The Director General

Maisons-Alfort, July 20th, 2012

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

concerning epidemiological studies on associations between exposure to perchlorate in drinking water and thyroid function in specific populations

1. REVIEW OF THE REQUEST

On 27 April 2012, 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 epidemiological studies that aimed to evaluate the associations between exposure to perchlorate in drinking water and thyroid function in pregnant women, foetuses, and newborns.

2. BACKGROUND AND PURPOSE OF THE REQUEST

Further to the publication of the ANSES opinion of 18 July 2011 on the assessment of the health risks associated with the presence of perchlorate in drinking water, the Directorate General for Health (DGS) requested on 1 August 2011 and 12 December 2011 that ANSES study the potential presence of perchlorate in infant formula, calculate dietary exposure to perchlorate in children aged 0 to 6 months, and examine the pertinence of taking into account goitrogenic anions present in the environment (specifically thiocyanate and nitrate) in health risk assessments.
The DGS sent a request to the Agency on 27 April 2012 concerning assessment of the possible health risks related to levels of perchlorate above the control limit of 15 µg/L in adults and above 4 µg/L in children under 6 months of age, on the basis of epidemiological data concerning a possible association between water-related exposure to perchlorate and changes in TSH concentrations and thyroid hormones in populations expected to be the most susceptible, i.e. pregnant women, foetuses and newborns. This request follows recent identification of perchlorate levels higher than control levels in source and municipal water supplies in several supply units in Nord-Pas de Calais.

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 Agency established an Emergency Collective Expert Assessment Group which met on 29 May and 20 June 2012 in order to examine published epidemiological studies on the association between exposure to perchlorate in drinking water and thyroid function in pregnant women and newborns.

4. Analysis and conclusions of the Emergency Collective Expert Assessment Group

4.1. Background concerning the method for establishing toxicity reference values for ingestion of perchlorate and control values for drinking water

4.1.1. *Toxicity reference values for ingestion of perchlorate*

In its opinion dated 18 July 2011, ANSES proposed a toxicity reference value (TRV) for ingestion of perchlorate of 0.7 µg/kg bw/d.
This TRV was primarily based on the study by Greer *et al.* (2002) carried out in healthy volunteers (21 women and 16 men) exposed to perchlorate in drinking water at doses of 0.007, 0.02, 0.1 and 0.5 mg/kg bw/d for 14 days. Among subjects in the group with the lowest exposure dose, the investigators found a decrease in uptake of radiolabelled iodide by the thyroid of 1.8%. In view of the relationship between inhibition of iodide uptake by the thyroid and changes in serum levels of thyroid hormones in humans, and uncertainties in this area, inhibition of 1.8% of iodine uptake by the thyroid through competition with the perchlorate in the sodium-iodide symporter is low inhibition that can be qualified as a biological effect that is not an adverse effect. Therefore, this dose of 0.007 mg/kg bw/d was retained as the no observed effect level (NOEL). In the study carried out by Greer *et al.*, no significant change in thyroid hormone serum concentrations was observed, irrespective of the tested exposure dose to perchlorate.

This NOEL of 7 µg/kg bw/d was retained as the basis for establishing the TRV in the ANSES opinion of July 2011 for the following reasons:

- Uptake of iodide by the thyroid is one the first steps in synthesis of thyroid hormones;

- The foetus has thyroid function as early as the end of the first trimester of pregnancy and foetal thyroid activity is high, even if iodine intake is sufficient, unlike the situation in adults in whom thyrocytes are mainly at rest. As a result, the adult thyroid is more able to adjust in the event of iodine deficiency. Moreover, states of hypothyroidism demonstrate that the main concern related to a deficiency in thyroid hormones in the foetus and in children is neurological development, which could be impaired in subjects with dysfunction of the hypothalamic-pituitary axis (Haddow *et al.*, 1999; Pop *et al.*, 1999). These findings mean that the foetus and the newborn can be considered from the outset as more susceptible to thyroid hormone deficiency;

- The choice of critical effect, of the pivotal study, of the reference dose used to determine the toxicity reference values and the intra-species uncertainty factor of 10 retained in the ANSES opinion of July 2011 have also been proposed by other Health Agencies, including the US National Academy of Sciences (NAS) and US Environmental Protection Agency

(EPA) in 2005, the Agency for Toxic Substances and Disease Registry (ATSDR) in 2009, and the French National Institute for Industrial Environment and Risks (INERIS) in 2011.

