Health effects and toxicological approaches for lead

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SOURCES OF LEAD EXPOSURE

National Poisons Information Service

Health Protection Agency

Environmental exposure:

- **Food**
- **Water (lead pipes)**
- **Soil**
- **Homemade/imported ceramics**
- **Imported toys**

SOURCES OF LEAD EXPOSURE

National Poisons Information Service

Health Protection Agency

Environmental exposure:

- 'Traditional' remedies or cosmetics
- Paint chips
- Petrol
- Snooker chalk

‘SNOOKER LOOPY’

Released in 1986 by Chas ‘n’ Dave

Lyrics based on lead induced neurotoxicity?

Snooker loopy nuts are we
Me and him and them and me
We'll show you what we can do
With a load of balls and a snooker cue

Pot the reds then, skrew back
For the yellow green brown blue pink and black
Snooker loopy nuts are we
We're all snooker loopy

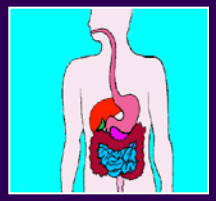
TOXICOKINETICS

National Poisons Information Service

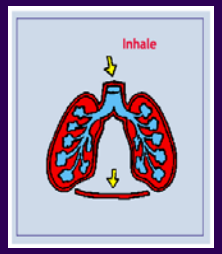
Health Protection Agency

Main route of exposure

Ingestion



Inhalation



Toxicological effects are the same regardless of the route of exposure

TOXICOKINETICS ABSORPTION

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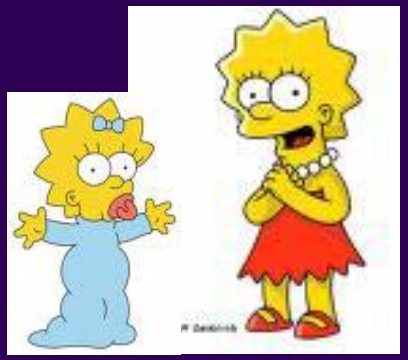
Health Protection Agency

5-15% of ingested or inhaled lead is absorbed into the blood stream



Up to 40% of ingested or inhaled lead is absorbed into the blood stream

TOXICOKINETICS DISTRIBUTION

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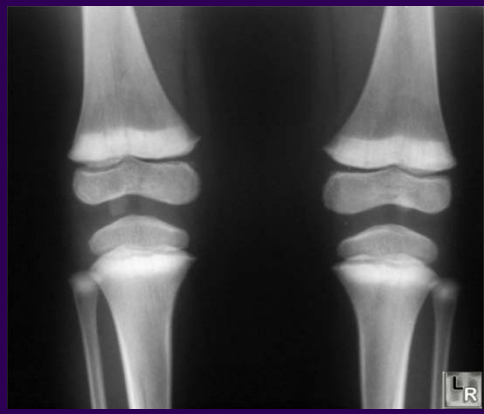
National Poisons Information Service

Health Protection Agency

- Lead is transported in red blood cells bound to plasma proteins
- Lead is distributed to soft tissues (liver and kidney) and bone
- Adults have a larger fraction of the body burden in bone (98.5%) compared to children (73%)



TOXICOKINETICS DISTRIBUTION

NPIS
National Poisons Information Service

Health Protection Agency

- Lead is mobilised from bone to the blood during pregnancy
- Readily transferred to the placenta and accumulates in bone
- Conc. of lead in cord blood may be 85-90% of maternal blood
- Poses a risk to the fetus

TOXICOKINETICS ELIMINATION

National Poisons Information Service

Health Protection Agency

Up to 85 % of ingested lead is eliminated unabsorbed

Up to 60 % of ingested lead is eliminated unabsorbed

ACUTE LEAD TOXICITY

National Poisons Information Service

Health Protection Agency

Lead is essentially a chronic toxin

Few health effects are seen following an acute exposure at low conc.

ACUTE LEAD TOXICITY

National Poisons Information Service

Health Protection Agency

At high concentrations, may see non-specific GI and CNS features

- **Tiredness, lethargy, headaches,**
- **Abdominal cramps (diffuse or colicky), anorexia, vomiting, constipation**

Other effects include

- **Kidney effects (reversible morphological changes)**
- **Cardiovascular effects (hypertension)**
- **Liver effects (inhibition of metabolic enzymes)**

ACUTE LEAD TOXICITY

Health Protection Agency

Blood [Pb]	
100-120 µg/dL	Encephalopathy (irritability, lethargy, dizziness, headache, memory loss, tremor, ataxia, convulsions, coma, death)
80 µg/dL	Encephalopathy (irritability, lethargy, dizziness, headache, memory loss, tremor, ataxia, convulsions, coma, death)
60-100 µg/dL	Anaemia
40-60 µg/dL	GI disturbances (anorexia, cramps, vomiting), anaemia
30 µg/dL	Decreased nerve velocity
10-15 µg/dL	Reduced haemoglobin levels
10 µg/dL	Cognitive impairment
	Hearing impairment

