The Importance of Toxicology in Managing Contaminated Land

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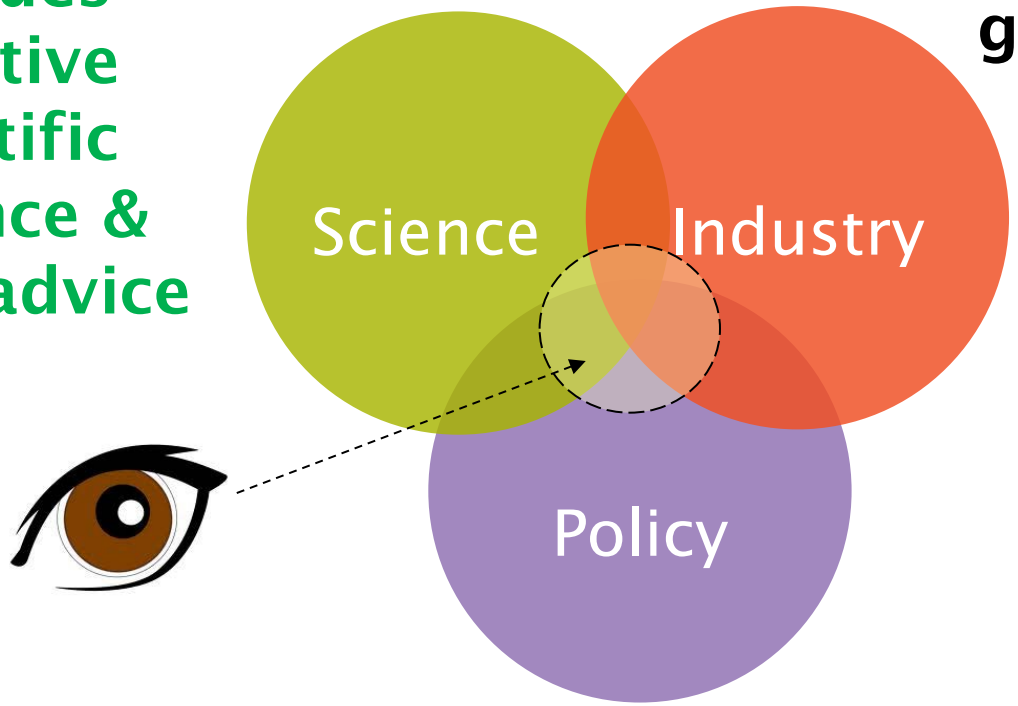
A Toxicologist…..

Provides objective scientific evidence & expert advice

Is not influenced by potential economic gains or savings



Does Not Make Policy Decisions!!

The Phillips Report on BSE

£27m and 630 witnesses

'175 cases of vCJD in UK, march 2011' (WHO)

1990

BSE is a fatal animal disease that causes rapid degeneration in the brain and spinal cord.

It is believed to be caused by feeding cattle the remains of other cattle in the form of meat and bonemeal.

Holly Mills Ages 14 and 23
(b. 1989, d. 2012) *(article in Mail-online)*

Observable cause and effect relationship

"We agree with the report that SEAC's *[Spongiform Encephalopathy Advisory Committee]* proper role was to advise government and not to be seen to be supporting the beef market. Later the report details how MAFF and the Department of Health virtually delegated policymaking to SEAC. A clear conclusion from the inquiry is that expert scientific committees should be restricted to giving advice and should not be setting policy."

The Lancet, editorial November 2000.

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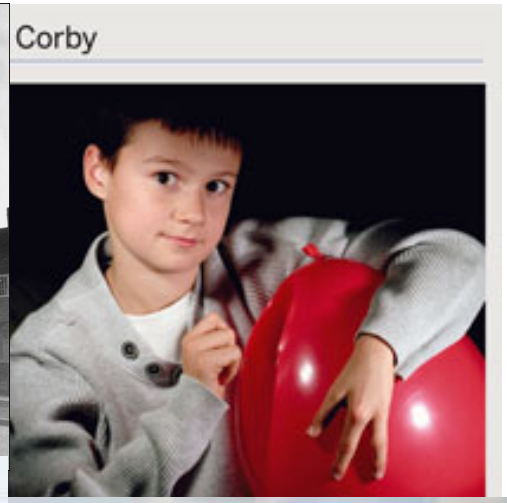
The Corby Case

The first case in the world to link airborne environmental chemicals from dusts to birth defects



Outcome of cause-effect judgement arguably influenced heavily by the evidence of the toxicologist

"What I can and do conclude is that the PAHs, dioxins, Cadmium, Nickel and Chromium were capable of causing the birth defects complained of by the Claimants."

From the judgment re: Corby Group Litigation, Re [2009] EWHC 1944 (TCC) (29 July 2009)

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From Understanding Poisons → Preventing Harm

Theophrastus Phillipus Auroleus Bombastus von Hohenheim (1493 - 1541)
aka Paracelsus
'The dose makes the poison'

Alfred Swaine Taylor, 19th-C
'A poison in a small dose is a medicine, and a medicine in a large dose is a poison.'

Rachel Carson 'Silent Spring'
Chemicals can cause cancer and Endocrine Disruption & Damage the environment

Erin Brockovich
Issues of Drinking water contamination with hexavalent chromium in California

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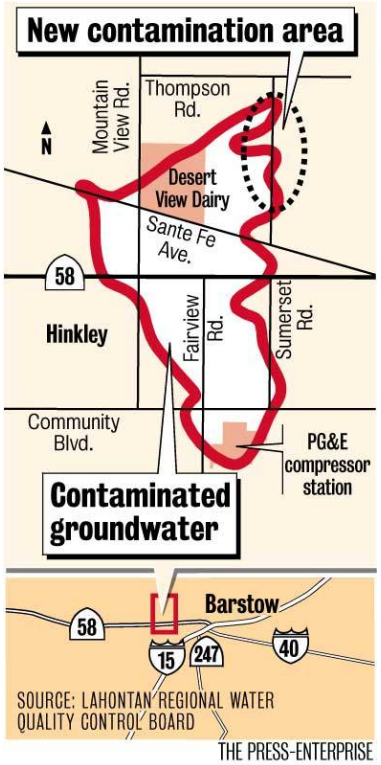
The ‘Erin Brokovich’ Case - CrVI

- Hexavalent chromium contamination in drinking water
  (N.B. trivalent chromium is much less toxic)



- Cancer cluster – Epidemiology data
  [Goodman et al, 2012 Cancer clusters in the USA : What do the last twenty years of state and federal investigations tell us? Critical Reviews in Toxicology, 42(6): 474–490.]

- California - highlighted a toxicology data gap
  → US National Toxicology Program 2008

Chromium VI – how new toxicology data were used to derive a Category 4 Screening Level (C4SL)

Chemical-related effects in man e.g.

Interpreting Toxicology Data Packages

A committee or a policy body

The Toxicologist (per chemical!!)

