

COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS

Regarding the “expert appraisal for recommending occupational exposure limits for chemical agents”

on the evaluation of biomarkers and recommendations of biological limit values and biological reference values for inorganic lead and its compounds

This document summarises the work of the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee) and the Working Group on biomarkers of exposure (biomarkers WG).

Presentation of the issue

On 11 March 2013, ANSES received a formal request from the French Directorate General for Labour to conduct the scientific expert appraisal work required for setting occupational exposure limits for lead. France has an 8h-OELV¹ for lead of 0.10 mg.m⁻³. The Directorate General for Labour asked the Agency to reassess this occupational exposure limit value (OELV) and the biological limit values for lead and its compounds, namely 400 µg.L⁻¹ for men and 300 µg.L⁻¹ for women and, if necessary, to propose new occupational exposure limit values based on health considerations.

Scientific background

Biological monitoring of exposure in the workplace has emerged as a complementary method to atmospheric metrology for assessing exposure to chemical agents. Biological monitoring assesses a worker's exposure by including all the routes by which a chemical penetrates the body (lung, skin, digestive tract). It is particularly effective when a substance has a systemic effect, and:

- when routes other than inhalation contribute significantly to absorption;
- and/or when the pollutant has a cumulative effect;
- and/or when the working conditions (personal protection equipment, inter-individual differences in respiratory ventilation...) determine large differences in internal dose that are not taken into account by atmospheric metrology.

With regard to prevention of chemical risk in the workplace, the French Labour Code provides the use of biological monitoring of exposure and biological limit values.

OEL Committee definitions

Biomarker of exposure: Parent substance or one of its metabolites, determined in a biological matrix, whose variation is associated with exposure to the agent targeted. Biomarkers of early and reversible effects are included in this definition when they can be specifically correlated to occupational exposure.

Biological limit value (BLV): This is the limit value for the relevant biomarkers.

¹ Art. R. 4412-149 of the French Labour Code

Depending on the available data, the recommended biological limit values do not all have the same meaning:

- If the body of scientific evidence is sufficient to quantify a dose/response relationship with certainty, the biological limit values (BLVs) will be established on the basis of health data (no effect for threshold substances or risk levels for non-threshold carcinogens);
- In the absence of such data for substances with threshold effects, BLVs are calculated on the basis of the expected concentration of the biomarker of exposure (BME) when the worker is exposed to the 8h-OEL. For carcinogens, in the absence of sufficient quantitative data, the biological limit value is calculated on the basis of another effect (pragmatic BLV). These last values do not guarantee the absence of health effects, but aim to limit exposure to these substances in the workplace.

Whenever possible, the OEL Committee also recommends biological reference values (BRVs). These correspond to concentrations found in a general population whose characteristics are similar to those of the French population (preferentially for biomarkers of exposure) or in a control population not occupationally exposed to the substance under study (preferentially for biomarkers of effects). These BRVs cannot be considered to offer protection from the onset of health effects, but do allow a comparison with the BME concentrations measured in exposed workers. These values are particularly useful in cases where it is not possible to establish a BLV.

Organisation of the expert appraisal

ANSES entrusted examination of this request to the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (OEL Committee). The Agency also mandated the Working Group on biomarkers (biomarkers WG) for this expert appraisal.

The methodological and scientific aspects of this group's work were regularly submitted to the OEL Committee. The report produced by the Working Group takes account of the observations and additional information provided by the Committee members.

This expert appraisal was therefore conducted by a group of experts with complementary skills. It was carried out in accordance with the French Standard NF X 50-110 "Quality in Expertise Activities".

Prevention of risks of conflicts of interest

ANSES analyses the links of interest declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert appraisal.

The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

Description of the method

Rapporteurs from the Biomarkers WG and the OEL Committee were appointed by the Agency to produce a summary report on biomarkers of exposure and the recommendation of biological limit values (BLVs) and biological reference values (BRVs) for the BME(s) considered relevant. ANSES employees also contributed to this report.

The summary report on the biomarkers of exposure for lead results from bibliographical information taking into account the scientific literature published on this substance. The rapporteurs reassessed the source articles or reports cited as references whenever they considered it necessary, or whenever the Committee requested it.

