The Director General

Maisons-Alfort, 18 July 2011

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

on the assessment of the health risks associated with the presence of perchlorate in drinking water

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its Opinions are made public.

1. REVIEW OF THE REQUEST

On 31 January 2011, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) received a formal request from the Directorate General for Health (DGS) for an opinion on the health risks associated with the presence of perchlorate in drinking water.

2. BACKGROUND AND PURPOSE OF THE REQUEST

The French Regional Health Agencies (ARS) of Aquitaine and Midi-Pyrénées notified the DGS of the presence of perchlorate in drinking water.
This contamination originated from industrial activities upstream from water catchment areas for the production of drinking water.
The purpose of the formal request was to seek an assessment of the health risks associated with the presence of perchlorate in drinking water.

3. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in compliance with Standard NF X 50-110 "Quality in expertise activities – general requirements of competence for an expertise activity (May 2003)".

The collective expert appraisal was carried out by the Working Group (WG) on Non-compliance, which applied the health risk assessment (HRA) approach related to situations in which quality limits and references for drinking water are exceeded, as presented in the AFSSA report dated September 2004.

A hearing with representatives from the French National Institute for Industrial Environment and Risks (INERIS) took place on 29 April 2011, following the publication of a report on the toxicological profile and choice of reference value for perchlorate in chronic oral exposure[1] (INERIS, 2011).

A hearing with representatives from SME (Safran Group) took place on 26 May 2011.

The opinion of the WG on Non-compliance relating to the assessment of the health risks associated with the presence of perchlorate in drinking water was adopted by the Expert Committee (CES) on Water on 3 May 2011 and by the CES on the Assessment of the physical and chemical risks in foods on 23 May 2011.

4. ANALYSIS AND CONCLUSIONS OF THE CES

4.1. Origins and sources of contamination

Ammonium perchlorate has many industrial applications, especially in the military and aerospace fields (ATSDR, 2009).

In particular, it is used:

- as an oxidant for rocket propellants;
- for the manufacture of pyrotechnic devices, flares and explosives for civil or military applications;
- in small quantities, in the powder for some firearms;
- mixed with sulphamic acid to produce a thick smoke or fog for military applications;
- in systems for triggering airbags;
- for the manufacture of oxygen candles used in confined environments (aircraft cabins, submarines, etc.) for civil and military applications;
- as a component of temporary adhesives for metal plates;
- to adjust the ionic strength of electroplating baths.

Cases of contamination associated with the use of Chilean saltpetre (sodium nitrate) containing perchlorate and used in granule form as an agricultural fertiliser have been reported in the USA (ATSDR, 2009).

Perchlorate ions have also been reported as impurities in industrial hypochlorite solutions used to disinfect water (Asami *et al.*, 2009).

[1] TRV proposed: 0.7 µg/kg bw/day established by the US Environmental Protection Agency (US EPA) in 2005 and also adopted by INERIS - proposed guideline value for drinking water: 6 µg/L established by OEHHA in 2004 (for details on the establishment of these values, see sections 4.6.9 and 4.7 of the opinion)

4.2. Physico-chemical properties

Perchlorate ions, ClO_4^-, are characterised by:

- their very high solubility in water related to their ionised form;
- the absence of formation of molecular compounds that can co-precipitate either with elements dissolved in water or elements added to the water during purification treatments;
- a very high oxidising power: $ClO_4^- + 8\ H^+ + 8\ e^- \rightarrow Cl^- + 4\ H_2O$, where $E_O = 1.287$ V. However, with a pH between 7 and 8, this oxidising power is sometimes lower than that of oxidants normally used to treat drinking water (at pH 7, $E_a = 0.867$; at pH 8, $E_a = 0.807$);
- the fact that the reduction of perchlorate to chloride is inhibited by the very high activation energy of the reaction (120 $kJ.mol^{-1}$), which promotes the stability of the chlorine atom at the valence +VII.

Ammonium perchlorate (NH_4ClO_4) is a solid that is highly soluble in water and releases ammonium NH_4^+ and perchlorate ClO_4^- ions after hydrolysis. Table I outlines its main physico-chemical characteristics.

Table I: Main physico-chemical characteristics of ammonium perchlorate (IUCLID, 2000)

CAS number	7790-98-9
Empirical formula	NH_4ClO_4
Molar mass	117.49
Melting point	130°C, begins to decompose at 439°C
Density	1.95 g/cm³
Solubility in water	200 g/L at 25°C

Ammonium perchlorate is relatively stable at ambient temperature. When heated, it decomposes into chlorine, water and nitrogen oxide, leaving no solid residue. In the presence of organic products or other oxidants (e.g. fuel oil), it leads to highly exothermic reactions.

4.3. Treatments reducing the level of perchlorate in water

In accordance with the provisions of Article R. 1321-1350 of the French Public Health Code, products and processes for treating drinking water must be authorised by the Ministry of Health before being placed on the market for the first time.

The Circular of 28 March 2000[2] lists the treatment products and processes authorised to date.

4.3.1 Retention methods

4.3.1.1 - Adsorption

Activated carbons have a low affinity for perchlorate. In addition, the ANSES WG considers that filtration of water on granular activated carbon (GAC) with a flow of 5 $m^3/m^2/h$ (or 5 BV/h) can only give acceptable results for periods of around 10 days.