Contaminated land officer receives – a single number
e.g. HCV → SGV, LLTC → C4SL

Toxicological Profile of Chromium VI

Effects

Dose in mg/kg/day

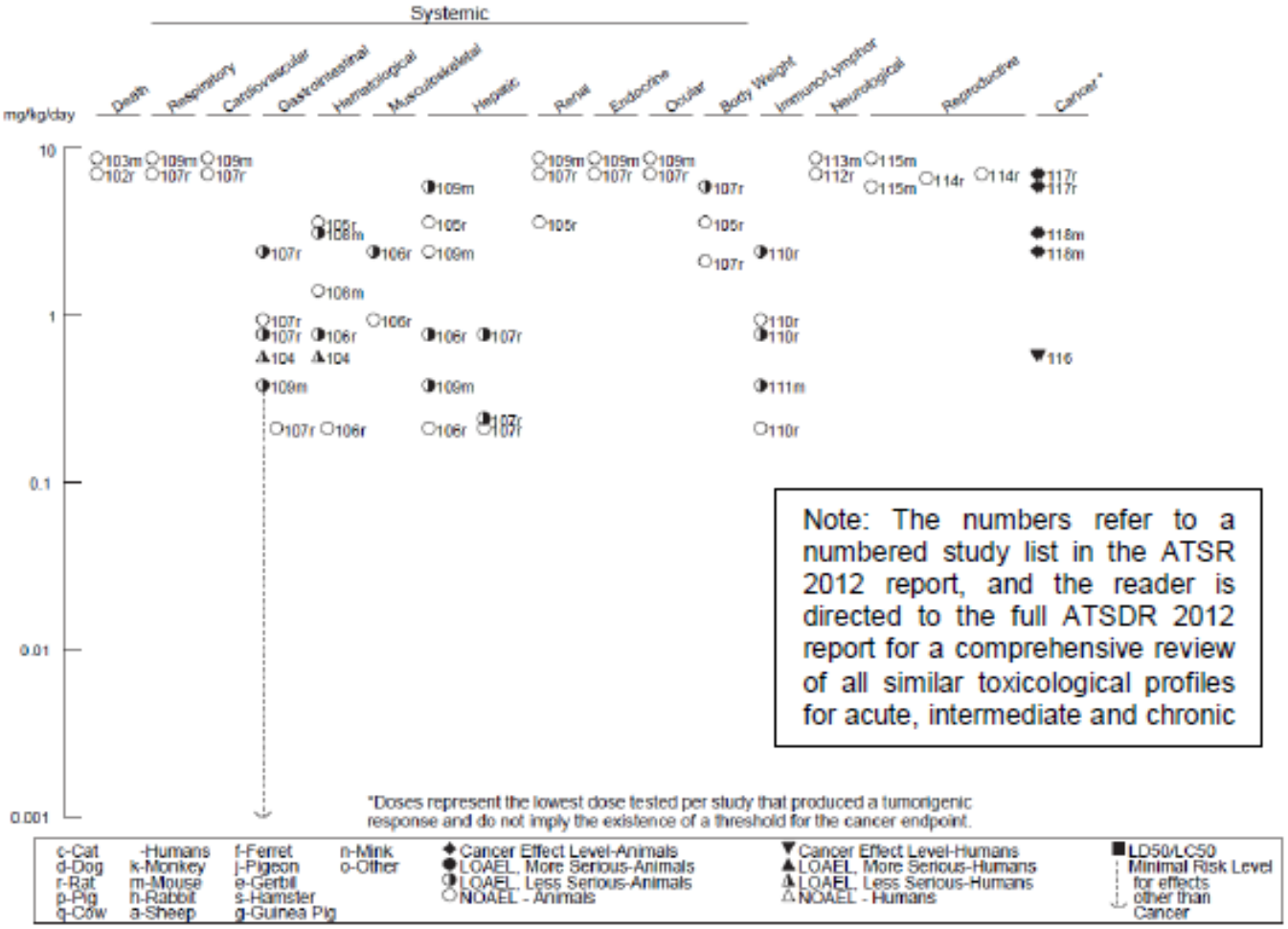


Figure 2.1: Example of all chronic (>365 days) animal and human study evaluations that lead to different adverse toxicological responses following oral exposure (ATSDR 2012)

Choice of pivotal study
Most Sensitive Endpoint

NTP 2 year bioassay (2008)

- 2 year drinking water study in male and female mice and rats administered sodium dichromate dehydrate

→ Diffuse duodenal epithelial hyperplasia

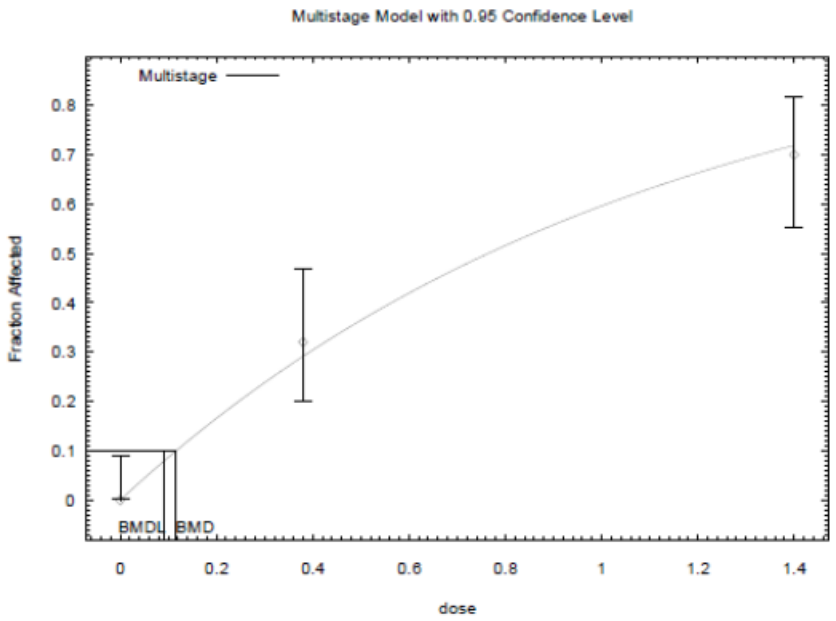


Figure 2.2: Reproduced from ATSDR (2012). Multistage model of diffuse epithelial hyperplasia in duodenum of female mice.

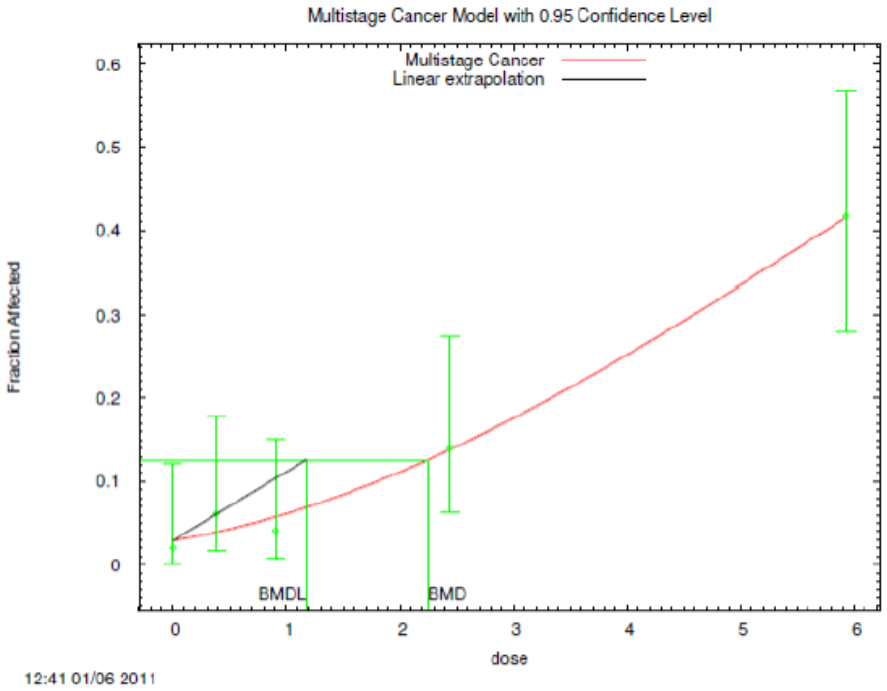
Dose is in mg Cr(VI) kg bw^{-1} day^{-1}, 95% confidence limits on the data are shown. The marked BMD is for BMD_{10}, a 10% extra risk of epithelial hyperplasia.

Choice of pivotal study
Most Sensitive Endpoint

NTP oral cancer study (2008)

- 2 year drinking water study in male and female mice and rats administered sodium dichromate dehydrate

→ Neoplasms of small intestines (duodenum, jejunum, or ileum) and squamous cell neoplams of oral cavity



Dose is in mg Cr (VI)kg bw $^{-1}$ day^{-1}, 95% confidence limits on the data are shown. The marked BMD is for BMD_{10}, a 10% extra risk of intestinal tumours.

Figure: 2.3: Reproduced from IPCS (2011). Multistage model of intestinal tumours (adenomas and carcinomas (in male mice).

CrVI study – Which endpoint to choose?

JUDGEMENT Re: TISSUE PATHOLOGY?

