Toxicology behind the scenes

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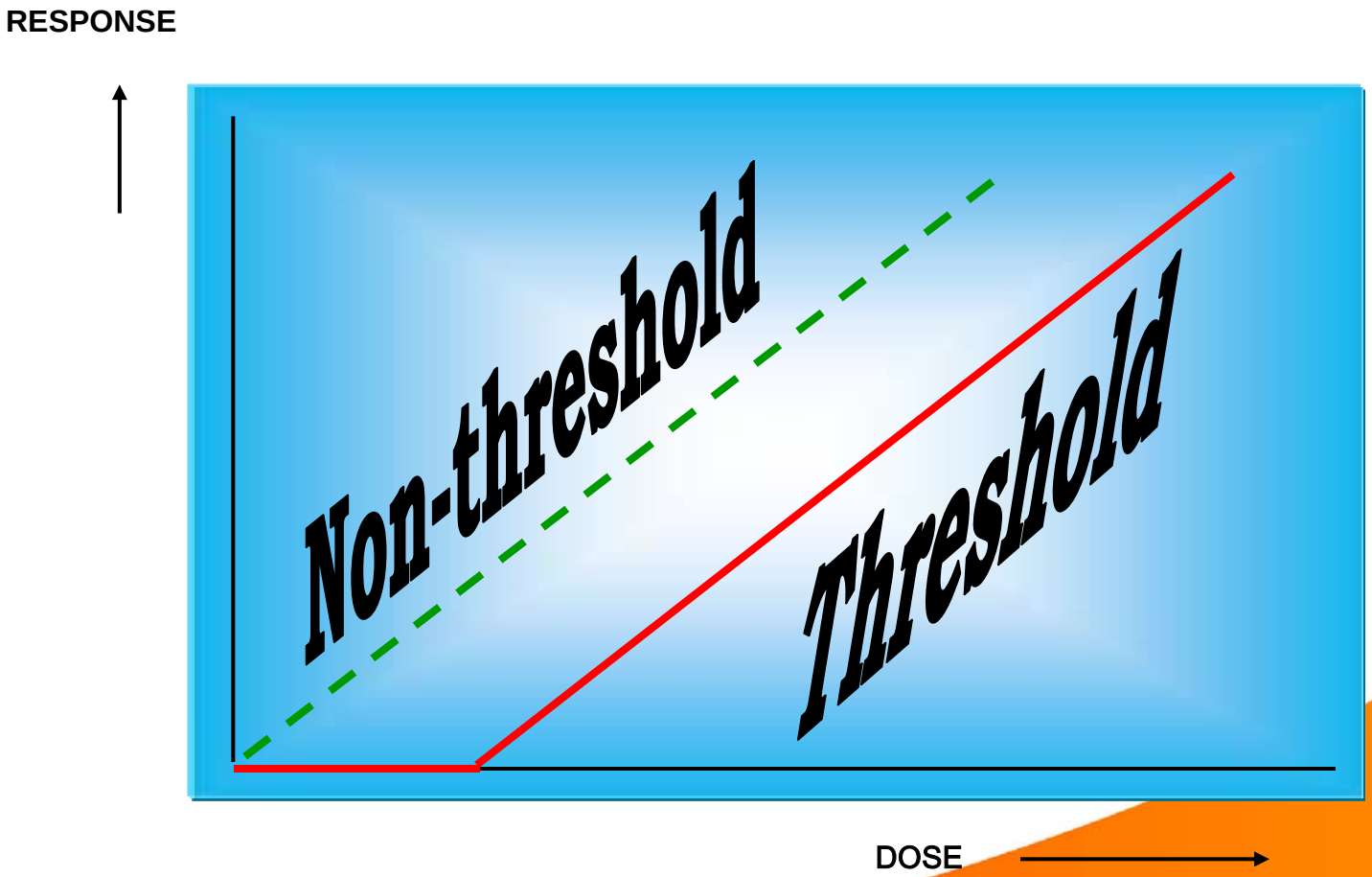
Threshold and non-threshold effects



Non-threshold chemicals

Usually genotoxic carcinogens.

Assumed that any exposure, no matter how small, has the potential to cause harm.

Cannot derive a level of exposure without risk.

Alternative = derive an exposure associated with *minimal risk*.

