels in California. Journal of Occupational and Environmental Medicine, 52, 1217–1524.

Stoker TE, Ferrell JM, Laws SC, Cooper RL and Buckalew A, 2006. Evaluation of ammonium perchlorate in the endocrine disruptor screening and testing program's male pubertal protocol: ability to detect effects on thyroid endpoints. Toxicology, 228, 58–65.

Sturniolo Gia, Gagliano E, Tonante A, Taranto F, Vermiglio F and Sturniolo Gio, 2013. Toxic multinodular goitre. Personal case histories and literature review. Il Giornale di Chirurgia, 34, 257–259.

Suh M, Abraham L, Hixon JG and Proctor DM, 2013. 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 and Environmental Epidemiology, doi:10.1038/jes.2013.67.

Sungur Ş and Atan MM, 2013. Determination of nitrate, nitrite and perchlorate anions in meat, milk and their products consumed in Hatay region in Turkey. Food Additives & Contaminants. Part B, 6, 6–10.

Sungur Ş and Sangün MK, 2011. Ion chromatographic determination of perchlorate in foods consumed in Hatay region. Food Chemistry, 126, 326–331.

Susarla S, Collette TW, Garrison AW, Wolfe NL and McCutcheon SC, 1999. Perchlorate identification in fertilizers. Environmental Science & Technology, 33, 3469–3472.

Téllez RT, Michaud Chacón P, Reyes Abarca C, Blount BC, Van Landingham CB, Crump KS and Gibbs JP, 2005. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid, 15, 963–975.

Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler, J and McGregor AM, 1991. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. The New England Journal of Medicine, 324, 532–536.

Thuett KA Roots EH, Mitchell LP, Gentles BA, Anderson TA, Kendall RJ and Smith EE. 2002a. In utero and lactational exposure to ammonium perchlorate in drinking water: effects on developing deer mice at postnatal day 21. Journal of Toxicology and Environmental Health. Part A, 65, 1061–1076.

Thuett KA Roots EH, Mitchell LP, Gentles BA, Anderson TA and Smith EE. 2002b. Effects of in utero and lactational ammonium perchlorate exposure on thyroid gland histology and thyroid and sex hormones in developing deer mice (*Peromyscus maniculatus*) through postnatal day 21. Journal of Toxicology and Environmental Health. Part A, 65, 2119–2130.

Tonacchera M, Pinchera A, Dimida A, Ferrarini E, Agretti P, Vitti P, Santini F, Crump K and 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.

Toro Guillen M, 1991. Reversibility of proliferative thyroid lesions. Dissertation Abstracts International C, 54, 1186.

Tran N, Valentín-Blasini L, Blount BC, McCuistion CG, Fenton MS, Gin E, Salem A and Hershman JM, 2008. Thyroid-stimulating hormone increases active transport of perchlorate into thyroid cells. American Journal of Physiology - Endocrinology and Metabolism, 294, E802–E806.

Trumpff C, De Schepper J, Tafforeau J, Van Oyen H, Vanderfaeillie J and Vandevijwere S, 2013. Mild iodine deficiency in pregnancy in Europe and its consequences for cognitive and psychomotor development of children: a review. Journal of Trace Elements in Medicine and Biology, 27, 174–183.

Trumpolt CW, Crain M, Cullison GD, Flanagan SJP, Siegel L and Lathrop S, 2005. Perchlorate: Sources, uses, and occurrences in the environment. Remediation Journal, 16, 65–89.

Urbansky ET, 1998. Perchlorate Chemistry: Implications for Analysis and Remediation. Bioremediation Journal, 2, 81–95.

Urbansky ET, 2002. Perchlorate as an Environmental Contaminant. Environmental Science and Pollution Research, 9, 187–192.

US-EPA (United States Environmental Protection Agency), 2005. Perchlorate and perchlorate salts. Integrated Risk Information System, 1007. Available at: http://www.epa.gov/iris/subst/1007.htm

US-EPA (United States Environmental Protection Agency), 2008. Interim Drinking Water Health Advisory for Perchlorate. Washington DC, Environmental Protection Agency, 1–41.

Valentin-Blasini L, Blount BC, Otero-Santos S, Cao Y, Bernbaum JC and Rogan WJ, 2011. Perchlorate exposure and dose estimates in infants. Environmental Science & Technology, 45, 4127–4132.

van den Hove MF, Beckers C, Devlieger H, de Zegher F and De Nayer P, 1999. Hormone synthesis and storage in the thyroid of human preterm and term newborns: effect of thyroxine treatment. Biochimie, 81, 563–570.

Völzke H, Schwahn C, Kohlmann T, Kramer A, Robinson DM, John U and Meng W, 2005. Risk factors for goiter in a previously iodine-deficient region. Experimental and Clinical Endocrinology and Diabetes, 113, 507–515.

Wang Z, Forsyth D, Lau BP, Pelletier L, Bronson R and Gaertner D, 2009. Estimated dietary exposure of Canadians to perchlorate through the consumption of fruits and vegetables available in Ottawa markets. Journal of Agricultural and Food Chemistry, 57, 9250–9255.

Wang Z, Lau BP, Tague B, Sparling M and Forsyth D, 2011. Determination of perchlorate in infant formula by isotope dilution ion chromatography/tandem mass spectrometry. Food Additives & Contaminants. Part A, 28, 799–806.

Wenzel KW and Lente JR, 1984. Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against an immunosuppressive action of thionamide drugs. Journal of Clinical Endocrinology and Metabolism 58, 62–69.

WHO (World Health Organization), 1998. Surface decontamination of fruits and vegetables eaten raw. Available at: http://apps.who.int/iris/bitstream/10665/64435/1/WHO_FSF_FOS_98.2.pdf?ua=1

WHO (World Health Organization), 2007. Iodine deficiency in Europe - A continuing public health problem. Available at: http://www.who.int/nutrition/publications/VMNIS_Iodine_deficiency_in_Europe.pdf

WHO (World Health Organization), 2009. Environmental Health Criteria 240. Principles and methods for the assessment of chemicals in food. Available at: http://www.who.int/iris/handle/10665/44065

WHO/IPCS ((World Health Organization - International Programme on Chemical Safety Evaluation), 2008. Uncertainty and Data Quality in Exposure Assessment. Part 1: Guidance document on characterizingand communicating uncertainty in exposure assessment. Part 2: Hallmarks of data quality in chemical exposure assessment. Available at: http://www.who.int/ipcs/publications/methods/harmonization/exposure_assessment.pdf

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

Yifru DD and Nzengung VA, 2007. Uptake of perchlorate by vegetation growing at field sites in arid and subhumid climates. Remediation Journal, 17, 53–68.

York RG, Barnett J Jr., Brown WR, Garman RH, Mattie DR and 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, 191–214.

York RG, Brown WR, Girard MF and Dollarhide JS. 2001b. Oral (drinking water) developmental toxicity study of ammonium perchlorate in New Zealand White rabbits. International Journal of Toxicology, 20, 199–205.

York RG, Brown WR, Girard MF and Dollarhide JS. 2001a. Two-generation reproduction study of ammonium perchlorate in drinking water in rats evaluates thyroid toxicity. International Journal of Toxicology, 20, 183–197.

York RG, Funk KA, Girard MF, Mattie D and Strawson JE, 2003. Oral (Drinking Water) Developmental Toxicity Study of Ammonium Perchlorate in Sprague-Dawley Rats. International Journal of Toxicology, 22, 453–464.

York RG, Lewis E, Brown WR, Girard MF, Mattie DR, Funk KA and Strawson JS, 2005a. Refining the effects observed in a developmental neurobehavioral study of ammonium perchlorate administered orally in drinking water to rats. I. Thyroid and reproductive effects. International Journal of Toxicology, 24, 403–418.

York RG, Lewis E, Brown WR, Girard MF, Mattie DR, Funk KA and Strawson JS, 2005b. Refining the effects observed in a developmental neurobehavioral study of ammonium perchlorate administered orally in drinking water to rats. II. Behavioral and neurodevelopment effects. International Journal of Toxicology, 24, 451–467.

Yu KO, Narayanan L, Mattie DR, Godfrey RJ, Todd PN, Sterner TR, Mahle DA, Lumpkin MH and Fisher JW, 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.

