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LA DIRECTRICE GÉNÉRALE

OPINION

of the French Food Safety Agency on the assessment of the health risks associated with non-compliance of barium in water intended for human consumption

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Context of the request

On 17 April 2003 the French Food Safety Agency (Afssa) was requested by the Directorate General for Health to issue an opinion on the assessment of health risks associated with non-compliance of barium in water intended for human consumption.

Method of expertise

After consulting the "Water" scientific panel on 3 May and 4 July 2007 and the "Chemical and Physical Contaminants and Residues" scientific panel on 6 June 2007, Afssa has issued the following opinion:

Whereas the initial procedure for assessing health risks associated with non-compliance in water intended for human consumption presented in volume 1 (June 2004 to April 2007) of Afssa's report;

Regulatory context

Whereas the quality limits set for barium by the order of 11 January 2007 on the quality references and limits of untreated water and water intended for human consumption mentioned in articles R. 1321-2, R. 1321-3, R. 1321-7 and R. 1321-38 of the public health code:
- at 0.7 milligram per litre in water intended for human consumption,
- at 1 mg/L in untreated surface water;

Hazard characterisation

Whereas barium is a substance with a threshold toxic effect;

Whereas, on the basis of cardiovascular effects, the World Health Organization (WHO) recommends a guideline value of 0.7 mg/L;

Whereas the limits of the detection methods for barium in water that were used when the epidemiological studies were carried out;

Whereas the US Environmental Protection Agency (US EPA), on the basis of nephropathies induced by barium observed in mice and rats, recommends a chronic oral reference dose (RfD) of 0.2 mg/kg bw/d;

Whereas the RfD recommended by the US EPA is considered to be the most relevant toxicological reference value for assessing the health risks associated with barium ingestion;

Estimation of exposure

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Whereas barium can be naturally present in water resources and also associated with anthropic activities practised in the catchment area;

Whereas food (solid foodstuffs and drinking water) is the main vector of barium exposure outside of the occupational context;

Whereas the absence of data enabling the dietary intake of barium in France to be estimated;

Whereas the assessments conducted particularly through Total Diet Studies (TDSs) carried out in Canada and the United Kingdom show that barium intake through food would be less than 2 mg/d for high consumers;

Whereas the data available in the SISE-Eaux database show that the maximum concentrations observed in water in France are around 2 mg/L;

Whereas concentrations in water exceeding 2 mg/L are exceptional due to the limit imposed by the solubility of barium salts in water;

Conclusions and recommendations

The French Food Safety Agency:

Recommends a scientific procedure described in sheet 18 appended for situations where the barium quality limit is exceeded,

Notes that ingesting water containing 2 mg/L of barium, similar to the maximum concentrations observed in France, exposes an individual to a lower dose (0.1 mg/kg bw/d) than the toxicological reference value recommended by the US EPA (0.2 mg/kg bw/d), with all dietary intakes taken into account,

Therefore estimates that there is no justification for setting a quality limit for barium.

The Director General of the French Food Safety Agency

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Key words: barium, exceeding the quality limits, drinking water

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Sheet 18: Assessment of the health risks associated with exceeding the quality limit of barium in water intended for human consumption

Quality limit: 0.7 mg/L

1 – Origin and sources of contamination

Barium in water is mainly of natural origin. This compound is spread in sedimentary and magmatic rocks in the form of sulphate (dominant form) or carbonate.
The main barium ore exploited is barium sulphate (or barite) ($BaSO_4$) which is found in sedimentary, metamorphic and igneous rocks. Other barium ores are benstonite $(Ba,Sr)_6(CO_3)_{13}(Ca,Mg,Mn)_7$) and sanbornite ($BaSi_2O_5$). Witherite ($BaCO_3$) and norsethite $BaMg(CO_3)_2$, rich in barium oxide (BaO) are not exploited much.
The highest concentrations are found in water of acid pH, in which barium solubility is higher. The concentrations in water are relatively stable.
Barium (metal or oxide) and its salts (particularly sulphate and carbonate) are used in a wide range of applications such as the manufacture of photographic paper, glass, paints, etc.