Non-threshold chemicals

Health Criteria Value =Index dose (ID)

'Estimate of the daily intake of a chemical that can be experienced *over a lifetime* with a minimal cancer risk'

Exposure should be "as low as reasonably practicable (ALARP)"

Derivation of HCVs for non-threshold chemicals

- Quantitative dose-response modelling

  quantitative risk assessment (QRA) on human data

- Non-quantitative extrapolation

  point of departure and large uncertainty factor on animal carcinogenicity bioassay data

Quantitative risk assessment (QRA)

Produces numerical estimates of cancer risk.

Based on estimates of the dose corresponding to an *excess lifetime cancer risk* (ELCR) of 1 in 100,000 (10^{-5}) (Defra, 2008)

If insufficient human data are available, data from animal carcinogenicity studies are often used.

COC does not recommend the use of QRA based on animal data for routine risk assessment

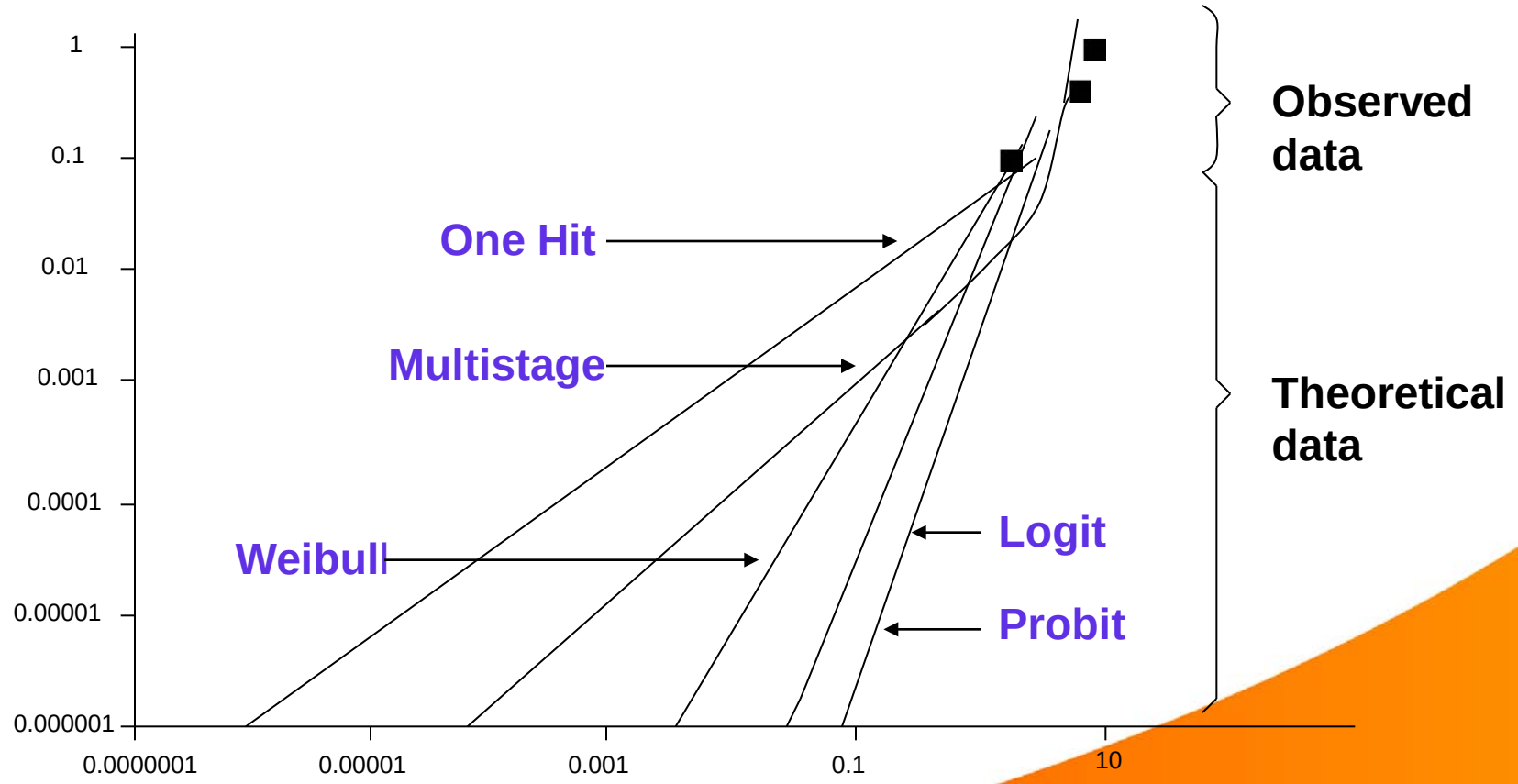
Quantitative risk assessment (QRA)

COC does not recommend the use of QRA based on animal data for routine risk assessment

Why?