On the basis of this NOEL, the TRV was established by applying an intra-species uncertainty factor of 10 to take into account the most susceptible human populations.

Adopting a TRV of 0.7 µg/kg bw/d is a conservative choice in that the retained effect is not based on a clinical observation (hypothyroidism) or on a directly causal biological change (decrease in serum levels of thyroid hormones) but on an early biomarker of dysfunction. In other words, it is not possible to interpret levels moderately exceeding the TRV in terms of occurrence of a directly observable clinical thyroid effect in individuals belonging to an exposed population.

In order to assess an inhibition of thyroid iodide uptake that would better reflect a significant change in thyroid hormone levels as an adverse effect, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) recently established a toxicity reference value for perchlorate on the basis of a benchmark dose (BMD) determined using the dose-response relationship in the Greer *et al.* (2002) study cited above. The benchmark response (BMR) retained by JECFA was an inhibition of 50% of thyroid iodide uptake expected to have no effect on blood thyroid hormone concentrations in adults, on the basis of clinical data for chronic and subchronic exposure in healthy adults (JECFA, 2011). After applying an intra-species uncertainly factor of 10, the TRV proposed by the JECFA is therefore higher (10 µg/kg bw/d) than the values suggested by other organisations.

4.1.2. *Drinking water guidelines for perchlorate retained by the DGS*

Further to publication of the Agency opinion of 18 July 2011 regarding assessment of the health risks associated with the presence of perchlorate in drinking water, the DGS retained a control value of 15 µg/L applicable to the adult population, on the basis of a proportion of water intake of 60% of the TRV retained by ANSES, and an exposure scenario for an adult weighing 70 kg bw consuming two litres of water per day. This approach, retained by ANSES in 2011, had been proposed as the interim value by the US EPA in 2005 (US EPA, 2005).
For children under six months of age, the retained control limit of 4 µg/L corresponds to a standard approach by the WHO for infants, i.e. a scenario of 0.75 litres of drinking water per day for a body weight of 5 kg (WHO, 2011).

4.2. Water-related exposure to perchlorate by ingestion in newborns and thyroid effects

The ten published epidemiological studies identified and listed in the Summary table in Annex 1 concern the study of associations between exposure to perchlorate through consumption of drinking water and thyroid function in newborns.

Generally, the iodine status of the population exposed to perchlorate via drinking water must be taken into account to interpret the possible thyroid effects observed. However, most epidemiological studies evaluated by the experts do not take this variable into account as a confounding factor, often because this variable is not available.

Most of the examined studies do not demonstrate an association between the presence of perchlorate in drinking water at concentrations lower than about 100 µg/L, and the occurrence of congenital hypothyroidism or changes in TSH or T4 levels in newborns (Lamm and Doemland, 1999; Crump *et al.*, 2000; Li *et al.* 2000a; Li *et al.* 2000b; Li *et al.* 2001; Kelsh *et al.*, 2003; Buffler *et al.*, 2006; Amitai *et al.*, 2007).

However, two epidemiological studies did show a relationship between these parameters (Brechner *et al.*, 2000; Steinmaus *et al.*, 2010).

Based on data concerning TSH levels in blood samples as part of the NBS (Newborn Screening) programme in the State of Arizona (USA) between October 1994 and the end of 1997, Brechner *et al*. studied an association between perchlorate contamination of drinking water and TSH levels in newborns. The exposed population was 1099 newborns in the city of Yuma (68,000 inhabitants) supplied with water sourced from Lake Mead, contaminated by perchlorate. The non-exposed population was 443 newborns in the city of Flagstaff (58,000 inhabitants).