Table 2.3: Proposed choices of oral LLTC values using different PODs and/or CSMs

	POD	Value (mg kg^{-1} bw day^{-1})	CSM /CSAF	LLTC (µg Cr(VI) kg^{-1} bw day^{-1})
Alternative (non-threshold)	BMD_{10}	0.12**	5000	0.024
Alternative (non-threshold)	$BMDL_{10}$	1.2	10000*	0.12
Proposed LLTC (non-threshold)	**BMD_{10}**	**2.2**	**5000**	**0.44**
Alternative (threshold)	$BMDL_{10}$	0.09	100	0.90
Alternative (threshold)	BMD_{10}	0.12	100	1.20
Current HCV (total Cr)I (EA 2002)	NOAEL	2.5	900	3.00

Minimal risk HCV

*Default margin

** Diffuse epithelial hyperplasia is considered by USEPA, ATSDR and WHO as a thresholded endpoint, although it may progress to cancer. LLTCs are therefore presented for both thresholded and non-thresholded opinions.

Cr VI – health based guidance value
(low level of toxicological concern for C4SL – use of BMD_{10})

Non-cancer

BMD_{10} = 120 µg/kg/day

÷ 100 (intraspecies 10, intrahuman 10)

LLTC = 1.2 µg/kg/day

N.B. UK COC has not reviewed the new NTP study to provide a UK view on the pathology

Cancer

BMD_{10} = 2200 µg/kg/day

÷ 5000

(10 intraspecies,
10 interhuman,
50 additional unknowns with regard to severity of effect
– but good quality data/study

LLTC = 0.44 µg/kg/day

÷ 10000

(precautionary default)

LLTC = 0.22 µg/kg/day

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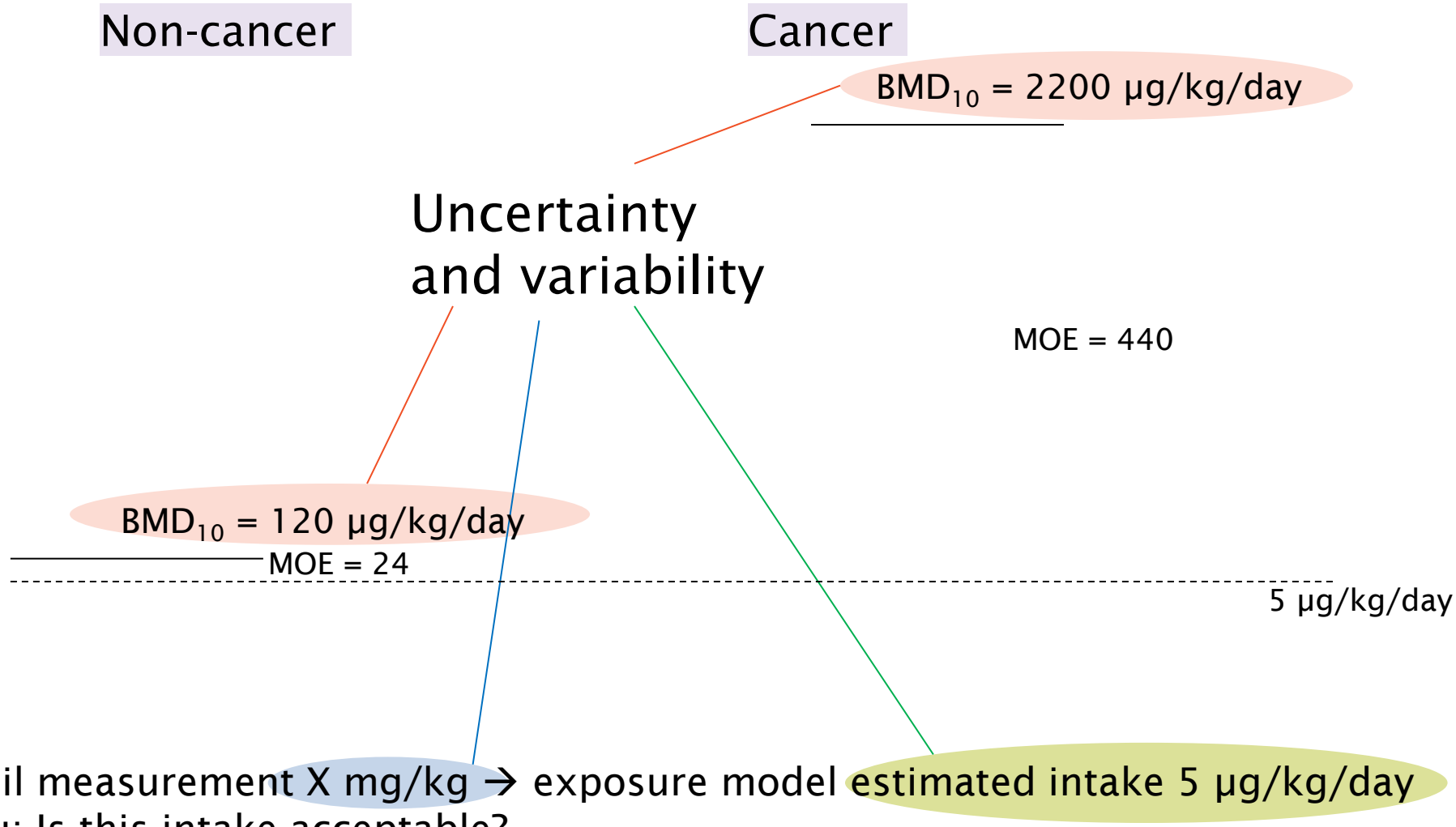
Cr VI – health based guidance value
(Use of BMD in Margin of Exposure approaches)



Soil measurement X mg/kg → exposure model estimated intake 5 µg/kg/day
Qu: Is this intake acceptable?

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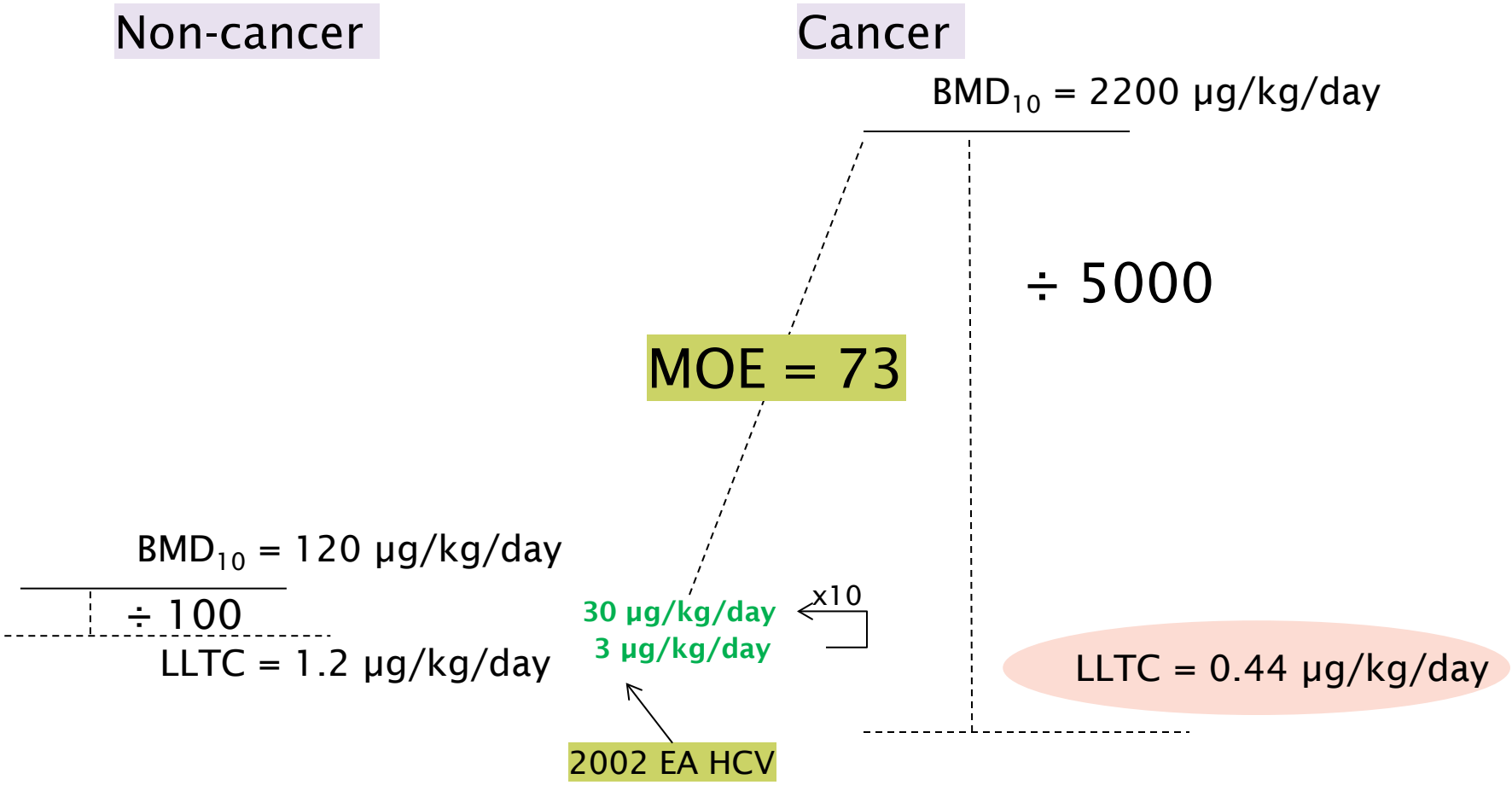
Cr VI – health based guidance value
(simple exposure proposals for deriving C4SLs)