ACUTE LEAD TOXICITY

National Poisons Information Service

Health Protection Agency

- Most patients with a blood [Pb] ≥ 50 µg/dL will show some symptoms

CHRONIC LEAD TOXICITY

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Health Protection Agency

Neurotoxicity

- Fatigue, headache, irritability, slurred speech, convulsions, muscle weakness, tremors, anxiety
- Decreases in reaction time, hand dexterity, IQ

In children:

5.6 µg/dL reported to cause IQ deficits

NON-THRESHOLD

CHRONIC LEAD TOXICITY

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National Poisons Information Service

Health Protection Agency

Cardiovascular toxicity

- Epidemiological data show a correlation between lead and blood pressure
- Hypertension (systolic)

Renal toxicity

- Renal tubular dysfunction
- Progressive renal impairment
- Hypertension

CHRONIC LEAD TOXICITY

Health Protection Agency

Neuropathy

- Nerve velocity
- Tendon reflexes lost
- Sensory loss
- Muscle weakness

Reproduction

- Spontaneous abortion
- Stillbirth
- Low birth weight
- Premature birth

Haematology

- Anaemia
- Reduced Hb formation
- Basophilic stippling
- Shortened RBC lifespan

Gastro-intestinal

- Abdominal cramps
- Nausea/vomiting
- Anorexia
- Excessive thirst

CHRONIC LEAD TOXICITY

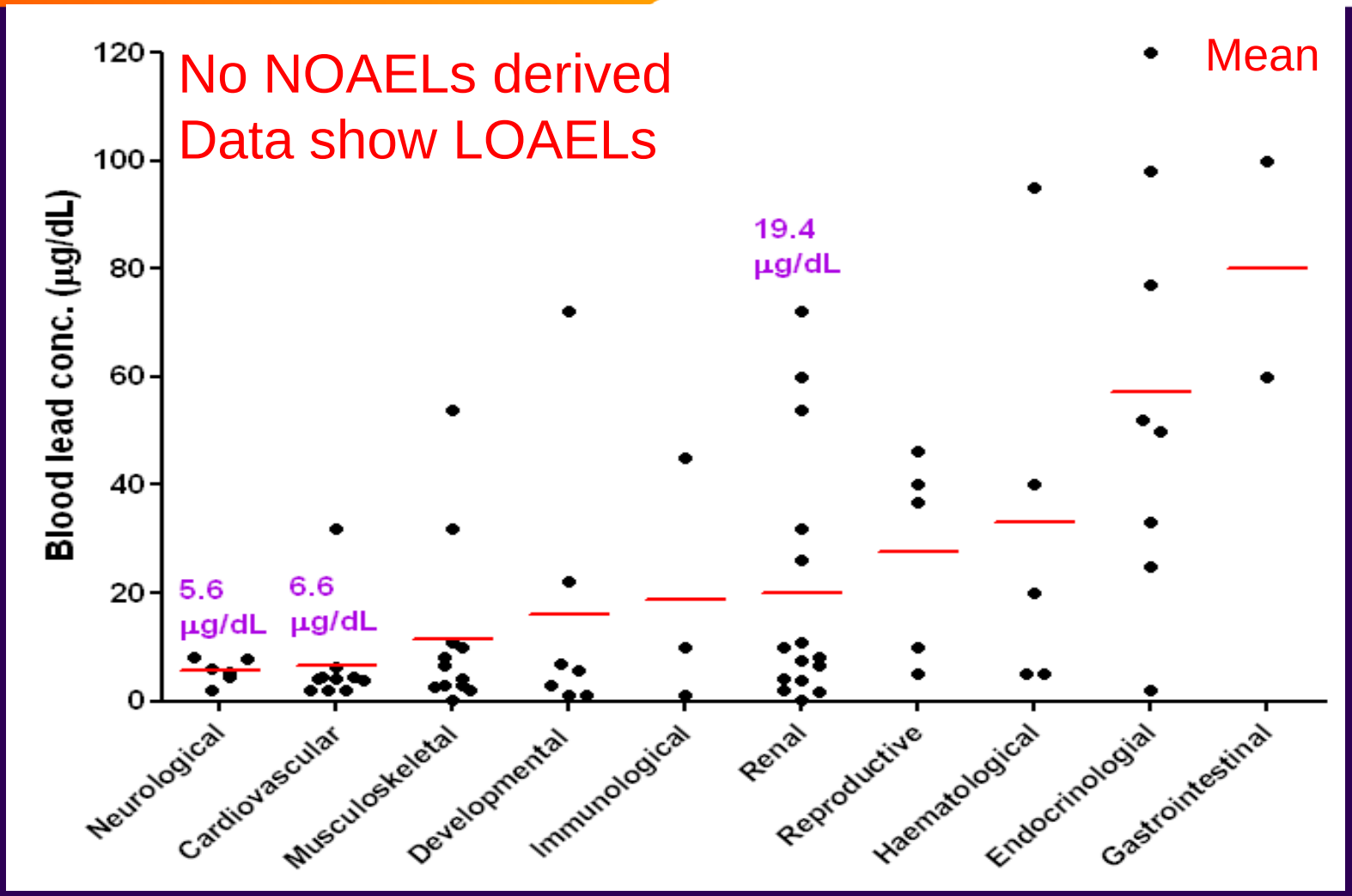
National Poisons Information Service

Health Protection Agency

Carcinogenicity

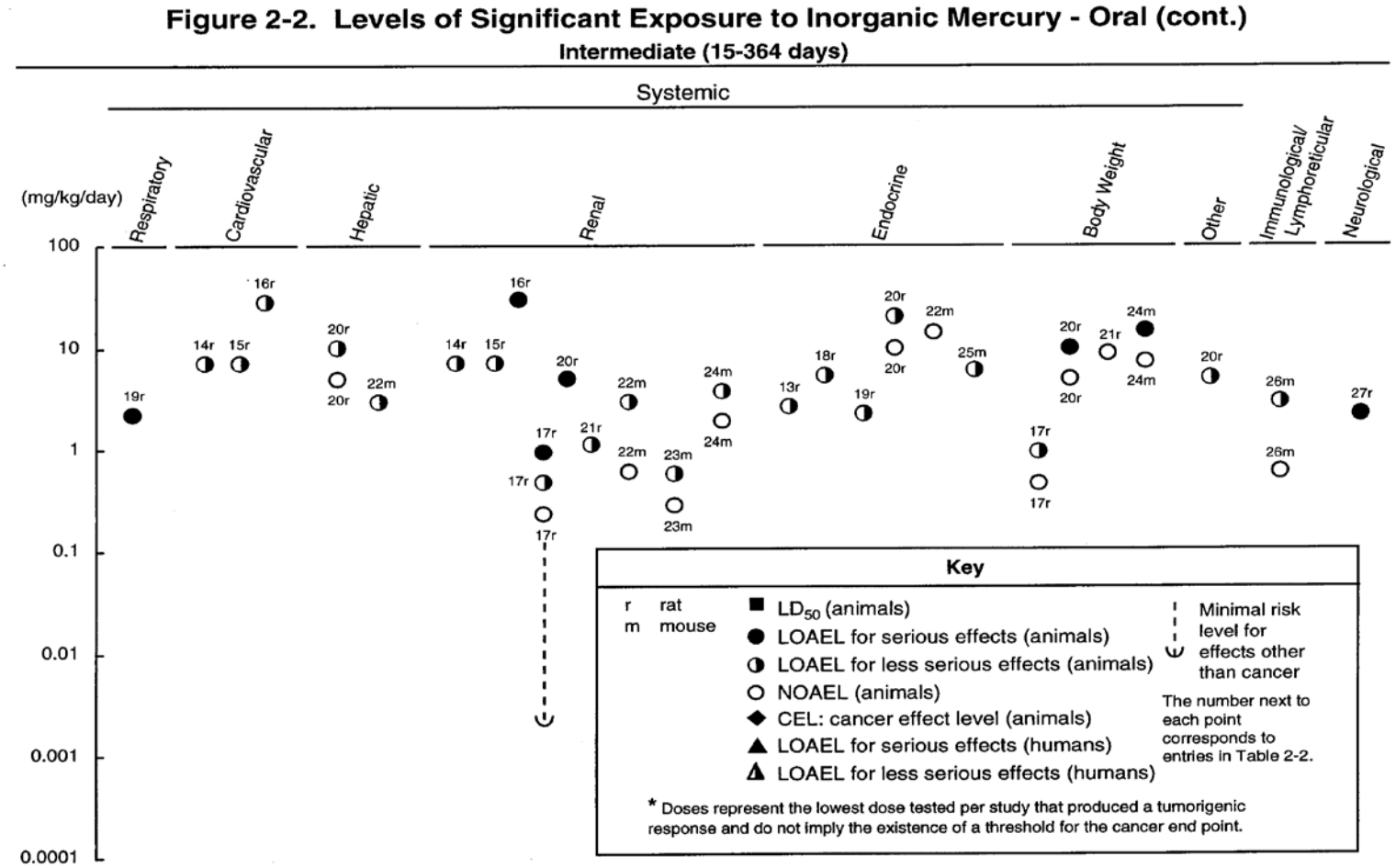
- IARC:
  - Lead - Group 2B – possibly carcinogenic in humans
  - Inorganic lead compounds – Group 2A – probably carcinogenic in humans
    - (little evidence in humans but sufficient evidence in animals)
- Little evidence that lead interacts with DNA
- Acts by production of reactive oxygen species and inhibition of DNA repair