The data concerning the quantification of contamination levels of water by perchlorate are not precise: the authors mention that in 1999, the perchlorate content in drinking water in the city of Yuma was about 6 µg/L, while perchlorate had not been detected in municipal water in Flagstaff (analytical limit of detection between 1 and 4 µg/L). After adjustment for age of the children at the time of measurement and the geographical origin, TSH levels in the newborns in Yuma were significantly higher than those in newborns from Flagstaff (median TSH level in Yuma of 19.9 µU/mL, interquartile range: 12.5 - 28.3 µU/mL; median TSH levels in Flagstaff of 13.4 µU/mL, interquartile range: 8.8 - 18.9 µU/mL). This ecological study showed an association between the presence of perchlorate in drinking water and TSH levels in newborns. The authors also reported a non-significant difference in the number of cases of congenital hypothyroidism between the two cities between October 1994 and August 1999 (4 cases in Yuma and none in Flagstaff). However, T4 levels in newborns were not significantly different in the two cities, after adjustment for geographic origin (Brechner *et al.*, 2000).

Other authors have questioned the interpretation of these results, pointing out that the ages of the newborns at the time of measurement of TSH were unbalanced in the two groups, and suggest that the differences observed may be more likely attributable to differing medical practices, demographic factors, and other geographic factors (influence of altitude between the cities, in particular) than to different exposure levels to perchlorate in Flagstaff and Yuma (Crump, 2001; Goodman, 2001; Lamm, 2003).

On the basis of data from the Californian programme for screening of congenital hypothyroidism between January and December 1998, Steinmaus *et al.* (2010) examined 497,458 results for TSH assays in newborns and stratified the results into two groups depending on the level of perchlorate contamination of drinking water supplying the cities where the children and their parents lived (> 5 µg/L *versus* < 5 µg/L). Water contamination was determined on the basis of concentrations of perchlorate between 1997 and 1998 (800 measurements of perchlorate for 200 sources supplying 66% of the Californian population). The median concentration of perchlorate in drinking water was about 8 µg/L and the maximum concentration 159 µg/L. Confounding factors taken into account in the study were: sex, geographic origin, birth weight, type of feeding, maternal age, family income, and age of the child at the time of sampling. When the comparison was limited to measurements of TSH carried out during the first 24 hours of life, the authors reported a significant difference between the frequency of TSH levels above 25 µU/mL (OR = 1.53; 95% CI = [1.24; 1.89]) or above 15 µU/mL (OR = 1.23; 95% CI = [1.16; 1.31]) in newborns in exposed towns *versus* those in non-exposed towns. However, when TSH was measured after the first 24 hours of life, there was no statistically significant difference between the newborns in exposed towns *versus* those in non-exposed towns, with a TSH threshold of 25 µU/mL (OR = 0.72; 95% CI = [0.41; 1.27]). Nonetheless, a statistically significant difference was reported when the TSH threshold was fixed at 8 µU/mL (OR = 1.27; 95% CI = [1.22; 1.33]).

This study found different results to those reported by Buffler *et al.* (2006) which demonstrated no relationship between the presence of perchlorate higher than 5 µg/L in drinking water supplying towns in California and the occurrence of congenital hypothyroidism or a variation in TSH levels assessed during neonatal screening.

In the studies by Buffler *et al.* (2006) and Steinmaus *et al.* (2010), the group of "non-exposed" newborns included those living in towns in California supplied by drinking water with a perchlorate concentration below 5 µg/L, with an analytical limit of detection of 4 µg/L. In these studies, there was no specific data on the distribution of contamination of drinking water by perchlorate in the “exposed” and “non-exposed” groups, which weakens the findings of these ecological studies.

4.3. Environmental exposure of pregnant women to perchlorate and thyroid effects

The five identified epidemiological studies in the Summary table given in Annex 2 concern an association between exposure to perchlorate through drinking water and thyroid function, specifically in pregnant women or in women of childbearing age.

Four of these studies did not show an association between the presence of perchlorate found in maternal urine, as a biomarker for exposure to perchlorate, and changes in TSH levels or thyroid hormones in pregnant women (Téllez Téllez *et al.*, 2005; Gibbs *et al.*, 2008; Pearce *et al.*, 2010; Pearce *et al.*, 2011).