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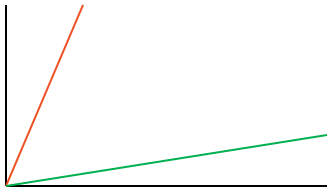
Cr VI – health based guidance value

(Defining the four category boundaries for Part 2A? Chemical specific)

Non-cancer



BMD_{10} = 120 µg/kg/day

÷ 100

LLTC = 1.2 µg/kg/day

1

2

3

Category 4

Cancer

BMD_{10} = 2200 µg/kg/day

÷ 5000

LLTC = 0.44 µg/kg/day

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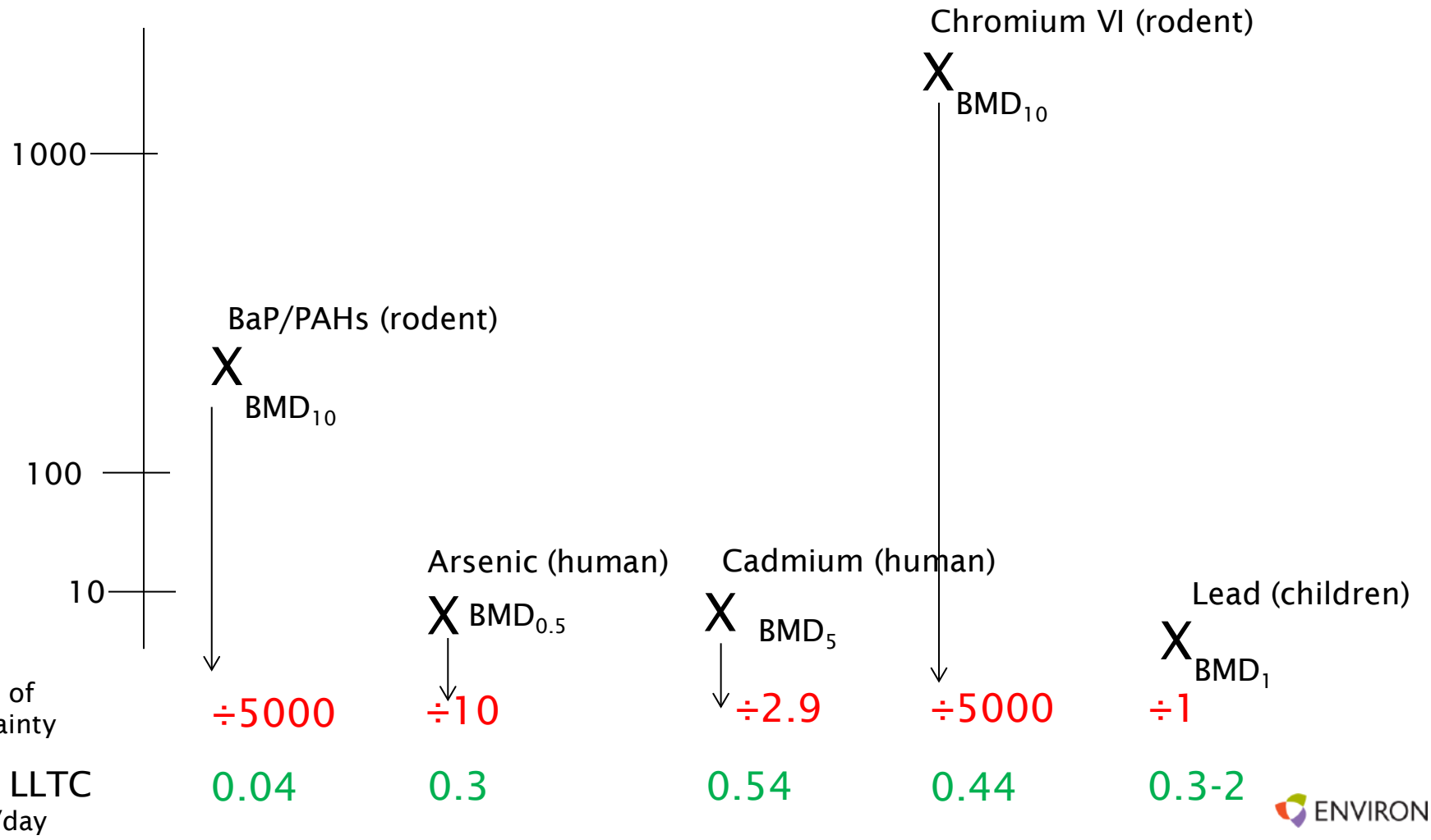
Comparison of Oral Benchmark Doses

For different substances



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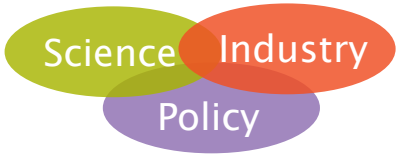
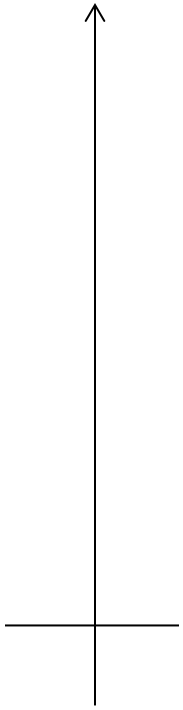
What happens above the LLTC

Decisions about acceptable risk in society?

Map the risk continuum

Exposure science
Toxicology
Social science
Socio-economic analysis





	Arsenic (human)	Cadmium (human)	Lead (children)
C4SL = Draft LLTC µg/kg/day	X $BMD_{0.5}$	X BMD_5	X BMD_1
	0.3	0.54	0.3-2

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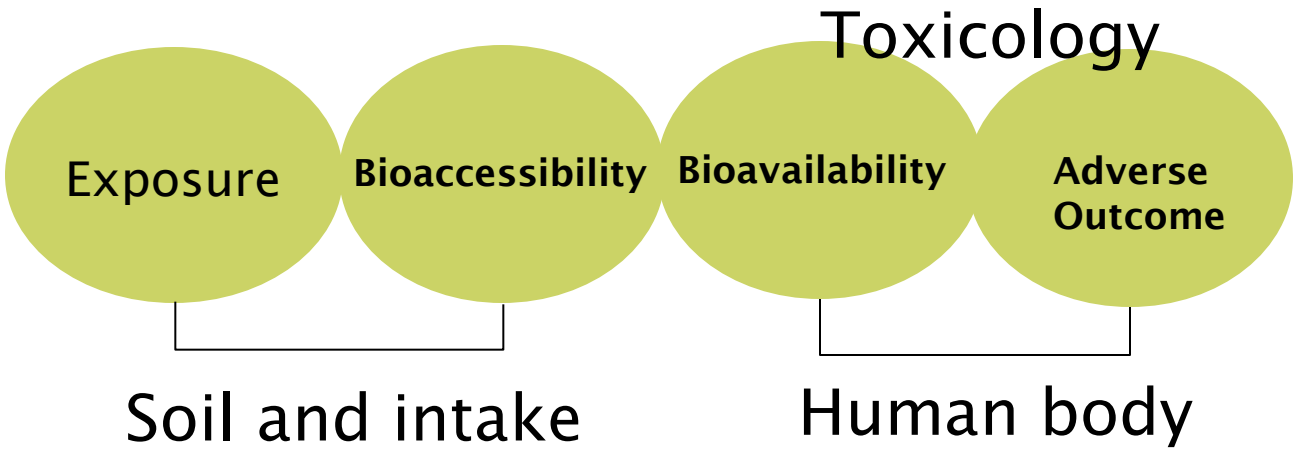
Refining the Science/Risk Assessment

Risk = *f* Exposure & Adverse Outcome



Site specific assessments DQRA

In: Arsenic: Exposure Sources, Health Risks, and Mechanisms of Toxicity. J.C. States, Ed., Wiley-Blackwell, NY (2014 In press).

