The EFSA scientific opinion on lead in food

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Vice-Chair of the EFSA Panel on Contaminants in the Food Chain (CONTAM)

Lead Ammunition Group Meeting, 29 September 2010
• FSA position prior to the EFSA opinion

• The EFSA opinion of March 2010

• The June 2010 evaluation of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)
Prior to the EFSA opinion

- JECFA Provisional Tolerable Weekly Intake (PTWI) of 25 µg/kg b.w.
- Originally set in 1986
- Level of exposure from all sources not expected to cause an increase in blood lead in young children
- Based on blood lead levels of UK infants at birth in early 1980s
- PTWI was endorsed by the EU Scientific Committee on Food (SCF) in 1990.
COT

- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
- Independent scientific advisory committee
- Provides advice to UK government departments
COT opinion on lead

• Not possible to identify a threshold identified for lead-associated intellectual deficits

• JECFA PTWI cannot be considered fully protective

• Efforts should continue to reduce lead exposure from all sources
EFSA

- European Food Safety Authority
- Established 2002
- To provide objective and independent scientific advice
- Scientific committee and 10 scientific panels
- Foundation for European policies and legislation
SCIENTIFIC OPINION

Scientific Opinion on Lead in Food

EFSA Panel on Contaminants in the Food Chain (CONTAM)

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Lead occurs primarily in the inorganic form in the environment. Human exposure is mainly via food and water, with some via air, dust and soil. In average adult consumers, lead dietary exposure ranges from 0.36 to 1.24, up to 2.43 μg/kg body weight (b.w.) per day in high consumers in Europe. Exposure of infants ranges from 0.21 to 0.94 μg/kg b.w. per day and in children from 0.80 to 3.10 (average consumers), up to 5.51 (high consumers) μg/kg b.w. per day. Cereal products contribute most to dietary lead exposure, while dust and soil can be important non-dietary sources in children. Lead is absorbed more in children than in adults and accumulates in soft tissues and, over time, in bones. Half-lives of lead in blood and bone are approximately 30 days and 10-30 years, respectively, and excretion is primarily in urine and faeces. The Panel on Contaminants in the Food Chain (CONTAM Panel) identified developmental neurotoxicity in young children and cardiovascular effects and nephrotoxicity in adults as the critical effects for the risk assessment. The respective BMDLs derived from blood lead levels in μg/L (corresponding dietary intake values in μg/kg b.w. per day) were: developmental neurotoxicity BMDLs, 12 (0.50); effects on systolic blood pressure BMDLs, 36 (1.50); effects on prevalence
Request from the Commission

• “a scientific opinion on the risks to human health related to the presence of lead in foodstuffs”
• Any new developments regarding the toxicity of lead since the SCF opinion of 1992
• Assess whether the PTWI of 25 µg/kg b.w. is still appropriate
• Updated exposure assessment, addressing exposure from food (incl. drinking water) and non-dietary sources
• Exposure for specific population groups (e.g. infants, children, people following specific diets)
• Indication of age group in which children would be most exposure
Overall database on lead toxicity

• Large amount of data on dose-response relationships in humans from occupationally exposed groups and the general population

• Studies in experimental animals generally support human data regarding effects and mode of action
Effects of lead

– Neurodevelopmental effects,
– Cardiovascular effects
– Nephrotoxicity
– Genotoxicity
– Carcinogenicity
– Endocrine effects
– Gastrointestinal effects
– Haematological effects
– Musculoskeletal effects
– Reproductive effects
– Developmental effects
Genotoxicity and carcinogenicity

- “there is sufficient evidence in experimental animals for the carcinogenicity of lead compounds”
- “there is limited evidence in humans for the carcinogenicity of lead compounds” (IARC 2006).
- “Lead may be a weak indirect genotoxin”
- Human exposure to lead through food is unlikely to represent a significant cancer risk
Neurodevelopmental effects

- Critical endpoint is decrease in full scale Intelligence Quotient (IQ) in children at ages 4 and higher, reflecting impaired cognitive ability
- Pooled analysis of Lanphear et al. (2005)
  - Association between IQ scores and blood lead (B-Pb) in 1333 children taken from seven studies published between 1989 and 2003.
  - Children aged 4 – 7 years in six cohorts and 5 - 10 years in one cohort
  - B-Pb measured as concurrent (i.e. closest to IQ testing), peak B-Pb level at any time, average lifetime, and early childhood
  - Adjusted for home environment, child’s birth weight; maternal education and maternal IQ
- Studies published since 2005 support the conclusions
Lanphear et al. (2005)

Figure 1. Restricted cubic splines and log-linear model for concurrent blood lead concentration. The dotted lines are the 95% CIs for the restricted cubic splines.

Figure 3. Log-linear model (95% CIs shaded) for concurrent blood lead concentration, adjusted for HOME score, maternal education, maternal IQ, and birth weight. The mean IQ (95% CI) for the intervals < 5 µg/dL, 5–10 µg/dL, 10–15 µg/dL, 15–20 µg/dL, and > 20 µg/dL are shown.

