EFSA scientific opinion on lead in food

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Trusted science for safe food

efsa
European Food Safety Authority

Occurrence of lead

- 94,126 analytical results (2003 to 2009) from food/tap water from 14 EU MS, Norway, 3 private entities used for assessment.
- 44% from Germany, 15% France, 10% Czech Republic/Romania
- 2/3 of samples < limit of detection (LOD)/limit of quantification (LOQ)
- Samples mainly on ‘Meat and meat products’ (20%), ‘Offal and offal products’ (20%), ‘Vegetables, nuts and pulses’ (12%), ‘Fish and fish products’ (7%) and ‘Cereals and cereal products’ (5%).

Occurrence of lead

- 2521 samples of ‘game meat’ (~ 60% < LOD) and 652 samples of ‘liver and kidney of game animals’ (25% < LOD)
- Mean UB content of ‘game meat’: 3.15 mg/kg, ‘liver and kidney of game animals’: 1.26 mg/kg
- High levels (> 0.1 mg/kg mean) in ‘Coffee, tea, cocoa’, ‘Meat and meat products and offal’, ‘Seafood and seafood products’ and ‘Miscellaneous/special dietary products’.
- 754 samples > 1 mg/kg, 106 > 10 mg/kg.
- These were mainly in ‘Game meat and offal’ and ‘Food supplements’ (maximum included in analysis was 867 mg/kg in wild boar muscle meat).
- One sample of wild boar meat (taken near entry of high velocity shot) had a content of 3 g/kg - excluded from assessment.

Food consumption data

- EFSA Concise European Food Consumption Database (now replaced by EFSA Comprehensive Consumption Database)
- Screening tool for exposure assessment
- Consumption data from 19 European countries, aggregated into 15 broad food groups and certain subgroups (total 28 groups)
- Average daily consumption linked with average occurrence value of each food group, bw considered
- Limited by broad categories, different methodologies for data collection, no mean European exposure can be assessed

Exposure assessment

Age Group	Exposure (µg/kg bw per day)			
	Lowest Mean LB	Highest Mean UB	Lowest P95 LB	Highest P95 UB
Adults	0.36	1.24	0.73	2.43
Infants	0.27	0.63	0.40	0.94
Children 1-3 years	1.10	3.10	1.71	5.51
Children 4-7 years	0.80	2.61	1.30	4.83
Developing fetus	*0.54*	*Single value derived using exposures of females of 20-40 years, applying fetal/maternal cord B-Pb ratio of 0.9.*		

Exposure assessment

- Cereal products, followed by potatoes, cereal grains, cereal-based dishes, leafy vegetables and tap water - main contributors to lead exposure in adults.

- Contribution of game meat small because of minimal consumption in average population

- Non-dietary exposures (µg/kg bw per day):
  - 0.001 - 000.3 (outdoor air),
  - 0.003 - 0.018 (smoking),
  - 0.009 - 0.037 (environmental tobacco smoke)

  of minor importance for the adult population.

- Oral exposure of children 2 years of age to lead in soil and house dust (µg/kg bw per day):
  - 0.18 and 0.8

  important contributor to exposure.

Exposure assessment

- In specific exposure scenarios for adults, high consumption of foods with high lead levels (game meat/offal, fungi, shellfish, algae food supplements) was assumed:

Food item	Lead level (mg/kg)	Consumption	Mean exposure µg/kg bw per day				
			Added to diet	Base diet		Total diet	
				LB	UB	LB	UB
Game meat	3.15*	28g/day or 200g/week	1.47	0.36	1.24	1.98	2.44
Game offal	1.26**	14g/day or 100g/week	0.30	0.36	1.24	0.81	1.27

* UB mean of 2521 game meat samples

**UB mean of 652 game liver/kidney samples

- Such scenarios were not calculated for children - lead exposures would be considerably higher.

Toxicokinetics

- Oral absorption is much higher in children as compared to adults and lower in the presence of food.
- About 90% of lead in adults is stored in bones while in children bone lead accounts for only about 70%.
- Increased mobilisation of bone lead during pregnancy and menopause.
- Lead crosses the placenta (fetal/maternal B-Pb ratio about 0.9) and is excreted in breast milk.
- Lead is primarily excreted via urine and faeces, half-live in blood ~30 days, in bone ~ 10-30 years.
- Blood lead (B-Pb) most appropriate indicator of current exposure.
- Bone lead (Tb-Pb) reflects long-term uptake.