Chapter 28

Considerations for a Biologically Based Risk Assessment for Arsenic[1]

Harvey J Clewell, III[1], Elaina M. Kenyon[2], P. Robinan Gentry[3], Annette M. Shipp[3], and Janice W. Yager[4]

[1]Hamner Institutes for Health Sciences, Research Triangle Park, NC, hclewell@thehamner.org; [2]National Health and Environmental Effects Research Lab, USEPA, Research Triangle Park, NC, kenyon.elaina@epa.gov; [3] ENVIRON International, 1900 N. 18th St. Monroe, LA, rgentry@environcorp.com; [4]University of New Mexico, Albuquerque, NM, 87131-00001, U.S.A., jwyager@salud.unm.edu

The Latest on Lead?

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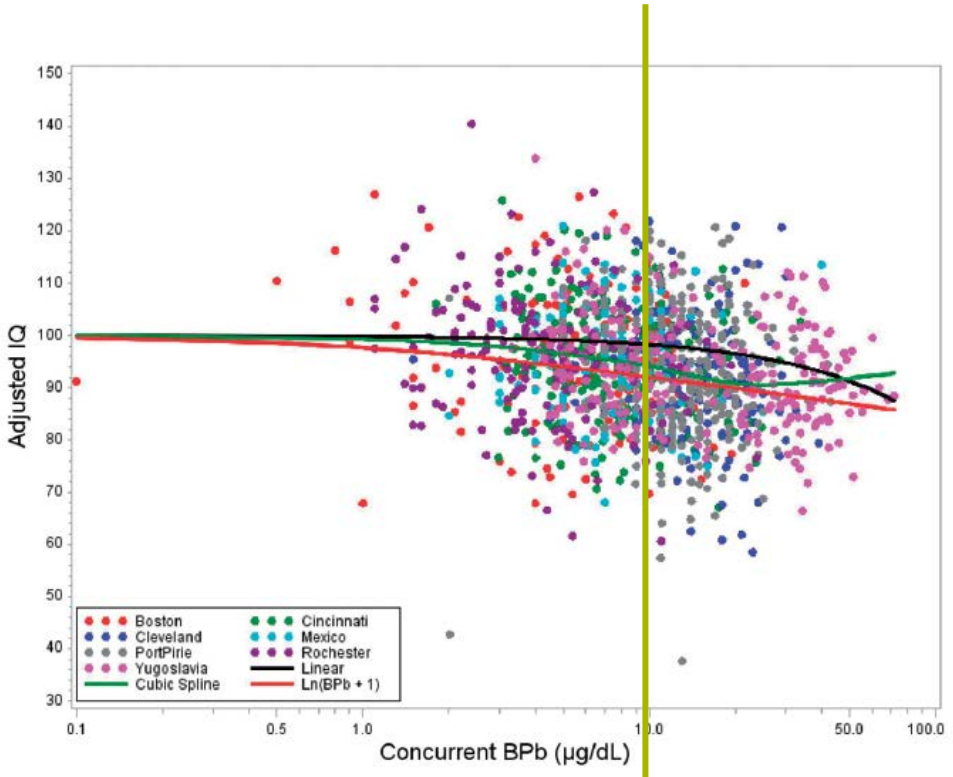
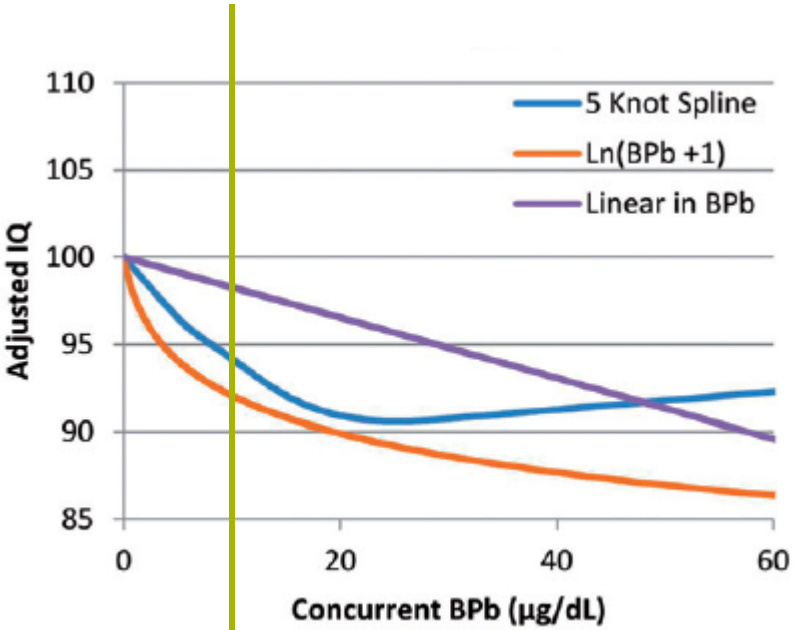
Crump et al., 2013 Crit Rev Toxicol, 2013; 43(9): 785–799.

A statistical re-evaluation of the data used in the Lanphear et al. (2005)





Withdrawn
2002 HCV 10 µg/dL

This work was conducted under contract awarded to ENVIRON International
by International Lead Zinc Research Organization (ILZRO)
Acknowledgement: Cynthia van Landingham (ENVIRON)

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Benchmark Dose Modelling of the 3 most sensitive health concerns

(as per EFSA 2010 modelling evaluations)

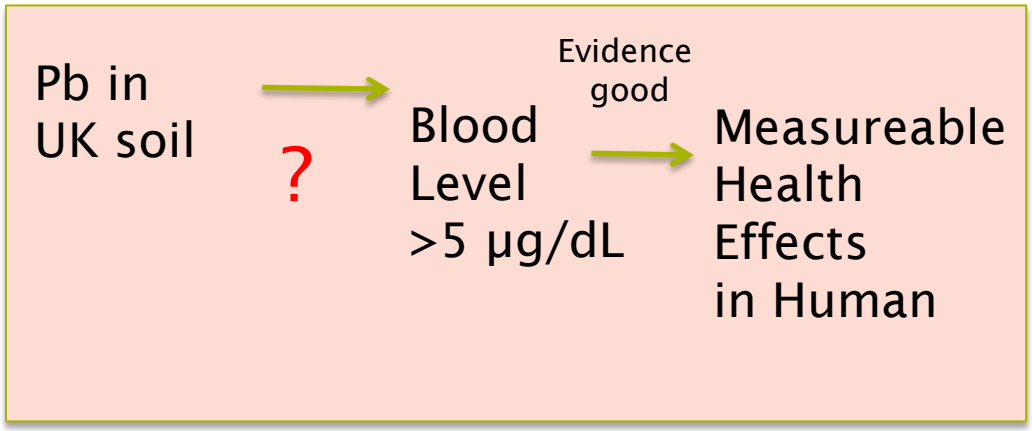
BMDL Value (µg/dL)	BMR	Effect	Human study/ Receptor
1.2	1 point reduction in IQ	Neurobehavioural	Child
1.5	10% increased incidence	Chronic kidney disease: glomerular filtration rates below 60 mL/min	Adult
3.6	1% increase above average 120 mm Hg systolic blood pressure	Cardiovascular	Adult