CHRONIC LEAD TOXICITY



http://www.atsdr.cdc.gov/toxprofiles/index.asp#P

ATSDR graphs



http://www.atsdr.cdc.gov/toxprofiles/index.asp#P

TOXICOLOGICAL APPROACHES

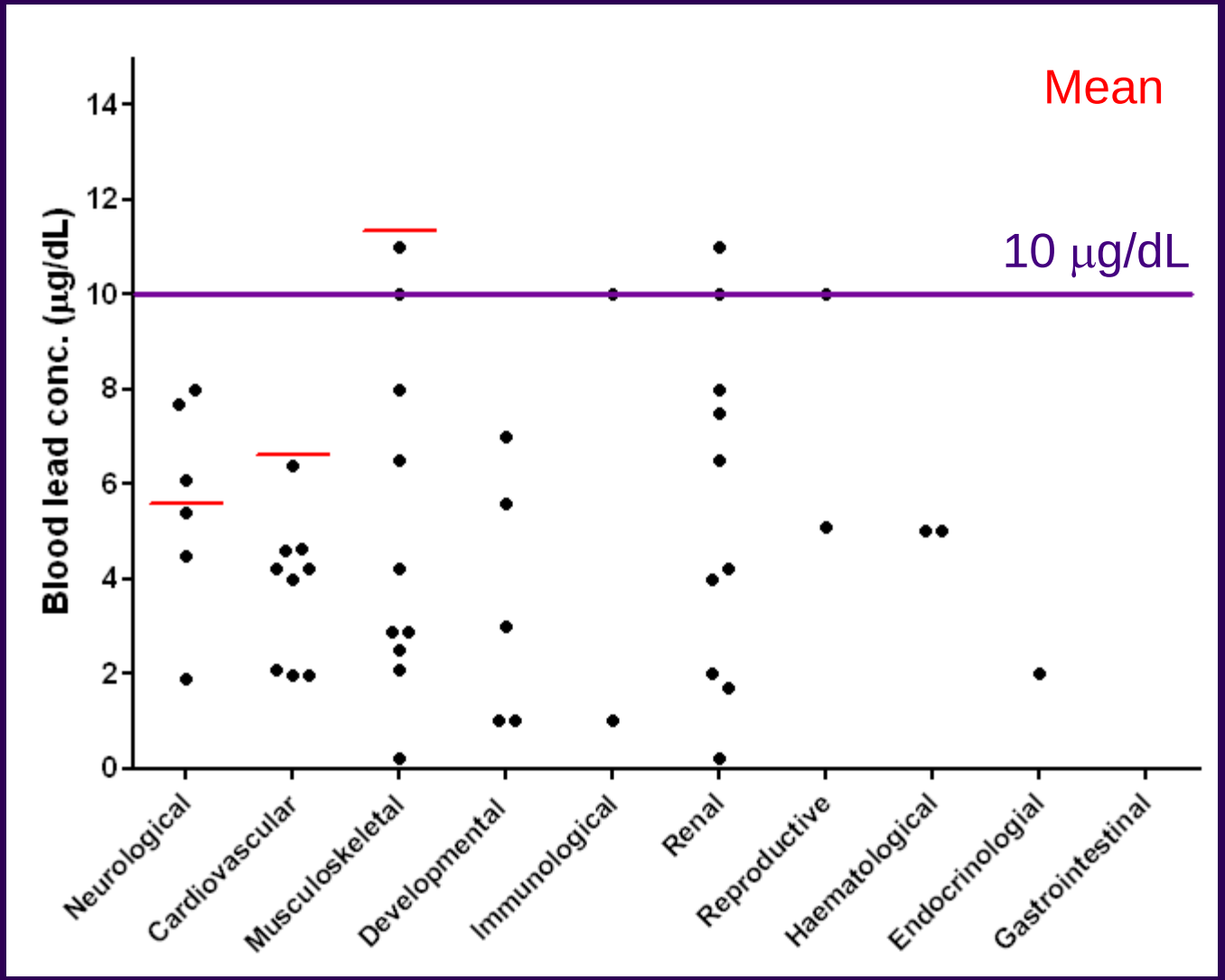
National Poisons Information Service

Health Protection Agency

Old approaches (TOX 6)

- Use PbB conc. of 10 µg/dL to derive the SGV
- Assume neurotoxicity doesn't have a threshold so exposures should be ALARP
- Takes account exposure from all routes and sources

HEALTH EFFECTS < 10 μg/dL
Old TOX value



TOXICOLOGICAL APPROACHES

JECFA

NPIS
National Poisons Information Service

Health Protection Agency

In 1993

- Provisional Tolerable Weekly Intake (PTWI) of 25 μg/kg bw (3.6 μg/kg bw/day)
  - Based on metabolic studies
  - Intake of 3-4 μg/kg bw/day does not result in an increase in PbB levels
  - Intake of 5 μg/kg bw/day resulted in lead retention
  - 1 μg lead intake per day = 0.16 μg/dL blood