2 – Treatments reducing barium content in water

According to the article R.1321-50 of the public health code, treatment processes and products placed on the market and intended for the treatment of water for human consumption must, under normal or predictable conditions of use, comply with the specific provisions defined by the order of the French Ministry of Health ensuring that (i) they are not liable, intrinsically or through their residues, to present a direct or indirect danger for human health or lead to an alteration in the composition of the water defined by the reference values set by this order; (ii) they are effective enough.

To date and pending the publication of an order on water treatment processes and products, the specific provisions to comply with are those defined by:

- the circular of 28 March 2000[1];
- the circular of 16 March 1995, in the case of the use of processes implementing membrane filtration modules.

The information gathered enables the identification of the following treatments for reducing barium content in line with the provisions regulating the authorisation of these treatments:

Precipitation
Barium can only be eliminated in its form $BaCO_3$ during the decarbonation of water. It is then coprecipitated by calcium carbonate.

Ion exchange
Strong cation ion exchangers have affinities which increase with the valency of ions. Accordingly, with sodic resins, calcium, magnesium, strontium and barium ions are exchanged by sodium ions.

Nanofiltration
Nanofiltration preferentially retains polyvalent ions. Barium ions are therefore retained like the alkaline earth elements: calcium, magnesium, strontium.

3 – Methods of analysis

The order of 17 September 2003[2] on the methods for analysing water samples and on their performance characteristics states that, in the case of barium, the quantification limit must not exceed 0.1 mg/L.

The main standardised methods are as follows:

[1] Circular DGS/VS 4 no. 2000-166 of 28 March 2000 on treatment process products of water intended for human consumption, STA: *MESP0030113C*
[2] Order of 17 September 2003 on the methods for analysing water samples and on their performance characteristics, STA: SANP0323688A, JORF of 7 November 2003, p. 19027 to 19033

- NF EN ISO 11885 (March 1998): assay of 33 elements by Inductively Coupled Plasma-Atomic Emission Spectroscopy.
- NF EN ISO 17294-2 (April 2005): application of Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) – Part 2 assay of 62 elements.

- NF EN ISO 14911 (October 1999): assay by ion chromatography of ions Li^+, Na^+, NH_4^+, K^+, Mn_2^+, Ca_2^+, Mg_2^+, Sr_2^+ and Ba_2^+ dissolved - Method applicable for water and wastewater. Since the quantification limit quoted in standard is 1 mg/L, this method is difficult to apply to health control.

Analytical uncertainty

The measurement uncertainty can be estimated through inter-laboratory tests determining the coefficient of reproducibility variation (CRV%). *(AGLAE, 2003)*
The maximum concentration tested in inter-laboratory tests is 0.18 mg/L; at this concentration, the CRV% value is 9.4%. The confidence interval at 95% is ± 0.017 mg/L. The top value of the analyses is therefore around 0.0196 mg/L (AGLAE, 2003).

4 – Exposure data

4.1 – Levels in the air

Low levels of barium are present in the air, in the form of particles from industrial emissions mostly, and more specifically the burning of coal, diesel and waste incineration. The concentration in the ambient air is estimated to be less than 0.05 µg/m^3 (IPCS, 1990). Concentrations in the air ranging from 0.0015 to 0.95 µg/m^3 were observed in the United States before 1984 (Health Canada, 1990, IRIS, 1998; WHO, 2004)

4.2 – Levels in water

The regulatory health control programme defined by the order of 11 January 2007[3] provides for the analysis of this parameter at the extraction point (from once every 5 years to 12 times a year) and after treatment (from once to more than 12 times a year).
A study of data available in the SISE-EAUX base (French Ministry of Health – DDASS – SISE-Eaux) for the period from January 2003 to December 2006 shows that:

- analyses[4] are available for 60% of water distribution units (i.e. 16,374 units),
- at least one non-compliant result was observed out of less than 0.5% of these water distribution units supplying a maximum of 337,000 people,
- the 50th percentile of the results of the 212 non-compliant analyses is 0.9 mg/L, the 95th percentile is 1.7 mg/L and the maximum values observed are around 2 mg/L.