N.B. 3 key effects at similar blood Pb levels; BMDL – lowest 95% confidence limit

Pb - What the science tells us

Toxicological quantitative evaluations for the three critical effects:

Neurobehavioural
Chronic kidney disease
Cardiovascular effects



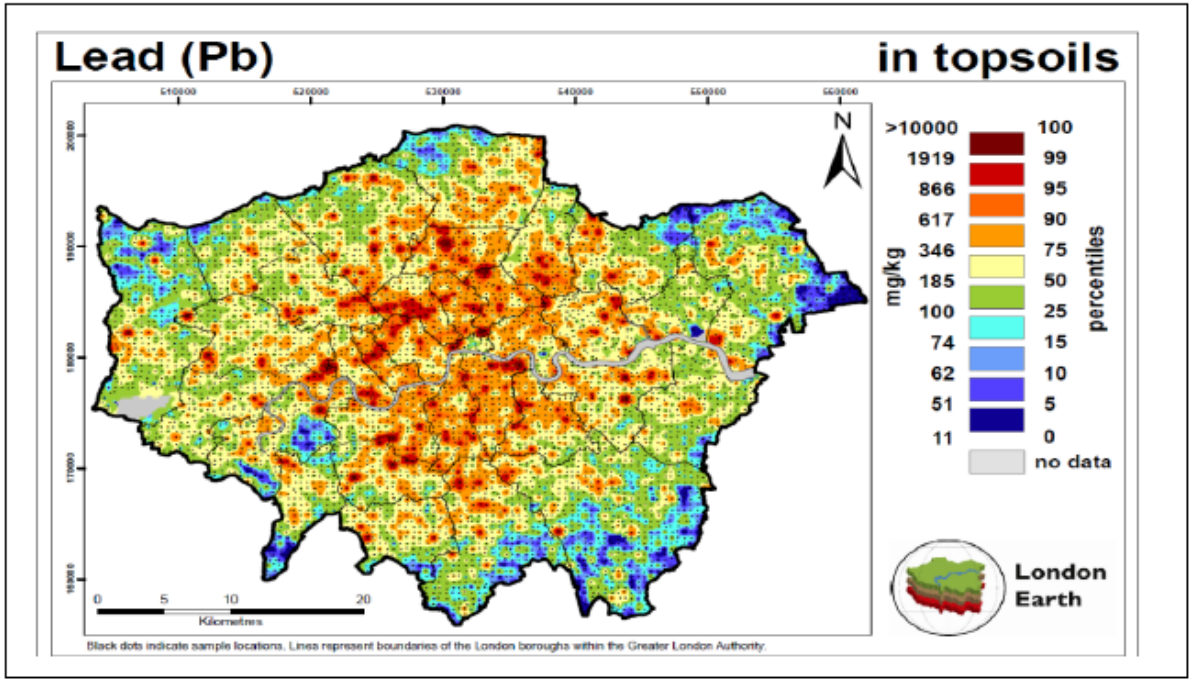
suggests no threshold, and there could be real health concerns to be investigated further in populations of children and adults exposed chronically to blood lead levels higher than 5 µg dL^{-1}.

Pb in Urban London Soil – 2011 data

From page 8 of the SOBRA 2011 Lead workshop report

Table 6: Typical concentrations of lead in London soils

(all mg/kg)	No. Samples	Minimum	Median	Mean	Maximum
London	6288	11	185	301	>10,000



British Geological Survey (2011). London Earth: Lead in surface soils. G-BASE geochemical map, Keyworth, Nottingham, UK

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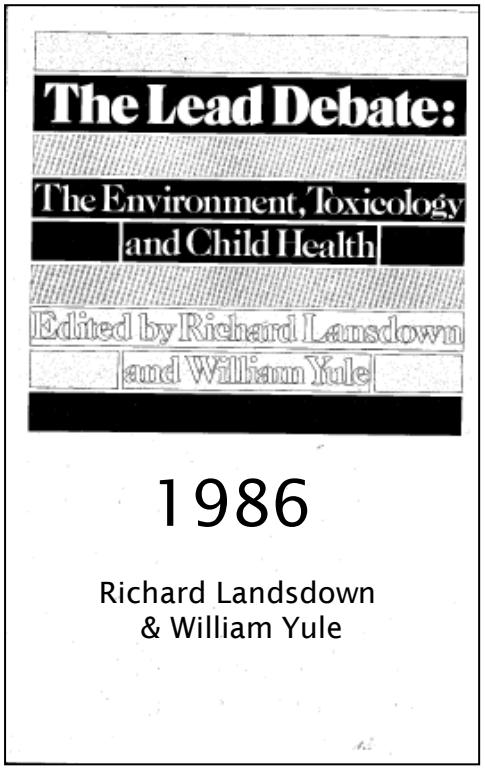
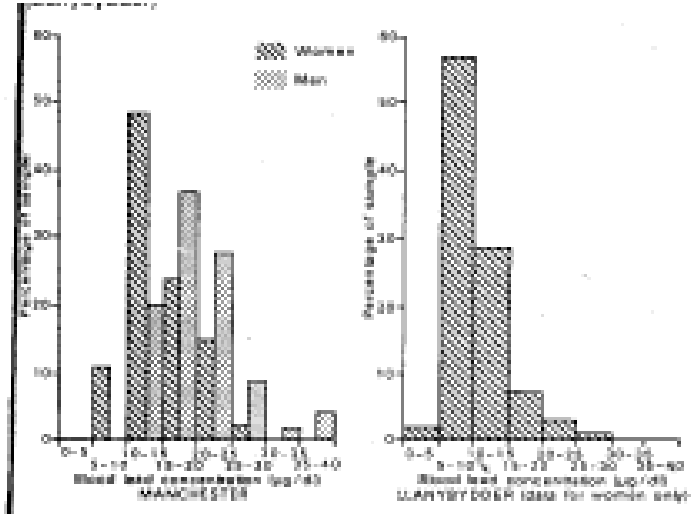
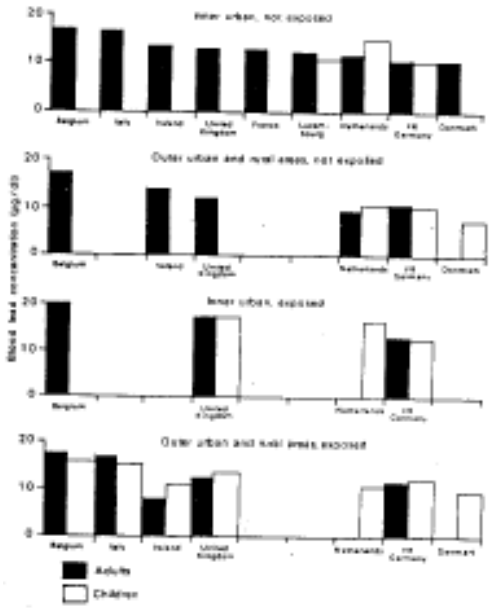
A Brief History of UK Lead Monitoring

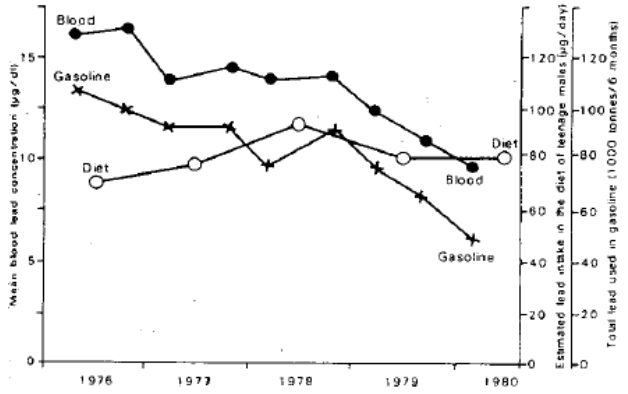


1986

Richard Landsdown
& William Yule







EEC Directive called for blood lead screening
UK studies in 1979 and 1981

UK Blood Lead Monitoring Programme 1984-1987
Dept of Environment – reduction of Pb in petrol