4.3.1.2 - Ion exchange

The ion exchange resins currently used and approved are not specific to perchlorate. Strong anionic resins, selective for perchlorate, have been synthesised. They use very long-chain quaternary ammoniums as the exchange group. There are resins with two exchange groups, one with long-chain quaternary ammonium, the other with short chains. The best regenerating reagent is the

[2] Circular DGS/VS 4 No. 2000-166 of 28 March on the products and processes for treating drinking water, NOR: MESP0030113C

ferrate ion ($FeCl_4^-$). Neither these resins nor the regenerating reagent have been approved by the French Ministry of Health and there is also the problem of dealing with regenerated substances.

4.3.1.3 - Membrane retention

The use of low cut-off (<100 Da) nanofiltration membranes could be considered for the retention of these ions, but would raise the problem of the fate of the concentrates.

4.3.2 Transformation methods

Chemical reduction or electro-reduction transformation methods are ineffective under normal drinking water production conditions.
Biological reduction processes require very long reaction times that do not suit the constraints of a drinking water production unit.

4.3.3 Conclusion

There is no really satisfactory and effective treatment process for removing perchlorate from drinking water (Srinivasan *et al.*, 2009).

4.4. Analytical methods for drinking water

4.4.1 Analytical principle

There are no standardised methods for assaying perchlorate in water apart from those published by the US EPA: EPA 314.0 (US EPA, 1999); EPA 314.1 (US EPA, 2005); EPA 314.2 (US EPA, 2008a) and EPA 332.0 (US EPA, 2005).

These methods are all based on the separation of ions by ion chromatography, with different pretreatment and/or detection techniques:

- Detection can be carried out without pretreatment, by conductometric detection [EPA 314.0]. This method is generally available in water control laboratories. It can be improved by inline pre-concentration of perchlorate [EPA 314.1], which improves the limit of quantification and reduces matrix effects.

- To reduce the risk of interference, the US EPA also proposes a method based on two-dimensional chromatography [EPA 314.2]. After an initial column separation, the collected fraction corresponding to the retention time of the perchlorate ions is injected onto a pre-concentration column and then to a second chromatography column with different selectivity from the first.

- A method of ion chromatography coupled with mass spectrometry detection is also available: IC-ESI-MS [EPA 332.0]. The mass of the ions usually selected are 101 ($_{37}Cl_{16}O_4^-$) and 99 in confirmation ($_{35}Cl_{16}O_4^-$). An internal standard ($_{35}Cl_{18}O_4^-$) with a mass of 107 can be used as a benchmark to improve the robustness of this method.

In France, to date, no laboratory has been approved or accredited for the analysis of perchlorate in water.

4.4.2 Preservation of samples

Samples are collected in vials of high density polyethylene (HDPE) or tinted inactinic glass. As perchlorate ions are not very sensitive to adsorption phenomena and not very photoreactive, there are no major constraints regarding analysis timeframes (28 days according to the US EPA).

However, due to the biodegradable nature of perchlorate ions, samples should be filtered with a mean cut-off threshold of 0.2 µm and kept in sterile vials.

4.4.3 Performance

The limit of quantification (LOQ) depends on the method used:

- It is generally of the order of a few µg/L for conductometric detection without pre-concentration, using large injection loops (1 mL) [EPA 314.0];
- With inline pre-concentration, it may be less than 1 µg/L [EPA 314.1];
- In two-dimensional chromatography [EPA 314.2] or with the IC-ESI-MS method [EPA 332.0], it can reach 0.1 µg/L depending on the operating conditions.

Information on uncertainties can be extrapolated from data derived from the same analytical principles and precision data from the US EPA. Intra-laboratory uncertainties are around 15 to 30% depending on the method and the concentration level, whereas inter-laboratory uncertainties range from 30 to 40% depending on the measured concentration levels.

4.4.4 Interference

In conductometric detection, interference mainly concerns the risk of co-elution of perchlorate ions with other compounds. Thus, due to the lack of specificity of this type of detector, it is advisable to confirm positive results on unknown matrices by the standard addition method.

Two-dimensional chromatographic methods [EPA 314.2] and the IC-ESI-MS method [EPA 332.0] are less affected by interference due to their separation principles and more specific detection.

4.5. Assessing exposure

4.5.1. Contamination of air

No data were found in the literature on contamination of the air by ammonium perchlorate relative to environmental exposure scenarios. In the workplace, cases of exposure to perchlorates by inhalation have been described (Lamm *et al.*, 1999; Braverman *et al.*, 2005). The effects observed in these studies are detailed in Section 4.6.6.

4.5.2. Data on food contamination and dietary exposure

At national level, there are no data on food contamination or dietary exposure from perchlorate. The main data come from publications relating to studies conducted in the USA.

Data on perchlorate contamination in food

El Aribi *et al.* (2006) detected perchlorate in food and beverages (fruit, vegetables, dairy products, etc.), among 350 samples with concentrations reaching values of around 400 µg/kg. These results were confirmed by Wang *et al*. (2009) for fruit and vegetables.

Between 2004 and 2005, the FDA conducted an exploratory study to estimate the level of perchlorate contamination in 28 categories of foods and beverages[3].

[3] The results of the 2004-2005 exploratory survey by the FDA are available on the Internet: http://www.fda.gov/food/foodborneillnesscontaminants/chemicalcontaminants/ucm2006788.htm

The FDA then undertook a sampling campaign as part of the survey for the US total diet study (TDS 2005-2006). Perchlorate was found in many foods (dairy products, eggs, oil, fruit, vegetables, meat, sugar, etc.), and was detected in 59% of samples. The foods contributing most to dietary exposure in children (aged 2, 6, 10 and 14-16 years) were dairy products (29-51%). In adults, vegetables were the main contributing foods (26-38%).