The report, as well as the summary and conclusions of the collective expert appraisal, were adopted by the Expert Committee on expert appraisal for recommending occupational exposure limits for chemical agents (2014-2016 mandate) on 10 May 2016.

The collective expert appraisal work and the summary report were submitted to public consultation from 17/11/2016 to 15/01/2017. The people or organizations who contributed to the public consultation are listed in appendix of the report (only available in French). The comments received were reviewed by the OEL Committee who adopted this version on 15 May 2017.

Result of the collective expert appraisal

With a view to revising the biological limit value for the biomonitoring of exposed workers, an analysis of the literature was carried out. This literature review drew on previous expert appraisal reports (ANSES 2013, US EPA 2006, NTP 2012, etc.) and more recent epidemiological studies (using the following key words: "lead", "biomarker", "biomonitoring", "biological monitoring" "urine", "blood" and "occupational"). This report results from bibliographic information taking into account the scientific literature published on this substance through to 2016.

Toxicokinetics data

Absorption

The amount of lead absorbed by the oral route is influenced by the physico-chemical characteristics of the substance (particle size, solubility, nature of the lead derivative, etc.), as well as by the physiological characteristics of the person (age, nutritional status in iron, calcium, etc.). Depending on the size of the particles breathed in, 30 to 50% of inhaled lead is absorbed by inhalation (ATSDR 2007).

Distribution

Lead absorbed by the digestive tract passes into the bloodstream (ATSDR 2007). In the blood, 98% of the lead is found in the intra-erythrocyte compartment, the remainder is bound to albumin. Blood lead is then distributed in bone tissue and soft tissues such as the brain, kidneys and liver. It is also found in the male reproductive system (epididymis, seminal vesicles, testes and prostate) as well as in seminal fluid. Lead also passes into breast milk. The concentrations found in breast milk are proportional to the blood concentrations in the mother (the ratio between breast milk and blood is between 0.01 and 0.48). Lead also crosses the placental barrier (Inserm, 1999).

In adults, the half-life of lead in blood and soft tissues is about 30 days (ATSDR, 2007) whereas in bone tissue, the half-life is between 10 and 30 years. Approximately 94% of the body burden of lead in an adult is found in the bones. Bone tissue is an endogenous reservoir of exposure to lead, even when exposure has ceased. Some of the bone lead can therefore be mobilised into plasma under certain pathophysiological conditions. During physiological stresses such as pregnancy, when suffering from a disease, or the age-related reduction in bone mass, and in cases of osteoporosis, the lead stored in the bones is released into the blood again. The accumulated lead can therefore be released into the blood over a person's entire lifetime (Inserm, 1999).

The relative amounts of lead in other tissues, as reported by Schroeder and Tipton (1968 cited by ATSDR, 2007), were distributed in the following manner: liver (33%), skeletal muscle (18%), skin (16%), connective tissue (11%), fat tissue (6.4%), kidneys (4%), lungs (4%) and brain (2%).

Excretion

Lead is excreted in the faeces (25%) and in urine (75%). Urinary excretion occurs by glomerular filtration with low tubular reabsorption. There is also low excretion via tissues rich in sulphur-containing proteins, nails and hair which, like urine and bones, can be used as matrices for screening for biomarkers.

Choice of biomarkers of exposure

Biomarkers of exposure to lead include measurements of lead in the different biological compartments, in particular blood lead levels, urine lead levels and lead in bones.

The blood lead level is the biomarker most commonly used in routine and is therefore the marker for which there is the most complete information relating to the dose-response relationship. Given that it is currently the only biological marker with a binding regulatory biological limit value, and on which there is the most information in the literature relating to the health effects, it was decided to focus the expert appraisal report on this biomarker of exposure.