Yu L, Canas JE, Cobb GP, Jackson WA and Anderson TA, 2004. Uptake of perchlorate in terrestrial plants. Ecotoxicology and Environmental Safety, 58, 44–49.

Zeiger E, 1998a. Salmonella mutagenicity testing of ammonium perchlorate (memorandum with attachment to Annie Jarabek). Department of Health and Human Services, National Institute of Environmental Health Services, Research Triangle Park, NC, USA.

Zeiger E, 1998b. Ammonium perchlorate MN test results [memorandum with attachment to Annie Jarabek]. Department of Health and Human Services, National Institute of Environmental Health Services Research Triangle Park, NC, USA.

Zoeller TR, 2003. Challenges confronting risk analysis of potential thyroid toxicants. Risk Analysis, 23, 143–162.

Zoeller TR, Dowling AL, Herzig CT, Iannacone EA, Gauger KJ and Bansal R, 2002. Thyroid hormone, brain development, and the environment. Environmental Health Perspectives 110 Suppl 3, 355–361.

APPENDICES

Appendix A. Occurrence

Table A1: Perchlorate occurrence levels under the scenario in which suspect samples were included presented according to FoodEx food categories and the proportion of left-censored data (% LC)

FoodEx Level 1	FoodEx Level 2 or 3[(c)]	Number of samples	% LC	Mean perchlorate concentration (µg/kg)		
				Lower Bound	Middle Bound	Upper Bound
Grains and grain-based products[(a)]	Grains for human consumption	90	100	0	1.9	3.8
	Grain milling products	17	100	0	1.1	2.2
	Pasta (Raw)	5	100	0	1	2
	Breakfast cereals	3	100	0	1	2
Vegetables and vegetable products	Vegetables and vegetable products (including fungi)	9	44	15	16	16
	Root vegetables	387	77	8.8	11	13
	Turnips (*Brassica rapa*)	3	0	230	230	230
	Bulb vegetables	138	94	2.2	4.8	7.4
	Fruiting vegetables	2 324	59	25	27	28
	Brassica vegetables	387	79	9.0	11	13
	Leaf vegetables	818	55	51	53	55
	Lamb's lettuce (*Valerianella locusta*)	212	48	280	280	280
	Lettuce, excluding Iceberg-type lettuce (*Lactuca sativa*)	586	44	720	720	720
	Legume vegetables	46	85	11	13	15
	Stem vegetables (Fresh)	313	93	1.4	4.5	7.5
	Celery (Apium graveolens var. dulce)	50	50	560	560	570
	Sugar plants	26	92	1.8	5.8	9.9
	Tea and herbs for infusions (Solid)	18	56	87	88	90
	Peppermint (Mentha × piperita)	7	43	130	130	130
	Vegetable products	5	0	110	110	110

Table continued overleaf.

Table A1: Perchlorate occurrence levels under the scenario in which suspect samples were included presented according to FoodEx food categories and the proportion of left-censored data (% LC) (continued)

FoodEx Level 1	FoodEx Level 2 or 3[c]	Number of samples	% LC	Mean perchlorate concentration (µg/kg)		
				Lower Bound	Middle Bound	Upper Bound
	Fungi, cultivated	147	96	4.1	6.4	8.7
	Fungi, wild, edible	32	94	0.59	1.9	3.1
Starchy roots and tubers	Starchy roots and tubers	1	100	0	2.5	5
	Potatoes and potatoes products	204	94	3.8	5.9	8.0
	Other starchy roots and tubers	6	100	0	2.8	5.7
Legumes, nuts and oilseeds	Legumes, beans, green, without pods	156	67	25	27	28
	Legumes, beans, dried	120	78	23	24	26
	Tree nuts	29	100	0	2.4	4.9
	Legumes, beans, green, with pods	8	63	8.4	9.9	12
Fruit and fruit products	Fruit and fruit products	1	100	0	5	10
	Citrus fruits	812	64	14	16	17
	Pome fruits	511	100	0.39	2.9	5.4
	Stone fruits	547	96	1.2	4.0	6.8
	Berries and small fruits	1 452	88	3.6	6.0	8.4
	Miscellaneous fruits	785	87	7.4	9.9	12
	Dried fruits	107	72	5.7	7.3	9.0
	Jam, marmalade and other fruit spreads	1	100	0	1	2
	Other fruit products (excluding beverages)	24	100	0	1.1	2.2
Milk and dairy products	Milk and dairy products	23	74	4.8	8.5	12
	Liquid milk[b]	148	18	4.9	5.3	5.7
	Concentrated milk	1	100	0	2.5	5
	Cream and cream products	1	100	0	2.5	5
	Fermented milk products	7	100	0	2.5	5
	Milk and milk product imitates	3	100	0	1	2
Fruit and vegetable juices	Fruit and vegetable juices	1	100	0	5	10

Table continued overleaf.

Table A1: Perchlorate occurrence levels under the scenario in which suspect samples were included presented according to FoodEx food categories and the proportion of left-censored data (% LC) (continued)

FoodEx Level 1	FoodEx Level 2 or 3[c]	Number of samples	% LC	Mean perchlorate concentration (µg/kg)		
				Lower Bound	Middle Bound	Upper Bound
	Fruit juice[b]	23	48	1.2	1.7	2.2
	Fruit nectar[b]	13	77	0.47	1.8	3.1
	Mixed fruit juice	1	100	0	1	2
	Vegetable juice	1	100	0	2.5	5
Non-alcoholic beverages	Non-alcoholic beverages	1	0	420	420	420
	Soft drinks	9	89	0.11	0.16	0.20
Alcoholic beverages	Beer and beer-like beverage	144	0	1.0	1.0	1.0
	Wine	114	29	4.0	4.4	4.8
	Alcoholic mixed drinks	1	100	0	5	10
Drinking water	Drinking water	523	83	1.2	1.8	2.4
Herbs, spices and condiments	Herbs	304	31	230	230	230
	Spices	40	58	29	30	32
	Herb and spice mixtures	4	25	56	58	59
Food for infants and small children	Food for infants and small children	90	78	3.5	5.5	7.5
	Infant formulae, powder[b]	75	36	6.6	7.1	7.6
	Follow-on formulae, powder	29	52	2.3	2.8	3.3
	Cereal-based food for infants and young children	20	100	0	1.3	2.6
	Ready-to-eat meal for infants and young children	67	99	0.1	1.8	3.5
	Fruit juice and herbal tea for infants and young children	21	100	0	3	6
	Infant formulae, liquid[b]	56	4	1.9	2.0	2.1
Products for special nutritional use	Dietary supplements	4	75	120	130	130
Composite food	Prepared salads	25	88	3.4	5.7	8.0

(a): Excluded from the exposure assessment due to the limited number of samples, to the fact that their results were all left censored, and to the fact that perchlorate is not expected to be present in these foods.
(b): Data from the literature included.
(c): Drinking water is reported at the first level of FoodEx whereas some of the vegetables and vegetable products (e.g. 'lamb's lettuce', 'lettuce and excluding Iceberg-type lettuce') were reported at the third level of the FoodEx system.

Appendix B. Consumption

Table B1: Dietary surveys used for the chronic and 'short term' dietary exposure assessments