Table II presents some of the results for food contamination by perchlorate from the FDA's exploratory survey between 2004 and 2005 as well as the US TDS from 2005-2006, according to the article by Murray *et al.* (2008).

Table II: Perchlorate concentrations in various foods, according to Murray *et al.* (2008)

Food	n	Mean (µg/kg)*	Source
Milk	125	5.8	FDA exploratory study
	8	7	FDA TDS
Iceberg lettuce	43	8.1	FDA exploratory study
	4	2.1	FDA TDS
Lettuce	26	10.6	FDA exploratory study
	2	4.4	FDA TDS
Spinach	36	115	FDA exploratory study
	4	40	FDA TDS
Cabbage	13	95.1	FDA exploratory study
	4	17.7	FDA TDS
Cucumber	20	6.6	FDA exploratory study
	4	19.1	FDA TDS
Tomato	73	13.6	FDA exploratory study
	4	78	FDA TDS
Melon	48	28.6	FDA exploratory study
	4	24.4	FDA TDS
Orange	10	3.4	FDA exploratory study
	4	2.7	FDA TDS
Grape	4	0.5	FDA TDS

* Mean concentrations with undetected data estimated to be half the value of the limit of detection.

Annex 1 presents the results of dietary intake of perchlorate from the US total diet study (US TDS) from 2005-2006 (Murray *et al.*, 2008).

Data on perchlorate contamination in breast milk

Pearce *et al.* (2007) assayed perchlorate in the breast milk of 49 women in the Boston area. Perchlorate was detected in all the samples at concentrations ranging between 1.3 and 411 µg/L, with a median concentration of 9.1 µg/L and a mean concentration of 33 µg/L. The authors did not identify any statistically significant correlation between the concentrations of perchlorate and iodide in the milk.
Kirk *et al*. (2005) analysed 36 samples of breast milk in 18 US states. The authors describe perchlorate concentrations ranging from 1.4 to 92.2 µg/L, with a mean concentration of 10.5 µg/L.
Téllez Téllez *et al.* (2005) analysed breast milk samples in Chile. The concentrations were highly variable and no statistically significant correlation could be established with urinary concentrations of perchlorate or concentrations of iodide in the milk.
Investigating some of the results of the NHANES-UCMR study, Blount *et al.* (2007) showed that one of the routes of excretion of perchlorate is breast milk and reported a significant difference in urinary concentrations of perchlorate between the group of pregnant women and women breastfeeding their babies.
Dasgupta *et al.* (2008) analysed 457 samples of breast milk from 13 breastfeeding women from Texas. Perchlorate concentrations were between 0.01 and 48 µg/L, with a median concentration of 7.3 µg/L and a mean of 9.3 µg/L.

4.5.3. Contamination of drinking water

In France, there is no screening for perchlorate during health inspection of drinking water, as defined by the Decree of 11 January 2007[4]. Consequently, there are no data in the Health & Environment Information System on Water (*SISE-Eaux*) database on ammonium perchlorate or perchlorate.

The available data provided by the ARS of Midi-Pyrénées and Aquitaine, which include the self-monitoring results from SME (Safran Group), show a dispersion of the values at the different sampling points, with a high threshold of quantification until 2009 (5 µg/L), which then decreased. Between October 2006 and January 2011, the maximum concentration of perchlorate observed at the consumer's tap was 11 µg/L.

4.6. Toxicity and toxicity reference values

According to the literature, the effects of perchlorate observed in humans and animals are mainly on thyroid function.

4.6.1. Data on absorption, distribution, metabolism and excretion

In humans

Studies in humans of potassium perchlorate ingestion via drinking water show that perchlorate is rapidly absorbed from the gastrointestinal tract. Peak blood concentrations are reached in a few hours (ATSDR, 2009).

Perchlorate is rapidly distributed in the body, especially to the thyroid gland. It competitively inhibits the uptake of iodide from the bloodstream by the thyroid follicular cells. The site of this inhibition action is a membrane protein, sodium-iodide symporter (NIS), located in the basement membrane of follicular cells adjacent to the thyroid capillaries, via an ATPase-dependent active transport mechanism. This is a reversible and saturable mechanism that is stimulated by pituitary TSH (thyroid-stimulating hormone). Several anions other than perchlorate (e.g. nitrate or thiocyanate) may compete here with iodide.

Perchlorate is not metabolised in humans and is rapidly eliminated in the urine (> 90%) (Anbar *et al.*, 1959).

In eight healthy volunteers to whom doses of 0.5 mg/kg bw/day were administered orally, the elimination half-lives in the blood varied from 6 to 9.3 hours (Greer *et al*., 2002). Perchlorate is found in humans in serum, plasma, urine, saliva and milk.

Blount *et al.* (2007) measured urinary concentrations of perchlorate in 2820 samples taken between 2001 and 2002 as part of the NHANES survey. The authors detected concentrations above 0.05 µg/L in all samples tested, with a median concentration of 3.6 µg/L and a 95th percentile of 14 µg/L. Women of childbearing age (15-44 years) had a median urinary perchlorate concentration of 2.9 µg/L and a 95th percentile of 13 µg/L. The population with the highest urinary concentrations was children (6-11 years), with a median concentration of 5.2 µg/L. The authors estimated the total daily intake of perchlorate for individuals aged over 20 years, calculating a median exposure dose of 0.066 µg/kg bw/d and a 95th percentile of 0.234 µg/kg bw/d.