Information on biomarkers of exposure identified as relevant for the biological monitoring of exposed workers

Name	BLOOD LEAD	
Other substances giving rise to this BME	None	
Concentrations found in exposed workers or volunteers	<ul style="list-style-type: none"> - <u>Field studies</u>: See section on the literature data on the correlation between blood lead levels and health effects - <u>Studies in volunteers</u>: Not reported (NR) 	
Concentrations in the general population ²	USA-NHANES (5,765 people from the general population) <ul style="list-style-type: none"> - 95th percentile: 35.7 µg.L⁻¹ (20 years and over) (NCEH, 2012) France ENNS (2,029 people from the general population, 18-74 years) <ul style="list-style-type: none"> - 95th percentile: 75 µg.L⁻¹ (smokers); 62 µg.L⁻¹ (non-smokers) (Fréry, 2011) - 95th percentile: 58 µg.L⁻¹ (women); 85 µg.L⁻¹ (men) (Fréry, 2011) Germany-GerES (4,648 people from the general population, 18-69 years) <ul style="list-style-type: none"> - 95th percentile: 76 µg.L⁻¹ (smokers); 64 µg.L⁻¹ (non-smokers) (UBA, 1998) - For exposure to lead and its compounds (except lead arsenate, lead chromate and alkyl compounds): blood lead = 70 µg.L⁻¹ (women) (reference value in the non-occupationally exposed working-age population) (BAR value 2012). Finland: 95 th percentile among non-exposed individuals: 0.09 µmol.L ⁻¹ (19 µg.L ⁻¹) (FIOH, 2015)	
Limit values for exposed workers	USA - ACGIH (BEI)	Elemental lead and inorganic compounds 200 µg.L ⁻¹ (ACGIH, 2016)
	Germany – MAK (BAT)	Lead and its compounds (except lead arsenate, lead chromate and alkyl derivatives) 300 µg.L ⁻¹ for men and women (over the age of 45) 70 µg.L ⁻¹ for women under the age of 45 (DFG, 2014)

² Or, failing this, in a non-occupationally exposed control population; 95th percentile, or failing this the median or the mean (number of people in the study, if this information is available).

	France - Ministry of Labour (INRS, 2015)	<p>400 µg.L⁻¹ (men) 300 µg.L⁻¹ (women)</p> <p>Article R. 4412-152 of the French Labour Code: The biological limit value not to be exceeded is set at 400 µg of lead per litre of blood for men and 300 µg.L⁻¹ for women</p> <p>Article R. 4412-160 of the French Labour Code: Enhanced health surveillance of workers is carried: 1) if exposure to a lead concentration in the air is greater than 0.05 mg/m³, calculated as a time-weighted average on an eight-hour basis; 2) or if a blood lead level higher than 200 µg.L⁻¹ of blood for men or 100 µg.L⁻¹ of blood for women is measured in a worker</p>
	Quebec - IRSST (BIE)	1.45 µmol.L ⁻¹ (IRSST, 2012) (300 µg.L ⁻¹)
	Finland - FIOH (BAL)	1.4 µmol.L ⁻¹ (FIOH, 2015) (290 µg.L ⁻¹)
Conversion factor	Molecular weight: 207.2 1 µg.L ⁻¹ = 0.005 µmol.L ⁻¹ 1 µmol.L ⁻¹ = 207 µg.L ⁻¹	

Study of the relationship between concentrations of BMEs and health effects

Several effects have been observed as a result of exposure to lead in the workplace. The following critical effects were analysed and discussed:

Neurological effects

The neurological effects of lead have been widely documented for exposures above 400 $\mu\text{g.L}^{-1}$. However, at lower blood lead levels, subtle effects which are difficult to interpret have been the subject of several studies, some of which are described in this section. The reported neurological effects mainly consist of a decrease in the conduction speed of peripheral sensory and motor nerves. An analysis of the neurological effects of lead was carried out from the various tables shown in Annex VI of the report by the US EPA (2006), classifying these effects into four categories: posture and stability, cognitive functions, nerve conduction and evoked potentials.

While the studies analysed in the collective expert appraisal report described heterogeneous results, some of them stand out and provide a body of evidence for determining a biological limit value (BLV), in particular the studies by Schwartz *et al.*, 2001, 2005, exploring different neurobehavioural functions.

These studies, conducted in a South Korean population that was monitored over about two years, showed a decrease in neurobehavioural performance measured through a battery of standard tests adapted from the WHO Neurobehavioural Core Test Battery and exploring various major neurobehavioural registers such as motor skills, executive functions, cognition and emotions. The results of the eight positive tests in these studies are sufficient to identify a health effect with which to establish a BLV, namely a significant decrease in performance.