- Significant uncertainties
  - Models are not based on biological mechanisms or carcinogenic processes
  - Different models give different cancer risk estimates
  - Data are extrapolated well outside the range of doses given to the animals.

Different quantitative cancer risk models



Non-quantitative extrapolation

Animal data used to derive a "*Minimal Risk Level (MRL)*"

"an estimate of daily human exposure to a chemical identified by expert judgement that is likely to be associated with a negligible risk of carcinogenic effect over a specified duration of exposure (usually a lifetime)" (COC, 2004)

"there is also an additional requirement to keep exposure to "as low as reasonably practicable (ALARP)"

Non-quantitative extrapolation

Pragmatic approach

Does not attempt to quantify cancer risk

Benchmark dose modelling of the tumour data

Application of a large UF (10,000) to the critical $BMDL_{10}$

Benchmark dose

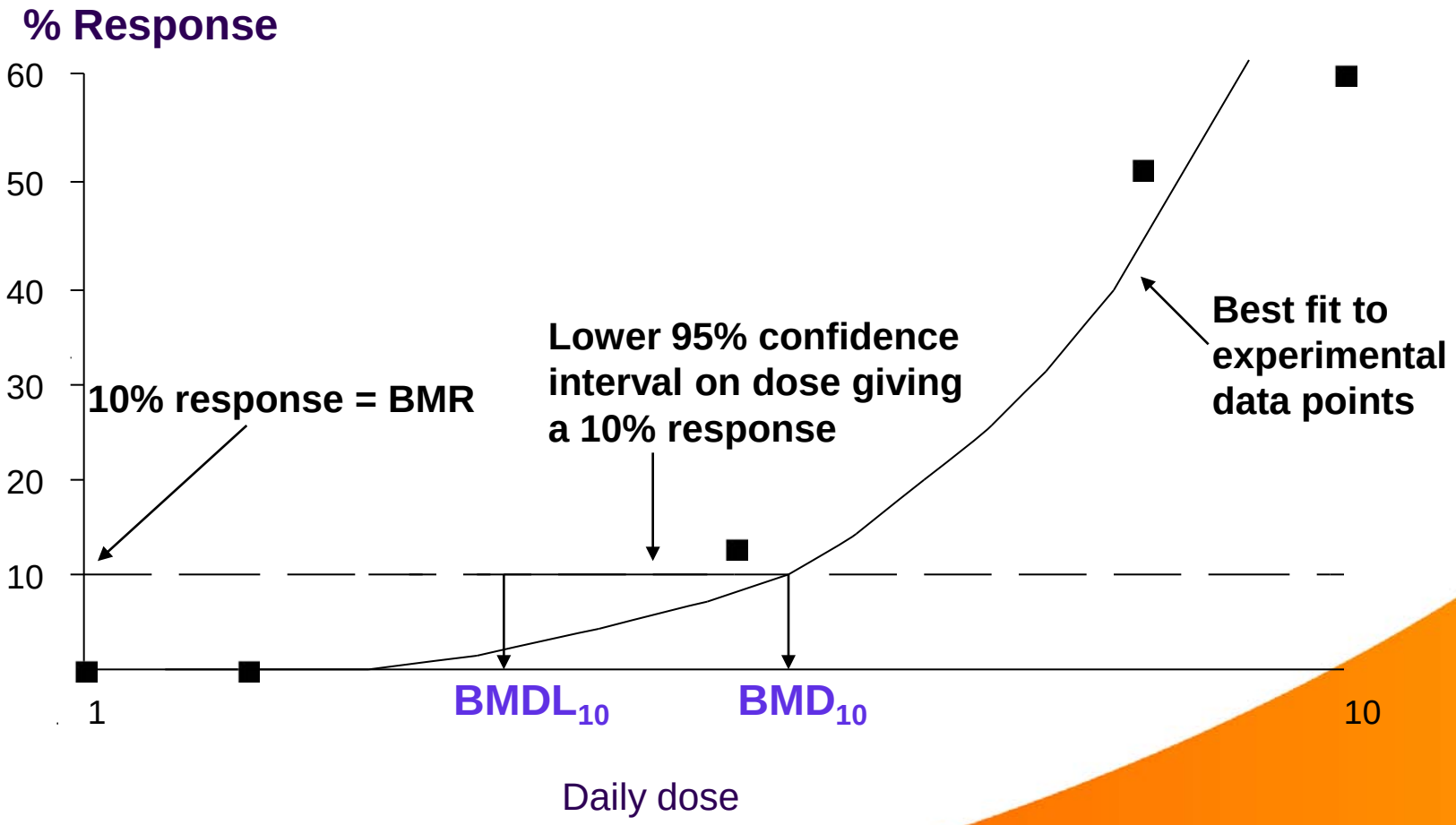
- Benchmark dose (BMD)