TOXICOLOGICAL APPROACHES

JECFA

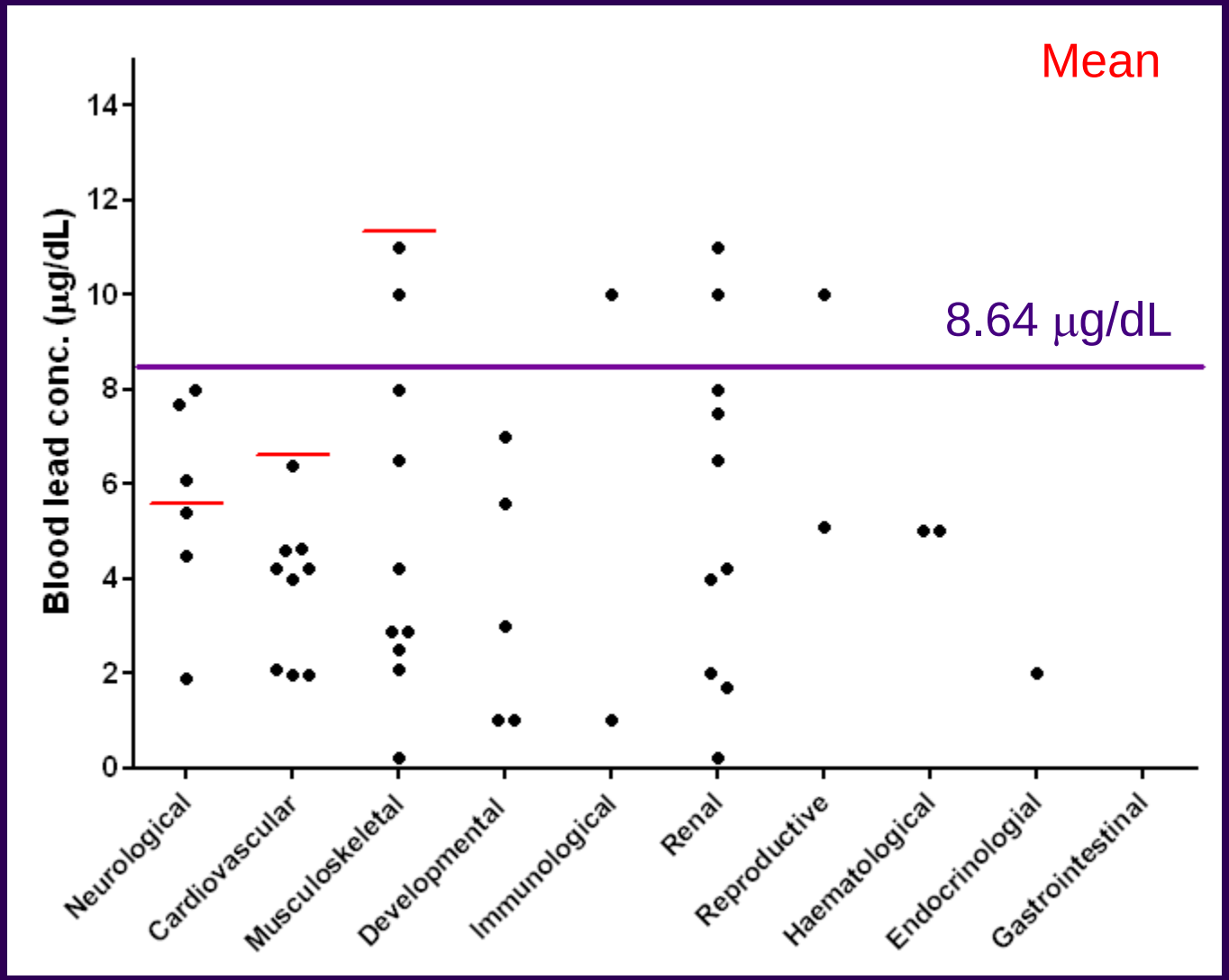
National Poisons Information Service

Health Protection Agency

In 1993

- Based on the Integrated Exposure Uptake Biokinetic (IEUBK) model (as used by EFSA for children)
  - 3.6 µg/kg bw/day equates to ~8.64 µg/dL

HEALTH EFFECTS < 8.64 µg/dL
JECFA value



TOXICOLOGICAL APPROACHES

JECFA

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Health Protection Agency

At 73rd meeting, 2010

- PTWI of 25 μg/kg bw (3.6 μg/kg bw/day) is associated with
  - At least 3 IQ points decrease and
  - Increase of systolic BP of 3 mmHg
- Effects may be insignificant at in individual level but important at the population level

Concluded that the PTWI could no longer be considered health protective and was withdrawn

TOXICOLOGICAL APPROACHES

JECFA cont…

National Poisons Information Service

Health Protection Agency

- Lead does not show a threshold for the key adverse effects
- The Committee concluded that it was not possible to establish a new PTWI that would be health protective

TOXICOLOGICAL APPROACHES

EFSA

National Poisons Information Service

Health Protection Agency

In 2010

- Scientific Opinion on Lead in Food

EFSA journal 2010; 8(4); 1570

Concluded that the JECFA PTWI was no longer appropriate as there was no evidence of a threshold

‘Compared to dietary exposure, non-dietary exposure to lead is likely to be of minor importance for the general population. House dust and soil can be an important source of exposure for children’

TOXICOLOGICAL APPROACHES

EFSA

National Poisons Information Service

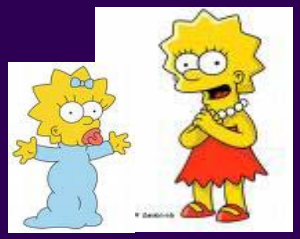
Health Protection Agency

- Developmental neurotoxicity in children
  - Full scale IQ

- Cardiovascular effects in adults
  - Systolic blood pressure (SBP)

- Chronic kidney disease in adults
  - Glomerular filtration rate (<60 ml/min)