Solubility varies depending on the anions present in the water: the solubilities of barium sulphate and barium carbonate are 10^{-10} and $10^{-8.3}$ respectively at 20℃ which, for a 9.5 mg/L sulphate content, gives a barium solubility limit of 0.14 mg/L.

4.3 - Levels in foodstuffs

Most foodstuffs contain less than 2 mg of barium per kg of food (Gormican, 1970; Ysart *et al.*, 1999). The foodstuffs that could contribute the most to dietary exposure are cereals and certain nuts, tea and cocoa.

Concentration factors in plants and aquatic organisms are unknown (ATSDR, 2005).

[3] Order of 11 January 2007 on the health control analysis and sample programme for the water supplied by a distribution network, in accordance with articles R. 1321-10, R. 1321-15 and R. 1321-16 of the public health code.
[4] Analyses carried out on the samples taken, from either production or distribution.

Dietary intake of barium has been estimated in old studies representative of Anglo-Saxon populations. The estimations range from 0.3 to 1.77 mg/d (IPCS, 1990).
Total Diet Studies have been conducted in various countries:

- in the United Kingdom in 1994, the average dietary intake of barium was estimated to be 0.58 mg/d for the whole population. Intake for high adult consumers was estimated to be 1.3 mg/d (Ysart *et al.*, 1999)
- in Canada from studies carried out between 1993 and 1999 (Health Canada, 2005), the average dietary intake of barium for different age groups was estimated to be around 0.6 mg/d for a 60 kg adult (see Table 18.1)

Table 18.1: Average daily dietary intakes of barium among the Canadian population per age group – Total Diet Study from 1993 to 1999

Age group	0-1 years old	1 to 4 years old	5 to 11 years old	12 to 19 years old	20 to 39 years old	40 to 64 years old	65 and over	Whole population
Daily intake µ g/kg bw./d	20 to 22.8	25.3	18.7	9.3 to 11.8	8.4 to 9.7	7.9 to 8.9	7.5 to 7.8	8.8

This study shows that the average daily intake is higher in young children.

A study conducted in France by Biego *et al.* (1998) allowed the intake for 3 month-old infants via the consumption of different types of milk to be estimated: while intake through maternal milk was only 4 µg/d, intake through different types of milk ranged from 39 to 59 µg/d.

The highest average intake was observed with the ingestion of soy milk (91µg/d)[5].

The crossing of food contamination data available in the United States (Gormican, 1970) and the United Kingdom (Ysart *et al.*, 1999) with food consumption data from the INCA 1999 study[6] resulted in the estimation of the average daily intakes at 0.63 mg/d, which is consistent with the estimations made in the United Kingdom and Canada.

4.4 – Share of exposure sources

Outside a given occupational context, food and water are the main source of barium exposure.

Estimations of these dietary intakes are not available for the French population. However, the assessments conducted particularly through Total Diet Studies (TDSs) in Canada and the United Kingdom show that barium intake through food would be less than 2 mg/d for high consumers;

Moreover, x-ray contrast agents based on barium sulphate were used. Barium sulphate is not very soluble, however, and is therefore little absorbed (WHO, 2004; IPCS, 2001).

[5] Intake is estimated by considering the ingestion of 700 mL of milk a day.
[6] The INCA 1999 survey (individual and national survey on food consumption) was carried out on 3,003 subjects representative of the French population.