Slope steeper at lower B-Pb
Not possible to identify a threshold
Benchmark dose (BMD)

- Reference point on the observed range of dose response curve
- Now preferred to no-observed-adverse-effect-level (NOAEL) risk characterisation as uses all of dose-response data
- Particularly valuable if NOAEL cannot be identified
- BMDL (lower 95% confidence limit of the BMD) takes into account uncertainty in the data related to quality of the study
Re-analysis conducted for EFSA

- BMD modelling of the raw data of Lanphear et al. (2005)
- Benchmark response (BMR) of loss of 1 IQ point
- Multiple regression models
- Adjustment for confounders (co-variates)
- Sensitivity analysis

- Budtz Jorgesen, 2010
Results of the reanalysis

<table>
<thead>
<tr>
<th>B-Pb concentration levels</th>
<th>logarithmic model</th>
<th>piecewise linear model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMD_{01} µg/L</td>
<td>BMDL_{01} µg/L</td>
</tr>
<tr>
<td>Concurrent lead</td>
<td>3.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Peak lead</td>
<td>3.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Life time lead</td>
<td>3.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Early childhood</td>
<td>5.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Subsample of n=583 children with B-Pb concentration &lt;100µg/L from the overlap region of the seven studies</td>
<td>7.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>
EFSA Conclusions on the BMDL

- Piecewise linear model preferred
- BMDL$_{01}$ of 12 µg/L B-Pb
- Decreased cognitive ability of 1 IQ point
- Impact on the socioeconomic status of a population
  - 4.5% increase in risk of failure to graduate from high school
  - Decrease of worker productivity of about 2%
Cardiovascular effects

- Increased systolic blood pressure (SBP) reported most frequently
- Identified 5 studies on dose response relationship between SBP and B-Pb or tibia bone Pb
- 1% annual increase in SBP in the whole population considered a health concern
  - 3.1% ↑ treatment for hypertension
  - 2.5% ↑ annual mortality from stroke or myocardial infarction
BMD modelling for cardiovascular effects

<table>
<thead>
<tr>
<th>Studies Selected</th>
<th>Slope of SBP per change in lead level</th>
<th>BMD$_{01}$</th>
<th>BMDL$_{01}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-Pb</strong></td>
<td>mmHg/µg/L (range)</td>
<td>µg/L</td>
<td>µg/L</td>
</tr>
<tr>
<td>Glenn et al. (2003) (longitudinal data)$^{(a)}$</td>
<td>0.025 (0.005-0.044)</td>
<td>48</td>
<td>29</td>
</tr>
<tr>
<td>Vupputuri et al. (2003) (cross-sectional data)$^{(b)}$</td>
<td>0.047 (0.014 - 0.08)</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Nash et al. (2003) (cross-sectional data)</td>
<td>0.032 (0.001- 0.0634)</td>
<td>38</td>
<td>21</td>
</tr>
<tr>
<td>Glenn et al. (2006) (longitudinal data)</td>
<td>0.009 (0.001 – 0.016)</td>
<td>133</td>
<td>78</td>
</tr>
<tr>
<td><strong>TB-Pb</strong></td>
<td>mmHg/µg/g TB (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng et al. (2001) (cross-sectional data)</td>
<td>0.10 (0.0015-0.20)</td>
<td>12</td>
<td>6.5</td>
</tr>
<tr>
<td>Glenn et al. (2003) (longitudinal data)</td>
<td>0.078 (0.024-0.13)</td>
<td>13</td>
<td>9.7</td>
</tr>
</tbody>
</table>
Results of the BMD modelling

• Average $\text{BMDL}_{0.1}$ of 36 $\mu$g/L for B-Pb (and 8.1 $\mu$g/g for TB-Pb)
Renal effects

- Chronic kidney disease (CKD) based on reduced glomerular filtration rate
- Data from USA, adjusted for wide range of confounders (Navas-Acien et al., 2009)
B-Pb vs CKD (Navas-Acien et al., 2009)

<table>
<thead>
<tr>
<th>B-Pb Quartiles µg/L</th>
<th>Median µg/L(n)</th>
<th>CKD Prevalence number of cases (%)</th>
<th>Odds ratio (95% CI) non-adjusted for cadmium</th>
<th>Adjusted for cadmium</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤11</td>
<td>8 (3242)</td>
<td>147 (4.5)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>11-16</td>
<td>13 (3167)</td>
<td>274 (8.7)</td>
<td>1.08 (0.79-1.47)</td>
<td>1.10 (0.80-1.51)</td>
</tr>
<tr>
<td>16-24</td>
<td>19 (3734)</td>
<td>468 (12.5)</td>
<td>1.25 (0.92-1.69)</td>
<td>1.36 (0.99-1.85)</td>
</tr>
<tr>
<td>&gt;24</td>
<td>32 (4635)</td>
<td>779 (16.8)</td>
<td>1.41 (1.07-1.86)</td>
<td>1.56 (1.17-2.08)</td>
</tr>
</tbody>
</table>