CRITICAL ENDPOINTS

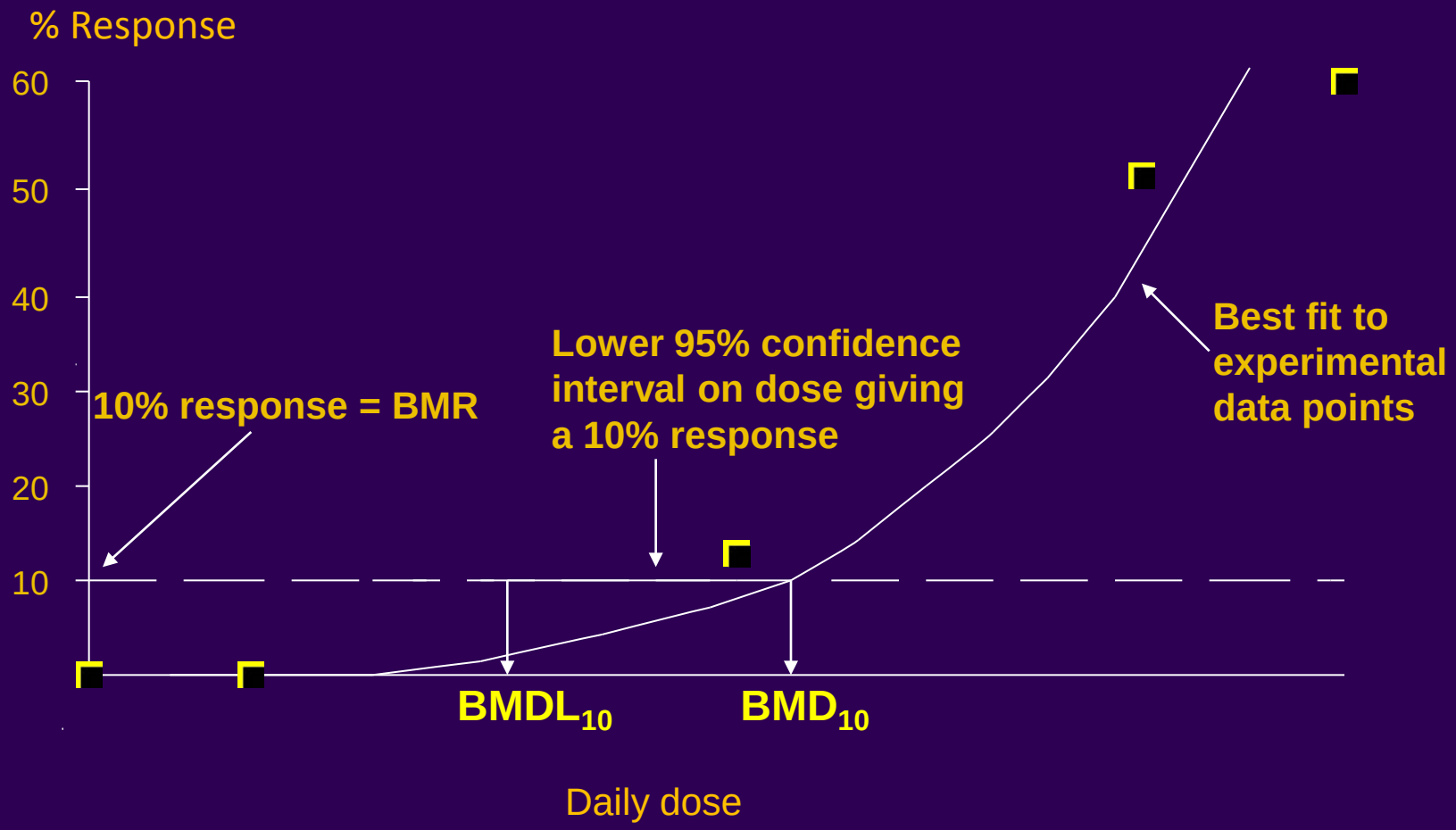
Neurodevelopment		$BMDL_{01}$ = 12 μg/L (1.2 μg/dL)
Cardiovascular toxicity		$BMDL_{01}$ = 36 μg/L (3.6 μg/dL)
Nephrotoxicity		$BMDL_{10}$ = 15 μg/L (1.5 μg/dL)

BENCHMARK DOSE (BMDL)

