The Director General

Maisons-Alfort, 23 January 2013

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

on the health effects of blood lead levels below 100 µg/L

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

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

Its opinions are made public. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 23 January 2013 shall prevail.

On 26 July 2011, ANSES received a request by the Directorate General of Health and the Directorate General for Risk Prevention (Ministry of the Environment) to investigate exposure to lead.

1. BACKGROUND AND PURPOSE OF THE REQUEST

The report entitled “Lead in Food”, published in April 2010 by the European Food Safety Authority (EFSA), mentions developmental neurotoxic effects in children as well as cardiovascular and kidney effects, associated with blood lead levels below 100 µg/L.
These data raise questions about the scientific basis for the threshold currently applied to treat children (blood lead levels above 100 µg/L) and about the public health measures that need to be taken to limit exposure of the general population to lead.

The Request concerned the following three questions:

1 – Do the studies suggesting that blood lead levels below 100 µg/L can have harmful effects provide a sufficiently robust scientific basis to justify taking specific risk-management measures?

2 – Have these questions been raised in other EU countries? If so, what measures and technical actions have been taken to bring blood lead levels below 100 µg/L?

3 – Is it possible to establish one or more critical doses on which to base the management of *moderate* blood lead levels[1], and if so, for which population group and concerning which effects? The study will exclude the population of workers exposed to lead.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

The Agency entrusted examination of Request No. 2011-SA-0219 "Request for an Opinion on exposure to lead" to the Expert Committee (CES) on Assessment of the risks related to chemical substances. The CES mandated the Working Group on "Toxicity reference values 1" (VTR 1) to carry out the assessment. An initial collective expert report on the first phase of the work (Questions 1 and 2) was validated by the CES on 19 January 2012.

Membership of the VTR Working Group was then renewed and the new WG (VTR 2) was formed on 25 October 2011. The VTR 2 Working Group was then mandated to address the third question.

The experts examined the plausibility of the effects of *moderate* blood lead levels taking especially into account the effects on the central nervous system, the kidneys, the cardiovascular system, the reproductive system and the immune system. For this purpose, it mainly leant on EFSA's "Lead in Food" report (2010), on the "Human Health State of the Science Report on Lead" report by Health Canada (2011), and also the report of the US National Toxicology Program (NTP, 2012).

The work of the VTR 2 Working Group was submitted at regular intervals to the CES. This report completes and replaces the interim report on the health effects associated with blood lead levels below 100 µg/L.

The work for the report gave rise to a collective expert appraisal memorandum that was adopted by the CES on Assessment of the risks related to chemical substances on 25 October 2012.

It should be noted that two experts in the VTR WG expressed divergent opinions on the expert report. Their positions are laid out in the "Divergent Positions" section of the report.

3. ANALYSIS AND CONCLUSIONS OF THE CES

The answers to the questions asked by the Directorate General for Health and the Directorate general for Risk Prevention expressed in the official Request are given below:

> 1 – Do the studies suggesting that blood lead levels below 100 µg/L can have harmful effects provide a sufficiently robust scientific basis to justify taking specific risk-management measures?

An analysis of the epidemiological data describing associations between blood lead levels and various health effects was carried out, on the basis of the source studies, meta-

[1] Moderate lead levels: blood levels of lead below the regulatory threshold of 100 µg/L.

analyses, analysis of pooled published data and recent expert assessments from international (EFSA) and national organisations (Health Canada and the NTP). The expert collective concluded that the studies showing the effects of lead on blood pressure and kidney functions in adults and those showing an adverse effect on the central nervous system (measured by a decrease in IQ) in children, provide a sufficiently robust scientific basis for concluding that lead can have adverse effects at blood levels below 100 µg/L. These conclusions concur with those expressed by the other international and national organisations mentioned above that have recently assessed the effects of lead.

> 2 – Have these questions been raised in other EU countries? If so, what measures and technical actions have been taken to bring blood lead levels below 100 µg/L?

In January 2012, ANSES consulted the Member States of the European Union (EU), the Accession Candidate Countries and the countries belonging to the European Free Trade Association (EFTA) on the "measures and technical actions" taken to bring blood lead levels below 100 µg/L. Ten countries responded, none of which reported having taken any specific measures.

> 3 – Is it possible to establish one or more critical doses on which to base the management of *moderate* blood lead levels, and if so, for which population group and concerning which effects?

The expert collective considered that the most sensitive and conclusive effects related to chronic exposure to lead are chronic kidney disease[2] in adults, and neurotoxicity in young children.