In a study carried out by Blount *et al.* (2006), the authors came to a different conclusion. The objective was to study a possible association between urine perchlorate concentrations and serum TSH and T4 concentrations in 1111 young women and girls aged more than 12 years included in the American NHANES 2001-2002 study. Multiple regression models including urine perchlorate concentrations and covariables known to have a probable relation to serum T4 and TSH levels were used (i.e. age, serum albumin level, serum cotinine level, estimated total caloric intake, pregnancy status, menopause status, premenstrual status, C-reactive protein serum levels, duration of fasting, body mass index, urine creatinine concentration, urine iodide, nitrate and thiocyanate concentrations, geographic origin and medication intake). The geometric mean of urine perchlorate concentrations was 2.84 µg/L (95% CI = [2.54; 3.18]). Urine perchlorate concentrations were associated with an increase in TSH and a decrease in T4 in young women and girls over 12 years of age who had a urine iodide concentration below 100 µg/L. In women who had a urine iodide concentration above 100 µg/L, the urine perchlorate concentration was predictive of the serum TSH level but not of the serum T4 level (Blount *et al.*, 2006).

The authors of this study aimed to evaluate the association between urine perchlorate concentrations and changes in TSH and T4 in young women and girls over 12 years of age. For a change in urine perchlorate concentrations from 0.19 to 100 µg/L, the authors observed a decrease in T4 of 2.43 µg/dL. However, the small increase in TSH associated with this significant decrease in T4 was unexpected on the basis of knowledge about the relationship between T4 and TSH concentrations which is near to negative exponential. Moreover, given the limited knowledge concerning the relationship between ingestion of perchlorate in water and urine excretion of perchlorate, analysis of these results does not make it possible to link exposure to perchlorate in water to changes in TSH and T4 in young women and girls over 12 years of age.

The results of this study highlight the importance of the iodine status in the population as a cofactor for evaluating possible associations between perchlorate exposure and changes in thyroid hormones.

4.4. Data on the iodine status of the population in France

4.4.1. *Sources of iodine intake*

The main source of intake is food, primarily through consumption of seaweed, seafood, salt-water fish, eggs and dairy products. Certain texture agents and colouring agents fortify foodstuffs in iodine. This is also the case for use of iodine disinfectants in veterinary practice. Salt fortified with iodine is a major source of intake in France.
Animal tissue, including meat and poultry, is naturally poor in iodine. Concentrations are also very low in plants and fruit (AFSSA, 2005).

Certain vitamin supplements for pregnancy are fortified with iodine. Unintentional iodine intake is related to certain drugs, skin disinfectants or radiological products.

4.4.2. *Iodine status of the general adult population in France*

The survey of vitamin and antioxidant mineral supplementation (SU.VI.MAX. 1994-1995) that included 12,014 adults (7154 women aged 35 to 60 years and 4860 men aged 45 to 60 years) showed median urine iodine levels of 85 µg/L in men and 82 µg/L in women. 22% of women and 16% of men had urine iodine levels lower than 50 µg/L. This rate of iodine deficiency increased with age. About 35% of subjects had urine iodine levels higher than 100 µg/L. There was an decreasing west-east gradient for urine excretion of iodide (Valeix *et al.*, 1999).

Based on the results of the National survey of nutrition and health (ENNS 2006-2007), the adult population residing in France had a satisfactory nutritional status for iodine according to the criteria of the World Health Organization (WHO), i.e. median urine iodine levels greater than 100 µg/L and the 20^{th} percentile of urine iodine distribution for this population above 50 µg/L. Results of the ENNS survey showed median adult urine iodine levels of 136 µg/L and the 20^{th} percentile of distribution of urine iodine of 72 µg/L.

Given the context surrounding this appraisal request, it can be emphasised in particular that for the geographic area Nord-Picardy-Normandy, the median urine iodine level in adults is 146 µg/L (95% CI [128-156]) and the 20^{th} percentile is 68 µg/L (95% CI [62-83]) (DREES, 2010).

4.4.3. *Iodine status of children under 1 year of age in France*

In a descriptive study conducted between January and March 2000, and then between January and May 2001, on the iodine status of 160 children (93 boys, 67 girls) aged 10 days to 6 years as part of maternal and child welfare consultations in the Lille metropolitan area, the median (range) of urine iodine concentrations and the percentage of concentrations in urine iodine > 100 µg/L were 196 µg/L (4-1042 µg/L) and 76%, respectively, in the total sample. In children under six months of age in particular, the median urine iodine concentration was 183 µg/L and the percentage of children with urine iodine concentrations greater than 100 µg/L was high (83%), indicating an absence of risk for iodine deficiency in this population (Pouessel *et al.*, 2003).