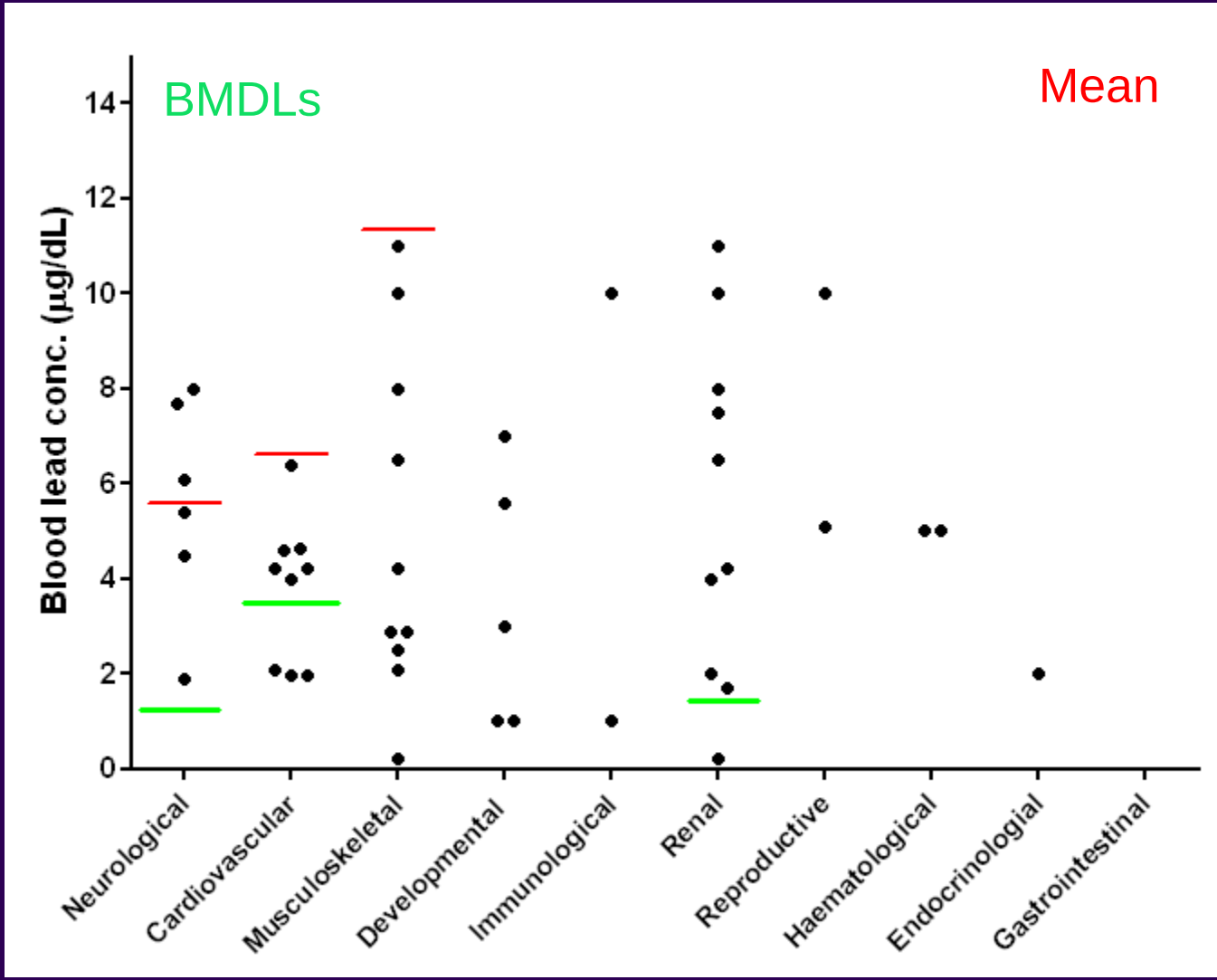
‘A dose that causes an increase in response in treated animals compared to controls i.e. the dose estimated to give a 1% increase in neurotoxicity or 10% increase in kidney effects’

Lower 95th confidence interval of the BMD01 is the *BMDL01*

BENCHMARK DOSE



EFSA BMDLs


BMDLs
Mean
Blood lead conc. (µg/dL)
0
2
4
6
8
10
12
14
Neurological
Cardiovascular
Musculoskeletal
Developmental
Immunological
Renal
Reproductive
Haematological
Endocrinologial
Gastrointestinal

NEUROTOXICITY

Could have significant consequences on population basis

Shift in the distribution of IQ by 1 point would have an impact on the socioeconomic status of the population and productivity

Decrease of 1 IQ point leads to :

= 4.5% increase in risk of failure to graduate

= 2% decrease in productivity

CARDIOVASCULAR TOXICITY

Could have significant consequences on a population level (increased cardiovascular morbidity and coronary heart disease)

Increase in SBP by 1% would increase:

= hypertension by 3.1%

= mortality from cerebral stroke by 2.6 %

= mortality from myocardial infarction by 2.4 %

NEPHROTOXICITY

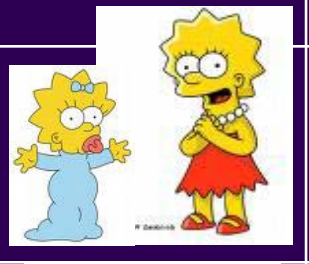
Health Protection Agency

Could have significant consequences on a population level

BLOOD LEAD LEVELS FROM FOOD AND SOIL/DUST

	BMDL (μg/L)	Average consumer B-Pb (μg/L)	High consumer B-Pb (μg/L)
Dietary exposure			
Children 1-3 years	12	18-48	28-77
Children 4-7 years	12	15-46	24-77
Female 20-40 years	12	9-31	16-62
Non-dietary exposure			
Soil and dust	12	4	15

CONVERSION BLOOD LEAD LEVELS TO INTAKE

Endpoint	Population	BMDL B-Pb (µg/L)	Dietary Pb exposure µg/kg bw/day
Neurotoxicity		12	0.5
Cardiovascular toxicity		36	1.5
Nephrotoxicity		15	0.63