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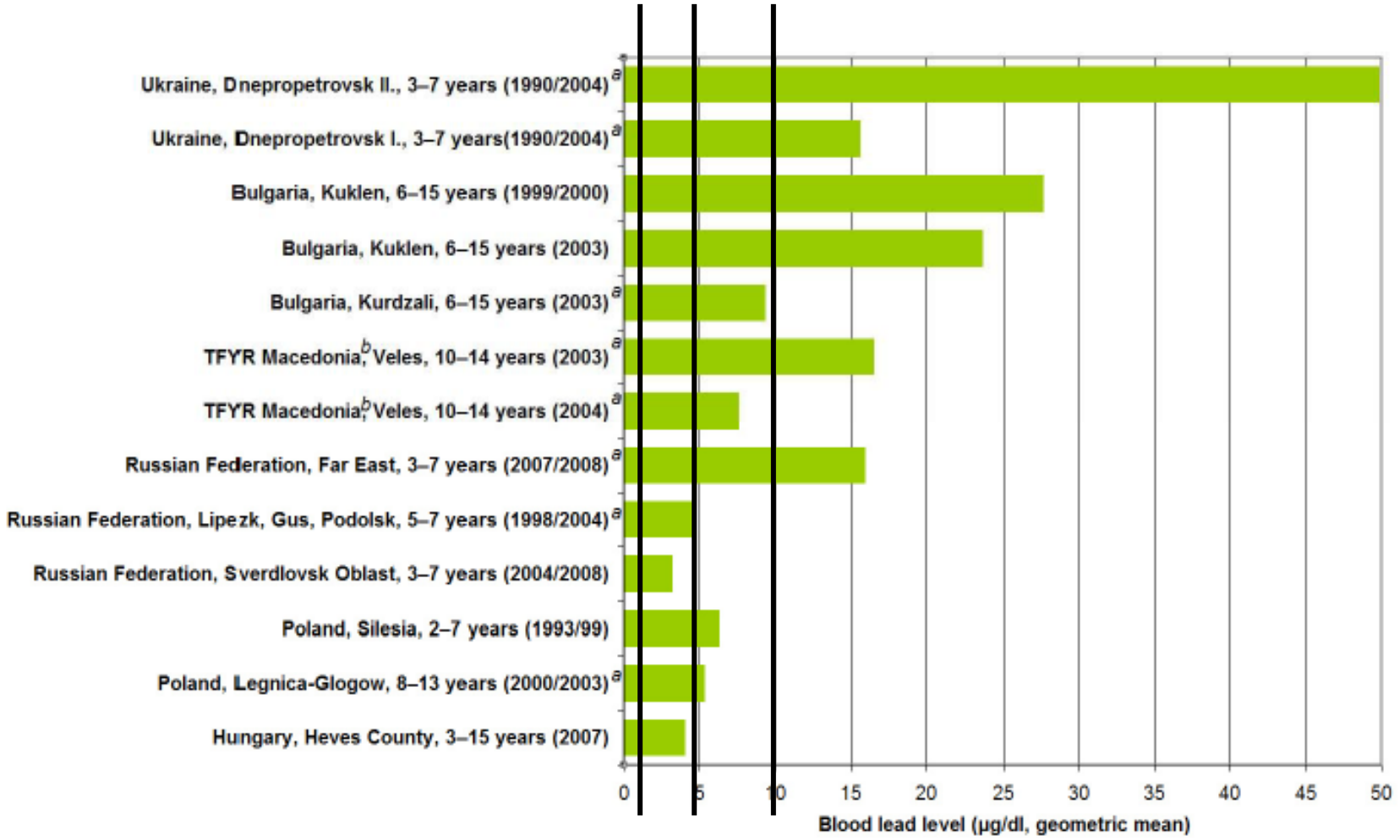
WHO/Europe

December2009

LEVELS OF LEAD IN CHILDREN'S BLOOD. FACT SHEET 4.5

Fig. 2. Mean blood lead levels in children measured in selected areas with specific local sources of lead exposure



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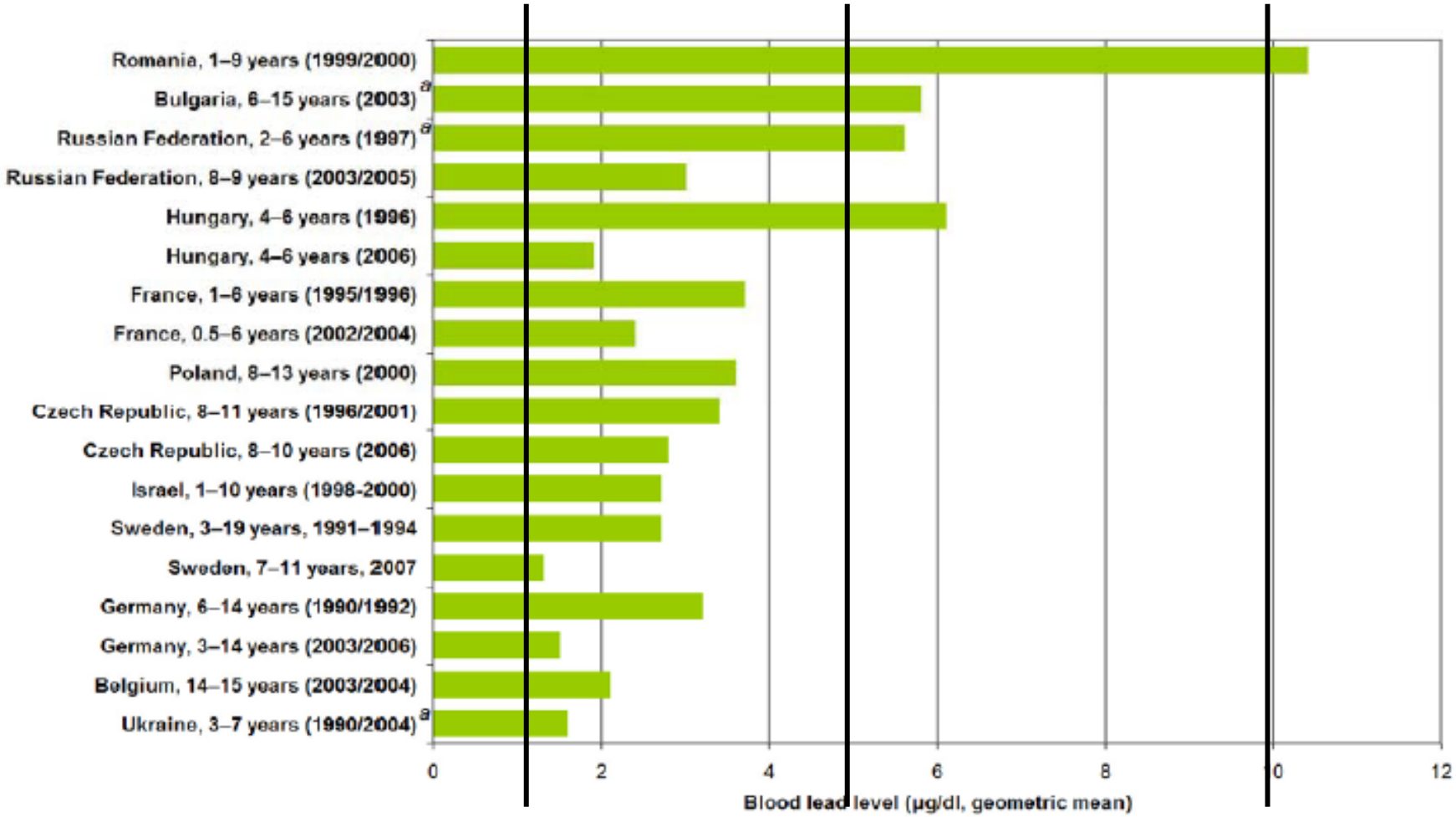
WHO/Europe

December2009

LEVELS OF LEAD IN CHILDREN'S BLOOD. FACT SHEET 4.5

Fig. 1. Mean blood lead levels of children measured in areas without significant local sources of lead exposure in selected European countries, 1991–2006



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Pb the Way Forward – a personal view