[4] Decree of 11 January 2007 on the sampling and analysis programme for health inspection of water supplied from a distribution system, pursuant to Articles R. 1321-10, R. 1321-15 and R. 1321-16 of the French Public Health Code amended by the Decree of 21 January 2010.

In animals

The characteristics of thyroid function differ between rats and humans to such an extent that only the qualitative aspects of the toxic effects associated with exposure to perchlorate can be used in risk assessment (IARC, 1999; NAS, 2005). In particular, there is a difference between rats and humans concerning the proteins related to the tri- and tetraiodothyronine thyroid hormones (T3 and T4) and their binding affinities. In humans, thyroid hormones bind mainly to thyroxin-binding globulin (TBG) with high affinity. Conversely, in rats, thyroid hormones bind to albumin and transthyretin with lower affinities, by a factor of at least 100, compared to TBG (Connors, 1997). Data indicate that the administration of perchlorate to rats inhibits the uptake of iodide in the same way as in humans. However, compensation for the lack of iodide in thyroid is faster in rats than in humans, due to the increase in NIS expression by the thyroid in response to TSH.

Physiologically based pharmacokinetic (PBPK) models have been developed for inter-species extrapolation of ingestion exposure to perchlorate between rats and humans. Their validity lies in the fact that the mechanism of competition between iodide and perchlorate in NIS exists in both species. However, this type of modelling is unsuitable for estimating the effects on thyroid hormone regulation (ATSDR, 2009).

4.6.2. Acute, subchronic and chronic toxicity, and carcinogenicity

Acute toxicity

Ammonium perchlorate has low acute toxicity via the oral route: between 3500 and 4200 mg/kg bw in rats; between 1900 and 2000 mg/kg bw in mice; between 750 and 1900 mg/kg bw in rabbits and 3310 mg/kg bw in hamsters (according to OEHHA, 2011).

Subchronic toxicity

In subchronic toxicity tests in rodents, the effects of perchlorate administered via drinking water concern disruption to thyroid hormone regulation, inducing hypertrophy and hyperplasia of the thyroid follicular cells, and leading to increased thyroid weight (ATSDR, 2009; Siglin *et al.*, 2000). Khan *et al.* (2005) showed histological changes to the thyroid in rats (colloidal depletion, hypertrophy and hyperplasia of the follicular epithelium), which were not however accompanied by changes in serum levels of thyroid hormones.

Long-term toxicity/carcinogenicity

The administration of concentrations of 1 to 1.2% potassium perchlorate and sodium perchlorate to rats and mice for 24 months led to the formation of thyroid tumours (follicular or papillary adenomas and/or carcinomas) at the highest doses (ATSDR, 2009). The estimated doses in these studies ranged from 928 to 2573 mg ClO_4/kg bw/d.
The US National Academy of Sciences (NAS, 2005) noted that, based on knowledge of the biology of thyroid tumours in humans and rodents, it is unlikely that perchlorate poses a risk of thyroid cancer in humans.

4.6.3. Genotoxicity

No studies in humans were identified of genotoxicity following exposure to perchlorate via the inhalation, oral or dermal routes. The rare information available from animal studies does not suggest that perchlorate is mutagenic or clastogenic (ATSDR, 2009).

4.6.4. Toxicity to reproduction and development

In a two-generation toxicity study conducted in Sprague-Dawley rats, ammonium perchlorate doses of 0; 0.3; 3 and 30 mg/kg bw/day were administered via drinking water to the P1 and F1 generations between weaning and the 19th week. An increase in the lactation index at the doses of 3 and 30 mg/kg bw/day was observed in the P1 generation. An increase in the fertility index was observed at all doses in the F1 generation, as well as an increase in the number of stillbirths from the F1 generation, at the maximum dose. An increase in thyroid weight was noted in the F1 generation in all dose groups for females, and at the doses of 3 and 30 mg/kg bw/day for males. Histological changes (hypertrophy and hyperplasia of thyroid follicles) were observed in all animals treated with 3 and 30 mg/kg bw/day in P1, F1 and F2. An increase in TSH concentration was observed at 30 mg/kg bw/day for the P1 and F1 generations. The authors identified a NOAEL[5] equal to 0.3 mg/kg bw/day. Perchlorate is not toxic to reproduction in rats when administered via drinking water at concentrations below 30 mg/kg bw/day (York *et al.*, 2001).
In a 90-day study conducted in rats with administration via drinking water at doses below 10 mg/kg bw/day, the authors did not report any macroscopic or microscopic changes to testes, epididymis, uterus, ovary or mammary glands (Siglin *et al.,* 2000). Nor did this study report any significant effects on sperm motility, count or morphology.

In several studies of developmental toxicity, the administration of low doses of perchlorate (≥ 0.009 mg/kg bw/day) to gestating animals led to changes in thyroid parameters being observed (serum concentrations of T3, T4 and TSH, as well as changes in the morphology of the thyroid gland) in newborns and young animals (ATSDR, 2009).

4.6.5. Studies in healthy volunteers

Greer *et al.* (2002) conducted a study to measure the uptake of iodide by the thyroid, hormone levels and excretion of iodide in the urine in a group of 37 healthy adult volunteers for 14 days. The main study involved twelve women and twelve men (four subjects of each sex for each of the three doses). An additional study involved six women and one man for the lowest dose and one subject of each sex for the other three doses. Potassium perchlorate was administered in drinking water at doses of 0.02; 0.1 and 0.5 mg/kg bw/day in the main study and at doses of 0.007; 0.1 and 0.5 mg/kg bw/day in the additional study. The study authors showed a 1.8% inhibition of the uptake of iodide by the thyroid after 24 hours for the group exposed to the lowest dose. Inhibition of 67.1% was demonstrated for the group exposed to the highest dose. Nevertheless, no significant difference was observed for serum concentrations of thyroid hormones (T4, total and free T3) in any of the groups tested. A NOEL[6] was identified by the authors for the inhibition of uptake of iodide by the thyroid at the dose of 7 mg/kg bw/day.