The study by Schwartz *et al.* (2005) shows statistically significant effects (decline in performance) with eight positive tests out of the 11 conducted, corresponding to the transition from the 25th to the 75th percentile. The value of 210 $\mu\text{g.L}^{-1}$ corresponds to the 25th percentile. Accordingly, the absence of effect is not demonstrated for a blood lead level of 210 $\mu\text{g.L}^{-1}$ (25th percentile), which results in this value being considered as a LOAEL. In a previous study (Schwartz *et al.* 2001), the authors mentioned a threshold value for blood lead levels (180 $\mu\text{g.L}^{-1}$) corresponding to a NOAEL was determined graphically (by the authors), as the value below which the effects of lead on certain tests do not seem to be observed.

Kidney effects

In the general population, chronic renal failure was the critical effect selected in ANSES's opinion (ANSES 2013) (blood lead levels below 15 $\mu\text{g.L}^{-1}$). In occupational populations, many studies have examined the potential kidney effects of lead. For the purposes of this report, the studied parameters were divided into three categories: indicators of clinical diagnosis, early indicators of glomerular impairment and early indicators of tubular impairment (proximal and distal). Although their use for diagnostic purposes is tending to grow, especially for screening for nephrotoxicity potentially induced by new drugs, the clinical significance of the early indicators has still not been clearly established (Xie *et al.*, 2013).

In conclusion, it would seem from the identified studies that lead exposure in workers has no measurable effect on renal function or on the early indicators of glomerular effects. The effects on the renal proximal tubules are not consistent as a whole. Although a NOAEL of 150 $\mu\text{g.L}^{-1}$ has been determined for these effects from data on urinary α_1 -microglobulin, this effect cannot be regarded as harmful ("adverse"). In accordance with the methodology of the OEL Committee, all the studies included in this section were carried out in an occupational environment. As they are spread out over time, the "non-exposed" groups in these studies have blood lead levels above the threshold of 15 $\mu\text{g.L}^{-1}$ mentioned at the beginning of this section and which aims to protect the general population

from chronic kidney disease. It is therefore impossible to verify the impact of occupational exposure possibly occurring around this low value from the data in this literature. Nevertheless, if there is a causal relationship between occupational exposure to lead measured by the blood lead levels and chronic kidney disease, one would expect to find a dose-effect and dose-response relationship between blood lead levels and the various indicators of kidney damage described here. However, neither the indicators of clinical diagnosis nor the early indicators of glomerular effects clearly show such an effect, even at blood lead levels several tens of times higher than the threshold of $15 \mu\text{g.L}^{-1}$. Only one early indicator of tubular effects, urinary $\alpha 1$ -microglobulin, suggests a slight effect on the renal tubule at 10 times the threshold of $15 \mu\text{g.L}^{-1}$, whereas the other recognised early indicators of tubular effects show no clear signs of tubular impairment.

Effects on male fertility

Over the last 20 years, many cross-sectional studies have shown associations between occupational exposure to lead and sperm abnormalities (decline in sperm count in particular). These observations are in agreement with the animal data. However, the results are sometimes contradictory and these studies may have methodological limitations (in particular selection bias, variability of the semen analysis and the multitude of factors to be taken into account). The European study by Bonde *et al.* (2002) helped identify a limit to the blood lead level below which the decline in sperm count is unlikely, at about $450 \mu\text{g.L}^{-1}$. This concentration can be considered as a NOAEL.

Effects on female fertility

As the studies were conducted in primarily male work environments, there are insufficient data for assessing the associations between exposure to lead and female fertility. The most recent studies (for lower exposures) do not show significant results.

Snijder *et al.* (2012), in a review of the literature on the impact of occupational exposure on the time needed to conceive, in which two of the studies were conducted in women, did not show any statistically significant effects below the current BLV of $300 \mu\text{g.L}^{-1}$.

Effects on development

Some studies analysed in this collective expert appraisal report quantified the relationship between the level of lead (in maternal or cord blood) and parameters of foetal growth in populations of mothers subjected to low levels of lead exposure. Significant relationships were observed in particular with birth weight.

In conclusion, the analysis of these studies seems to suggest that lead induces reprotoxic effects (intra-uterine growth retardation, low birth weight, risk of spontaneous abortion and delayed post-natal development) at blood lead levels below $100 \mu\text{g.L}^{-1}$.