– dose that causes a pre-determined change in response (5 or 10%)

- BMDL10

– 95% confidence limit on the dose that causes 10% increase in tumour response

The benchmark dose



Non-quantitative extrapolation

Approach is similar to threshold chemicals:

$$ID = \frac{POD}{Uncertainty\ factors}$$

Point of Departure (POD) = BMDL or T25.

Uncertainty Factor = 10,000

(interspecies and intraspecies differences, seriousness of endpoint and no threshold)

Risk characterisation

Comparison between the estimated human exposure and the HCV

Exposure < HCV = risk to humans is not of concern

Exposure > HCV = implications are dependent on whether the HCV is based on threshold or non-threshold effects

Risk characterisation

In the context of Part 2A –

Exposures ≤ ID = low level of risk

Exposures > ID = increased risk to health (*might* represent a significant possibility of significant harm)

The significance of an exceedance requires expert judgement, but often will not be quantifiable.

Risk characterisation

Points to consider are:

How much is the HCV exceeded by?

For how long is the HCV exceeded?

What endpoint is the HCV based on? Is it a chronic effect or an acute effect?

How steep is the dose-response curve?

Must be considered on a case-by-case basis

The *Margin of Exposure* (MOE) approach may be useful

Margin of Exposure approach for genotoxic carcinogens

A technique developed to assist in the management or communication of risks from genotoxic carcinogens (or in risk characterisation)

Ratio between the Point of Departure (POD) and estimated chemical exposure (in mg/kg bw/day or mg/m^3)

$$MOE = \frac{POD}{Exposure}$$

MOE – Current COC recommendations

MOE Band	Interpretation
<10,000	May be a concern
10,000 – 1,000,000	Unlikely to be a concern
>1,000,000	Highly unlikely to be concern

Current RA approaches (oral)

CURRENT EA GUIDANCE (TOX 2)

- Index Dose (ID) for BaP – “Regulatory equivalent limit”
- Based on WHO GV for water
- ELCR of 1 in 100,000
- Forestomach tumours in mice
- Minimal risk - doesn’t cover other PAHs

Possible alternative approaches

- Quantitative risk assessment
  - not endorsed by COC for risk assessment
- Assess individual PAHs (non-quantitative extrapolation)
  - not enough data for all PAHs
- Toxic equivalency factors (TEF) approach
- Surrogate marker approach

TEFs

Things to consider:-

- Do PAHs have a common mechanism of action?
- Can TEFs be generated for enough PAHs to reflect mixtures present in environmental matrices?
- Are TEFs derived from inhalation or skin painting studies a sufficient basis for comparison?
- Can TEFs reflect potential synergistic or antagonistic modulation of PAH carcinogenicity?
- Can high potency PAHs, such as DB[a,l]P be assessed by TEFs?

TEFs

Opinion by authoritative bodies:

✗ EFSA's CONTAM Panel, US EPA and COC do not support a TEF approach for PAHs

✓ TEFs have been endorsed by RIVM to derive Maximum Permissible Risk Levels

✓ CCME used a potency equivalence factors approach (PEF) in the derivation of soil quality guidelines for PAHs

Surrogate Marker

Things to consider:-

- Is the surrogate marker (BaP) is present in all soil samples?
- Is the Culp study representative?
  - Uses a coal tar mixture from manufactured gas plant waste sites
  - Unknown levels of DB[a,l]P
  - Low levels of DB[a,h]A
- Is the profile of PAHs in soil, relative to surrogate marker, similar in all samples and similar to toxicity study?
- Does the carcinogenicity of mixture increase linearly with dose?