Braverman *et al.* (2006) administered potassium perchlorate capsules to 13 healthy volunteers (four men and nine women) once a day for 6 months. The estimated exposure doses were 0; 0.5 and 3 mg/kg bw/day which, according to the authors, led to equivalent water-related exposure of 250; 500 and 1500 µg/L for daily consumption of 2 litres of water. The parameters measured were serum concentrations of thyroid hormones, inhibition of iodide uptake by the thyroid after 24 hours, serum concentration of thyroglobulin, urinary concentrations of iodide and perchlorate, and serum concentrations of perchlorate. No statistically significant change was measured in the rate of uptake of radiolabelled iodide by the thyroid gland. Nor were there any statistically significant changes in serum levels of T3, the free T4 index, concentrations of TSH or Tg during exposure compared with the baseline level or the post-exposure period. Urinary concentrations of iodide at the highest dose were higher than the baseline concentrations, but this was not statistically significant.

[5] No Observed Adverse Effect Limit
[6] No Observed Effect Limit

4.6.6. Occupational studies

Exposure to perchlorate via inhalation was estimated in the workplace from air concentrations of total perchlorate and particulate perchlorate, as well as through the measurement of urinary concentrations in 37 exposed workers (35 men and two women) and 21 workers producing azide who were used as a control group. The air concentrations of particulate perchlorate led to daily doses ranging from 0.004 to 167 mg perchlorate/day. The workers were grouped into four exposure categories based on the average dose: 1, 4, 11 and 34 mg/day. Thyroid function was determined by serum assays of T4, T3, TSH and anti-thyroid antibodies. The authors reported that there was no difference in the parameters of thyroid function assessed between the groups exposed by inhalation and the control group. Based on these observations, the authors proposed a NOAEL of 34 mg/day for perchlorate exposure by inhalation in the workplace (Lamm *et al.*, 1999).

Braverman *et al.* (2005) studied the thyroid uptake of radiolabelled iodide and thyroid hormone levels in 29 workers employed for at least 1.7 years in the perchlorate production plant used as a framework for the study by Lamm *et al.* (1999) as well in 12 volunteers not working in this plant. Subjects worked three consecutive days for 12 hours and then had three days off. Biological measurements were taken before and after the work periods and concerned serum levels of perchlorate, thiocyanate, nitrite, T3, T4, free T4 index, Tg and TSH, as well as urinary concentrations of perchlorate and iodide. The workers' mean serum concentrations of perchlorate increased from 2 µg/L to 838 µg/L between the beginning and the end of the work periods. There was a significant decrease in the uptake of radiolabelled iodide, from 21.5% to 13.5%, between the beginning and the end of the work period. However, the observed rate of uptake of radiolabelled iodide was 14.4% in the controls, which is significantly lower than the rate in workers before starting work and very similar to the level observed in workers after their work period. After starting work, the workers showed a modest but significant increase in T3, T4 and the free T4 index. According to the authors, greater absorption of perchlorate during the work periods led to a 38% decrease in the uptake of iodide by the thyroid compared to that observed following a rest period of 3 days.

It should be noted that these two studies were conducted on a small sample and concern a population of workers that is not representative of the most vulnerable populations (newborns, foetuses and pregnant women). It is debatable whether these studies, in which subjects are exposed to perchlorate via inhalation, can be used for deriving a toxicity reference value for the oral route. In addition, the exposure to perchlorate was discontinuous and recovery phenomena were observed in subjects during the rest periods.
Furthermore, the results from the study by Braverman *et al.* (2005) raise certain questions. In particular, the serum and urinary concentrations of perchlorate in the controls were zero, which is surprising given the results of the NHANES survey (2001-2002), in which traces of perchlorate were detected in all the urine samples from the 2820 individuals surveyed (Blount *et al.,* 2007). Braverman *et al.* (2007) observed a significant increase in serum levels of T4 and T3 which, although considered very low by the authors, still remains unexplained, even in another paper by the same team.

4.6.7. Environmental epidemiological studies

In its 2005 report, the NAS identifies the epidemiological studies that have examined possible associations between exposure to perchlorate in drinking water at concentrations between 4 and 120 µg/L and the occurrence of thyroid diseases. None of these studies, that were mostly ecological in nature, were able to show a causal link. Confounding biases such as the presence of ions other than perchlorate (thiocyanate and nitrate) inhibiting the sodium-iodide symporter are generally not taken into account. The same is true with the other substances with endocrine disrupting toxicity. The majority of studies relate to short-term exposure (NAS, 2005).

Lastly, environmental epidemiological studies were not selected for the characterisation of the ammonium perchlorate hazard in drinking water. In their review published in 2010, Tarone *et al.*

concluded that epidemiological studies on environmental exposure to perchlorate do not provide robust evidence of their adverse effects on thyroid function (changes in concentrations of thyroid hormones or congenital hypothyroidism measured in newborns).

4.6.8. Classification regarding carcinogenicity

Ammonium perchlorate has not been classified as carcinogenic by any international body.