In a prospective study between 1 January and 31 May 2005 which concerned all children under 1 year of age in the general paediatrics sector of the Lille University Hospital Centre (CHRU de Lille), 95 (83%) out of 114 children under 1 year hospitalised over this period were evaluated for iodide levels in urine samples, and 60% of these 95 infants were evaluated for TSH as part of their blood workup.
Median urine iodine was 328 µg/L (range: 12 - 1580 µg/L): 24 infants (25%) had excess iodine with urine levels greater than 400 µg/L, while 19 children (20%) had an iodine deficiency with urine levels lower than 100 µg/L. Among these children, 5 had a clinical iodine deficiency with urine levels lower than 20 µg/L. Statistical analysis did not demonstrate a significant relationship between the iodine status and the following parameters: family history of thyroid disease, intake of medication by the mother during pregnancy, pregnancy term, type of delivery, socio-professional category of the parents, age, sex, type of feeding, child nutritional status, and presence of chronic disease. There was no abnormal elevation of TSH levels in the infants with iodine deficiency. The authors of this study did not show an association between iodine deficiency and occurrence of hypothyroidism in children (Pouessel *et al.*, 2008).

4.4.4. *Iodine status of pregnant women in France*

In three studies carried out in pregnant women at the end of pregnancy, iodine intake was equivalent to less than 50% of population reference intakes (PRIs) for pregnant women (PRI of 200 µg/day) (Caron *et al*. 1997; Leleu, 1999; Pivot, 2003 *in* AFSSA, 2005).

In a study performed at the Nice University Hospital Centre (CHU de Nice) including 108 pregnant women at the end of the second trimester of pregnancy, the median urine iodine level was found to be 59 µg/L. Urine iodine was lower than 50 µg/L in 51% of women and lower than 30 µg/L in 25%. 86% of these patients had urine iodine levels lower than 100 µg/L. 6.5% of subjects had urine iodine levels greater than 150 µg/L (Brucker-Davis *et al.*, 2004).

The increase in iodine requirements during pregnancy (200 µg/24 h) is related to higher renal clearance of iodide and constitution of an intra-thyroid iodine pool in the foetus, required after 18-20 weeks of pregnancy for synthesis of thyroid hormones by the foetal thyroid.

4.5. Neonatal screening of congenital hypothyroidism

Given that correct functioning of the thyroid is essential for development in children, neonatal screening of congenital hypothyroidism has been mandatory since 1978 in all newborns, under the control of the French association for screening and prevention of disabilities in children (AFDPHE). Screening is performed three days after birth using TSH assay as a marker in a blood sample taken from the newborn child. This timeline is justified since blood TSH is elevated in the first hours of life and levels stabilise thereafter.

In the publication by Steinmaus *et al.* (2010), the levels retained as a threshold limit for TSH in statistical analysis by logistic regression were 25 µU/mL and 8 µU/mL. Although neonatal screening for congenital hypothyroidism is not performed using the same method in France and in the United States, it is possible to interpret the value of 25 µU/mL as equivalent to the value retained in France for the screening of congenital hypothyroidism by blood sampling blot three days after birth. The value of 8 µU/mL is the value concerning the 95th percentile of the distribution of assay results for TSH in the blood. This value could be considered moderately elevated in the newborn.

4.6. Conclusions and recommendations

The results from the evaluated epidemiological studies do not enable conclusions to be drawn concerning the possible association between TSH levels and perchlorate concentrations in drinking water in pregnant women and newborns. In most of these studies, these concentrations ranged from levels below the analytical limit of detection (most often 4 µg/L) to about 100 µg/L[1]. The absence of information concerning the iodine status of the studied populations makes it difficult to interpret the published epidemiological data.

Hypothyroidism states indicate that the main concern related to insufficient thyroid hormone production in the foetus and in children is neurological development which could be impaired if there is dysfunction of the hypothalamic-pituitary axis (Haddow *et al.*, 1999; Pop *et al.*, 1999). The changes that have been demonstrated in children whose mothers had severe hypothyroidism during pregnancy correspond to extreme situations when compared to the subtle changes in TSH and thyroid hormone levels that may be associated with environmental exposure to perchlorate.