5 – Health effects

The soluble forms of barium salts are quickly absorbed from the intestinal tract. Absorption rates have been determined in rats after exposure to low doses (around 30 mg/kg bw). Chloride salt is absorbed better than sulphate and carbonate (Taylor *et al*. 1962).
Animal tests have been carried out with barium chloride ($BaCl_2$) and barium nitrate [Ba $(NO_3)_2$] which are the most soluble in water.

Barium can be transported or incorporated in various tissues, depending on mechanisms about which little is known but which are probably similar to those involved in the fate of calcium and strontium (IPCS, 1990). Barium is preferentially deposited in bones (Beliles, 1994; IPCS, 1990). The half-life of barium in the bone is estimated to be 50 days (Machata, 1988). Barium activates the secretion of adrenal medullary catecholamines; it can shift calcium from cell membranes, which modifies the permeability of it and stimulates muscle cells. Excretion is mainly through faeces, around 90%. A small amount (2%) is eliminated through urine.

5.1 – Subchronic and chronic toxicity

Animal studies

The chronic toxicity of barium has above all been studied by oral administration to rats and mice, focusing on the cardiovascular pathology, given the clinical cases observed in humans (Roza & Berman, 1971).

Dihydrated barium chloride was administered for 4 to 13 weeks (Tardiff *et al*. 1980, US NTP 1994) or for more than five months (Perry *et al*. 1989, Mc Cauley *et al*. 1985, US NTP 1994).

Schroeder and Mitchener (1975a) exposed rats to barium acetate in water (0 or 5 mg/L). They observed an increase in the frequency of proteinuria, revealed by reagent strip. There were no other significant anomalies. One LOAEL[7] of 0.61 mg/kg bw/d was recommended. Perry *et al.* (1983, 1985, 1989) exposed rats to barium doses in drinking water ranging from 0.098 mg/kg bw/d to 7.4 mg/kg bw/d for 16 months. They observed an increase in systolic blood pressure from the 8th month of exposure until the end of the study. **However, the authors of these studies pointed out that the animals' food did not comply with the recommended dietary intakes and could therefore constitute a bias.**

Mc Cauley *et al*. (1985) did not observe any organ damage after exposing male rats for 36 to 68 weeks and females for 46 weeks; The total doses of barium through drinking water (form not specified) ranged from 1 to 38 mg/kg bw. These authors detected glomerular alterations at doses of 150 mg/kg bw/d in unilaterally nephrectomised rats. On the cardiovascular level, exposure to 250 mg/L of barium in drinking water (i.e. a LOAEL of 38 mg/kg bw/d in total intakes) modifies the response to the epinephrine test, without the physiopathological significance of this observation being clear. Possible effects on blood pressure have been studied on rats with normal blood pressure and rats sensitive to hypertension (Dahl salt-sensitive). The study lasted 16 weeks and no effect was observed, which resulted in a NOAEL[8] of 150 mg/kg bw/d.

The US National Toxicology Program (US NTP, 1994) conducted studies on mice (B6C3F1) and rats (F334/N), male and female, with exposure durations to barium chloride in drinking water from 103 to 105 weeks. A significant increase in the incidence of nephropathies characterised by tubular effect was observed in the male and female mice exposed to doses of 160 and 200 mg/kg bw/d respectively. The US NTP anatomopathologists concluded that these lesions were morphologically distinct from the spontaneous degenerative renal lesions commonly observed in elderly mice. The severity of the nephropathies was moderate to marked for males and females in these groups. In rats, a nephropathy was observed in the treated groups and the control groups, but an increase in the kidney weight in females was only observed in the group ingesting 2500 mg/L of barium in drinking water.

Epidemiological studies

Brenniman *et al.* (1979, 1981, 1984) studied the cardiovascular consequences of barium exposure through drinking water. An initial study reports the results of a retrospective mortality study (1971-1975)

[7] Lowest Observed Adverse Effect Level

[8] No Observed Adverse Effect Level

conducted in the communities of Northern Illinois exposed to high concentrations of barium (2-10 mg/L). The authors compared the death rates of cardiovascular cause among these communities with those of matching groups (demographic characteristics and socio-economic status) exposed to low concentrations (less than or equal to 0.2 mg/L). Barium was the only parameter to exceed the regulatory limits in water. The death rates due to cardiovascular problems, arteriosclerosis and all types of causes were high for men and women in the communities exposed to barium-rich water. The authors highlighted the fact that variables were not taken into account, which could have influenced the results, such as population mobility, the use of water softeners, smoking, food habits and physical exercise.