Surrogate marker

Opinion by authoritative bodies:

✓ Has been used in risk assessment of food by EFSA

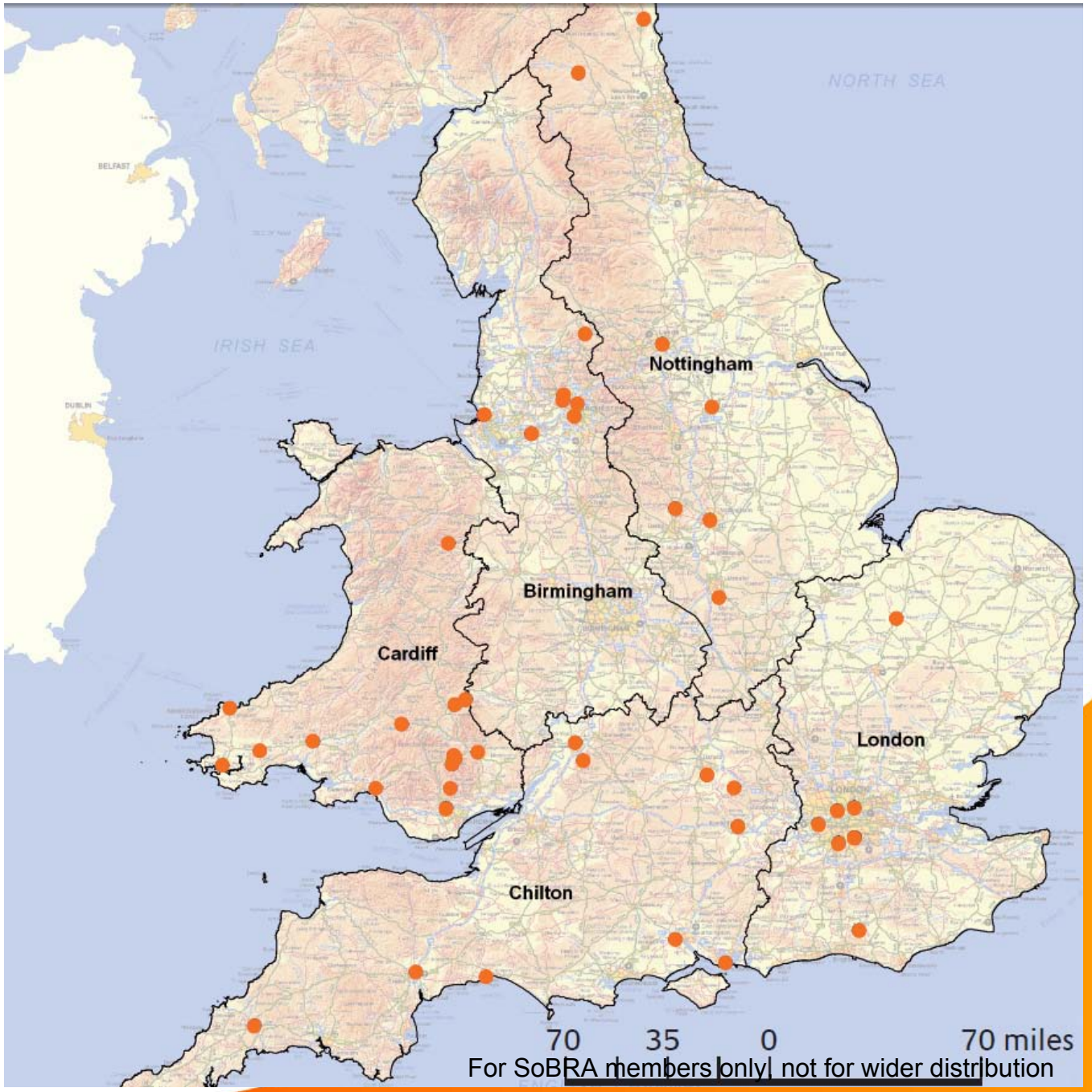
✓ Favoured approach by US EPA

✗ RIVM stated ‘surrogate marker approach cannot be used for oral exposure to PAH at soil contaminated sites due to the wide variety in composition of PAH mixtures at such sites’

