Chemical health risk assessment

Dispelling urban myths about uncertainty factors

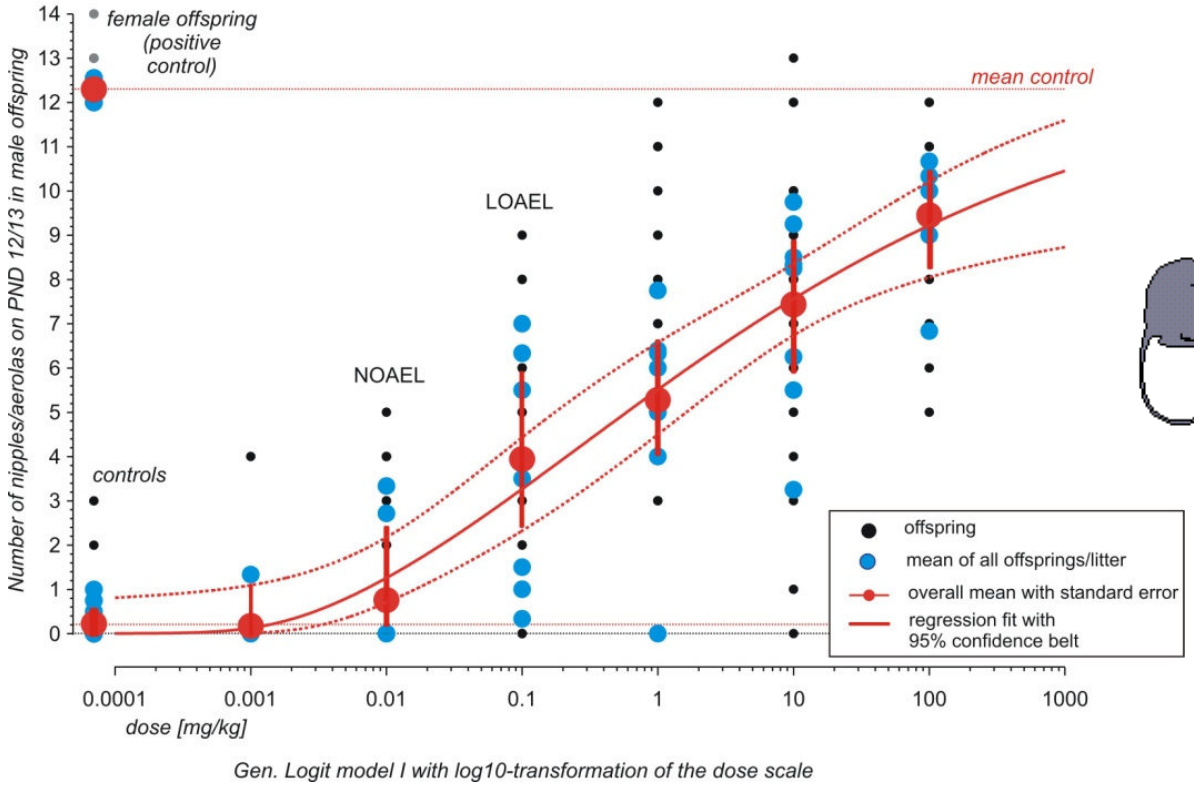
Olwenn Martin
Institute for the Environment,
Brunel University

FOOD PACKAGING FORUM WORKSHOP
17TH OCTOBER 2013, *ZURICH*

Brunel UNIVERSITY LONDON

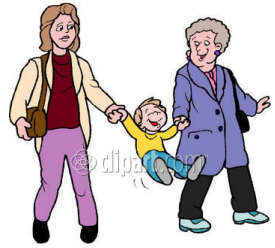
OAK FOUNDATION

Do default uncertainty factors protect against mixture effects?



Gen. Logit model I with log10-transformation of the dose scale

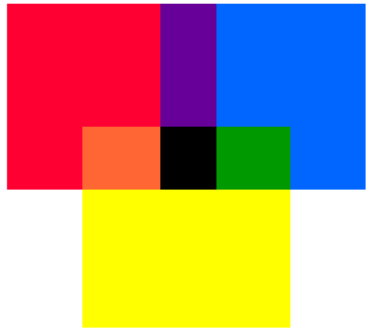
/100



Brunel UNIVERSITY LONDON

OAK FOUNDATION

Do default uncertainty factors protect against mixture effects?