Toxicity

- In laboratory animals, lead is neuro-, cardio-, nephro- and haematotoxic, induces tumours (e.g. kidney, adrenal gland, testes, prostate, lung).
- In humans, early symptoms of acute poisoning are abdominal pain, nausea, vomiting, anorexia. Children are particularly prone to develop toxic encephalopathy.
- CNS main target organ for chronic toxicity in humans - effects on central information processing, visuospatial organisation, short term-verbal memory, psychiatric symptoms, impaired manual dexterity.
- Developing brain is particularly vulnerable.
- In children, increased B-Pb associated with reduced IQ, reduced cognitive functions leading to reduced adult grey matter volume.
- Nonlinear dose-effect relationship between B-Pb and IQ - greater relative impact of at lower levels.
- Association between increased B-Pb and elevated systolic blood pressure (SBP) as well as chronic kidney disease (CKD).

Toxic mode of action in humans

Neurotoxicity

- Disruption of Ca homoeostasis leading to neuron damage (particular vulnerability of fetus/infant due to immature blood-brain barrier/lack of Pb binding proteins)
- Interference with dopaminergic/cholinergic system (blocked release of acetylcholine, diminishing cholinergic function)

Cardiovascular effects

- Constrictive effect on vascular smooth muscle likely mediated by inhibition of Na-K-ATPase activity and elevation of Ca^{2+} levels

Kidney effects

- Formation of intranuclear inclusion bodies leading to inhibition of enzymes, binding to mitochondria in the in the proximal tube leading to abnormal respiratory function

Critical effects/Dose response analysis

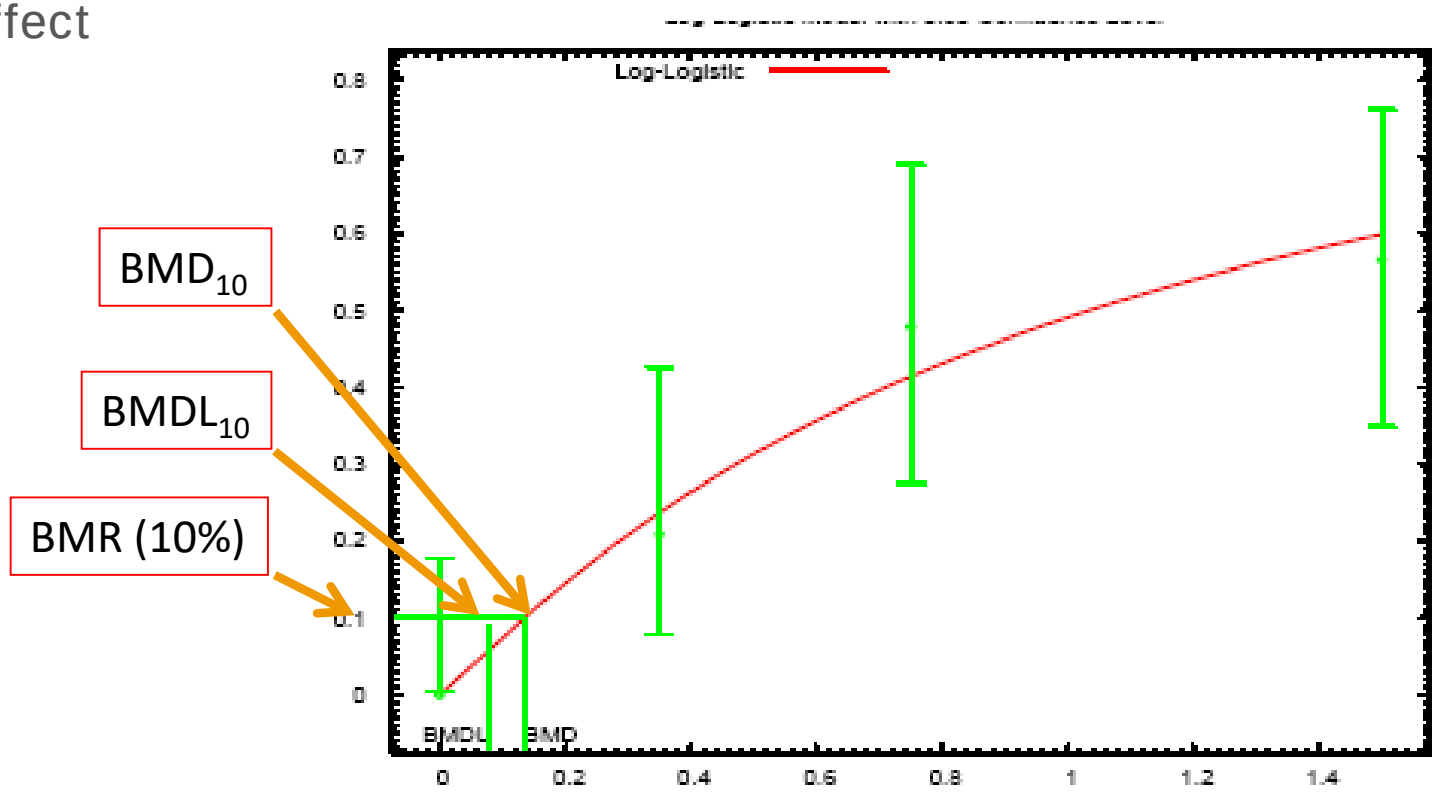
- Critical effects:
  - developmental neurotoxicity in young children
  - cardiovascular and kidney effects in adults

- Endpoints for dose response analyses:
  - full Scale IQ score in children
  - changes in systolic blood pressure (SBP) and prevalence of chronic kidney disease (CKD) in adults.