Country	Dietary survey acronym	Method	Days	Number of subjects[a]/ days[b]						
				Infants	Toddlers	Other children	Adolescents	Adults	Elderly	Very elderly
Austria	ASNS	24-h recall	1					–/2 123		
Belgium	Diet National 2004	24-h recall	2				584/1 187	1 304/2 648	518/1 045	712/1 448
Belgium	Regional Flanders	record	3		36[c]/108	625/1 875				
Bulgaria	NUTRICHILD	24-h recall	2	860/1 720	428/867	433/856				
Bulgaria	NSFIN	24-h recall	1				–/162	–/691	–/151	–/200
Cyprus	Childhealth	record	3				303/909			
Czech Republic	SISP04	24-h recall	2			389/798	298/596	1666/3332		
Germany	DONALD 2006	record	3		92/276	211/633				
Germany	DONALD 2007	record	3		85/255	226/678				
Germany	DONALD 2008	record	3		84/252	223/669				
Germany	National Nutrition Survey	24-h recall	2				1 011/2 022	10 419/20 838	2 006/4 012	490/980
Denmark	Danish Dietary Survey	record	7			490/3 426	479/3 398	2 822/19 722	309/2 159	20[c]/140
Greece	Regional Crete	record	3			839/2 508				
Spain	AESAN	24-h recall	2					410/828		
Spain	AESAN-FIAB	record	3				86/226	981/2 748		
Spain	NUT INK05	24-h recall	2			399/798	651/1 302			
Spain	enKid	24-h recall	2		17[c]/34	156/312	209/418			
Estonia	NDS_1997	24-h recall	1					–/1866		
Finland	DIPP	record	3		497/1 486	933/2 773				
Finland	FINDIET 2007	48-h recall	2					1 575/3 150	463/926	
Finland	STRIP	record	4			250/1 000				
France	INCA2	record	7			482/3 315	973/6 728	2 276/15 727	264/1 824	84/571
Hungary	National Repr Surv	record	3					1 074/3 222	206/618	80/240
Ireland	NSFC	record	7					958/6 706		
Italy	INRAN-SCAI 2005-06	record	3	16[c]/48	36[c]/108	193/579	247/741	2 313/6 939	290/870	228/684
Latvia	EFSA_TEST	24-h recall	2			189/377	470/949	1 306/2 655		
Netherlands	DNFCS 2003	24-h recall	2					750/1 500		
Netherlands	VCP kids	record	3		322/644	957/1 914				
Poland	IZZ_FAO_2000	24-h recall	1		–/79	–/409	–/666	–/2 527	–/329	–/124
Sweden	RIKSMATEN 1997-98	record	7					1 210/8 466		

Country	Dietary survey acronym	Method	Days	Number of subjects[a]/ days[b]						
				Infants	Toddlers	Other children	Adolescents	Adults	Elderly	Very elderly
Sweden	NFAn	24-h recall	4			1 473/5 875	1 018/4 047			
Slovakia	SK_MON_2008	24-h recall	1					–/2 763		
Slovenia	CRP_2008	24-h recall	1					–/407		
United Kingdom	NDNS	record	7					1 724/12 068		

(a): Number of available subjects for chronic exposure assessment in each age class;
(b): Number of available days for acute exposure assessment in each age class;
(c): 95th percentile calculated over a number of observations lower than 60 require cautious interpretation as the results may not be statistically robust (EFSA, 2011a).

Appendix C. Dietary exposure

Table C1: Chronic dietary exposure under the scenario in which suspect samples were excluded by age class, country, survey, and scenarios under the lower-, middle- and upper-bound assumptions

Age group	Country	Survey	Number of subjects	Exposure (µg/kg b.w. per day)					
				Lower Bound		Middle Bound		Upper bound	
				Mean	P95	Mean	P95	Mean	P95
Infants	Bulgaria	NUTRICHILD	860	0.13	0.32	0.22	0.45	0.30	0.61
Infants	Italy	INRAN_SCAI_2005_06	16	0.40		0.47		0.54	
Toddlers	Belgium	Regional_Flanders	36	0.18		0.25		0.32	
Toddlers	Bulgaria	NUTRICHILD	428	0.24	0.47	0.33	0.59	0.42	0.72
Toddlers	Germany	DONALD_2006_2008	261	0.22	0.42	0.29	0.51	0.37	0.62
Toddlers	Spain	enKid	17	0.24		0.32		0.40	
Toddlers	Finland	DIPP	497	0.33	0.66	0.42	0.81	0.50	0.97
Toddlers	Italy	INRAN_SCAI_2005_06	36	0.29		0.36		0.42	
Toddlers	The Netherlands	VCP_kids	322	0.18	0.34	0.25	0.42	0.32	0.53
Other children	Belgium	Regional_Flanders	625	0.15	0.33	0.21	0.40	0.27	0.48
Other children	Bulgaria	NUTRICHILD	433	0.24	0.53	0.31	0.63	0.37	0.72
Other children	The Czech Republic	SISP04	389	0.14	0.30	0.18	0.36	0.23	0.43
Other children	Germany	DONALD_2006_2008	660	0.14	0.28	0.18	0.34	0.22	0.40
Other children	Denmark	Danish_Dietary_Survey	490	0.20	0.36	0.24	0.43	0.29	0.50
Other children	Spain	enKid	156	0.18	0.43	0.23	0.49	0.27	0.56
Other children	Spain	NUT_INK05	399	0.13	0.24	0.17	0.31	0.21	0.37
Other children	Finland	DIPP	933	0.24	0.44	0.30	0.54	0.36	0.63
Other children	Finland	STRIP	250	0.15	0.25	0.18	0.29	0.21	0.34
Other children	France	INCA2	482	0.17	0.34	0.20	0.39	0.24	0.45
Other children	Greece	Regional_Crete	839	0.10	0.27	0.15	0.32	0.19	0.38
Other children	Italy	INRAN_SCAI_2005_06	193	0.24	0.60	0.28	0.62	0.32	0.69
Other children	Latvia	EFSA_TEST	189	0.07	0.19	0.10	0.23	0.13	0.27
Other children	The Netherlands	VCP_kids	957	0.12	0.28	0.18	0.34	0.23	0.42
Other children	Sweden	NFA	1 473	0.12	0.23	0.15	0.29	0.19	0.36

Table continued overleaf.

Table C1: Chronic dietary exposure under the scenario in which suspect samples were excluded by age class, country, survey, and scenarios under the lower-, middle- and upper-bound assumptions (continued)

Age group	Country	Survey	Number of subjects	Exposure (µg/kg b.w. per day)					
				Lower Bound		Middle Bound		Upper bound	
				Mean	P95	Mean	P95	Mean	P95
Adolescents	Belgium	Diet_National_2004	584	0.06	0.13	0.07	0.15	0.08	0.17
Adolescents	Cyprus	Childhealth	303	0.08	0.18	0.10	0.20	0.11	0.23
Adolescents	The Czech Republic	SISP04	298	0.10	0.21	0.13	0.24	0.15	0.30
Adolescents	Germany	National_Nutrition_Survey_II	1 011	0.06	0.15	0.08	0.18	0.10	0.20
Adolescents	Denmark	Danish_Dietary_Survey	479	0.11	0.21	0.13	0.25	0.16	0.29
Adolescents	Spain	AESAN_FIAB	86	0.12	0.27	0.14	0.30	0.15	0.33
Adolescents	Spain	enKid	209	0.10	0.24	0.12	0.26	0.14	0.29
Adolescents	Spain	NUT_INK05	651	0.08	0.15	0.10	0.19	0.12	0.22
Adolescents	France	INCA2	973	0.09	0.19	0.10	0.21	0.12	0.24
Adolescents	Italy	INRAN_SCAI_2005_06	247	0.15	0.32	0.17	0.35	0.19	0.39
Adolescents	Latvia	EFSA_TEST	470	0.05	0.13	0.07	0.16	0.09	0.21
Adolescents	Sweden	NFA	1 018	0.07	0.14	0.09	0.17	0.11	0.20
Adults	Belgium	Diet_National_2004	1 304	0.06	0.14	0.08	0.16	0.09	0.19
Adults	The Czech Republic	SISP04	1 666	0.07	0.15	0.08	0.17	0.10	0.20
Adults	Germany	National_Nutrition_Survey_II	10 419	0.07	0.16	0.09	0.18	0.11	0.21
Adults	Denmark	Danish_Dietary_Survey	2 822	0.09	0.17	0.11	0.21	0.13	0.24
Adults	Spain	AESAN	410	0.12	0.27	0.14	0.29	0.16	0.33
Adults	Spain	AESAN_FIAB	981	0.14	0.31	0.17	0.34	0.19	0.37
Adults	Finland	FINDIET_2007	1 575	0.09	0.18	0.11	0.21	0.13	0.25
Adults	France	INCA2	2 276	0.09	0.19	0.11	0.22	0.13	0.25
Adults	The United Kingdom	NDNS	1 724	0.07	0.15	0.09	0.17	0.11	0.20
Adults	Hungary	National_Repr_Surv	1 074	0.11	0.22	0.12	0.24	0.14	0.27
Adults	Ireland	NSIFCS	958	0.07	0.13	0.09	0.16	0.11	0.20
Adults	Italy	INRAN_SCAI_2005_06	2 313	0.14	0.33	0.16	0.36	0.18	0.38
Adults	Latvia	EFSA_TEST	1 306	0.04	0.11	0.06	0.13	0.07	0.16
Adults	The Netherlands	DNFCS_2003	750	0.06	0.14	0.08	0.16	0.10	0.19
Adults	Sweden	Riksmaten_1997_98	1 210	0.06	0.10	0.07	0.13	0.09	0.17

Table continued overleaf.