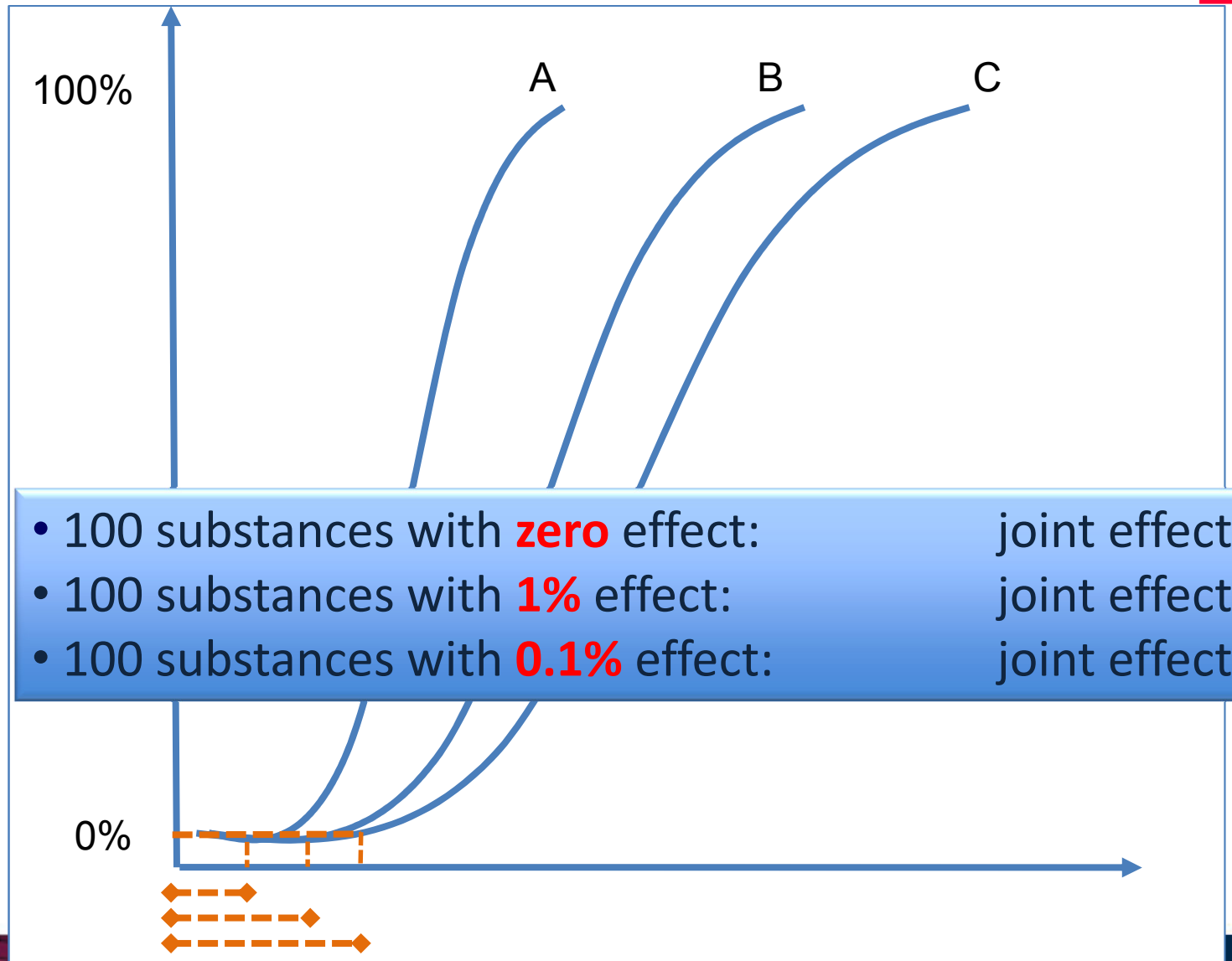
Mixture toxicology

- Similar mode-of-action → **Concentration addition**
- Dissimilar mode-of-action → **Response addition**
- Interactions (potentiation, synergism, antagonism)