4.6.9. Toxicity reference values

Several chronic threshold TRVs for the oral route have been identified by the experts. There is no non-threshold effect TRV for perchlorate.

US Environmental Protection Agency (US EPA)

Since 1998, the US EPA has revised the chronic TRV for the oral route (RfD) for perchlorate several times.

Based on the study by Greer *et al.* (2002) conducted in healthy volunteers (21 women and 16 men) exposed to perchlorate at doses of 0.007 - 0.02 - 0.1 and 0.5 mg/kg bw/day for 14 days, the US EPA proposed establishing an oral RfD for this compound. The critical effect selected is the inhibition of the uptake of radioactive iodide by the thyroid, with a no observed effect level (NOEL) of 0.007 mg/kg bw/day. An uncertainty factor of 10 was applied to take intra-species uncertainty into account, mainly due to the fact that vulnerable populations, especially foetuses and pregnant women, may have hypothyroidism or an iodide deficiency.
The US EPA therefore proposed selecting as the RfD for perchlorate and perchlorate salts the value of **7.10^{-4} mg/kg bw/d** (US EPA, 2005).

Agency for Toxic Substances and Disease Registry (ATSDR)

In 2009, the ATSDR proposed selecting as the TRV for chronic oral exposure to perchlorate the value of **7.10^{-4} mg/kg bw/d**, retaining the same pivotal study and the same criteria as the US EPA in 2005.

Joint FAO/WHO Expert Committee on Food Additives (JECFA)

In 2010, JECFA proposed selecting a provisional maximum tolerable daily intake (TDI) of **0.01 mg/kg bw/day.** The monograph detailing the method used to develop this value was unavailable at the time of this opinion's publication. The starting point of this toxicity reference value was a $BMDL_{50}$ of 0.11 mg/kg bw/day estimated from data in healthy volunteers and selecting the inhibition of radiolabelled iodine capture by thyroid cells as the critical effect. JECFA proposed applying an uncertainty factor of 10 to take vulnerable populations into account: pregnant women, foetuses and newborns. However, it deemed it unnecessary to include an additional uncertainty factor to take account of the short duration of exposure in the pivotal study.

Office of Environmental Health Hazard Assessment (OEHHA)

In 2004 and in its draft report of 2011, the OEHHA proposed selecting the study on healthy volunteers by Greer *et al.* (2002) as the pivotal study in order to establish a $BMDL_5$ of 0.0037 mg/kg bw/day as the starting point for establishing a chronic TRV for the oral route for perchlorate. The OEHHA proposed applying an intra-species uncertainty factor of 10 to take account of the susceptibility of the following populations: women with low iodine intakes, foetuses, infants and young children, breastfed children, breastfeeding mothers and pregnant women. Like the US EPA and the WHO, this organisation did not consider it appropriate to apply an uncertainty factor related

to the short duration of the pivotal study. Accordingly, the TRV selected for perchlorate is **$3.7x10^{-4}$ mg/kg bw/day**.

Table III summarises the chronic TRVs for the oral route for perchlorate identified in the literature.

Table III: Chronic toxicity reference values for the oral route for perchlorate

Organisation	Pivotal study	Critical effect	Critical dose (mg/kg bw/d)	Uncertainty factor	TRV (mg/kg bw/d)
US EPA (2005)	Greer *et al.*, 2002	Inhibition of the absorption of radioactive iodide by the thyroid gland	NOAEL = 0.007	10	$7x10^{-4}$
ATSDR (2009)			*ditto* US EPA	10	$7x10^{-4}$
OEHHA (2004, 2011)			$BMDL_5$ = 0.0037	10	$3.7x10^{-4}$
JECFA (2010)			$BMDL_{50}$ = 0.11	10	$1x10^{-2}$

Choice of a toxicity reference value

In 2005, the NAS conducted a review of the human and animal data and concluded that human data were more reliable than animal data for the determination of a critical dose (point of departure) for assessing the health risk associated with perchlorate : "The rat is a good *quantitative* model for assessing inhibition of iodide uptake by the thyroid caused by perchlorate exposure, but it is only a good *qualitative* model for the [study of the] effects of this inhibition" (NAS, 2005). Therefore, animal studies will not be used to establish a TRV, due to variations in thyroid physiology between rodents and humans and the heightened sensitivity of the rat.

The inhibition of iodide uptake by the thyroid associated with exposure to perchlorate is a relevant thyroid effect in humans, because it is a precursor event, in terms of a toxic mechanism of action. In other words, without inhibition of iodide uptake by the thyroid, there would be no deleterious effect, which is why this critical effect was selected for this health risk assessment.

The study in healthy volunteers chosen for the establishment of a TRV was that of Greer *et al.* (2002), which is the only study available for examining the chosen critical effect associated with water-related exposure to perchlorate. An examination of this study nevertheless raises a number of comments:

- it is not a very powerful study (small number of individuals) based on a short observation period (14 days);
- the study population consisted of healthy adult volunteers, and is therefore not representative of newborns, foetuses and pregnant women (the amount of iodine in the thyroid gland is lower in newborns compared to adult subjects);
- possible dietary intake of perchlorate (excluding water-related exposure) was not taken into account;
- the ways in which healthy volunteers were chosen for inclusion in the study, based on serum and urine assays of iodide, are not explained in the paper. However, there are iodine-deficient populations. In its 2005 report, AFSSA showed that the French adult population is at risk of mild iodine deficiency, with women more exposed to this risk than men (AFSSA, 2005)[7].