The same authors conducted a morbidity study in two communities, McHenry (1,197 adults) and West Dundee (1,203 adults), similar in demographic and socio-economic terms but with different barium intake levels: this was 70 times higher in the West Dundee community (7.3 mg/L). Three blood pressure measurements were taken and a medical questionnaire was filled in. No difference in the blood pressure figures or frequency of cardiac diseases, infarction, arterial hypertension or renal diseases was observed.

Two sub-groups of 85 people from each community with no water softener or treatment for hypertension and living in the community for over ten years were formed. For all the elements measured or researched by questionnaire, the two groups were identical.

Wones *et al.* (1990), noting that the epidemiological studies did not reveal a clear link between barium exposure through drinking water and cardiovascular effects, exposed eleven volunteers to concentrations in drinking water (intake of 1.5 L/d) of 0 mg/L for 2 weeks, then 5 mg/L for 4 weeks, then 10 mg/L for a final 4 weeks. They did not observe any significant impact on cardiovascular risk factors or on the parameters measured (ECG, blood pressure, metabolic parameters). The 10 mg/L dose corresponding to 0.21 mg/kg/bw/d was selected by the authors as the NOAEL.

To conclude, the chronic studies in animals by oral route do not reveal any cardiovascular effects, but do reveal a tubular nephropathy.

The epidemiological studies do not reveal any cardiovascular effect or renal disease up to a concentration in drinking water of 7.3 mg/L. However, no functional marker of renal nephropathy was sought.

It should, however, be pointed out that at the time these epidemiological studies were carried out, the methods of analysis were characterised by interferences and a high quantification threshold. Given the solubility of barium sulphate, such concentrations in water are only possible if the level of sulphates in the water is less than 1 mg/L.

5.2 – Genotoxicity, mutagenesis and carcinogenesis

Information on genotoxicity is limited. No *in vivo* study has been published. Virtually all *in vitro* studies conclude that barium nitrate and barium chloride do not induce genetic mutations in bacterial trials with or without metabolic activation (US NTP 1994, Monaco *et al.* 1990, Rossman *et al.* 1991). Two *in vitro* studies on mammal cells (CHO cells - Chinese hamster ovary) conducted by the NTP (1994) are negative, only one study on lymphoma cells in mice gives a positive result with metabolic activation (NTP, 1994).

Carcinogenesis studies have not revealed an increase in tumour frequency, whatever the animal species or dose used (US NTP, 1994).

5.3 – Reprotoxicity and teratogenesis

Dietz *et al.* (1992) studied the barium effect (dihydrated chloride) on reproduction in rats and mice. The males of both species were exposed 60 days before mating and the females 30 days. In the rat, they observed a fall in the weight of newborns in the group exposed to the highest dose of 200 mg Ba/kg bw/d with recovery on the fifth day. In the mouse, a fall in the number of babies per litter does not depend on the dose.

The effects observed are therefore transitory or unconnected to the dose.

Given the effects observed during barium exposure and the absence of genotoxicity of this substance, barium is a substance with a threshold toxic effect.

6 – Toxicological reference values

6.1 – Chronic toxicological reference values

Table 18.2 summarises the method for establishing the toxicological reference values recommended by various bodies. The critical studies retained are described below.