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Response addition



- 100 substances with **zero** effect: joint effect = **0%**
- 100 substances with **1%** effect: joint effect = **63%**
- 100 substances with **0.1%** effect: joint effect = **9.5%**

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Urban myths about the default factor

1. Intended to protect against mixture effects
2. A worst-case scenario
3. Overly conservative
   - Interspecies differences
   - Intraspecies differences
   - Multiplication

Historical background

Data

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Mixture effects

Lehman and Fitzhugh (1954)

- Inter-species (animal-to-human) variability
- Inter-individual (human-to-human) variability
- Sensitive human populations due to illness
- **Possible synergistic action of contaminants**.

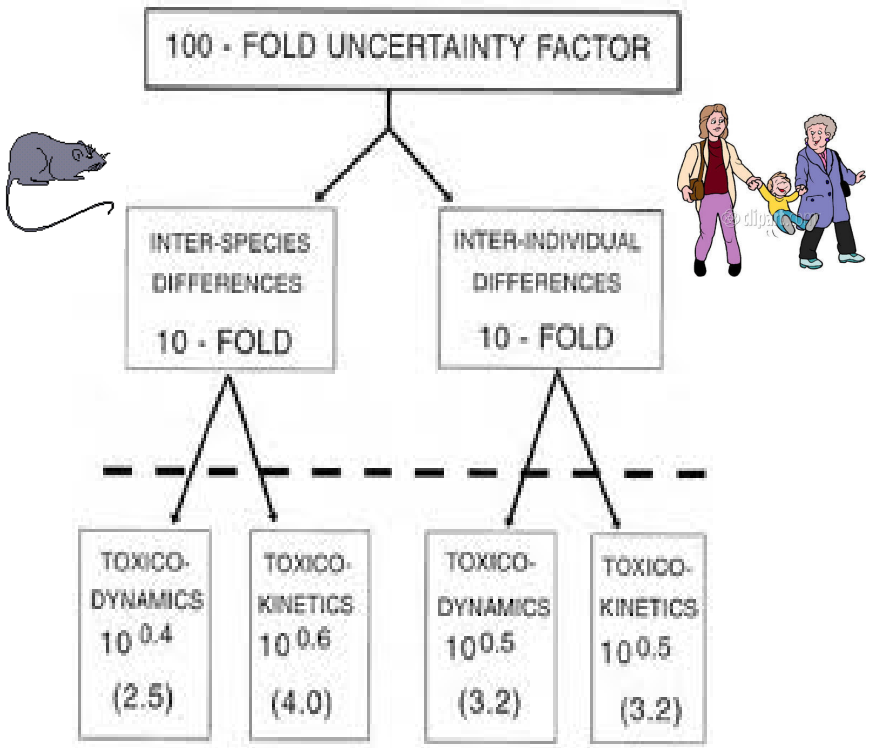
Vetorazzi (1977)

- Differences in susceptibility between animals and humans,
- Variations in sensitivities in the human population
- The fact that the number of animals tested is small
- Difficulty in estimating human intake
- **Possibility of synergistic action among chemicals**

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Mixture effects



Yes, the default factor of 100 was originally intended to account for mixtures

BUT, this intention was abandoned 30 years ago.