Cardiovascular effects and effects on blood pressure in pregnant women

The report by the US EPA (2006) identified a number of studies conducted on occupational populations, including Glenn *et al.* (2003), Schwartz *et al.* (2000), Sokas *et al.* (1997), Tepper *et al.* (2001), Maheswaran *et al.* (1993), Telişman *et al.* (2004), Lee *et al.* (2001), Lustberg *et al.* (2004), Nomiyama *et al.* (2002), Wu *et al.* (1996) and a meta-analysis by Nawrot *et al.* (2002).

According to the report by the US EPA (2006), in an occupational environment, there is an effect on the variation of blood pressure in workers exposed to lead, for blood lead levels below $400 \mu\text{g.L}^{-1}$. However, no increase in the risk of high blood pressure is observed at blood lead levels below the current BLV of $400 \mu\text{g.L}^{-1}$ and $300 \mu\text{g.L}^{-1}$ in women.

Concerning pregnant women, eight studies (four cross-sectional, three prospective and one case-control) focused on mean maternal blood lead levels (or cord blood levels for two studies) that were significantly lower than $100 \mu\text{g.L}^{-1}$. All show a relationship between higher blood lead levels and increased blood pressure during pregnancy, or even a risk of hypertension, with the exception of one highlighting a positive association with bone lead (and not blood). In conclusion, these studies show that there is an effect on the variation of blood pressure in pregnant women for blood lead levels below $100 \mu\text{g.L}^{-1}$. However, it is not possible to identify a threshold without effect.

Genotoxicity and carcinogenicity

The genotoxicity studies show that lead can be responsible for DNA damage and an increase in micronuclei levels. However, there does not appear to be any increase in levels of chromosomal aberrations during exposure to lead. Epidemiological studies carried out in an occupational environment suggest a relationship between lead and lung or stomach cancer, but the evidence is limited by the presence of various potential confounding factors (co-exposure to arsenic or cadmium, smoking and dietary habits). The National Toxicology Program (NTP, 2003 and 2004) and the International Agency for Research on Cancer (IARC, 2006) have concluded that lead compounds are probably carcinogenic (limited evidence in humans and sufficient indications in animals).

Effects on the immune system

The epidemiological studies suggest an association between exposure to lead and an effect on the immune system in workers, which appears for blood lead levels higher than the current BLV of 400 $\mu\text{g.L}^{-1}$.

Effects on the haematopoietic system

The epidemiological studies reported here on the possible associations between exposure to lead and an effect on the haematopoietic system do not report significant effects in workers for blood lead levels below the current BLV of 400 $\mu\text{g.L}^{-1}$. There are effects on ALAD and PPZ which are not significant in health terms.

Establishment of biological limit values and choice of biological reference values

Concerning the occupationally exposed subjects, the analysis of the health effects resulting from exposure to lead in the workplace showed a neurological effect highlighted by the neurobehavioural tests. The studies by Schwartz *et al.* (2001 and 2005) found a significant decrease in performance in the aptitude tests below 210 $\mu\text{g.L}^{-1}$. According to the authors, the blood lead level of 180 $\mu\text{g.L}^{-1}$ can be regarded as a no-effect threshold (NOAEL). As the BLV was established from an epidemiological study based on sensitive tests able to identify an early effect, the OEL Committee considered that no adjustment factor was necessary.

This value of 180 $\mu\text{g.L}^{-1}$ is adopted for establishing a BLV.

Although a NOEL of 150 $\mu\text{g.L}^{-1}$ was determined for the effects on the renal proximal tubules from data on urinary α_1 -microglobulin, this effect cannot be regarded as harmful ("adverse") and is not adopted for establishing a BLV.

Concerning pregnant women, studies show that there is an effect on the variation of blood pressure in women for blood lead levels below the current BLV (300 $\mu\text{g.L}^{-1}$), without a threshold for establishing a BLV being identified.

According to the report by the NTP (NTP, 2012), studies have shown that there is an association between maternal blood lead levels below 100 $\mu\text{g.L}^{-1}$ and reprotoxic effects (premature birth rate, stillbirth and low birth weight).