BMDL$_{10}$ of 15 µg/L was calculated
## Conversion of B-Pb to dietary exposure values

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Population</th>
<th>BMDL</th>
<th>Corresponding dietary Pb exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B-Pb (µg/L)</td>
<td>µg/kg b.w./day</td>
</tr>
<tr>
<td>Developmental neurotoxicity</td>
<td>Children</td>
<td>12</td>
<td>0.50</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Adults</td>
<td>15</td>
<td>0.63</td>
</tr>
<tr>
<td>Cardiovascular effects</td>
<td>Adults</td>
<td>36</td>
<td>1.50</td>
</tr>
</tbody>
</table>
Risk characterisation

- Could not establish PTWI since no evidence of a threshold
- Calculated margin of exposure (MOE)

\[
\frac{\text{BMDL}}{\text{Dietary exposure}}
\]
## Estimated MOEs for dietary exposure

<table>
<thead>
<tr>
<th>Population/Diet</th>
<th>Exposure Average/high (µg/kg bw/day)</th>
<th>End-point</th>
<th>MOE Average consumer</th>
<th>MOE High consumer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>0.36/2.43</td>
<td>SBP</td>
<td>1.21 - 4.17</td>
<td>0.62 - 2.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CKD</td>
<td>0.51 - 1.75</td>
<td>0.26 - 0.86</td>
</tr>
<tr>
<td>Vegetarians</td>
<td>0.46/2.24</td>
<td>SBP</td>
<td>1.20 - 3.26</td>
<td>0.67 - 1.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CKD</td>
<td>0.50 - 1.37</td>
<td>0.28 - 0.79</td>
</tr>
<tr>
<td>Specific diet (game meat)</td>
<td>1.98/2.44</td>
<td>SBP</td>
<td>0.76</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CKD</td>
<td>0.32</td>
<td>0.26</td>
</tr>
<tr>
<td>Infants 3 months breast milk</td>
<td>0.21/0.32</td>
<td>IQ</td>
<td>2.38</td>
<td>1.56</td>
</tr>
<tr>
<td>Infants 3 months formulae</td>
<td>0.27/0.94</td>
<td>IQ</td>
<td>0.79 - 1.85</td>
<td>0.53 - 1.25</td>
</tr>
<tr>
<td>Children 1-3 years</td>
<td>1.10/5.51</td>
<td>IQ</td>
<td>0.16 - 0.45</td>
<td>0.09 - 0.29</td>
</tr>
<tr>
<td>Children 4-7 years</td>
<td>0.8/4.83</td>
<td>IQ</td>
<td>0.19 - 0.63</td>
<td>0.10 - 0.38</td>
</tr>
<tr>
<td>In utero exposure</td>
<td>0.38/2.60</td>
<td>IQ</td>
<td>0.39 - 1.32</td>
<td>0.19 - 0.74</td>
</tr>
</tbody>
</table>
Non-dietary exposure

- Soil and dust (esp. young children)
- Outdoor air
- Smoking
- Environmental tobacco smoke
Key EFSA Conclusions

- Possibility of a risk to some adult consumers cannot be excluded
- Consumer groups with higher lead exposure levels include high consumers of game meat
- Possibility of a risk to children cannot be excluded
- Not possible to estimate the potential numbers of children who might be affected, as even in average consumers the MOE was < 1
- Not possible to exclude a risk to the developing fetus through exposure of some pregnant female consumers
- Work should continue to reduce exposure to lead, both from dietary and non-dietary sources
JECFA conclusions - 1

- Impaired neurodevelopment in children is generally associated with lower blood lead concentrations than the other effects.
- For adults, the adverse effect associated with lowest blood lead concentrations for which the weight of evidence is greatest and most consistent is a lead-associated increase in systolic blood pressure.
- Previously established PTWI of 25 µg/kg bw is associated with a decrease of at least 3 IQ points in children and an increase in SBP of approximately 3 mmHg. These changes are important when viewed as a shift in the distribution of IQ or blood pressure within a population. The Committee therefore concluded that the PTWI could no longer be considered health protective, and it was withdrawn.
JECFA conclusions - 2

- Not possible to establish a new PTWI that would be considered to be health protective

<table>
<thead>
<tr>
<th>Population group</th>
<th>Exposure (µg/kg bw per day)</th>
<th>Change in endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>0.3</td>
<td>↓ 0.5 IQ points</td>
</tr>
<tr>
<td>Children</td>
<td>1.9</td>
<td>↓ 3 IQ points</td>
</tr>
<tr>
<td>Adults</td>
<td>1.2</td>
<td>↑ SBP by 1mm Hg</td>
</tr>
<tr>
<td>Adults</td>
<td>3.0</td>
<td>↑ SBP by 2mm Hg</td>
</tr>
</tbody>
</table>
Overall conclusions

- Recent conclusions of EFSA and JECFA are similar, and consistent with view previously expressed by COT
- The PTWI for lead has been withdrawn because it is no longer considered health protective
- Effects in some subgroups, especially children, are possible at current exposure levels
- Efforts should continue to reduce exposure to lead