A review of calculations of critical doses by estimating benchmark doses (BMD) from the study by Greer *et al.* (2002) was conducted by the NAS in 2005. The original data available (OEHHA, 2004, 2011; WHO JECFA, 2010) were examined. Although the approach of hazard characterisation by benchmark dose proved to be more inclusive, with regard to the available data in the pivotal study, than the NO(A)EL/LO(A)EL approach, the experts considered that there was no clear argument for the benefit of using the BMD specifically on data from Greer *et al.* (2002).

Consequently, the no observed effect level (NOEL) of 7 µg/kg bw/d was finally selected. An intra-species uncertainty factor of 10 was applied, leading to a TRV for the oral route of **0.7 µg/kg bw/d**.

[7] Population Reference Intake (PRI) = 150 pg Iodine/24 hrs for adults

4.7. Limit values for perchlorate in drinking water

No quality limit nor reference limit for perchlorate or perchlorate salts has been established to regulate drinking water quality by the French Public Health Code.

Several recommendations were found in the literature. These values are shown in Table IV.

Table IV: Limit values for perchlorate in drinking water proposed by different organisations

US EPA (2008b,c)	OEHHA (2004)	OEHHA (2011)	MassDEP (2006)
15 µg/L	6 µg/L	1 µg/L	2 µg/L

US Environmental Protection Agency (US EPA)

The US EPA proposed a limit in drinking water (interim value) of **15 µg/L** for chronic exposure (US EPA, 2008b, c, 2009a, b). This value is based on the RfD of $7x10^{-4}$ mg/kg bw/day established in 2005. The exposure scenario used to develop this limit value is that of an adult individual of 70 kg bw consuming 2 litres of water daily throughout their entire life. To estimate the share of the RfD attributed to oral water intake, the US EPA estimated exposure to perchlorate via the oral route from knowledge about the distribution of urinary concentrations of perchlorate from the CDC's NHANES survey and data on water contamination from the UCMR survey. Estimating the 90th percentile of the distribution of dietary exposure to perchlorate (excluding water) in pregnant women to be 0.263 µg/kg bw/d, the share of the RfD attributed to water-related exposure was estimated at 62% for this population, which is more vulnerable than the general population to effects on the thyroid.

Office of Environmental Health Hazard Assessment (OEHHA, 2004)

The limit value proposed by the OEHHA in 2004 was established from the threshold TRV of $3.7x10^{-4}$ mg/kg bw/d for chronic effects via the oral route. Assuming that 60% of this TRV can be attributed to water intake in pregnant women (the population considered to be at greatest risk in dietary exposure to perchlorate) and estimating the ratio of body weight in this population to its daily consumption of drinking water to be 25.2 $kg.L^{-1}.d^{-1}$, the limit value for perchlorate in drinking water is estimated to be equal to **6 µg/L**.

Office of Environmental Health Hazard Assessment (OEHHA, draft, 2011)

The limit value proposed in 2011 in the OEHHA draft report is based on the threshold TRV for chronic effects via the oral route of $3.7x10^{-4}$ mg/kg bw/d. The population selected as being at greatest risk related to oral exposure to perchlorate is that of children aged under 6 months. The OEHHA assumed the ratio of body weight in this population to its daily consumption of drinking water to be 4.3 $kg.L^{-1}.d^{-1}$. Using data from Shier *et al.* (2009), who analysed perchlorate in 15 samples of infant formula, the mean oral exposure for children aged under 6 months is estimated at 0.1 µg/kg bw/d. Based on this result, the OEHHA considers that 73% of the TRV can be attributed to water-related exposure. Thus, a draft limit in drinking water of **1 µg/L** is proposed.

Massachusetts Department of Environmental Protection (MassDEP)

Development of the limit value for perchlorate in drinking water by the MassDEP in 2006 is detailed in the article by Zewdie *et al.* (2010). After identifying the health arguments for developing this value, the authors note that hypochlorite solutions used for disinfecting drinking water may contain chlorate that can in turn be oxidised into perchlorate. According to Greiner *et al.* (2008), at the maximum dose of a hypochlorite solution used for disinfecting drinking water, i.e. 10 mg/L (in the USA), perchlorate concentrations would be between 0.03 and 29 µg/L. Forty per cent of the hypochlorite solutions tested would lead to the treated water having perchlorate concentrations greater than 1 µg/L, and 29% would lead to concentrations greater than 2 µg/L. To ensure the efficacy of disinfection while still conforming to the toxicity data for perchlorate, the MassDEP proposed a limit value for risk management in drinking water of **2 µg/L**.

The details of how the limit values were established are given in Table V.

Table V: Details of the establishment of limit values for perchlorate in drinking water.

Source	Toxicity reference value (µg/kg bw/d)	Relative water-related exposure contribution to the TRV	Individual body weight (kg bw)	Daily consumption of drinking water (L/d)	Limit value in drinking water (µg/L)
US EPA (2008b, c)	0.7	62%	70	2	15 (draft)
OEHHA (2004)	0.37	60%	bw/Consumption$_{water}$ = 25.2 kg.L^{-1}.d^{-1} in pregnant women		6
OEHHA (2009)	0.37	73%	bw/Consumption$_{water}$ = 4.3 kg.L^{-1}.d^{-1} in children aged under 6 months		1 (draft)
MassDEP (2006)	Risk management value				2

Establishment of a limit value in drinking water

Value in adults

The default approach of the WHO, for establishing a limit value in drinking water for a substance with a threshold for toxicological effects, is to select 10% of the oral TRV as being attributed to water-related exposure, when there are no specific data that would enable this share to be refined (WHO, 2004). In the case of perchlorate, according to estimates by the US EPA in 2005, the available data mean that the share of the TRV attributed to water-related oral exposure in adults is around 60%.
Adopting this value and assuming chronic exposure to drinking water of an individual of 70 kg body weight consuming 2 litres of water per day and based on a chronic oral TRV of 0.7 µg/kg bw/d, a limit value in drinking water for perchlorate equal to **15 µg/L** can be proposed.