Table C1: Chronic dietary exposure under the scenario in which suspect samples were excluded by age class, country, survey, and scenarios under the lower-, middle- and upper-bound assumptions (continued)

Age group	Country	Survey	Number of subjects	Exposure (µg/kg b.w. per day)					
				Lower Bound		Middle Bound		Upper bound	
				Mean	P95	Mean	P95	Mean	P95
Elderly	Belgium	Diet_National_2004	518	0.06	0.14	0.08	0.16	0.09	0.19
Elderly	Germany	National_Nutrition_Survey_II	2 006	0.06	0.14	0.08	0.17	0.10	0.20
Elderly	Denmark	Danish_Dietary_Survey	309	0.08	0.16	0.11	0.19	0.13	0.23
Elderly	Finland	FINDIET_2007	463	0.08	0.17	0.10	0.20	0.12	0.23
Elderly	France	INCA2	264	0.11	0.21	0.13	0.24	0.15	0.27
Elderly	Hungary	National_Repr_Surv	206	0.12	0.19	0.13	0.21	0.15	0.23
Elderly	Italy	INRAN_SCAI_2005_06	290	0.16	0.47	0.18	0.49	0.20	0.51
Very elderly	Belgium	Diet_National_2004	712	0.06	0.14	0.07	0.16	0.09	0.19
Very elderly	Germany	National_Nutrition_Survey_II	490	0.06	0.13	0.08	0.16	0.10	0.19
Very elderly	Denmark	Danish_Dietary_Survey	20	0.08		0.10		0.13	
Very elderly	France	INCA2	84	0.11	0.20	0.13	0.23	0.15	0.26
Very elderly	Hungary	National_Repr_Surv	80	0.11	0.20	0.12	0.22	0.14	0.25
Very elderly	Italy	INRAN_SCAI_2005_06	228	0.15	0.33	0.17	0.35	0.19	0.37

b.w.: body weight; P95: 95th percentile.

Table C2: Number of dietary surveys per age class under the scenario in which suspect samples were excluded and according to the percentage mean contribution of the FoodEx Level 1 category to the total mean chronic dietary exposure to perchlorate

Age class	FoodEx Level 1 category	Number of dietary surveys (% mean perchlorate contribution under the Middle Bound scenario)						
		< 1 %	1–5 %	5–10 %	10–25 %	25–50 %	50–75 %	75–90 %
Infants	Vegetables and vegetable products (including fungi)		1		1			
	Starchy roots and tubers	1	1					
	Legumes, nuts and oilseeds	1	1					
	Fruit and fruit products		1	1				
	Milk and dairy products				1			1
	Fruit and vegetable juices	1	1					
	Non-alcoholic beverages (excepting milk based beverages)	2						
	Alcoholic beverages	2						
	Drinking water	1			1			
	Herbs, spices and condiments	1	1					
	Food for infants and small children			1	1			
	Products for special nutritional use	2						
	Composite food (including frozen products)	2						
Toddlers	Vegetables and vegetable products (including fungi)				4	3		
	Starchy roots and tubers		5	2				
	Legumes, nuts and oilseeds	3	4					
	Fruit and fruit products			3	4			
	Milk and dairy products				1	5	1	
	Fruit and vegetable juices	1	4	2				
	Non-alcoholic beverages (excepting milk based beverages)	6	1					
	Alcoholic beverages	7						
	Drinking water		4	3				
	Herbs, spices and condiments	5	2					
	Food for infants and small children	2	3	2				
	Products for special nutritional use	7						
	Composite food (including frozen products)	7						

Table continued overleaf.

Table C2: Number of dietary surveys per age class under the scenario in which suspect samples were excluded and according to the percentage mean contribution of the FoodEx Level 1 category to the total mean chronic dietary exposure to perchlorate (continued)

Age class	FoodEx Level 1 category	Number of dietary surveys (% mean perchlorate contribution under the Middle Bound scenario)						
		< 1 %	**1–5 %**	**5–10 %**	**10–25 %**	**25–50 %**	**50–75 %**	**75–90 %**
Other children	Vegetables and vegetable products (including fungi)				3	10	2	
	Starchy roots and tubers		8	6	1			
	Legumes, nuts and oilseeds	10	4	1				
	Fruit and fruit products			6	9			
	Milk and dairy products				3	10	2	
	Fruit and vegetable juices	1	9	5				
	Non-alcoholic beverages (excepting milk based beverages)	11	3	1				
	Alcoholic beverages	15						
	Drinking water	1	9	5				
	Herbs, spices and condiments	10	5					
	Food for infants and small children	15						
	Products for special nutritional use	15						
	Composite food (including frozen products)	12	2	1				

Table continued overleaf.

Table C2: Number of dietary surveys per age class under the scenario in which suspect samples were excluded and according to the percentage mean contribution of the FoodEx Level 1 category to the total mean chronic dietary exposure to perchlorate (continued)

Age class	FoodEx Level 1 category	Number of dietary surveys (% mean perchlorate contribution under the Middle Bound scenario)						
		< 1 %	1–5 %	5–10 %	10–25 %	25–50 %	50–75 %	75–90 %
Adolescents	Vegetables and vegetable products (including fungi)				1	7	4	
	Starchy roots and tubers		4	6	2			
	Legumes, nuts and oilseeds	4	7	1				
	Fruit and fruit products			6	6			
	Milk and dairy products				8	3	1	
	Fruit and vegetable juices	1	10		1			
	Non-alcoholic beverages (excepting milk based beverages)	7	4	1				
	Alcoholic beverages	10	2					
	Drinking water	1	7	3	1			
	Herbs, spices and condiments	8	4					
	Food for infants and small children	12						
	Products for special nutritional use	12						
Adults	Vegetables and vegetable products (including fungi)				1	8	6	
	Starchy roots and tubers		7	6	2			
	Legumes, nuts and oilseeds	5	9	1				
	Fruit and fruit products			11	4			
	Milk and dairy products			5	9	1		
	Fruit and vegetable juices	6	8	1				
	Non-alcoholic beverages (excepting milk based beverages)	4	2	8	1			
	Alcoholic beverages		6	9				
	Drinking water		9	4	2			
	Herbs, spices and condiments	11	4					
	Food for infants and small children	15						
	Products for special nutritional use	15						
	Composite food (including frozen products)	13	1	1				

Table continued overleaf.

Table C2: Number of dietary surveys per age class under the scenario in which suspect samples were excluded and according to the percentage mean contribution of the FoodEx Level 1 category to the total mean chronic dietary exposure to perchlorate (continued)

Age class	FoodEx Level 1 category	Number of dietary surveys (% mean perchlorate contribution under the Middle Bound scenario)						
		< 1 %	1–5 %	5–10 %	10–25 %	25–50 %	50–75 %	75–90 %
Elderly	Vegetables and vegetable products (including fungi)					4	3	
	Starchy roots and tubers		5	2				
	Legumes, nuts and oilseeds	2	4	1				
	Fruit and fruit products			1	6			
	Milk and dairy products		1	4	2			
	Fruit and vegetable juices	3	4					
	Non-alcoholic beverages (excepting milk based beverages)	1	3	3				
	Alcoholic beverages		3	4				
	Drinking water	1	3	3				
	Herbs, spices and condiments	5	2					
	Food for infants and small children	7						
	Products for special nutritional use	7						
	Composite food (including frozen products)	7						
Very elderly	Vegetables and vegetable products (including fungi)					3	3	
	Starchy roots and tubers		2	4				
	Legumes, nuts and oilseeds	1	4	1				
	Fruit and fruit products			1	5			
	Milk and dairy products			4	2			
	Fruit and vegetable juices	3	3					
	Non-alcoholic beverages (excepting milk based beverages)	1	2	3				
	Alcoholic beverages		2	4				
	Drinking water	1	4	1				
	Herbs, spices and condiments	3	3					
	Food for infants and small children	6						
	Products for special nutritional use	6						
	Composite food (including frozen products)	6						

