SCIENTIFIC OPINION

Scientific Opinion on Lead in Food[1]

EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Lead is an environmental contaminant that occurs naturally and, to a greater extent, from anthropogenic activities such as mining and smelting and battery manufacturing. Lead is a metal that occurs in organic and inorganic forms; the latter predominates in the environment. Control measures have been taken to regulate lead in paint, petrol, food cans and pipes in Europe since the 1970s. Human exposure to lead can occur via food, water, air, soil and dust. Food is the major source of exposure to lead. The primary techniques for analysing lead in food samples are based on atomic absorption spectrometry, atomic emission spectrometry and mass spectrometry after digestion of organic material with concentrated acids.

Following a call for data, 14 Member States and Norway submitted approximately 140,000 results of lead concentrations in various food commodities and tap water. A total of 94,126 results covered the period from 2003 to 2009 and were suitable for calculating lead concentrations in the various food categories. The lead level in approximately two thirds of the samples was below the limit of detection or limit of quantification. Sampling adjustment factors were applied when aggregating food sub-category averages to category averages in order to fit the information structure of the European Food Safety Authority (EFSA) Concise European Food Consumption Database.

Mean and 95th percentile lead dietary exposures were calculated separately for each country recorded in EFSA Concise European Food Consumption Database for the whole and subgroups of the population, including infants, children and vegetarians, using a deterministic approach. The Panel on Contaminants in the Food Chain (CONTAM Panel) also performed a probabilistic exposure

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assessment using lower bound and upper bound values for the non-quantifiable samples. This approach resulted in similar exposure values for average consumers as the deterministic approach. To maintain consistency with its opinions on other heavy metals, the CONTAM Panel therefore decided to use the deterministic approach for its assessment of dietary exposure to lead. Lead dietary exposure for average adult consumers in 19 European countries ranged from 0.36 to 1.24 µg/kg body weight (b.w.) per day (lower bound for country with lowest average exposure – upper bound for country with highest average exposure) and from 0.73 to 2.43 µg/kg b.w. per day for high consumers, respectively. Overall, cereals, vegetables and tap water were the most important contributors to lead exposure in the general European population. More specifically, the following food groups were identified as the major contributors to lead exposure: cereal products, followed by potatoes, cereal grains (except rice), cereal-based mixed dishes and leafy vegetables and tap water. Considerable variation between and within countries in the contribution of different food categories/groups exists.

The available evidence for women of child-bearing age and vegetarians does not indicate a dietary exposure that is different from that of the general adult population. Lead levels in breast milk are highly variable but exposure of infants is estimated to be 0.21 µg/kg b.w. per day on average or 0.32 µg/kg b.w. per day for high consumers. For infants fed with ready-to-consume infant formula, the average exposure estimates range from 0.27 to 0.63 µg/kg b.w. per day, based on lower bound and upper bound assumptions, respectively; for high consumers, lead exposure estimates range from 0.40 to 0.94 µg/kg b.w. per day. For children aged 1-3 years mean lead dietary exposure estimates range from 1.10 to 3.10 µg/kg b.w. per day based on lower bound and upper bound assumptions, respectively; for high consumers, lead exposure estimates range from 1.71 to 5.51 µg/kg b.w. per day. For children aged 4-7 years mean lead dietary exposure estimates range from 0.80 to 2.61 µg/kg b.w. per day based on lower bound and upper bound assumptions, respectively; for high consumers, lead exposure estimates range from 1.30 to 4.83 µg/kg b.w. per day.

Compared to dietary exposure, non-dietary exposure to lead is likely to be of minor importance for the general population in the European Union (EU). House dust and soil can be an important source of exposure to lead for children.

Absorption of lead from the gastrointestinal tract depends on host characteristics and on the physicochemical properties of the ingested material. Absorption of ingested soluble lead compounds appears to be higher in children than in adults. Absorption is lower in the presence of food. Absorption of inhaled sub-micron sized particles occurs in the respiratory tissues whereas larger-sized particles are transferred into the pharynx and are then swallowed. Absorbed lead is transported in the blood primarily within erythrocytes and then transferred to soft tissues, including liver and kidneys, and to bone tissue, where it accumulates with age. Maternal transfer of lead occurs through the placenta and subsequently during breast feeding. Enhanced mobilisation of lead from bones occurs during pregnancy. Half-lives for inorganic lead in blood and bone are approximately 30 days and between 10 and 30 years, respectively, and excretion primarily is in urine and faeces.