As a result and given currently available data, though levels moderately exceeding the level of 15 µg/L in adults (particularly in pregnant women) and the level of 4 µg/L in newborns do not seem to be associated with clinically detectable effects, it is not possible to quantify the health risk related to exposure to levels higher than 15 µg/L in adults and 4 µg/L in children under 6 months of age. It is therefore also not possible to establish another quantitative threshold above the management values.

Recommendations:

Perform a feasibility study on the iodine status of the populations in areas where municipal water supplies are the most contaminated by perchlorate. This study could be used to assess the pertinence of applying control measures that would involve restricting consumption of tap water in a portion of the population in Nord-Pas de Calais exposed to perchlorate levels in drinking water higher than the health values indicated in the opinion of 18 July 2011.

A feasibility study is currently underway at the French Institute for Public Health Surveillance (InVS) concerning use of data collected as part of systematic screening for congenital hypothyroidism in Nord-Pas de Calais to initiate an epidemiological study aimed at quantifying the relationship between thyroid function in newborns and perchlorate drinking water contamination levels. The results of this

[1] This value of approximately 100 µg/L is moreover close to the limit value in drinking water that would be established on the basis of the TRV proposed by the JECFA in 2011 (estimate obtained using the TRV of the JECFA (10 µg/kg bw/d) converted to equivalent doses in drinking water, following a scenario in adults of 70 kg bw, 2 litres per day, 50% of TRV attributed to perchlorate intake via tap water.

type of study may in time make it possible to contribute to revision of control values currently used by the DGS.

5. CONCLUSION AND RECOMMENDATIONS OF THE AGENCY

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusion and recommendations of the Emergency Collective Expert Assessment Group.

The Director General

Marc Mortureux

KEY WORDS

PERCHLORATE, DRINKING WATER, FOOD, THYROID

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<u>Annex 1:</u> Summary table (1/3) for epidemiological studies on the associations between exposure to perchlorate through water and changes in thyroid parameters in newborns.

Authors, year of publication	Region	Description of exposure groups	Level of exposure to perchlorate in drinking water	Study duration	Confounding factors	Thyroid parameters	Results
Lamm and Doemland (1999)	6 counties in California and 1 county in Nevada (USA)	700,000 newborns	Perchlorate detected in drinking water in 7 counties	Between 1996 and 1997	none	TSH (neonatal screening for congenital hypothyroidism)	No association between detection of perchlorate in drinking water and prevalence of congenital hypothyroidism
Brechner *et al.* (2000)	2 cities in Arizona (USA): Flagstaff and Yuma	1099 newborns in Yuma (presence of perchlorate) 443 newborns in Flagstaff (absence of perchlorate)	In Yuma, in August 1999: 6 µg/L In Flagstaff: absence of detection	Between October 1994 and December 1997	age of child at time of sampling; geographic origin	TSH T4	Association between detection of perchlorate in drinking water and increase in mean TSH levels No association between detection of perchlorate in drinking water and T4 levels
Crump *et al.* (2000)	3 towns in Chile (Taltal, Chañaral and Antofagasta)	163 schoolchildren between 6 and 8 years 11,967 newborns	In Taltal: concentrations between 100 and 120 µg/L (mean = 112 µg/L) In Chañaral: concentrations between 5.3 and 6.7 µg/L (mean = 6.2 µg/L) In Antofagasta: absence of detection (LoD = 4 µg/L)	Study in Chilean schoolchildren in September 1999 For newborns, data from neonatal screening between February 1996 and January 1999	sex; age; urine iodine levels (for schoolchildren)	TSH Free T4	No association between the detection of perchlorate in drinking water and an increase in mean TSH levels in newborns No association between the detection of perchlorate in drinking water and TSH levels or the prevalence of goitre in schoolchildren Association between detection of perchlorate in drinking water and increase in levels of free T4 considered of no clinical relevance by the authors

Annex 1 Summary table (cont'd 2/3)