- **“Benchmark doses”** calculated for use as reference points

Benchmark dose (BMD)

- Better option than NOAEL/LOAEL for the dose response analysis:
  - Independent from experimental design
  - Can be used both for thresholded and **non-thresholded** effects
  - Uses all available information available in the study
- Modelling benchmark dose (BMD) for selected Benchmark Response (BMR) typically 5-10% extra risk of the critical effect)
- BMDL = 95% lower confidence limit of the BMD extra risk of the critical effect



Critical effects/Dose response analysis

- B-Pb levels were converted into dietary exposures using PBPK models

- For renal/cardiovascular effects the equation of Carlisle and Wade (1992) was applied: *([food exposure (µg/kg b.w. per day)*b.w. *0.4]+[soil and dust lead level (mg/kg)*0.025*0.18]+[air lead level (µg/m³)*16.4] = B-Pb (µg/L))*

- For neurodevelopmental effects the Integrated Exposure Uptake Biokinetic (IEUBK 1.1) model was applied

Critical effects/dose response analysis

- Developmental neurotoxicity: Association between IQ scores and B-Pb seen in 7 studies (Lanphear et al., 2005)
  - $BMDL_{01}$ = 12 µg/L(B-Pb) = 0.5 µg/kg bw per day.
- Effects on systolic blood pressure: Association between SBP and B-Pb seen in 5 epidemiological studies
  - $BMDL_{01}$ = 36 µg/L (B-Pb); = 1.5 µg/kg bw per day
- Effects on kidney: Association between chronic kidney disease (CDK) and B-Pb seen in an epidemiological study (NHANES 1999-2006)
  - $BMDL_{10}$ = 15 µg/L (B-Pb) = 0.63 µg/kg bw per day
- Previously established provisional tolerable weekly intake (PTWI) of 25 µg/kg bw is no longer appropriate.

Margin of exposure MOE

- A **threshold** for these effects could not be identified, therefore a health-based guidance value (e.g. TWI) could not be set but a **margin of exposure** (MOE) approach was applied.
- Interpretation of the MOE depends on nature of effect, dose metric used, relevance of the population used, range of intake estimates (LB/UB).
- For effects on SBP or kidney in adults, MOE of ≥10 between BMDL and exposure *"should be sufficient to ensure that there was no appreciable risk*", even at a MOE > 1 *"the risk would be very low".*
- For neurodevelopmental toxicity, a MOE ≥10 between BMDL and exposure *"should be sufficient to ensure that there is no appreciable risk",* at a MOE of < 10 but >1 *"the risk is likely low but not such that it could be dismissed as potential concern".*

Risk characterisation

- Mean LB/UB exposures of adults below the $BMDL_{01}$ SBP of 1.50 µg/kg bw per day, MOEs vary from 1.2 to 4.2.
- Several UB exposures of adults higher than the $BMDL_{10}$CKD of 0.63 µg/kg bw per day (MOEs range 1.8 for lowest LB to 0.51 for highest UB). "*Adverse effects in some consumers cannot be excluded".*
- Mean LB/UB exposure levels of consumers of game meat (1.98/2.44 µg/kg bw per day) and game offal (0.81/1.27 µg/kg bw per day) within or at the higher end of the range of the respective BMDL values. "*The possibility of an effect in some consumers of a game meat rich diet cannot be excluded".*
- Mean LB/UB exposures in children ≤ 7 years exceed the $BMDL_{01}$ of 0.5 µg /kg bw per day for neurodevelopmental effects. "*Thus, effects in some children cannot be excluded".*
- Breast-fed 3-month old infants exposures < the $BMDL_{01}$ 0.5 µg/kg bw per day at LB levels but UB P95 exposures exceeded this. "*The possibility of effects in some infants cannot be excluded".*
- Exposure of the fetus (calculated in a special scenario) was 0.54 µg/kg bw per day, thus at/above the $BMDL_{01}$ for neurodevelopmental effects. "*A risk to the developing fetus through exposure of some pregnant female consumers cannot be excluded".*

Uncertainties

- B-Pb concentration measured at one time point does not reflect adequately systemic exposure (e.g. concentration in brain) or chronic exposure
- Use of IQ tests for the assessment of neurotoxicity in children
- Possible reverse causation of higher B-Pb levels because of nephrotoxicity
- Heterogeneity in study outcomes on hypertension
- Occurrence data might not reflect the whole of the EU
- Influence of non-detects on exposure estimate (LB/UB)
- Dietary exposure estimates from B-Pb