Most of the information on human exposure to, and the health effects of, lead is based on blood lead (B-Pb) data. Lead levels in bone and teeth provide information on past exposure to lead.

Due to its long half-life in the body, chronic toxicity of lead is of most concern when considering the potential risk to human health. Studies with rodent and non-human primate models have demonstrated that chronic low-level exposure to lead causes neurotoxicity, particularly learning deficits in the developing animal. Evidence, albeit limited, for lead-induced increases in blood pressure and nephrotoxicity in experimental animals has been reported. Lead may be a weak indirect genotoxic metal. There is extensive experimental evidence that at high doses lead can induce tumours at a number of different sites in rodents. The International Agency for Research on Cancer classified inorganic lead as probably carcinogenic to humans (Group 2A) in 2006.

In humans, the central nervous system is the main target organ for lead toxicity. In adults, lead-associated neurotoxicity was found to affect central information processing, especially for visuospatial

organisation and short-term verbal memory, to cause psychiatric symptoms and to impair manual dexterity. There is considerable evidence demonstrating that the developing brain is more vulnerable to the neurotoxicity of lead than the mature brain. In children, an elevated blood lead level is inversely associated with a reduced Intelligence Quotient (IQ) score and reduced cognitive functions up to at least seven years of age. There is some evidence that this subsequently leads to a reduced adult grey matter volume, especially of the prefrontal cortex. The dose-effect relationship between blood lead levels and IQ indicates a nonlinear curve that reflects a greater relative impact at lower lead concentrations. A number of studies in adults have identified an association between blood lead concentration, elevated systolic blood pressure (SBP) and chronic kidney disease (CKD), at relatively low B-Pb levels.

Lead in blood is considered to be the best indicator of the concentration of lead in soft tissues, reflecting recent and, to some extent, past exposure, whereas bone lead in vivo reflects the long-term uptake and body burden. A non-specific biomarker for lead exposure is the inhibition of haem metabolism.

The CONTAM Panel identified developmental neurotoxicity in young children and cardiovascular effects and nephrotoxicity in adults as potential critical adverse effects of lead on which to base the risk assessment. Full Scale IQ) score (was chosen as the most sensitive and most relevant endpoint for children. Dose-response analysis of cardiovascular effects identified blood pressure as the most sensitive endpoint, and SBP was the preferred critical endpoint. Nephrotoxicity was analysed for the prevalence of CKD based on a reduction in the glomerular filtration rate (GFR) to values below 60 mL/min. Dose metrics available in published studies were B-Pb concentration measured both concurrently with the examination for health effect and in early childhood, as average or as peak concentration over the lifetime, in units of µg lead per litre (L) blood. When available the CONTAM Panel used also tibia bone concentration measured concurrently or in the past in units of µg lead/g bone mass.

Using the complete individual data from the seven studies described by Lanphear et al. (2005) the CONTAM Panel determined the 95th percentile lower confidence limit of the benchmark dose (BMD) of 1 % extra risk ($BMDL_{01}$) of 12 µg B-Pb/L as a reference point for the risk characterisation of lead when assessing the risk of intellectual deficits in children measured by the Full Scale IQ score. A 1 % increase of SBP annually or on average in the whole population was considered a public health issue, since it would result in an increased risk of cardiovascular morbidity and coronary heart disease (CHD) mortality in a population. Assuming an average SBP of 120 mmHg and critical Benchmark Response level of 1 %, the dose associated with an increase of SBP by 1.2 mmHg, then this corresponds to a BMD_{01}. BMD and $BMDL_{01}$ values were based on the slope estimates derived from the five selected studies on blood and tibia bone lead concentration. Longitudinal data allowed the calculation of a BMD_{01} for the mean annual increase of SBP by 1 % in an individual, whereas cross-sectional data allowed only calculation of the BMD_{01} on a population-based increase of the means. The CONTAM Panel determined four $BMDL_{01}$ values for SBP ranging from 15 to 71 µg/L (longitudinal 27 and 71 µg/L, cross-sectional studies 15 and 21 µg/L). Given the strong overlap of the study results and the absence of any obvious design deficiencies in the studies, the CONTAM Panel calculated a mean $BMDL_{01}$ for SBP of 36 µg/L from the four studies and a $BMDL_{01}$ = 8 µg/g for tibia bone lead concentrations. For CKD, no model was acceptable when using the criterion that the fitted model should not be significantly different from a statistical point-of-view from the full model at a p-value not smaller than 0.10. Considering the high precision of the incidence rates due to the large sample size using the cross-sectional data from the National Health and Nutrition Examination Survey (1999-2006) that criterion was reduced to a value of 0.01. Two models gave an acceptable fit: the probit model and the multistage model gave the same values, i.e. BMD10= 16 µg/L and $BMDL_{10}$=15 µg/L, respectively.