Authors, year of publication	Region	Description of exposure groups	Level of exposure to perchlorate in drinking water	Study duration	Confounding factors	Thyroid parameters	Results
Li *et al.* (2000a)	2 cities in Nevada (USA): Las Vegas and Reno	17,308 newborns in Las Vegas (presence of perchlorate) 5882 newborns in Reno (absence of perchlorate)	In Las Vegas: over period A of 7 months, drinking water had concentrations of 9 to 15 µg/L; over period B of 8 months, absence of detection (< 4 µg/L) In Reno, absence of detection (LoD = 4 µg/L)	Between April 1998 and June 1999	birth weight; age of child at time of sampling	T4	No association between the presence of perchlorate in drinking water and mean T4 levels in newborns
Li *et al.* (2000b)	2 cities in Nevada (USA): Las Vegas and Reno	407 newborns in Las Vegas (presence of perchlorate) 133 newborns in Reno (absence of perchlorate)	*Ditto* Li *et al.* (2000a)	Between December 1998 and October 1999	age; sex	TSH	No association between the presence of perchlorate in drinking water and mean TSH levels in newborns
Li *et al.* (2001)	Towns in Clark county *versus* towns in Washoe county and Towns in Clark county *versus* all towns in other counties in Nevada (USA)	176,847 patients in Medicaid programme selected on the basis of thyroid disease	Towns in Clark county: presence of perchlorate at about 8 µg/L between 1997 and 1998 Other counties in Nevada (including Washoe): absence of detection	Between January 1997 and December 1998	none	Thyroid disease (simple non-specific goitre, non-toxic nodular goitre, thyrotoxicosis with or without goitre, congenital hypothyroidism, acquired hypothyroidism, thyroiditis, thyroid cancer, other thyroid disease)	No association between the presence of perchlorate in drinking water and the prevalence of thyroid diseases in patients in the Medicaid programme
Kelsh *et al.* (2003)	Towns in southern California (USA): Redlands *versus* the other towns in San Bernardino and Riverside counties	15,090 newborns in Redlands (presence of perchlorate) 685,161 newborns in the other towns in San Bernardino and Riverside counties (absence of perchlorate)	In Redlands: between 4 and 130 µg/L in raw or treated water. A municipal report for 2001/2002 records concentrations between < 4 µg/L and 9 µg/L Other counties in San Bernardino and Riverside: absence of detection	Between 1983 and 1997	age of child at time of sampling; sex; geographic origin; birth weight; number of pregnancies of mother; year of birth	Occurrence of congenital hypothyroidism TSH	No association between the presence of perchlorate in drinking water and the occurrence of cases of congenital hypothyroidism No association between the presence of perchlorate in drinking water and TSH levels in newborns

Annex 1 Summary table (cont'd 3/3).

Authors, year of publication	Region	Description of exposure groups	Level of exposure to perchlorate in drinking water	Study duration	Confounding factors	Thyroid parameters	Results
Buffler *et al.* (2006)	Towns in California (USA)	50,326 newborns in 24 exposed towns *versus* 291,931 newborns in 287 towns not exposed to perchlorate	Towns supplied with drinking water with a perchlorate concentration > 5 µg/L *versus* < 5 µg/L	In 1998	birth weight; geographic origin; sex; multiple pregnancy status	Occurrence of congenital hypothyroidism TSH	No association between the presence of perchlorate in drinking water and occurrence of congenital hypothyroidism No association between the presence of perchlorate in drinking water and TSH levels in newborns
Amitai *et al.* (2007)	3 towns in Israel (Ramat Hasharon, Hertzlia and Morasha)	97 newborns in Morasha (highly exposed zone) 216 newborns in Ramat Hasharon (exposed zone) 843 newborns in Hertzlia (non-exposed zone)	In Morasha: concentration > 340 µg/L In Ramat Hasharon: 42 to 94 µg/L In Hertzlia: < 3 µg/L	Between January and September 2004	age; sex; birth weight; duration of pregnancy	T4	No association between the presence of perchlorate in drinking water and T4 levels in Israeli newborns
Steinmaus *et al.* (2010)	Towns in California (USA)	497,458 newborns	Towns supplied with drinking water with a perchlorate concentration of > 5 µg/L *versus* < 5 µg/L	Between January and December 1998	sex; geographic origin; birth weight; type of feeding; age of mother; income; age of child at time of sampling	TSH	Association between the presence of perchlorate in drinking water at concentrations higher than 5 µg/L and TSH levels in newborns

<u>Annex 2:</u> Summary table (1/2) for epidemiological studies on the associations between exposure to perchlorate through water and changes in thyroid parameters, particularly in pregnant women or women of childbearing age.