Table 18.2: summary of the toxicological reference values recommended by various bodies

Source	Chronic TRVs		Study type	Species	Critical effect	Study reference
ATSDR 2005 Draft	Chronic duration oral MRL[1]	0.6 mg Ba /kg bw/d	Chronic study (2 years)	Mice	nephropathy	US NTP, 1994
US EPA IRIS, 2005	Reference Dose for Chronic Oral Exposure (RfD)	0.2 mg Ba/kg bw/d	Chronic study (2 years)	Mice	nephropathy	US NTP, 1994
WHO, 2003	Guideline value	0.7 mg Ba/L	Epidemiological study	Humans	Increase in blood pressure	Brenniman & Levy, 1984
Health Canada 1990	MAC[2]	1 mg Ba/L	Epidemiological study Medium and long-term study	Humans Rats	Increase in blood pressure	Brenniman & Levy, 1984 Perry et al., 1983 et 1985

[1] MRL: Minimal Risk Level

[2] MAC: Maximum acceptable concentration

In 2005, the **Agency for Toxic Substance and Disease Registry** (ATSDR) used the chronic study in mice B6C3F1 carried out by the National Toxicology Program (US NTP, 1994). A benchmark dose (BMD_{05}) of 80 mg/kg bw/d, corresponding to a 5% increase in the incidence of nephropathies, was calculated; the low value of the confidence interval at 95% of this BMD_{05} ($BMDL_{05}$) is 61 mg/kg bw/d. The Minimum Risk Level (MRL) was established on the basis of this $BMDL_{05}$ of 61 mg/kg bw/d with the application of a safety factor of 100: 10 for extrapolation from animal to human and 10 for interindividual variability.

The **US Environmental Protection Agency** (US EPA) in 2005 used the same study as the ATSDR. The RfD is based on the $BMDL_{05}$ determined for male rats of 63 mg/kg bw/d. The US EPA justifies this choice by indicating that the $BMDL_{05}$ in males and females are very similar, but that the uncertainty is less for the BMD_{05} in the estimation carried out in male mice.
A safety factor of 300 is applied: 10 for extrapolation from animal to human, 10 for the interindividual variability and 3 due to a lack of data, particularly in the field of reprotoxicity.

The **World Health Organization** (WHO) estimates, despite proven nephrotoxicity of barium in laboratory animals, that the critical effect of barium at low concentration for humans is the effect on blood pressure.
Considering that the epidemiological study it deems the most relevant (Brenniman & Levy, 1984) does not reveal effects on blood pressure in subjects ingesting water containing 7.3 mg/L of barium (see 5.1

– Subchronic and chronic effects), WHO recommends a guideline value of 0.7 mg/L by applying a safety factor of 10 (interindividual variability) to this NOAEL.

Health Canada keeps the Maximum Acceptable Concentration (MAC) of 1.0 mg/L recommended in its previous recommendations of 1978, in view of the epidemiological study by Brenniman and the toxicological studies in animals by Perry et al., 1983, 1985 which resulted in similar values.

6.2 – Reference values for drinking water

Concerning drinking water, the quality limit is set at 0.7 mg/L by the order of 11 January 2007[9]. Various recommendations and parametric values, presented in Table 18.3, have been found in the literature.

Table 18.3: Reference values for drinking water recommended by various bodies

Directive 98/83/EC value - Annex IB	WHO guideline value 2004	Health Canada (1990)	US EPA
/	0.7 mg/L	1 mg/L	2 mg/L

7 – Risk assessment

7.1 Choosing the chronic toxicological reference value

Historically, the guideline value proposed by WHO considers arterial hypertension (AH) to be the critical effect. This body bases its guideline value in drinking water on a NOAEL corresponding to a concentration of barium with which arterial hypertension in humans is not associated (Brenniman & Levy, 1984).

However, no cardiovascular sign has been observed in epidemiological or experimental studies and no human data allows for the disproval or confirmation of the hypothesis of a link between barium consumption through drinking water and the occurrence of arterial hypertension, which is a complex multi-factor disease.