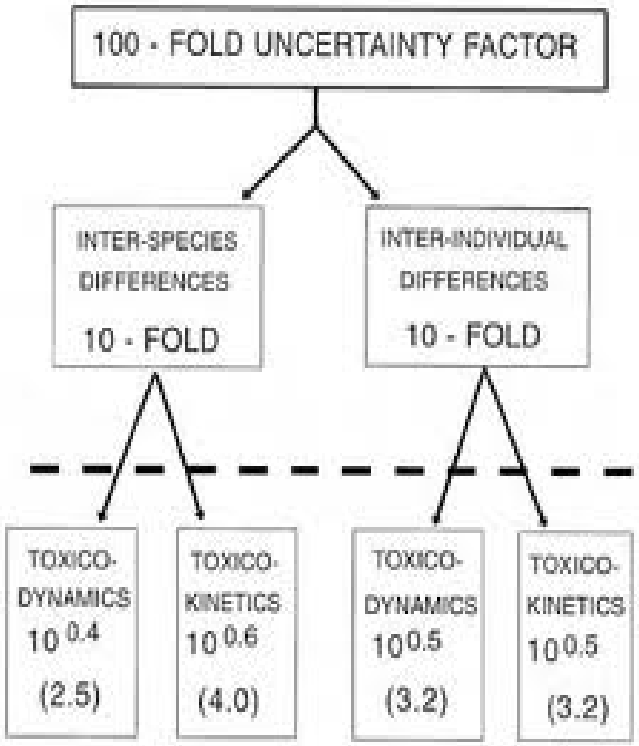
Renwick, 1993 - IPCS

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Worst-case scenario?

Renwick, 1991



Renwick, 1993 - IPCS

Trans-species extrapolation	
1	Toxicity due to a metabolite not detected in humans; impaired elimination and/or higher sensitivity than humans
10	Toxicity due to a parent compound or a metabolite with similar AUC; expected differences in kinetics
100	Greater elimination or impaired sensitivity in animals; toxicity due to a metabolite with higher AUC in humans
Human heterogeneity	
1	Limited absorption
10	Compound eliminated by pathways showing normal variability (2-3-fold) and toxicity not immunologically mediated.
100	Compound metabolised by enzyme showing great inter-individual variability or toxicity immunologically mediated

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Level of protection

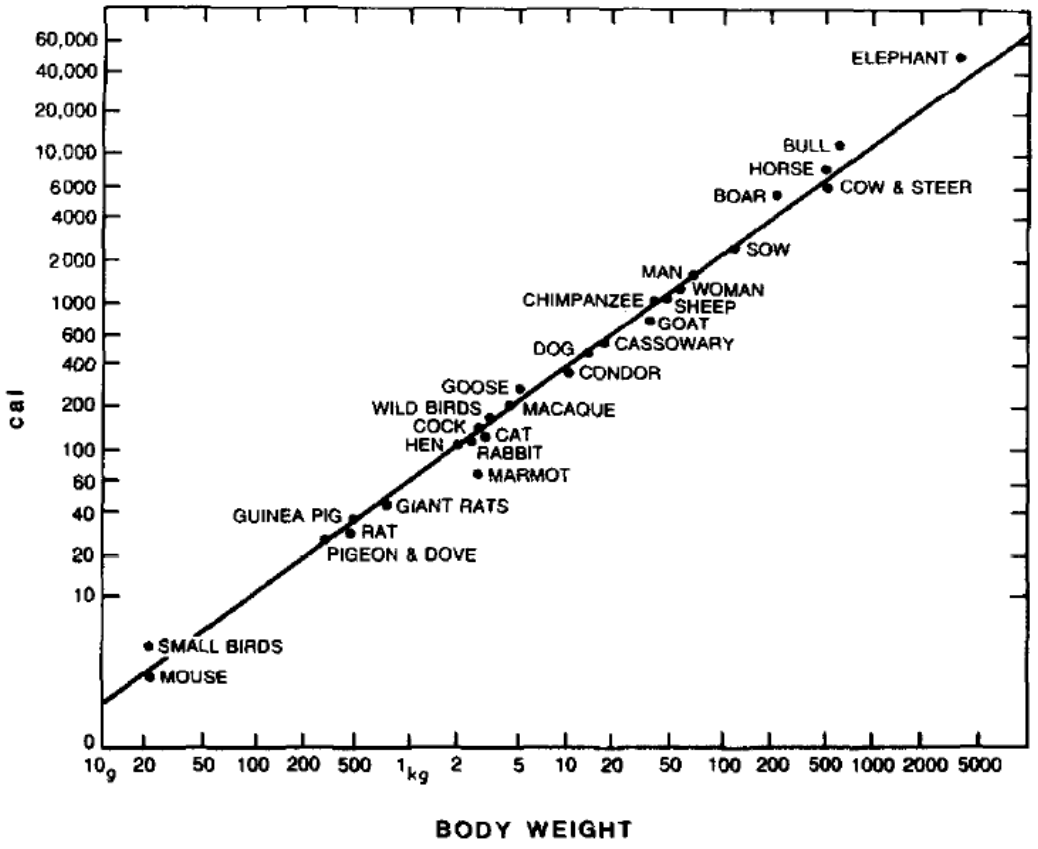
Acceptable Daily Intake
"the daily dosage of a chemical, which, during an entire lifetime, appears to be **without appreciable risk** on the basis of all the facts known at the time" (JECFA 1962).