The relationship between dietary lead intake and blood lead levels in adults was estimated using the Carlisle and Wade (1992) model that takes into account dietary lead and lead from soil, dust and air, although in adults it was concluded that direct exposure via soil and dust is negligible. Using this

model, BMDL dietary lead intake values in adults of 1.50 µg/kg b.w. per day and 0.63 µg/kg b.w. per day were derived for the cardiovascular and kidney effects, respectively. The relationship between dietary lead intake and blood lead levels in children up to age seven was estimated using the Integrated Exposure Uptake Biokinetic (IEUBK) model for lead in children. Using the IEUBK model, a $BMDL_{01}$ dietary intake value of 0.50 µg/kg b.w. per day for developmental neurotoxicity was derived.

The CONTAM Panel concluded that the provisional tolerable weekly intake (PTWI) of 25 µg/kg b.w. set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and endorsed by the Scientific Committee of Food is no longer appropriate and that as there was no evidence for a threshold for a number of critical endpoints including developmental neurotoxicity and nephrotoxicity in adults, it would not be appropriate to derive a PTWI. The CONTAM Panel does consider it appropriate to calculate margins of exposure to support the risk characterisation.

Estimates of dietary exposure to lead based on lower bound assumptions and upper bound assumptions for the level of reporting for average adult consumers in Europe are lower than the BMDL intake value for effects on SBP (1.50 µg/kg b.w. per day), but vary from above to below the BMDL intake value for effects on the prevalence of CKD (0.63 µg/kg b.w. per day). The respective MOEs range from 1.2 to 4.2 and from 0.51 to 1.81, respectively. Hence, if exposure were closer to the upper bound estimates, the possibility of an effect on some consumers cannot be excluded.

The limited available evidence does not indicate a different average dietary exposure or risk for vegetarians from the adult population, consumer groups with higher lead exposure levels include high consumers of game meat (1.98 to 2.44 µg/kg b.w. per day) and high consumers of game offal (0.81 to 1.27 µg/kg b.w. per day). The estimated dietary exposures of these groups are also within, or at the higher end of the range of the respective BMDL intake values.

Breast-fed 3-month old infants are predicted to have a lead exposure that is below the $BMDL_{01}$ intake value of 0.50 µg/kg b.w. per day for neurodevelopmental effects. Lead exposure based on lower bound assumptions in both average and high 3-month old infant consumers of infant formula is below the $BMDL_{01}$, but may exceed this level, based on upper bound estimates. Therefore, the possibility of a risk to infants cannot be excluded.

Estimated exposure in children up to age seven exceeds the $BMDL_{01}$ intake level of 0.50 µg/kg b.w. per day for neurodevelopmental effects. The MOE in average 1 to 3 year old child consumers ranged from 0.16 to 0.45, and was only slightly higher in 4 to 7 year old children. Therefore, the MOE is such that the possibility of an effect in some children cannot be excluded. It was not possible to estimate the potential numbers of children who might be affected, as even in average consumers the MOE was <1.

Women of 20 to 40 years of age were used as a surrogate for pregnant women to calculate the risk of lead exposure in utero on neurodevelopment in the offspring. Estimates of exposure were at or above the BMDL for neurodevelopmental effects, and the CONTAM Panel concluded that it was not possible to exclude a risk to the developing fetus through exposure of some pregnant female consumers.

The CONTAM Panel concluded that the risk of clinically important effects on either the cardiovascular system or kidneys of adult consumers, at current levels of lead exposure is low to negligible. In infants, children and pregnant women, there is potential concern at current levels of exposure to lead for effects on neurodevelopment. Protection of children and women of child-bearing age against the potential risk of neurodevelopmental effects should be protective for all other adverse effects of lead, in all populations.

KEY WORDS

lead, occurrence, dietary exposure, food consumption, risk assessment, adults, children, margin of exposure