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# The EFSA scientific opinion on lead in food

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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

Committee on \_\_\_\_\_  
**TOXICITY**

# 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<sup>1</sup>

#### EFSA Panel on Contaminants in the Food Chain (CONTAM)<sup>2,3</sup>

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  $\mu\text{g}/\text{kg}$  body weight (b.w.) per day in high consumers in Europe. Exposure of infants ranges from 0.21 to 0.94  $\mu\text{g}/\text{kg}$  b.w. per day and in children from 0.80 to 3.10 (average consumers), up to 5.51 (high consumers)  $\mu\text{g}/\text{kg}$  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  $\mu\text{g}/\text{L}$  (corresponding dietary intake values in  $\mu\text{g}/\text{kg}$  b.w. per day) were: developmental neurotoxicity BMDL = 12 (0.50); effects on systolic blood pressure BMDL = 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  $\mu\text{g}/\text{kg}$  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

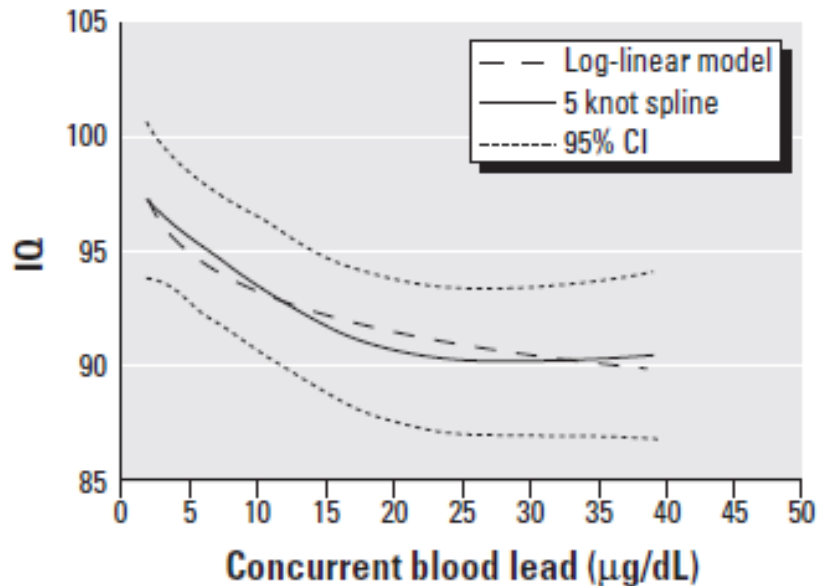
# Genotoxicity and carcinogenicity

- “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

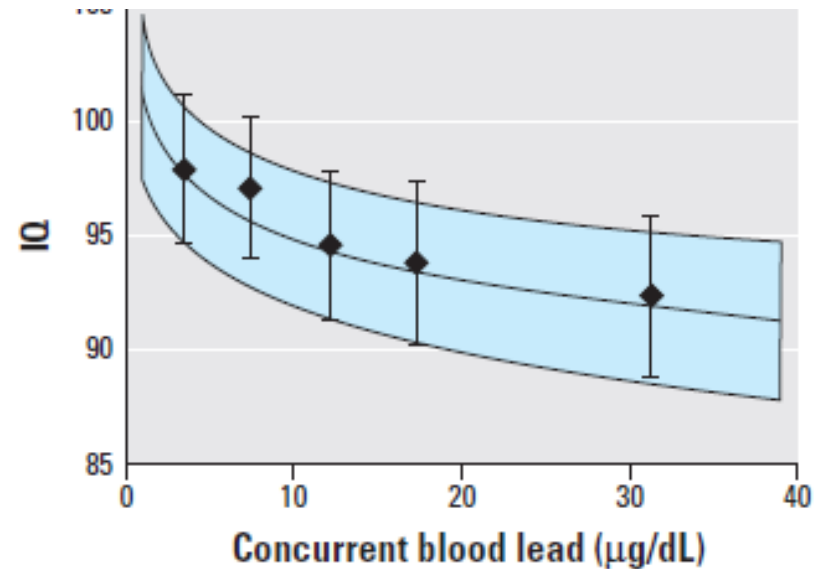
# Neurodevelopmental effects

- 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  $< 5 \mu\text{g/dL}$ ,  $5\text{--}10 \mu\text{g/dL}$ ,  $10\text{--}15 \mu\text{g/dL}$ ,  $15\text{--}20 \mu\text{g/dL}$ , and  $> 20 \mu\text{g/dL}$  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