"Straw Man" Proposal (Hattis et al. 2002)
• The daily dose rate that is expected (with 95% confidence) to produce less than **1/100,000 incidence over background** of a minimally adverse response in a standard **general population** of mixed ages and genders, or
• The daily dose rate that is expected (with 95% confidence) to produce less than **1/1,000 incidence over background** of a minimally adverse response in a definable **sensitive subpopulation**.

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Over-conservative? Allometry



Mouse-to-elephant diagram according to Benedict (1938). Correlation for caloric turnover rate and body weight for various species (Davidson et al., 1986)

$Y = a\ BW^n$
n = 0.67 for body surface area
n = 0.75 for metabolic rate

Neurotoxicity
Relative brain weight and oxygen consumption (e.g. Pb, PCBs)
Reproductive toxicity
Relatively low male fertility (sperm count at the lower limit required for full fertility) compared with experimental animals

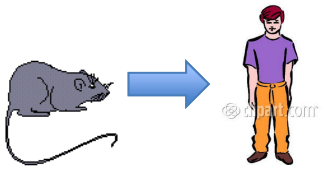
Brunel UNIVERSITY LONDON

OAK FOUNDATION

Over-conservative?

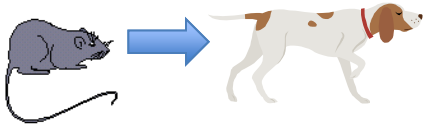
Differences between animal and humans

- 9 datasets
- Mostly acute toxicity of chemotherapeutic drugs
- Medians in agreement with allometry
- $LD10_{rat}/MTD_{human}$ > 10 for ~ 20% chemotherapeutic drugs



Differences between animals species

- 8 datasets
- Wider range of chemicals
- Medians in agreement with allometry
- Factor 10 = 71st percentile (Bokkers, 2007)



Limitations

- MTD associated with toxic effects
- Short-term studies of acute toxicity rather than chronic exposure
- Endpoints may differ
- Chemotherapeutic drugs administered by injection
- Not representative of the universe of general chemicals
- MTDs in humans likely to be more sensitive to toxic effects than healthy adults

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Over-conservative?

Genetic factors
Age (infants, elderly)
Disease

Gender
Stress, diet, pregnancy …

Data from animals (Dourson & Stara (1983), data from Weil (1972))

- Dose-response slopes from 490 acute lethality of carcinogenic agents
- Default factor of 10 would cover **88% of chemicals**

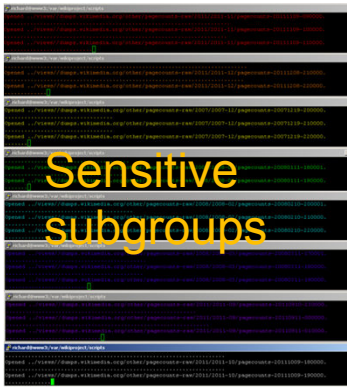
Inter-individual differences in healthy adults