Authors, year of publication	Region	Description of exposure groups	Level of exposure to perchlorate in drinking water	Study duration	Confounding factors	Thyroid parameters	Results
Téllez Téllez *et al.* (2005)	3 towns in Chile (Taltal, Chañaral and Antofagasta)	60 pregnant women per town seen for three medical consultations (2 before delivery and one after)	In Taltal: concentrations between 72 and 139 µg/L (mean = 114 µg/L) In Chañaral: concentrations between 4.7 and 7.3 µg/L (mean = 5.8 µg/L) In Antofagasta: absence of detection (LoD = 4 µg/L)	Between November 2002 and April 2004	urine iodine; anti-thyroid peroxidase antibodies; anti-thyroglobulin antibodies	T3 Free T4 TSH Tg	No association between the presence of perchlorate in drinking water and levels of thyroid parameters evaluated in pregnant women No association between the presence of perchlorate in drinking water and birth weight, head circumference or length in newborns
Blount *et al.* (2006)	USA	1188 males and 1111 females over 12 years of age included in the American NHANES 2001-2002 study	Estimation of exposure by measuring the urine concentration of perchlorate	2001-2002	age, serum albumin; serum cotinine; estimated total caloric intake; pregnancy status; menopausal status; premenstrual status; C-reactive protein; duration of fasting; body mass index; urine creatinine; urine iodine; urine nitrate; urine thiocyanate; geographic origin; medication intake	T4 TSH	No association between urine perchlorate concentration and serum concentrations of TSH and T4 in men Association between urine perchlorate concentration and serum TSH and T4 concentration in women with urine iodine < 100 µg/L No association between urine perchlorate concentrations and serum T4 concentrations but association with serum TSH in women with urine iodine > 100 µg/L

Annex 2 Summary table (cont'd 2/2).

Authors, year of publication	Region	Description of exposure groups	Level of exposure to perchlorate in drinking water	Study duration	Confounding factors	Thyroid parameters	Results
Gibbs *et al*. (2008)	Chile	Observations from the study by Téllez Téllez *et al.* (2005) for three towns carried out during 3 medical examinations were pooled (i.e. 202 measurements of free T4 in 149 pregnant women and 220 measurements of TSH in 155 pregnant women)	Estimation of exposure by measuring urine perchlorate concentration	Between November 2002 and April 2004	age, weeks of pregnancy, tobacco consumption, urine iodine, urine creatinine	Free T4 TSH	No association between urine perchlorate concentration and free T4 or TSH in pregnant women for urine iodine levels lower or higher than 100 µg/L (only 17 TSH results and free T4 results concerned pregnant women with urine iodine levels lower than 100 µg/L)
Pearce *et al.* (2010)	Cardiff (UK) and Turin (Italy)	1st sub-cohort: 374 pregnant women in Cardiff and 261 women in Turin who all had high TSH serum concentrations and low	Estimation of exposure by measuring urine perchlorate concentration	2002-2006	anti-thyroid peroxidase antibodies; thiocyanate and nitrate urine concentrations	Free T4 TSH	No association in the two sub-cohorts between urine perchlorate concentration and serum free T4 or TSH levels in

		serum T4 levels at 1st trimester 2nd sub-cohort: 480 euthyroid women in Cardiff and 526 euthyroid women in Turin					pregnant women at the 1st trimester of pregnancy, even if urine iodine level was < 100 µg/L
Pearce *et al.* (2011)	Los Angeles (USA) and Cordoba (Argentina)	134 pregnant women in the 1st trimester of pregnancy in Los Angeles 107 pregnant women in the 1st trimester of pregnancy in Cordoba	Estimation of exposure by measuring urine perchlorate concentration (median of 7.8 µg/L in Los Angeles and 13.5 µg/L in Cordoba)	2004-2007	urine iodine; anti-thyroid peroxidase antibodies; duration of pregnancy; urine creatinine	TSH Free T4 index total T3	No association in either city between urine perchlorate concentration and thyroid parameters studied in pregnant women in the 1st trimester of pregnancy, even if urine iodine level was < 100 µg/L