HPA research

- Data from 52 sites

(1848 samples)



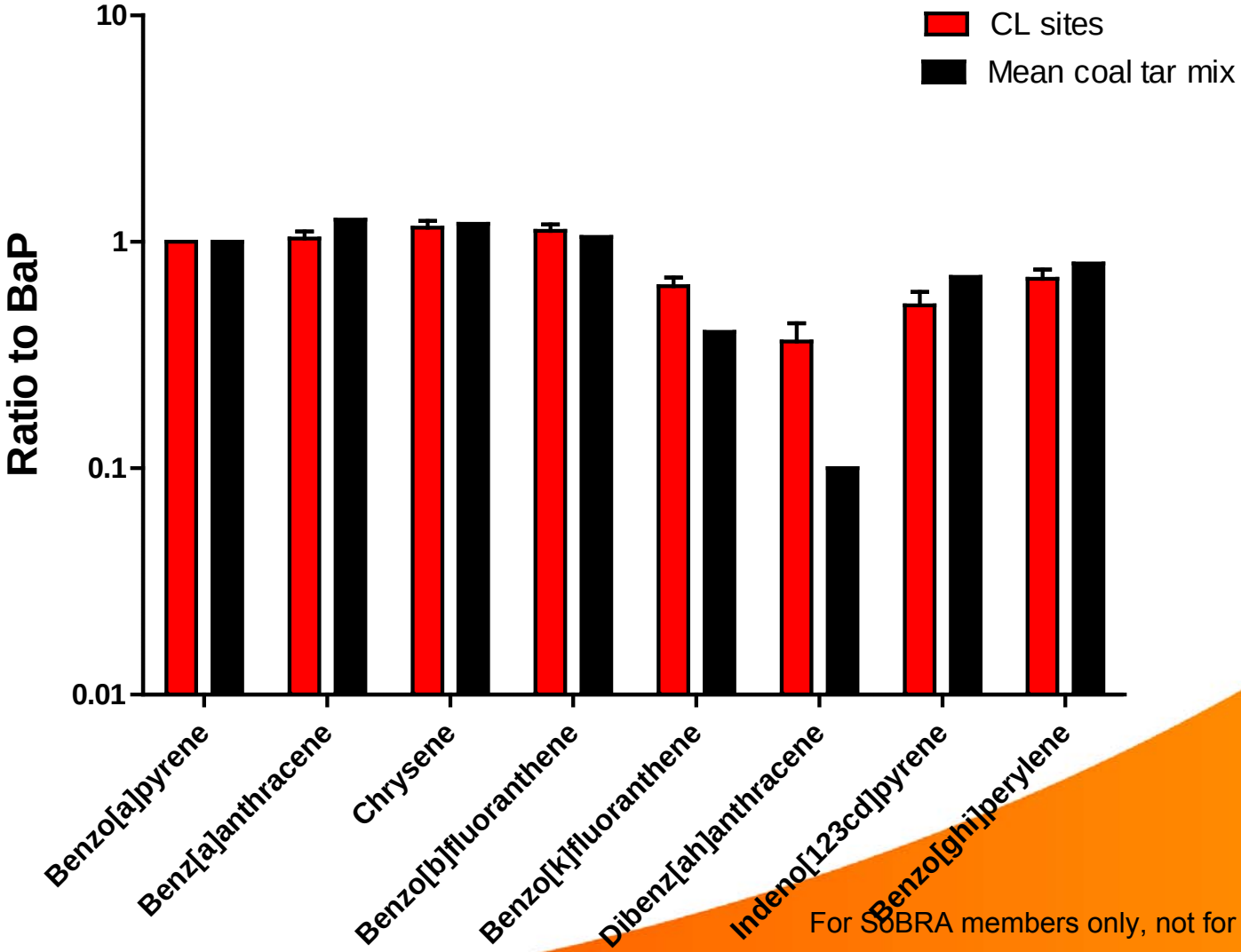
HPA research – site data

- BaP present in all sites
- Absolute conc. of BaP is variable but ratios to BaP are similar
- Narrow confidence range indicates levels stable relative to BaP and BaP good predictor of PAHs in soil