Table C3: Chronic dietary exposure estimates to perchlorate under the scenario in which suspect samples were included

Age class	Number of surveys[a]	Chronic dietary exposure (µg/kg b.w. per day)											
		Mean						P95					
		Minimum		Median		Maximum		Minimum		Median		Maximum	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Infants	2 (1)	0.28	0.48	–	–	0.46	0.61	–[b]	–	–	–	–	–
Toddlers	7 (4)	0.24	0.41	0.35	0.52	0.52	0.73	0.47	0.71	0.76	1.1	1.0	1.4
Other children	15	0.10	0.17	0.24	0.37	0.52	0.68	0.26	0.38	0.61	0.70	1.5	1.6
Adolescents	12	0.08	0.13	0.15	0.20	0.33	0.38	0.17	0.24	0.37	0.44	1.0	1.0
Adults	15	0.07	0.11	0.17	0.21	0.44	0.49	0.15	0.24	0.43	0.49	1.1	1.2
Elderly	7	0.11	0.17	0.17	0.24	0.36	0.41	0.25	0.33	0.43	0.51	0.83	0.90
Very elderly	6	0.11	0.16	0.16	0.21	0.32	0.36	0.23	0.32	0.46	0.51	0.81	0.86

b.w.: body weight; P95: 95th percentile; LB: lower bound; UB: upper bound.
(a): The number in parentheses is the number of surveys presenting more than 60 subjects and for which it was considered possible to calculate the 95th percentile of exposure.
(b): For infants, only one dietary survey included more than 60 subjects, that could be used to calculate a 95th percentile dietary exposure of 0.75–1.0 (LB-UB) µg/kg b.w. per day.

Table C4: Highest reliable percentile of occurrence used to assess 'short-term' dietary exposure

Food groups (FoodEx level 2)	Food groups (FoodEx level 3)	Under the scenario in which suspect samples were excluded			Under the scenario in which suspect samples were included		
		Number of samples	Perchlorate level (µg/kg)	Percentile used	Number of samples	Perchlorate level (µg/kg)	Percentile used
Vegetables and vegetable products (including fungi)	Vegetables and vegetable products (including fungi)	9	16	Mean	9	16	Mean
	Root vegetables	320	38	P99	387	180	P99
	Turnips (*Brassica rapa*)	2	350	Mean	3	230	Mean
	Bulb vegetables	106	5	P95	138	13	P95
	Fruiting vegetables	1 745	270	P99	2 324	310	P99
	Brassica vegetables	331	130	P99	387	190	P99
	Leaf vegetables	675	950	P99	818	950	P99
	Lamb's lettuce (*Valerianella locusta*)	166	240	P95	212	880	P95
	Lettuce, excluding Iceberg-type lettuce (*Lactuca sativa*)	352	2 300	P99	586	8 700	P99
	Legume vegetables	42	23	P90	46	23	P90
	Stem vegetables (Fresh)	265	5	P95	313	34	P99
	Celery (Apium graveolens var. dulce)	25	5	P75	50	1 600	P90
	Sugar plants	26	5	P75	26	5	P75
	Tea and herbs for infusions (Solid)	17	72	P75	18	95	P75
	Peppermint (Mentha × piperita)	4	30	Mean	7	130	Mean
	Vegetable products	4	67	Mean	5	110	Mean
	Fungi, cultivated	141	5	P95	147	25	P95
	Fungi, wild, edible	32	2.5	P90	32	2.5	P90
Starchy roots and tubers	Starchy roots and tubers	–	–	–	1	5	Mean
	Potatoes and potatoes products	191	5	P95	204	8.0	P95
	Other starchy roots and tubers	5	4.8	Mean	6	5.7	Mean
Legumes, nuts and oilseeds	Legumes, beans, green, without pods	134	80	P95	156	150	P95
	Legumes, beans, dried	95	30	P95	120	120	P95
	Tree nuts	19	1	P75	29	5	P75
	Legumes, beans, green, with pods	8	12	Mean	8	12	Mean

Table continued overleaf.

Table C4: Highest reliable percentile of occurrence used to assess 'short-term' dietary exposure (continued)

Food groups (FoodEx level 2)	Food groups (FoodEx level 3)	Under the scenario in which suspect samples were excluded			Under the scenario in which suspect samples were included		
		Number of samples	Perchlorate level (µg/kg)	Percentile used	Number of samples	Perchlorate level (µg/kg)	Percentile used
Fruit and fruit products	Fruit and fruit products	–	–	–	1	10	Mean
	Citrus fruits	639	100	P99	812	190	P99
	Pome fruits	458	5	P99	511	5	P99
	Stone fruits	460	15	P99	547	20	P99
	Berries and small fruits	1 246	60	P99	1 452	81	P99
	Miscellaneous fruits	624	120	P99	785	180	P99
	Dried fruits	107	25	P95	107	25	P95
	Jam, marmalade and other fruit spreads	1	2	Mean	1	2	Mean
	Other fruit products (excluding beverages)	24	1	P75	24	1	P75
Milk and dairy products	Milk and dairy products	23	10	P75	23	10	P75
	Liquid milk	148	9.2	P95	148	9.2	P95
	Concentrated milk	1	5	Mean	1	5	Mean
	Cream and cream products	1	5	Mean	1	5	Mean
	Fermented milk products	7	5	Mean	7	5	Mean
	Milk and milk product imitates	–	–	–	3	2	Mean
Fruit and vegetable juices	Fruit and vegetable juices	–	–	–	1	10	Mean
	Fruit juice	23	2.4	P75	23	2.4	P75
	Fruit nectar	13	2.5	P75	13	2.5	P75
	Mixed fruit juice	1	2	Mean	1	2	Mean
	Vegetable juice	1	5	Mean	1	5	Mean
Non-alcoholic beverages (excepting milk based beverages)	Non-alcoholic beverages	–	–	–	1	420	Mean
	Soft drinks	5	0.28	Mean	9	0.20	Mean
	Tea (Infusion)	475	9.1	P99	523	16	P99
	Coffee (Beverage)	475	9.1	P99	523	16	P99
Alcoholic beverages	Beer and beer-like beverage	144	6	P95	144	6	P95
	Wine	114	21	P95	114	21	P95
	Alcoholic mixed drinks	1	10	Mean	1	10	Mean

Table continued overleaf.

Table C4: Highest reliable percentile of occurrence used to assess 'short-term' dietary exposure (continued)

Food groups (FoodEx level 2)	Food groups (FoodEx level 3)	Under the scenario in which suspect samples were excluded			Under the scenario in which suspect samples were included		
		Number of samples	Perchlorate level (µg/kg)	Percentile used	Number of samples	Perchlorate level (µg/kg)	Percentile used
Drinking water	Drinking water	475	9.1	P99	523	16	P99
Herbs, spices and condiments	Herbs	238	270	P95	304	1 800	P99
	Spices	35	80	P90	40	60	P90
	Herb and spice mixtures	3	75	Mean	4	59	Mean
Food for infants and small children	Food for infants and small children	90	12	P95	90	12	P95
	Infant formulae, powder	75	33	P95	75	33	P95
	Follow-on formulae, powder	29	3.4	P75	29	3.4	P75
	Cereal-based food for infants and young children	20	1	P75	20	1	P75
	Ready-to-eat meal for infants and young children	67	2.5	P95	67	2.5	P95
	Fruit juice and herbal tea for infants and young children	21	2.5	P75	21	2.5	P75
	Infant formulae, liquid	56	3.6	P90	56	3.6	P90
Products for special nutritional use	Dietary supplements	3	5	Mean	4	130	Mean
Composite food	Prepared salads	24	2.5	P75	25	2.5	P75

Appendix D. Perchlorate concentrations in urine and breast milk from different studies