LEAD INTAKE FROM FOOD AND SOIL/DUST

	BMDL intake (µg/kg bw/day)	Average consumer B-Pb (µg/kg bw/day)	High consumer B-Pb (µg/kg bw/day)
Dietary exposure			
Children 1-3 years	0.5	1.1-3.1	1.71-5.51
Children 4-7 years	0.5	0.8-2.61	1.3-4.83
Female 20-40 years	0.5	0.38-1.28	0.68-2.6
Non-dietary exposure			
Soil and dust	0.5	0.18-0.8	0.18-0.8

RISK CHARACTERISATION
MARGIN OF EXPOSURE

$$\text{Margin of exposure} = \frac{\text{BMDL}}{\text{Exposure}}$$

- MOE of >10 should not give rise to appreciable risk of clinically sig. effects
- MOE >1 risk likely to be low but could not be dismissed as of no potential concern

RISK CHARACTERISATION MARGIN OF EXPOSURE

MOE >1 risk likely to be low but could not be dismissed as of no potential concern	Endpoint	Average consumer	High consumer
Adults	Cardiac effects	1.2-4.2	0.62-2.1
	Nephotox	0.51-1.8	0.26-0.86
Children 1-3 years	Neurotox	**0.16-0.45**	**0.09-0.29**
Children 4-7 years	Neurotox	**0.19-0.63**	**0.1-0.38**
Female 20-40 years (in utero exposure)	Neurotox	0.39-1.3	0.19-0.79

MARGIN OF EXPOSURE - NEUROTOXICITY

Bottle fed infants

<BMDL01 intake MOE>1

- may exceed the BMDL01, so the possibility of an effect of lead cannot be excluded

1-3 year old children

>BMDL01 intake MOE<1 in even average consumers

- the possibility of an effect of lead cannot be excluded

4-7 year old children

> BMDL01 intake MOE<1 in even average consumers

- the possibility of an effect of lead cannot be excluded

EFSA CONCLUSIONS

Health Protection Agency

Risk of clinically significant effects on the cardiovascular system or kidneys in adults is low to negligible

Infants, children and pregnant women, there is potential concern at current levels of exposure for neurodevelopment

Protection of children and women of child bearing age against the risk of neurodevelopmental effects would protect against all adverse effects of lead in the population

OTHER TOXICOLOGICAL APPROACHES

National Poisons Information Service

Health Protection Agency

Extrapolation from other guideline values

- WHO water guideline value of 10 μg/L
  - Based on PTWI
  - JECFA state it is not protective of health

OTHER TOXICOLOGICAL APPROACHES

National Poisons Information Service

Health Protection Agency

Extrapolation from other guideline values

- WHO air quality guideline of 0.5 μg/m3
  - Based on the objective that 98% of the population should have a PbB level of <10 μg/L (median = 5.4 μg/L)
  - Know of adverse effects < 10 μg/L
  - Sufficiently protective?

OTHER TOXICOLOGICAL APPROACHES

NPIS
National Poisons Information Service

Health Protection Agency

Extrapolation from other guideline values

- EPAQS air quality standard of 0.25 μg/m3
  - Assume 1 IQ point is the limit of detection
  - Assume increase of 5 μg/dL will reduce IQ by 1 point
  - Limit in air that causes a decrease of 1 IQ in the population is unacceptable
  - 1 μg/m3 increases PbB level by 5 μg/dL = decrease 1 IQ point = unacceptable

OTHER TOXICOLOGICAL APPROACHES

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National Poisons Information Service

Health Protection Agency

Extrapolation from other guideline values

- US EPA
- Inappropriate to set a reference dose
- Neurobehavioral development may occur at blood lead levels so low as to be without a threshold

- ATSDR
- Chose not to derive any minimum risk levels
- Lack of clear threshold for health effects

OTHER AGENCY APPROACHES

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Health Protection Agency

- Calafornia Office of Environmental Health hazard Assessment (OEHHA)
- Conc. in soil that would lead to an increase in PbB levels of up to 1 μg/dL

- US EPA
- Child should have no more than 5% risk of exceeding PbB levels of 10 μg/L

SOIL GUIDELINE VALUES

National Poisons Information Service

Health Protection Agency

- RIVM (NL)
  - Based on a Maximum Permissible Risk Level of 3.6 μg/kg bw/day (from the PTWI)

- IEUBK model
  - Based on a PbB level of 10 μg/dL

WHERE ARE WE TO DATE?

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National Poisons Information Service

Health Protection Agency

- Based on intake (PTWI)
  - Not health protective

- Based on PbB
  - What PbB level to use?
  - 10 μg/dL not health protective
  - EFSA BMDL of 1.2 μg/dL protective but very low

IMPACT ON SGV

National Poisons Information Service

Health Protection Agency

If BMDL01 is used

- **With no UF**
  - **SGV = ~ 50 mg/kg* (old value 450 mg/kg)**

- **With a provisional UF* (to account for differences in population and lack of threshold)**
  - **SGV = ~ 5 mg/kg***

- **Most of UK would exceed the SGV**

***Largely demonstrative purposes only and should NOT be used or cited**

WHAT DOES THIS MEAN FOR SOIL?