There also seems to be an association between the risk of both spontaneous abortion and delayed post-natal development for blood lead levels ranging between 50 $\mu\text{g.L}^{-1}$ and 100 $\mu\text{g.L}^{-1}$.

In conclusion, from the identified studies, it would seem that exposure to lead has an effect on reproduction and during pregnancy for blood lead levels below the current BLV of 300 $\mu\text{g.L}^{-1}$.

The French ENNS study, in the general population aged 18 - 74 years, is adopted for defining the biological reference values (distinction according to sex and age) (Fréry *et al.*, 2011). The blood lead levels, corresponding to the 95th percentile of the distributions in this study, are:

- 44 $\mu\text{g.L}^{-1}$ in women aged 18-39 years,

- 58 $\mu\text{g.L}^{-1}$ in women aged 40-59 years,
- 58 $\mu\text{g.L}^{-1}$ in all women (regardless of age)
- 85 $\mu\text{g.L}^{-1}$ in men.

The biological reference values adopted for blood lead levels are:

- 45 $\mu\text{g.L}^{-1}$ for women of childbearing age,
- 60 $\mu\text{g.L}^{-1}$ for women,
- 85 $\mu\text{g.L}^{-1}$ for men.

For women of childbearing age, the OEL Committee recommends not exceeding the BRV of 45 $\mu\text{g.L}^{-1}$ insofar as it is not possible to identify a precise threshold with no effect on reproduction.

Conclusions of the collective expert appraisal

The biological limit values (BLVs) and biological reference values (BRVs) proposed for monitoring exposure to inorganic lead are as follows:

Biological limit values - blood lead	
Based on the neurobehavioural effects (sampling time irrelevant)	180 $\mu\text{g.L}^{-1}$
Biological reference values - blood lead	
Men	85 $\mu\text{g.L}^{-1}$
Women	60 $\mu\text{g.L}^{-1}$
Women of childbearing age	45 $\mu\text{g.L}^{-1}$

The OEL Committee considers that the BLV does not ensure protection against the effects on reproduction. It should be noted that following the recommendations of the French High Council for Public Health, the health authorities in France decided, by Order dated 8 June 2015, to decrease from 100 to 50 $\mu\text{g.L}^{-1}$ the blood lead level threshold defining childhood lead poisoning (a notifiable disease). As a point of reference for the French population, the OEL Committee provides here a biological reference value of 45 $\mu\text{g.L}^{-1}$ corresponding to the 95th percentile of blood lead levels observed in women of childbearing age.

Sampling method and factors that may affect the interpretation of results

Blood lead exhibits multiphasic elimination kinetics because of blood exchanges with the different compartments and also according to the nature of the exposure (past chronic exposure, recent exposure, single exposure...).

Given the multiphasic kinetics, an isolated blood lead level measurement can represent both short-term and long-term exposure, depending on the profile and history of the exposure (US EPA, 2006). The half-life of lead in human blood is about 30 days, with large interindividual variations, and becomes longer with the duration of the exposure (INRS BIOTOX sheet 2015).

Sampling time: irrelevant

Determining blood lead levels requires a perfect sampling technique given the risk of sample contamination: sampling must be conducted outside the work premises, in subjects who have showered and are not wearing their work clothing.

The skin must be fully washed before sampling (non-coagulated, non-decanted total blood), which must be done using a vacuum extraction device into a tube guaranteed as lead-free (including the stopper), onto anticoagulant (EDTA or heparin).

The tube must be turned over slowly 7 to 8 times after sampling to ensure proper homogenisation and contact with the anticoagulant.

Samples can be kept for five days before transport at between +2 and +8°C, and should be delivered at the earliest opportunity to the Medical Biology Laboratory (UCL, 2010).

Samples should preferably be transported at a temperature of between +2 and +8°C, but shipping at ambient temperature is nevertheless accepted by several French laboratories performing this analysis (INRS, 2012).