Subjects	n	Perchlorate in urine (µg/L)			Perchlorate in breast milk (µg/L)			Concentration in drinking water (µg/L)	Estimated exposure	Reference
		median	mean	range	median	mean	range	mean		
Age 6–11 years	374	–	4.93[(a)]	4.22–5.76						
Age 12–19 years	828	–	3.80[(a)]	3.44–4.20	–	–	–	–	0.066	Blount et al. (2006)
Age ≥ 20 years	1 618	–	3.35[(a)]	3.08–3.65					(0.060–0.071)	
Age 6–11 years	314	4.32	–	3.67–5.09						
Age 12–19 years	721	3.62	–	3.19–4.12	–	–	–	–	–	CDC (2009)
Age ≥ 20 years	1 487	3.05	–	2.75–3.38						
Pregnant women (Antofagasta)										
1st prenatal	61	–	24.5 ± 23.9	–	–	81.6 ± 277.1	–	0.46	–	
2nd prenatal	35	–	16 ± 14.3	–						
Postpartum	6	–	22.3 ± 23.8	–						
Pregnant women (Chañaral)										
1st prenatal	53	–	66.7 ± 84.9	–	–	18.3 ± 17.7	–	5.82	–	Téllez et al. (2005)
2nd prenatal	36	–	73.2 ± 178.1	–						
Postpartum	4	–	17.5 ± 10	–						
Pregnant women (Taltal)										
1st prenatal	59	–	132.9 ± 103.9	–	–	95.6 ± 54.6	–	113.9	–	
2nd prenatal	27	–	128.9 ± 127	–						
Postpartum	16	–	49.1 ± 35.2	–						
Pregnant women	64	3.1	–	0.2–22.4	4.4	–	0.5–29.5	–	–	Leung et al. (2012)
Infants (1–3 month)	64	4.7	–	0.3–25.3						
Pregnant women	150	–	2.9[(a)]	P95 = 7.71	–	–	–	–	–	Blount et al. (2009)
NHANES – 2007–08	1 007	3.9	5.98	0.36–47.8	–	–	–	–	–	Steinmaus et al. (2013)
Iodine-deficient pregnant women										
From Turin, Italy	261	5	–	0.4–168	–	–	–	–	–	Pearce et al. (2010)
From Cardiff, Wales	374	2	–	0.02–368	–	–	–	–	–	
Lactating women	57	3	8.2 ± 19	0.37–127	9.1	33 ± 77	1.3–411			Pearce et al. (2007)
infants	92		1.21[(a)]	0.86–1.69	–	–	–	–	–	Cao et al. (2010)
Pregnant women										
From California	134	7.8	–	0.4–284	–	–	–	–	–	Pearce et al. (2011)
From Argentina	107	13.5	–	1.1–676	–	–	–	–	–	
Women > 12 years of age	1 111		2.84[(a)]	2.54–3.18	–	–	–	–	–	Blount et al. (2006)

Appendix D. Perchlorate concentrations in urine and breast milk from different studies (continued)

Subjects	n	Perchlorate in urine (µg/L)			Perchlorate in breast milk (µg/L)			Concentration in drinking water (µg/L)	Estimated exposure	Reference
		median	mean	range	median	mean	range	mean		
NHANES – 2007-08	1 007	3.9	5.98	0.36–47.8	–	–	–	–	–	Steinmaus et al. (2013)
NHANES – 2001-02										
Men (age 6–19)	501	4.9	6.2 ± 0.25	–	–	–	–	–	–	
Men (age 20–85)	509	4.2	5.79 ± 0.31	–						
Women (age 6–14)	332	4.8	6.34 ± 0.33	–						Schreinemachers et al. (2011)
Women (age 15–49) not pregnant	491	3.2	4.33 ± 0.19	–						
Women (age 50–85)	168	2.7	3.94 ± 0.31	–						
Women (age 16–38) pregnant	93	3.7	5.94 ± 0.82	–						
Pregnant women (Greece)	134	4.1	–	0.2–118.5	–	–	–	–	–	Pearce et al. (2012)
NHANES – 2003-08; female										
Pregnant	235		3.03[(a)]	2.54–3.62[(b)]	–	–	–	–	–	Jain et al. (2013)
Non-pregnant	1 792		2.93[(a)]	2.73–3.14[(b)]						
Infants consuming									0.255(1.83[(c)])	
breast milk	92	3.9	4.97	< 0.05–25.8	–	–	–	–	0.420	Valentin-Blasini et al. (2011)
cow milk formula	51	2.2	2.89	< 0.05–13.1					0.280	
soy based formula	63	0.58	1.07	< 0.05–5.49					0.065	
Lactating women (age 24–35 years)	20	–	–		–	10.61±7.33	2.2–28.6	–	–	Kirk et al. (2012)
Lactating women (age 24–35 years)	13	–	3.6	–	–	–	–	0.46	0.186	Kirk et al. (2013)
Human milk	36	–	–	–		10.5	0.6–92.2	–	–	Kirk et al. (2005)
California residents	31	–	6.44[(a)]	1.08–32.2	–	–	–	2.4–2.5[(d)]	0.112	English et al. (2011)
Breastfeeding women (age 24–34 years)	13	3.2	4.0 ± 3.4	0.6–80	7.3	9.3 ± 7.5	0.01–48	–	–	Dasgupta et al. (2008)
Lactating women	10	–	–	–	4	5.8 ± 6.2	0.5–39.5	–	–	Kirk et al. (2007)
NHANES – 2007-08										
male	970	–	4.3	1–18.4[(e)]	–	–	–	–	–	Mendez and Eftim (2012)
female	970	–	3.4	0.7–15.6[(e)]	–	–	–	–	–	

n: number of subjects.
(a): geometric mean;
(b): colostrum samples – perchlorate detected in 43 of 46 samples;
(c): 95 % confidence limits;
(d): maximum estimated perchlorate dose
(e): N = 68 water samples, negative results, excluding two samples;
(f): 5th–95th percentile.

Appendix E. Benchmark dose modelling

E1. Benchmark dose modelling of adverse effects in clinical use of potassium perchlorate

The increased incidence of cutaneous effects reported in clinical studies on the medicinal use of potassium perchlorate was selected for the dose-response analysis. Information was taken from three independent reports (Crooks and Wayne, 1960; Krüskemper, 1960; Morgans and Trotter, 1960). As treatment doses in the three reports were reported as ranges without consistent information on the effects observed at discrete doses, the lowest doses of the ranges (minimum doses) were selected for the dose-response analysis. In the benchmark dose (BMD) analysis the doses, reported as mg potassium perchlorate/person per day in the original publications, were converted to mg perchlorate/kg b.w. per day for a 70-kg person.

The BMDL was calculated by means of the software BMDS v2.4 (US-EPA). All models for dichotomous (quantal) data were selected for the analysis at the default benchmark response (BMR) of 10 % (95 % confidence level) advised by the EFSA guidance on the use of BMD for quantal data (EFSA, 2009). In addition, calculation at a BMR of 1 % were also carried out. The models, allowing for restrictions, were run without the selected default restrictions.

Table E1: Incidence data

Dose groups as reported in the original publication (mg $KClO_4$/person per day)	400–600[(a)]	600–1 000[(b)]	1 200–1 600[(c)]	1 500–2 000[(b)]
Minimum doses (converted to mg perchlorate ion/kg body weight per day)	4	6	12	15
Number of subjects	881	200	67	50
Cases of cutaneous effects	11[(d)]	1[(e)]	10[(f)]	5[(e)]

(a): Krüskemper (1960);
(b): Crooks and Wayne (1960);
(c): Morgans and Trotter (1960);
(d): Cutaneous symptoms (translated from original publication in German);
(e): Skin rash;
(f): Combined incidence of skin rash alone (eight cases) and skin rash with fever (two cases).

BMR: 0.01 and 0.1 (extra risk)

Model acceptability criteria: Due to the larger than usual sample sizes available when combining the three human studies and accounting for the higher power to reject models, models with a goodness-of-fit test with p-values greater than 0.01 were accepted.

Table E2: BMDL results

Models	Restriction	Number of parameters	Log-likelihood	p-value	Accepted	BMD_{10}	$BMDL_{10}$	BMD_{01}	$BMDL_{01}$
						(mg/kg b.w. per day)			
Null model	–	1	−129.09	–	–	–	–	–	–
Gamma	No restriction	3	−113.22	0.010	No	13.0	10.9	6.6	3.2
Logistic	No restriction	2	−113.88	0.019	**Yes**	13.1	11.7	4.9	4.0
LogLogistic	No restriction	3	−113.34	0.009	No	13.0	10.8	6.1	3.1
LogProbit	No restriction	3	−112.99	0.013	**Yes**	12.9	11.0	6.9	3.5
Multistage	No restriction	3	−112.41	0.026	**Yes**	14.6	12.2	11.6	4.0
Probit	–	2	−113.66	0.024	**Yes**	12.9	11.2	4.5	3.7
Weibull	–	3	−113.43	0.008	No	13.0	10.8	6.0	3.1
Quantal–Linear	–	1	−118.16	< 0.001	No	24.0	17.8	2.3	1.7
Full model	–	4	−109.93	–	–	–	–	–	–

–: not relevant; BMD_{10}: benchmark dose-response of 0.1 (extra risk); $BMDL_{10}$: 95 % lower confidence limit for the benchmark dose-response of 0.1 (extra risk); BMD_{01}: benchmark dose-response of 0.01 (extra risk); $BMDL_{01}$: 95 % lower confidence limit for the benchmark dose-response of 0.01 (extra risk); b.w.: body weight.