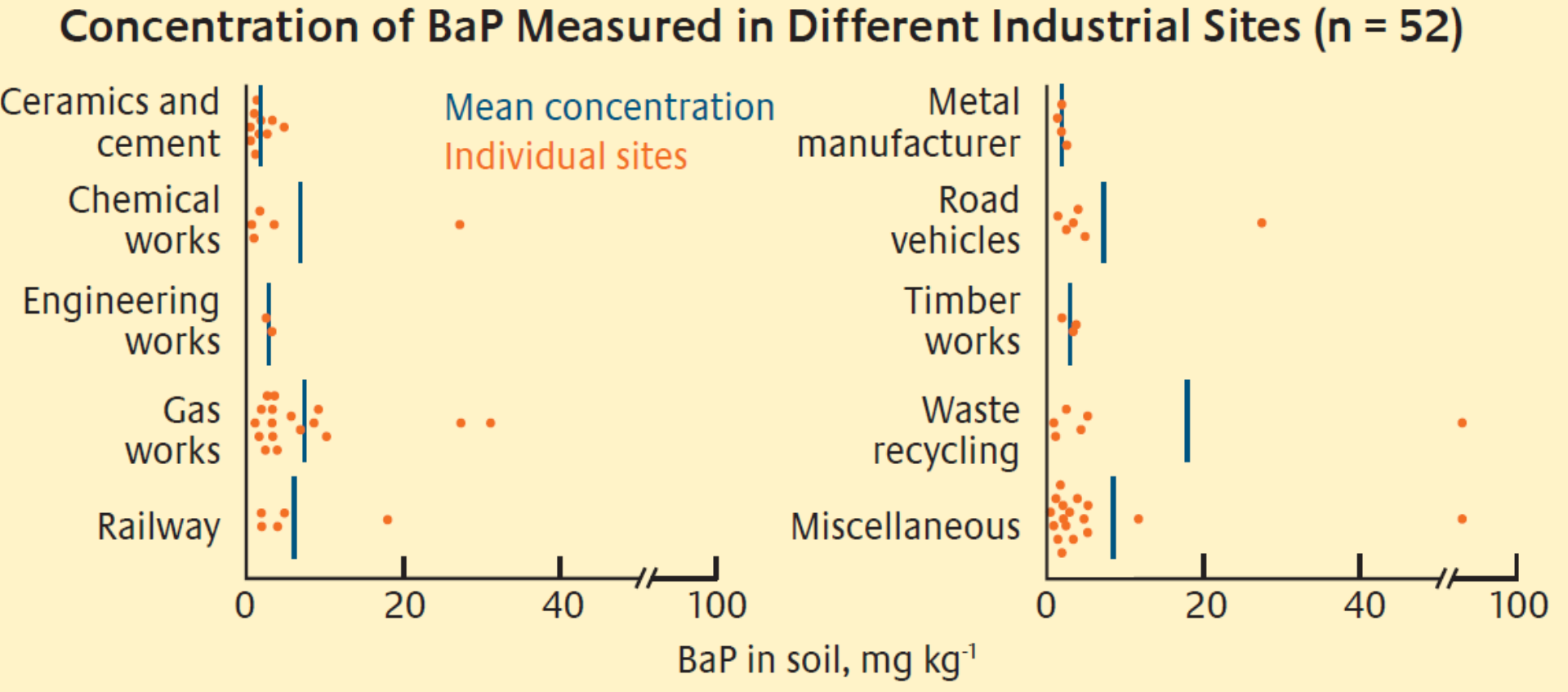
HPA research – site data

PAH	Mean ratio to BaP	Minimum	Maximum	Lower confidence limit	Upper confidence limit	Confidence range
Benz[a]anthracene	**1.03**	0.47	2.16	0.95	1.11	**1.17**
Chrysene	**1.15**	0.60	2.09	1.07	1.23	**1.15**
Benzo[b]fluoranthene	**1.12**	0.54	1.67	1.05	1.19	**1.13**
Benzo[k]fluoranthene	**0.64**	0.28	1.15	0.58	0.70	**1.21**
Dibenz[ah]anthracene	**0.37**	0.07	1.36	0.30	0.44	**1.47**
Indeno[123-cd]pyrene	**0.53**	0.15	1.71	0.45	0.61	**1.35**
Benzo[ghi]perylene	**0.70**	0.35	1.74	0.64	0.76	**1.19**