Moreover, animal experimental data show a dose-response relationship for nephropathies induced by barium in male or female mice, the most sensitive species given the results. Based on this critical effect, the US EPA proposed a Reference Dose (RfD) of 0.2 mg/kg bw/d in 2005 (US EPA, 2005). **In the framework of this assessment, the working group therefore suggests retaining this toxicological reference value of 0.2 mg/kg bw/d.**

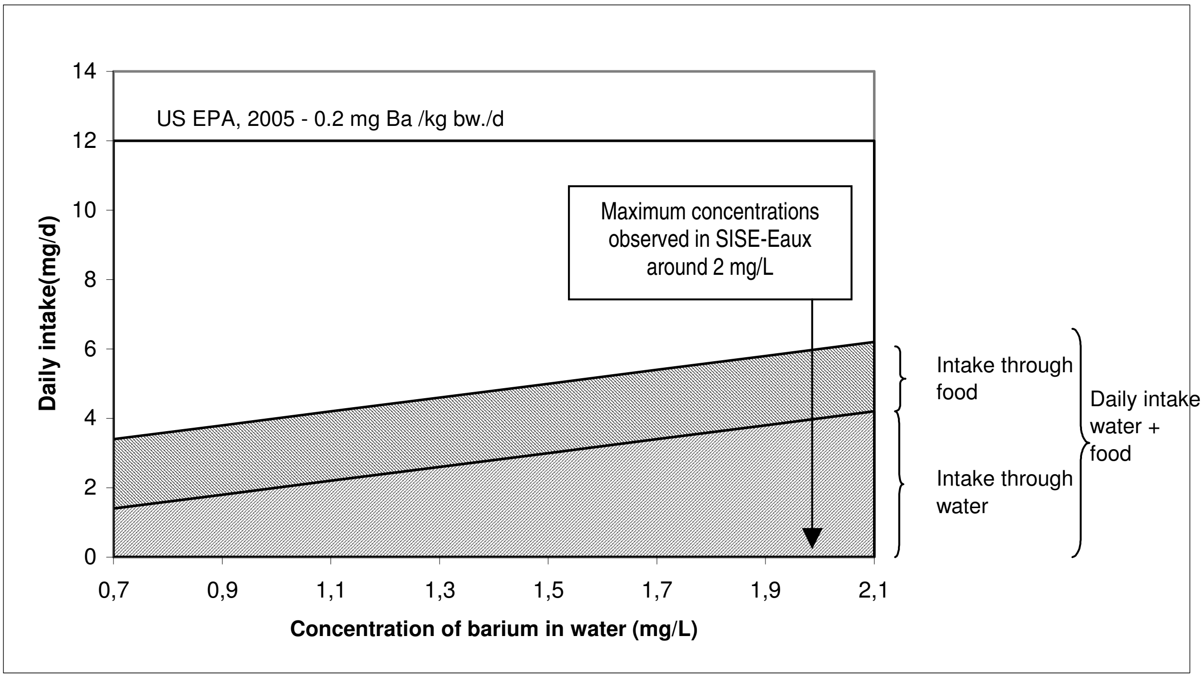
7.2 Estimation of barium intakes and comparison with the chronic toxicological reference value

Dietary intake estimations are not available for the French population. However, the assessments conducted particularly through Total Diet Studies (TDSs) in Canada and the United Kingdom show that barium intake through food would be less than 2 mg/d for high consumers.

The maximum concentrations observed in drinking water in France are around 2 mg/L. The ingestion of such water exposes a 60 kg adult ingesting 2 litres of water a day to a lower dose than 0.07 mg/kg bw/d.

According to these conservative hypotheses, total intake (from water and solid foods) is lower than the toxicological reference value proposed by the US EPA (Graph 18.1).

[9] Order of 11 January 2007 on the quality references and limits of untreated water and water intended for human consumption mentioned in articles R. 1321-2, R. 1321-3, R. 1321-7 and R. 1321-38 of the public health code



Graph 18.1: Barium intake through water and food for an increasing concentration in drinking water – adult consuming 2 litres of water a day.

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