Comments on results

The Logistic, Multistage, LogProbit and Probit models satisfied the defined goodness-of-fit acceptability criteria when compared with the full model (p-value greater than 0.01).

The calculated $BMDL_{10}$ values were in the range 11.0–12.2 mg/kg b.w. per day. The calculated $BMDL_{01}$ values were in the range 3.5–4.0 mg/kg b.w. per day. The lowest BMDL values were calculated by the LogProbit model (plot reported in Figure E1 below for $BMDL_{01}$).

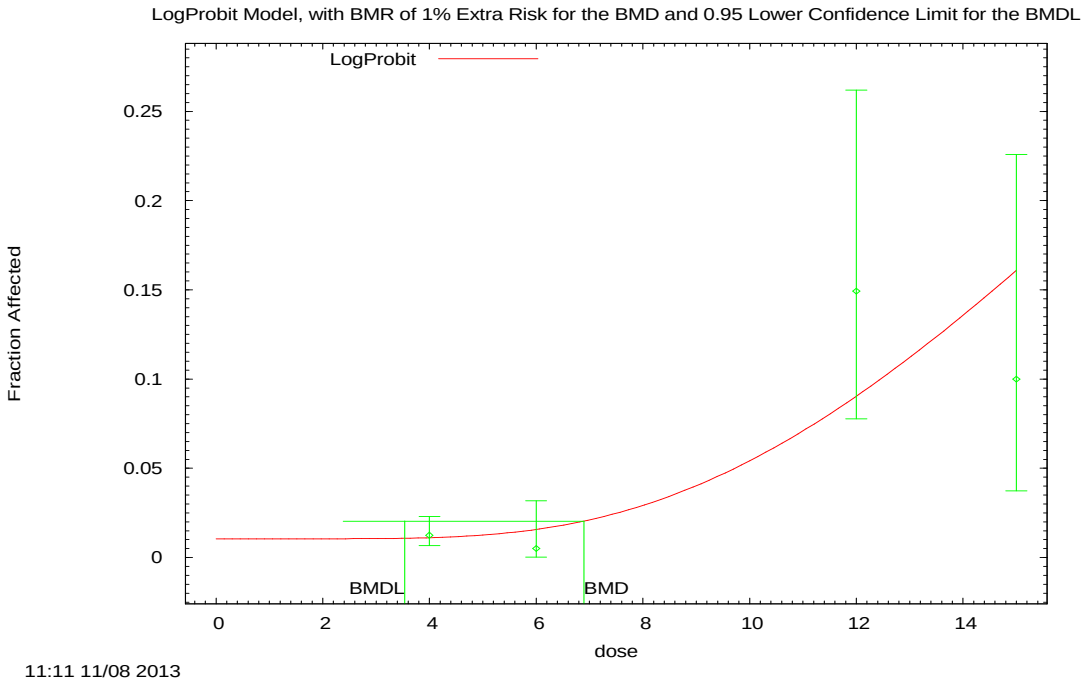


Figure E1: $BMDL_{01}$ plot (LogProbit model)

E2. Benchmark dose modelling of the thyroid iodine inhibition in human adult volunteers

The data on thyroid iodine inhibition from the Greer et al. (2002) study in human volunteers were used for the BMD modelling. Similarly to the approach followed by JECFA (FAO/WHO, 2011), the data on the percentage of radioactive iodine uptake measured at different timepoints during the exposure period and relative to the baseline uptake measured before the exposure to perchlorate were selected for the analysis. Since each subject's baseline values were used as his or her own control levels, the percentile baseline level was set at 100 % for each subject.

BMDL was calculated by means of the software PROAST38.9 (RIVM). The nested models for continuous data were selected for the analysis at the default BMR of 5 % (95 % confidence level) advised by the EFSA guidance on the use of the BMD for continuous data (EFSA, 2009) and at the BMR of 50 % selected by JECFA (FAO/WHO, 2011). Data for different timepoints were combined using time as a covariate in the analysis. The results of the fitting showed no differences compared with the modelling of the combined data without the definition of time as covariate. Since the results of the BMD calculations at a BMR of 5 % were outside the observation range (i.e. the $BMDL_{05}$ calculated by means of the Hill and Exponential models were lower than the lowest dose tested in the Greer et al. (2002) study), the BMD(L) at BMRs of 10 % and 20 % were also calculated.

Table E3: Thyroid radioactive iodine uptake levels relative to baseline levels measured in human volunteers exposed to perchlorate for 14 consecutive days (adapted from Greer et al., 2002)

Time	Dose (mg/kg b.w. per day)	Percent of baseline		Number of subjects
		Mean	Standard deviation	
Day 2, 8 hours	0.007	NA	NA	NA
	0.02	83.8	17.82	8
	0.1	59.4	5.66	8
	0.5	31.6	8.20	8
Day 14, 8 hours	0.007	93.8	23.81	7
	0.02	81.8	13.28	10
	0.1	56.7	15.60	9
	0.5	32.6	10.44	10
Day 2, 24 hours	0.007	NA	NA	NA
	0.02	82.8	15.84	8
	0.1	59.2	9.90	8
	0.5	30.6	7.35	8
Day 14, 24 hours	0.007	98.2	21.96	7
	0.02	83.6	12.97	10
	0.1	55.3	12.33	10
	0.5	32.9	12.02	10

b.w: body weight; NA: not applicable.

BMR: 0.05 and 0.5

Model acceptability criteria: as indicated by EFSA (2009).

Table E4: Benchmark dose results

Analysis with exponential models - the selected model is indicated in bold

Model	Converged	npar	Loglik
Full	1	19	36.03
full-v	1	22	38.65
m1-	1	2	–110.03
m2-	1	3	6.85
m2-a	1	6	6.89
m2-b	1	6	6.9
m2-ab	1	9	6.92
m3-	1	4	32.85
m4-	**1**	**4**	**33.58**
m5-	1	5	34.87
m4-b	1	7	34.16

Analysis with Hill models – the selected model is indicated in bold

Model	Converged	npar	Loglik
Full	NA	19	36.03
m1-	1	2	–110.03
m2-	1	3	19.63
m2-a	1	6	22.44
m2-b	1	6	22.46
m2-ab	1	9	22.51
m3-	1	4	34.49
m4-	1	4	34.6
m5-	**1**	**5**	**34.92**
m5-b	1	8	35.06

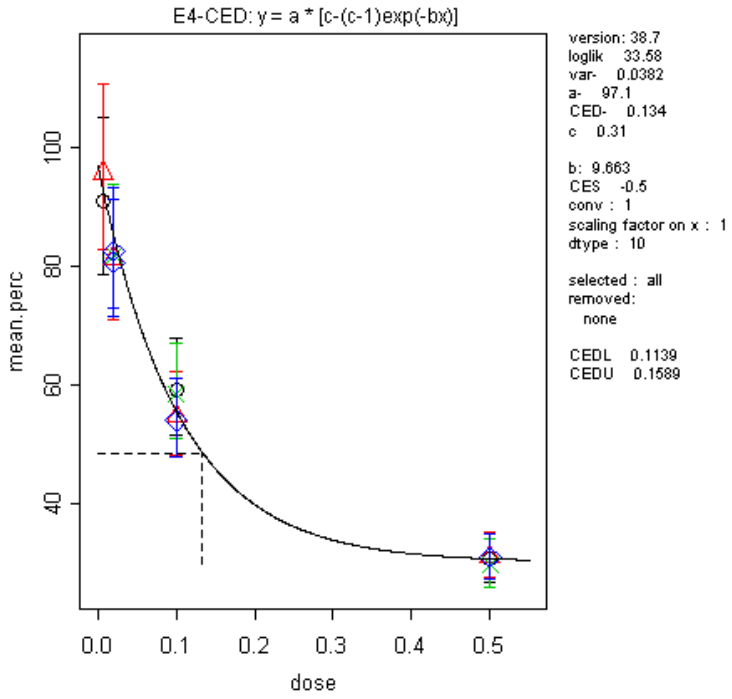
NA: not applicable.