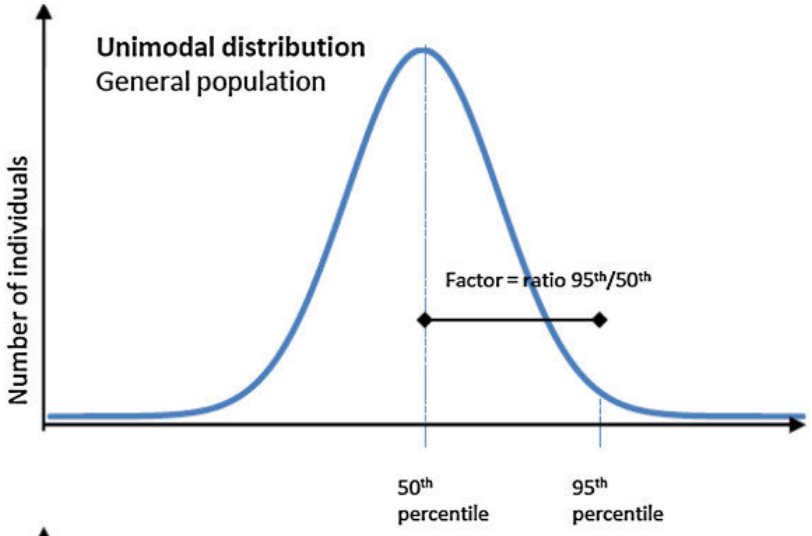
- Data from therapeutic or occupational exposures
- Renwick and Lazarus (1998) - about **162 persons/million**
- Hattis *et al* (1999) - **8 persons/100,000** (median); **2-3 persons/1,000** (95% of chemicals)

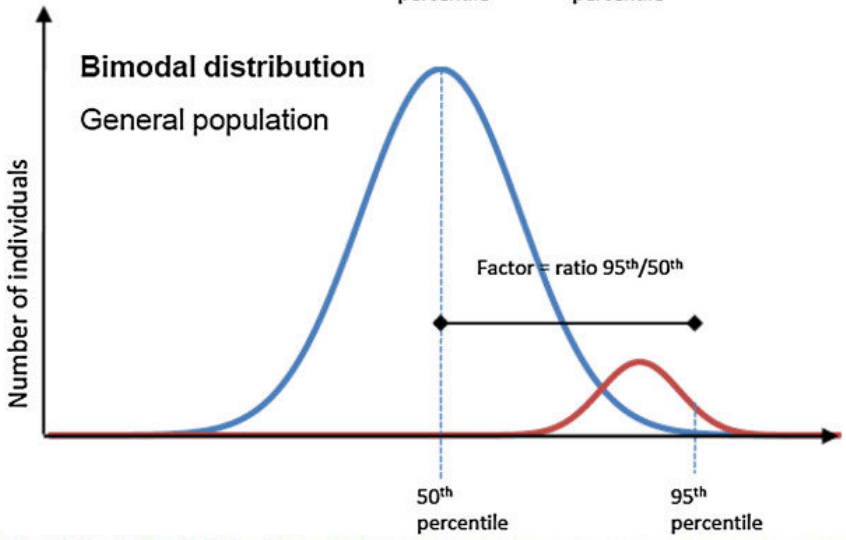
Brunel UNIVERSITY LONDON

OAK FOUNDATION

Over-conservative?







Brunel UNIVERSITY LONDON

OAK FOUNDATION

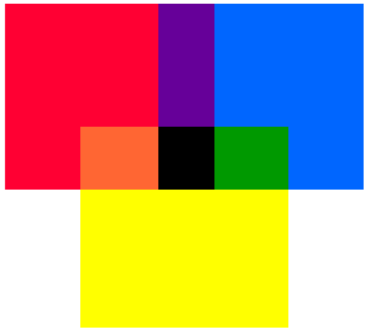
Over-conservative?

Reference	Interspecies data	Intraspecies data	Result
Sheehan et al. 1990	190 chemicals, Animal species	238 chemicals, Adult and newborn animals	GM: 6 100: 88th percentile
Baird et al. 1996	69 pesticides, Animal species	Dose-response from 490 acute lethality experiments in rats	GM: 10/21 100: 64/83th percentile
Vermeire et al. 1999, 2001	184 substances, Animal species	Theoretical (P99 = 10)	GM: 16 100: 88th percentile
Gaylor and Kodell, 2000	500 substances, Aquatic species	Dose-response from 490 acute lethality experiments in rats	Median = 1 P95 = 46 P99 = 230
Schneider et al. 2005	63 chemotherapeutics, Humans and animals	Human database for healthy adults (Hattis et al. 1999)	GM = 15 100: 85th percentile
Hasegawa et al. 2010	63 chemotherapeutics, Humans and animals	18 industrial chemicals Young and newborn rats	GM = 12 P95 = 88

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Implications for risk assessment