Value in children aged 0-6 months

Thyroid hormones are essential for the proper functioning of cellular respiration and for the metabolism of cells and organs. Situations of hypothyroidism show that the main concern associated with thyroid hormone deficiency in the foetus and child relates to neurological development, which could be impaired in the event of malfunction of the hypothalamic-pituitary axis (Haddow *et al.*, 1999; Pop *et al.*, 1999). In addition, the amount of iodine in foetuses and children is lower than in adults, and its turnover is faster.

Based on the recommendations of the French Paediatric Society (Bocquet *et al.,* 2003), the scenario of four infant bottles of 210 mL and seven levelled 5-gram measures of formula per bottle proposed for children aged from 4 to 6 months was chosen as the "worst-case" for the 0-6 months age group.

Her *et al.* (2010) assayed perchlorates in 26 formulations for powdered infant formula from four different commercial brands on the market in South Korea. The average level of perchlorates was 7.83 ± 0.22 µg/kg food (minimum content 1.49 ± 0.01 µg/kg; maximum content 33.3 ± 0.49 µg/kg).

For a child with 5 kg of body weight, daily exposure to perchlorate is 0.21 µg/d, or 6% of the toxicity reference value of 0.7 µg/kg bw/d for the lowest infant formula contamination scenario according to the data from Her *et al.* (2010) (i.e. 1.5 µg/kg food). For the high level of infant formula contamination of about 33 µg/kg, from the same publication, the dietary exposure exceeds the toxicity reference value.
Schier *et al.* (2009) measured perchlorate concentrations in 15 infant formulas made with milk powder to which was added water uncontaminated by perchlorate. The geometric means for perchlorate concentrations varied from 0.18 to 1.72 µg/L (maximum value equal to 5.05 µg/L). These contamination data corresponded to geometric means for daily exposure doses ranging from 0.02 µg/kg bw/d to 0.35 µg/kg bw/d (maximum exposure equal to 1.016 µg/kg bw/d).

The contamination data reported in the publications by Her *et al.* (2010) and Schier *et al.* (2009) show levels higher than those reported by the US survey conducted by the US FDA as part of the 2005/2006 total diet study. Perchlorate was quantified in infant formula up to 3.6 µg/L (the arithmetic mean for the 12 results was 1.42 µg/L, if values below the analytical limit of detection of 1 µg/L were estimated to be equal to half the limit of detection) (FDA, 2008).

In the absence of national contamination data for perchlorates in infant formulas, and in view of the bibliographic data available, consumption of water contaminated with perchlorate is not recommended for children aged 0 to 6 months.

4.8. Conclusion

The CES on Water:

- notes that perchlorate ions are difficult to eliminate with the methods used in drinking water treatment plants;

- recommends, in view of the current toxicological data, a limit value in drinking water of 15 µg/L for perchlorate in order to prevent the health risks associated with consumption of water supplied to adult consumers, under normal conditions;

- recommends that a national survey be conducted on perchlorate contamination of food, in particular to clarify the levels found in formulations of powdered infant formula used in the preparation of infant bottles;

- advises avoiding water contaminated by perchlorate for the preparation of infant bottles for infants aged up to 6 months;

- recommends that health authorities compile inventories of the water intakes intended to produce drinking water that are affected by industrial emission of perchlorate.

5. AGENCY CONCLUSION AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety adopts the conclusion and recommendations of the CES on Water.

Following the Opinion's adoption by the CES on Water and the CES on the Assessment of the physical and chemical risks in foods, the French Agency for Food, Environmental and Occupational Health & Safety received information on perchlorate contamination of powdered infant milk marketed in France, based on a small quantity of data (n = 2) with a quantified maximum value of 2 µg/kg. This value should be compared with the maximum contamination of 33 µg/kg found during the bibliographic analysis and used to calculate exposure, that led to the recommendation advising against the use of water contaminated by perchlorate for the preparation of infant bottles for infants aged up to 6 months.

The Director General

Marc MORTUREUX

KEY WORDS

Ammonium perchlorate, perchlorate, drinking water.

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ANNEX 1: DATA ON EXPOSURE TO PERCHLORATE – US TDS - 2005-2006

(according to Murray *et al.* 2008)

Age groups		Lower bound[8] (µg/kg bw/d)	Upper bound[9] (µg/kg bw/d)
Infant – 6-11 months		0.26	0.29
Child – 2 years		0.35	0.39
Child – 6 years		0.25	0.28
Child – 10 years		0.17	0.20
Women	14 – 16 years	0.09	0.11
	25 – 30 years	0.09	0.11
	40 – 45 years	0.09	0.11
	60 – 65 years	0.09	0.10
	Over 70 years	0.09	0.11
Men	14 – 16 years	0.12	0.12
	25 – 30 years	0.08	0.11
	40 – 45 years	0.09	0.11
	60 – 65 years	0.09	0.11
	Over 70 years	0.11	0.12

[8] Undetected data estimated to be equal to 0

[9] Undetected data estimated to be equal to the limit of detection (1 µg/kg)