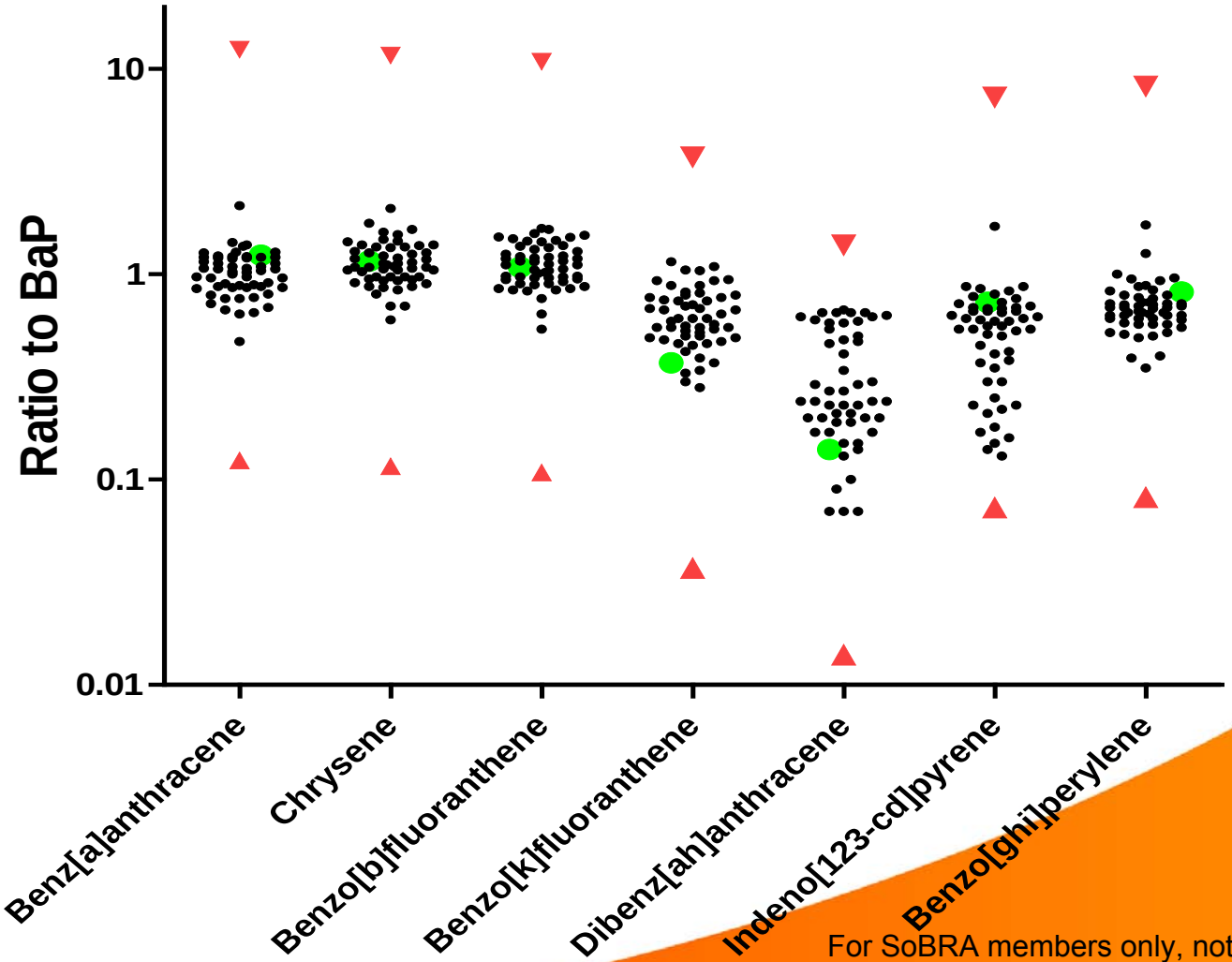
Profile of PAHs in UK soils compared to Culp et al study



EA Industrial profiles



Profile of PAHs in individual sites compared to Culp et al study



Conclusion - TEFs

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Conclusion – surrogate marker

- Is the BaP is present in all soil samples?
- Is the profile of PAHs in soil, relative to surrogate marker, similar in all samples and similar to toxicity study?
- Does the carcinogenicity of mixture increase linearly with dose?
- Is the Culp study appropriate?
- Overall – prudent to use surrogate marker approach?

Conclusions

This is interim advice pending publication of the EA non-statutory guidance.

The approach is being considered by EA in developing their revised guidance