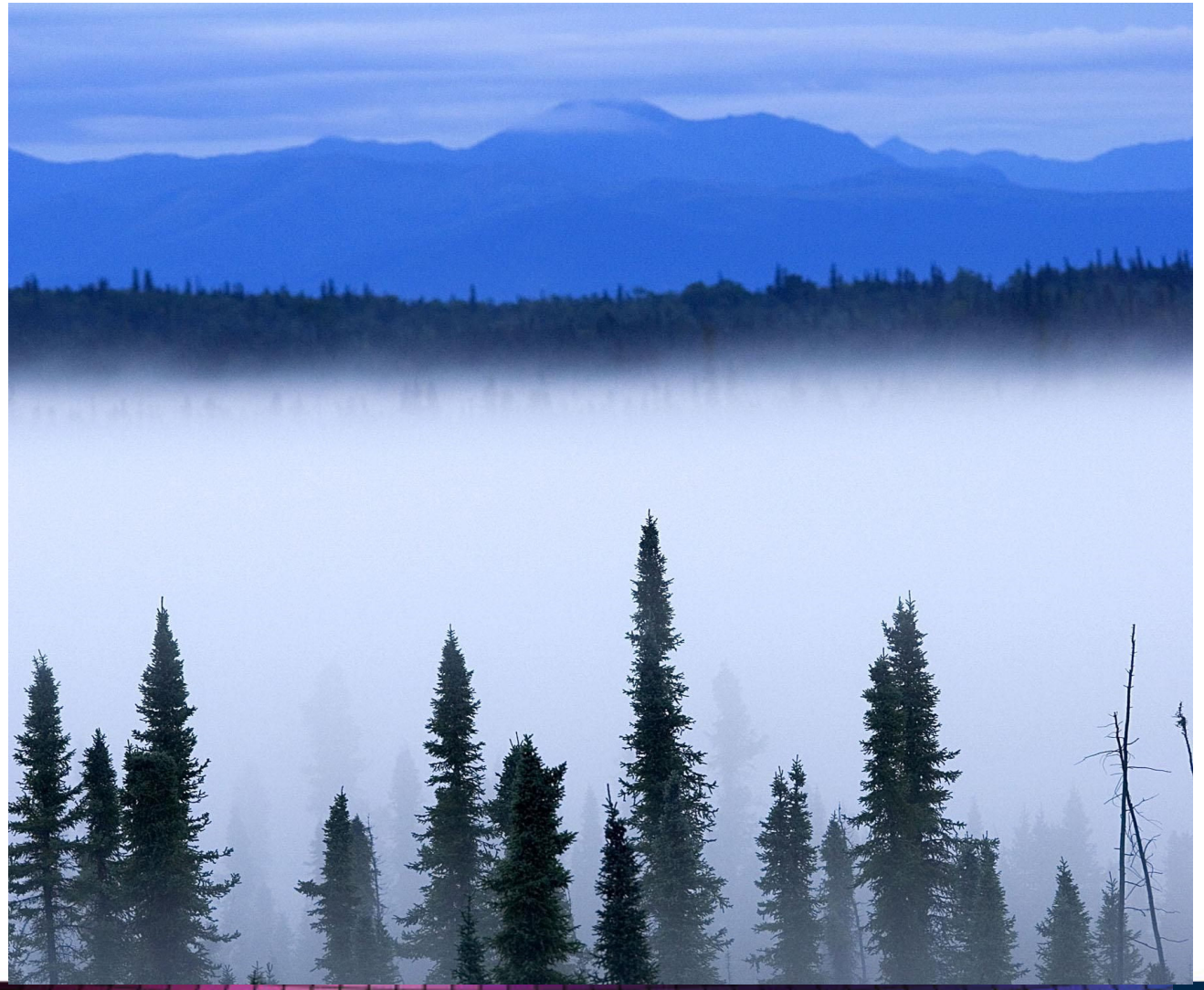
- ADI = no absolute zero-risk
- Desired level of protection?
- Intractable uncertainty

→ Pragmatic approach, incentive to generate better data

Brunel UNIVERSITY LONDON

OAK FOUNDATION

Thank you!



Brunel UNIVERSITY LONDON

OAK FOUNDATION