BMD results at BMR 5 % and 50 % (expressed in mg/kg b.w. per day)

Model family	Selected model	BMR	BMD	BMDL	BMDU
Exponential	**m4-**	**5 %**	0.0078	**0.0067**	0.0092
		50 %	0.13	**0.11**	0.16
Hill	**m5-**	**5 %**	0.0036	**0.0012**	0.0088
		50 %	0.14	**0.11**	0.17

BMD: benchmark dose; BMDL: lower confidence limit of the benchmark dose; BMDU: upper confidence limit of the benchmark dose; BMR: benchmark response.

(a)



(b)

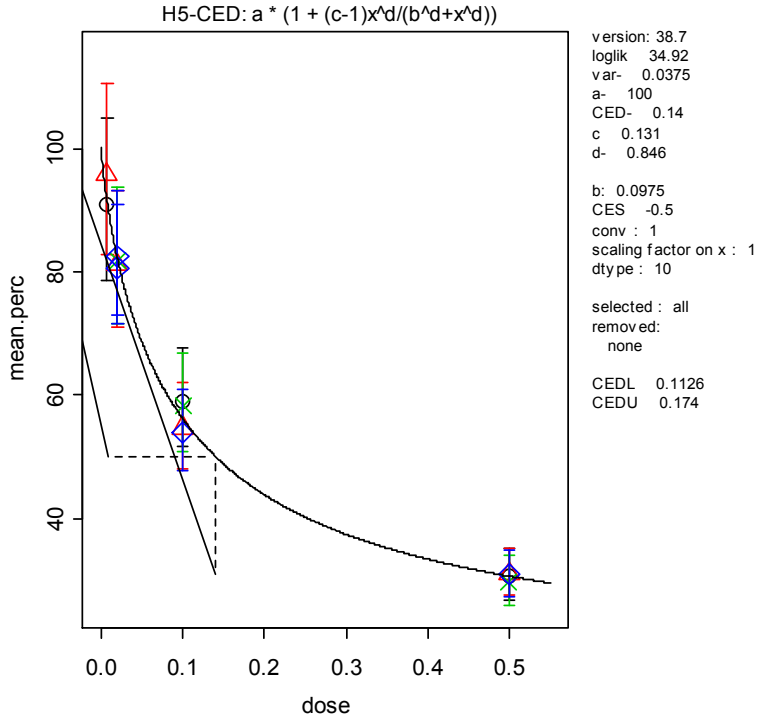
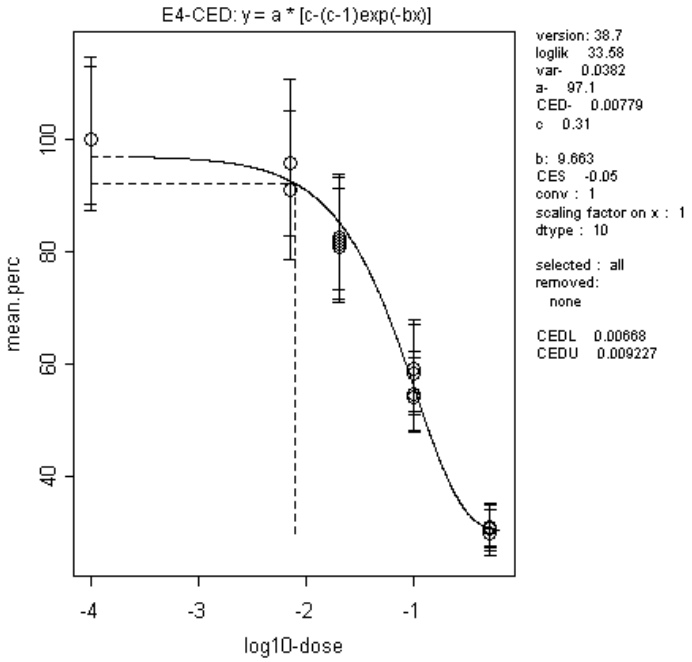


Figure E2: Illustrative graphs for (a) exponential model and (b) Hill model (both at BMR 50 %)

(a)



(b)

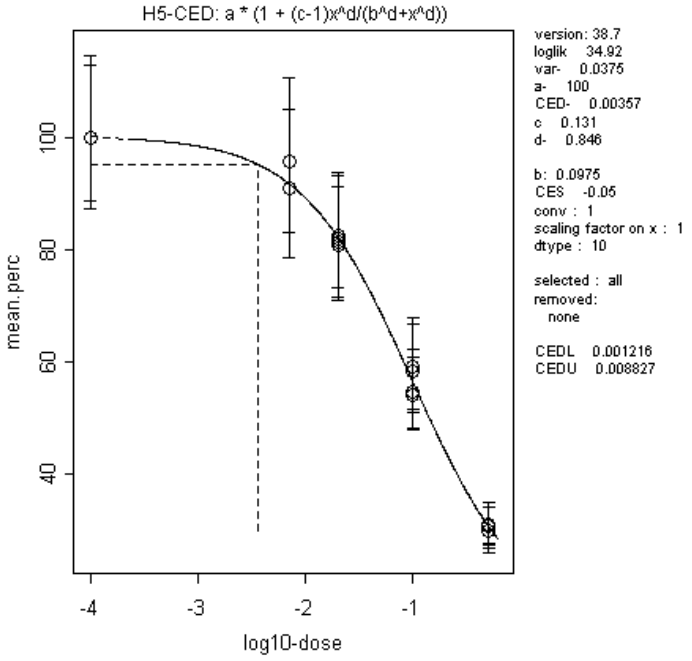


Figure E3: Illustrative graphs for (a) exponential model and (b) Hill model (both at BMR 5 %) using semi logarithmic plots

ABBREVIATIONS

ADD	Acceptable daily dose
AI	Adequate intake
ANSES	l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail
ARfD	Acute reference dose
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	Area under the curve
BBDR	Biologically based dose-response
BfR	Bundesinstitut für Risikobewertung
BIOHAZ Panel	EFSA Panel on Biological Hazards
BMD	Benchmark dose
BMDL	Lower confidence limit of the benchmark dose
$BMDL_{05}$	95 % lower confidence limit for the benchmark dose response of 5 % extra risk
$BMDL_{50}$	95 % lower confidence limit for the benchmark dose response of 50 % extra risk
BMDU	Upper confidence limit of the benchmark dose
BMR	Benchmark response
CDPH	Californian Department of Public Health
CFSAN	Center for Food Safety and Applied Nutrition
CI	Confidence interval
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	US Food and Drug Administration
GD	Gestation day
GI	Gastro-intestinal
HBGV	Health-based guidance value
HPT	Hypothalamic-pituitary-thyroid
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LB	Lower bound
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LOD	Limit of detection
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect-level
LOQ	Limit of quantification
MB	Middle bound
MCL	Maximum contaminant level
MDEP	Massachusetts Department of Environmental Protection
MRL	Maximum residue level
NDA Panel	EFSA Panel on Dietetic Products, Nutrition and Allergies
NHANES	National Health and Nutrition Examination Survey
NIS	Sodium iodide symporter protein (Na-I symporter)
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect level
NRC	National Research Council
OEHHA	Office of Environmental Health Hazard Assessment
P95	95th percentile
PBK	Physiologically based kinetic
PMTDI	Provisional maximum tolerable daily intake
PND	Postnatal day

PRIMo	Pesticide Residue Intake Model
QuPPe	Quick Polar Pesticides Method
RfD	Reference dose
RP	Reference point
TBG	Thyroxine-binding globulin
TDI	Tolerable daily intake
TDS	Total diet study
TSH	Thyroid-stimulating hormone
T_3	Triiodothyronine
T_4	Thyroxine
UB	Upper bound
UI	Urinary iodine
USA	United States of America
US-EPA	United States Environmental Protection Agency
WHO	World Health Organization