Based on the study by Lanphear *et al.* (2005), EFSA established a critical blood lead level for children of 12 µg/L, this level being associated with a drop of one point of Intellectual Quotient (IQ) in a population. On the basis of the available information and the additional hearings held by the Working Group on the significance that may be attributed to a reduction of one point of IQ, the experts considered that:

- IQ tests were not developed for the purpose of assessing the neurotoxicity of chemicals,
- the determination of IQ is subject to wide intra- and inter-individual variations as well as variations in test conditions,
- a drop of one point of IQ may be statistically significant across an entire population but is not significant at individual level,
- due to the lack of data and to analytical limitations, it is difficult to correlate IQ with blood lead levels below 10 µg/L.

The expert group considered that a reduction of one point of IQ cannot be used for a quantitative assessment of the health risk.

The expert group also considered that a blood lead level established with kidney effects in adults as the critical effect would protect the entire population, including children, against all the adverse effects of lead identified to date.

The study by Navas-Acien *et al*. (2009) of the NHANES 1999–2006 survey was chosen as the key study for defining kidney toxicity of lead and for establishing critical blood lead levels ($BMD_{10\%}$ and $BMD_{10\%}L_{95\%}$). This study, on 14,778 subjects over the age of 20,

[2] "Chronic kidney disease is defined as a glomerular filtration rate of less than 60 mL/1.73 m^2 of body surface area/min for more than 3 months." *Evaluation de la fonction rénale et de la protéinurie pour le diagnostic de la maladie rénale chronique chez l'adulte* [Evaluation of glomerular filtration rate and proteinuria for the diagnosis of chronic kidney disease]. Nephrol Ther 2009; 5:302-305.

showed associations between blood levels of lead and reduction in glomerular filtration rate.
On the basis of this study, EFSA modelled the relationship between lead levels and the prevalence of chronic kidney disease (defined by the persistence for longer than 3 months of a glomerular filtration rate of less than 60 mL/min/1.73 m^2 of body surface area). A critical blood lead level of **15 µg/L** was determined (the value associated with an increase of 10% in the prevalence of chronic kidney disease). This value can be considered as protecting against effects on the central nervous system in children.

No kidney effect was observed in children (under the age of 12) for blood lead levels below 50 µg/L (NTP, 2012). Kidney effects observed in adults may be consecutive to lifetime exposure (since childhood). Consequently, nephrotoxicity was selected as the critical effect for the entire population irrespective of age.

Levels of atmospheric and oral exposure to lead can be estimated in children up to the age of 7, using the Integrated Exposure Uptake Biokinetic[3] (IEUBK) model developed by the US EPA (US EPA, 1994), and in adults using the equation of Carlisle and Wade[4].
In children, for example, daily exposure by the oral route (assuming negligible exposure by contact with soil) of 0.63 µg of lead per kilo of body weight per day would result in a blood lead level of 15 µg/L.

[3] http://www.epa.gov/superfund/lead/products.htm#ieubk. Integrated Exposure Uptake Biokinetic Model for Lead in Children, Windows® version (IEUBKwin v1.1 build 11) **(**February, 2010) 32-bit version
[4] Lead level (µg/L) = [dietary exposure (µg/kg/day) x weight x 0.4] + [concentration in soil and dust (mg/kg) x 0.025 x 0.18] + [atmospheric concentration (µg/m^3) x 16.4].

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of the CES on Assessment of the risks related to chemical substances, on the health effects of lead associated with blood lead levels below 100 µg/L.

The Agency emphasises that:

- in France, 50% of children in the 1 to 6 age range and 75% of adults in the 18 to 74 age range present blood lead levels in excess of 15 µg/L (see the survey *Imprégnation des enfants par le plomb en France en 2008-2009*, Etchevers *et al*. 2010, and the National Nutrition & Health Study discussed in Fréry *et al.*, 2011);

- dietary exposure (foodstuffs and drinking water) is the principal route of exposure to lead. According to the "Total Diet Study 2" (TDS 2) (ANSES 2011), mean dietary exposure to lead of the French population is estimated at 0.20 µg/kg bw/day in adults and 0.27 µg/kg bw/day in children. At the 95th percentile, exposure is estimated at 0.35 µg/kg bw/day in adults and at 0.57 µg/kg bw/day in children.

Domestic dust and soil contaminated by lead are also an important source of exposure in children.

The Agency also recommends:

- in view of the new data available, reviewing all the reference values based on blood lead levels, including those applicable in occupational environments,

- continuing with efforts to reduce the exposure of the population to lead,

- continuing biomonitoring studies in order to monitor blood lead levels for the entire population.

The Director General

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KEY WORDS

Lead, IQ, neurotoxicity, nephrotoxicity, cardiotoxicity, toxicity reference values, critical dose, uncertainty factors, health effects, general population, children

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