Biometrology

BLOOD LEAD					
Interlaboratory quality control		Institute and Out-patient Clinic for Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg (Germany): G-EQUAS National Institute of Public Health of Quebec, Toxicology Centre: PCI			
Analytical technique	Limit of Detection (LoD) Limit of Quantification	Reliability	Precision	Reference standard	Bibliographic reference
Electrothermal atomic absorption spectrometry (Oven-AAS)	LoD: 0.5 µg.L ⁻¹ (standard tubes) LoD: 0.1 µg.L ⁻¹ (graphite tubes)	Standard deviation = 0.5 µg.L ⁻¹ (between 5.9 and 50.7 µg.L ⁻¹)	NR		Fleischer (2012)
Inductively coupled plasma mass spectrometry (ICP-MS)	LoD: 1 µg.L ⁻¹ (5 nmol.L ⁻¹)	Intra-daily < 3% SD Inter-daily < 7% SD at 380 nmol.L ⁻¹	NR	NR	HSL (2013)

References

- ACGIH (ACGIH) (2016). Lead. (American Conference of Governmental Industrial Hygienists, Cincinnati).
- Agency for Toxic Substances and Disease Registry (ATSDR) (2007). Toxicological Profile for Lead. U.S. Department of Health and Human Services.
- ANSES (2013). Exposition au plomb : effets sur la santé associés à des plombémies inférieures à 100 µg/L. [Exposure to lead: health effects associated with blood lead levels below 100 µg/L] (French Agency for Food, Environmental and Occupational Health & Safety). 146 p
- ANSES (2014). Second French Total Diet Study (TDS 2).
- Bonde, J. P.; Joffe, M.; Apostoli, P.; Dale, A. Kiss, P.; Spano, M.; Caruso, F.; Giwercman, A.; Bisanti, L.; Porru, S.; Vanhoorne, M.; Comhaire, F.; Zschesche, W. (2002) Sperm count and chromatin structure in men exposed to inorganic lead: lowest adverse effect levels. *Occup. Environ. Med.* 59: 243-242.
- FIOH (2015). Biomonitoring of exposure to chemical. Guideline for specimen collection. Helsinki, Finland: Finnish Institute of Occupational Health Biomonitoring services. 44p.
- Fréry N, Saoudi A, Garnier R, et al. (2011). Exposition de la population française aux substances chimiques de l'environnement – Tome 1. (Institut de veille sanitaire: Saint-Maurice, France). 151 p.
- INRS. (2012). Plomb. In 'Base Biotox'. (Institut National de Recherche et de Sécurité: Paris, France). Available on website <http://www.inrs.fr/accueil/produits/bdd/biotox.html> consulted 26/04/2016.
- Inserm. (1999). Plomb dans l'environnement: quels risques pour la santé ? Rapport. Paris : les éditions Inserm, 1999 XIV-461 p. (Expertise collective).
- NTP (2012). NTP monograph on health effects of low-level lead. (National Toxicology Program US. Department of Health and Human Services).
- Schwartz, B. S.; Lee, B. K.; Lee, G. S.; Stewart, W. F.; Lee, S. S.; Hwang, K. Y.; Ahn, K.-D.; Kim, Y.-B.; Bolla, K. I.; Simon, D.; Parsons, P. J.; Todd, A. C. (2001a) Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with neurobehavioral test scores in South Korean lead workers. *Am. J. Epidemiol.* 153: 453-464.
- Schwartz, B. S.; Lee, B.-K.; Bandeen-Roche, K.; Stewart, W.; Bolla, K. I.; Links, J.; et al. (2005) Occupational lead exposure and longitudinal decline in neurobehavioral test scores. *Epidemiology* 16: 106-113.
- UCL. (2010). Plomb: sang. In 'Monitoring biologique de l'exposition aux substances 6 industrielles'. (UCL, Unité de Toxicologie Industrielle et de Médecine du Travail: Brussels, 7 Belgium). Available on website http://www.toxi.ucl.ac.be/documents/pb_sg.htm consulted 26/04/2016.
- US EPA (2006). Air quality criteria for lead. National Center Environmental Assessment-RTP Division Office of Research and Development. (U.S. Environmental Protection, Agency, Research Triangle Park, NC).
- Vyskocil, A., Smejkalova, J., Tejral, J., Emminger, S., Vincentova, M., Ettlerova, E., Lauwerys R., Bernard A. (1992). Lack of renal changes in stainless steel welders exposed to chromium and nickel. *Scand. J of Work, Enviro. and health* 18:252-256