- Too many uncertainties on whether current Pb in UK soil actually results in blood Pb levels of >5 µg/dL, >10 µg/dL etc

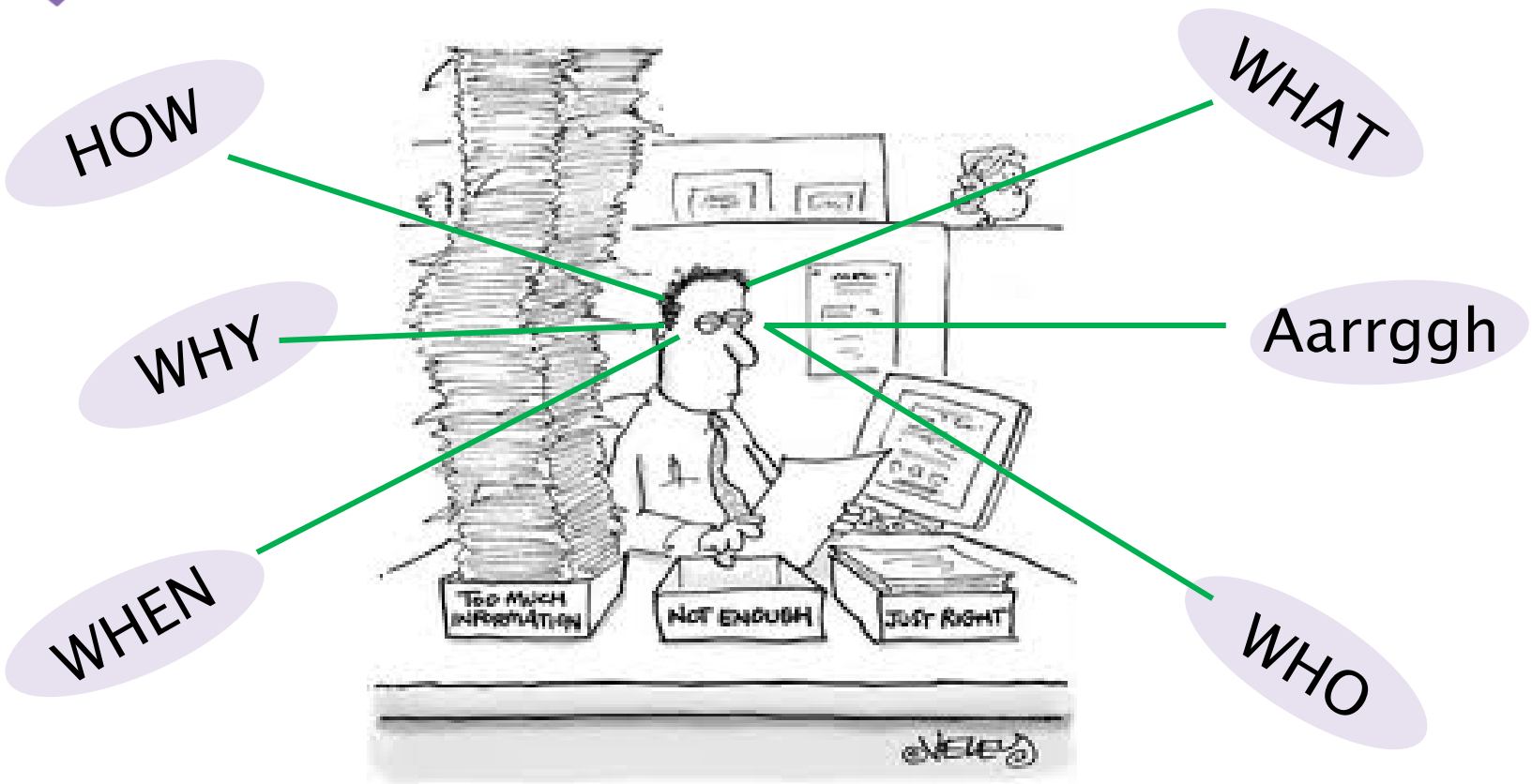
Is there an issue to address for Pb in UK soil?

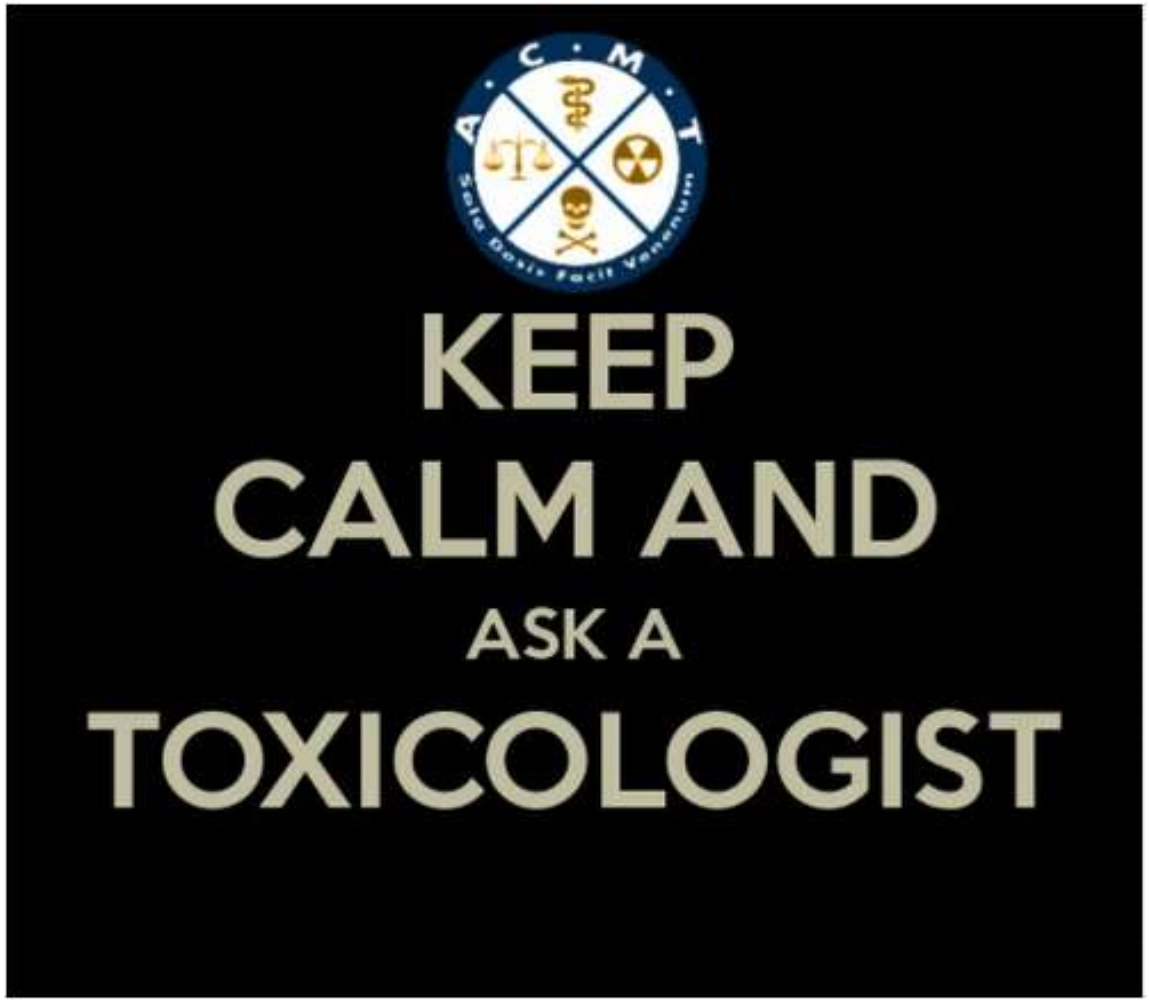
→ We don't know

Calls for: A multi-disciplinary exercise on the design, benefits and risks of undertaking blood biomonitoring of Pb in UK populations

Health scientists, toxicologists, child health specialists, exposure modellers, biomonitoring scientists, policy makers, socio-economic analysts, statisticians etc.

Arsenic, Cadmium, Lead – What to do?




KEEP
CALM AND
ASK A
TOXICOLOGIST