| B-Pb concentration levels   | logarithmic model         |                            | piecewise linear model    |                            |
|---|---------------------------|----------------------------|---------------------------|----------------------------|
|   | BMD <sub>01</sub><br>µg/L | BMDL <sub>01</sub><br>µg/L | BMD <sub>01</sub><br>µg/L | BMLD <sub>01</sub><br>µg/L |
| Concurrent lead   | 3.5                       | 2.6                        | 18.0                      | 12.0                       |
| Peak lead   | 3.9                       | 2.7                        | 10.3                      | 6.9                        |
| Life time lead  | 3.6                       | 2.5                        | 14.8                      | 9.7                        |
| Early childhood   | 5.6                       | 3.4                        | 37.7                      | 16.1                       |
| Subsample of n=583 children with B-Pb concentration <100µg/L from the overlap region of the seven studies | 7.1                       | 2.1                        | -                         | -                          |

# EFSA Conclusions on the BMDL

- Piecewise linear model preferred
- BMDL<sub>01</sub> 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

| <b>Studies Selected</b>  | <b>Slope of SBP per change in lead level</b>   | <b>BMD<sub>01</sub></b>    | <b>BMDL<sub>01</sub></b>   |
|--|--|----------------------------|----------------------------|
| <b>B-Pb</b>  | <b>mmHg/<math>\mu</math>g/L (range)</b>        | <b><math>\mu</math>g/L</b> | <b><math>\mu</math>g/L</b> |
| Glenn et al. (2003)<br>(longitudinal data) <sup>(a)</sup>        | 0.025 (0.005-0.044)                            | 48                         | 29                         |
| Vupputuri et al. (2003)<br>(cross-sectional data) <sup>(b)</sup> | 0.047 (0.014 - 0.08)                           | 26                         | 16                         |
| Nash et al. (2003)<br>(cross-sectional data)                     | 0.032 (0.001- 0.0634)                          | 38                         | 21                         |
| Glenn et al. (2006)<br>(longitudinal data)                       | 0.009 (0.001 – 0.016)                          | 133                        | 78                         |
| <b>TB-Pb</b>   | <b>mmHg/<math>\mu</math>g/g TB<br/>(range)</b> |                            |                            |
| Cheng et al. (2001)<br>(cross-sectional data)                    | 0.10 (0.0015-0.20)                             | 12                         | 6.5                        |
| Glenn et al. (2003)<br>(longitudinal data)                       | 0.078 (0.024-0.13)                             | 13                         | 9.7                        |

# Results of the BMD modelling

- Average  $BMDL_{01}$  of 36  $\mu\text{g}/\text{L}$  for B-Pb (and 8.1  $\mu\text{g}/\text{g}$  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)

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

**BMDL<sub>10</sub> of 15 µg/L was calculated**

# Conversion of B-Pb to dietary exposure values

| Endpoint                    | Population | BMDL                     | Corresponding dietary Pb exposure |                          |
|-----------------------------|------------|--------------------------|-----------------------------------|--------------------------|
|                             |            | B-Pb ( $\mu\text{g/L}$ ) | $\mu\text{g/kg}$<br>b.w./day      | $\mu\text{g/person/day}$ |
| Developmental neurotoxicity | Children   | 12                       | 0.50                              | 10 (20kg)                |
| Nephrotoxicity              | Adults     | 15                       | 0.63                              | 37.5 (60kg)              |
| Cardiovascular effects      | Adults     | 36                       | 1.50                              | 90 (60kg)                |

# 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

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

# 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/73/SC



**Food and Agriculture Organization  
of the United Nations**



**World Health  
Organization**

**JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES**  
**Seventy-third meeting**  
**Geneva, 8–17 June 2010**

**SUMMARY AND CONCLUSIONS**  
*Issued 24 June 2010*

# 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  $\mu\text{g}/\text{kg}$  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

| Population group | Exposure ( $\mu\text{g}/\text{kg}$ bw per day) | Change in endpoint |
|------------------|--|--------------------|
| Children         | 0.3  | ↓ 0.5 IQ points    |
| Children         | 1.9  | ↓ 3 IQ points      |
| Adults           | 1.2  | ↑ SBP by 1mm Hg    |
| Adults           | 3.0  | ↑ SBP by 2mm Hg    |

# 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