Imperial College London

Transitioning from the current paradigm for chemical risk assessment

Alan R Boobis

Imperial College London

a.boobis@imperial.ac.uk

EFSA's 10 Year Anniversary - Scientific Conference
Challenging boundaries in risk assessment – sharing experiences

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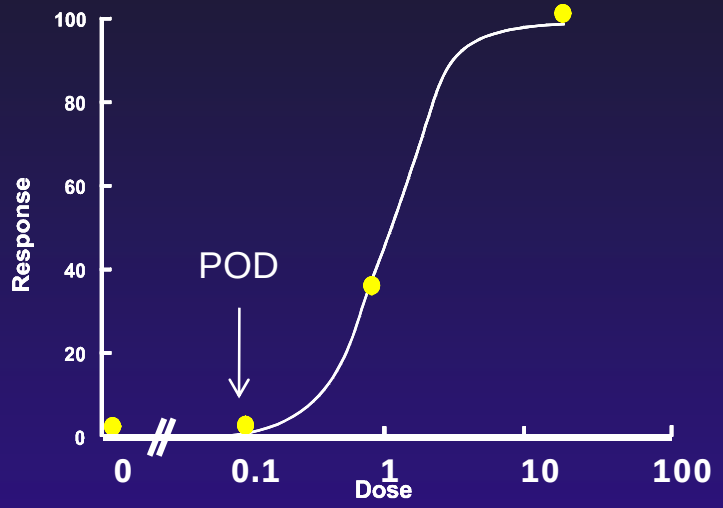
Parma, Italy

Purpose of toxicity prediction

- Product development
  - Screening to design or select least hazardous substances for further development
- Prioritisation of substances for further evaluation
- Classification and labelling
  - Indication of worst case effects (e.g. for emergencies during transport and other accidents)
- As part of an approvals or authorisation process
  - Intentional exposure (e.g. drugs, personal care products)
  - Incidental exposure that can be controlled (e.g. occupational)
  - Incidental exposure of general public (e.g. from water, food, air)
- As part of risk assessment of compounds to which people are already being exposed

Risk assessment

Hazard ID
Hazard characterisation



Uncertainty factor

Reference value (e.g. ADI)
[RV] = POD/UF

Exposure assessment
Risk characterisation

MOE = POD/Exposure

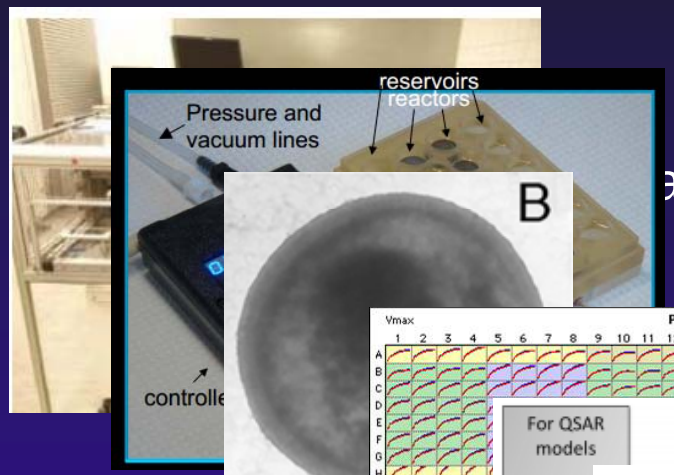
Some advances in risk assessment methodology

- Physiologically-based pharmacokinetic modelling
  - Clewell & Anderson (1985)
- Chemical specific adjustment factors
  - Renwick (1993)
- Thresholds of toxicological concern
  - Munro et al (1996)
- Mode of action
  - US EPA (1996); Sonich-Mullin et al (2001)

Why does toxicity testing have to change (further)

- Large numbers of chemicals with limited toxicity information
  - HPVs, REACH, etc
  - 90,000 chemicals on the EPA TSCA inventory; 140,000 chemicals preregistered under REACH, ~70,000 will require toxicity data
  - Metabolites and degradation products, process intermediates, mixtures and combined exposures
- Novel materials and processes, e.g. nanomaterials
- Accuracy of risk assessments, based on laboratory species
  - Coverage of all relevant endpoints and sub-populations?
- Use of laboratory animals in toxicity testing
  - 3R's – reduction, refinement and replacement

Risk assessment



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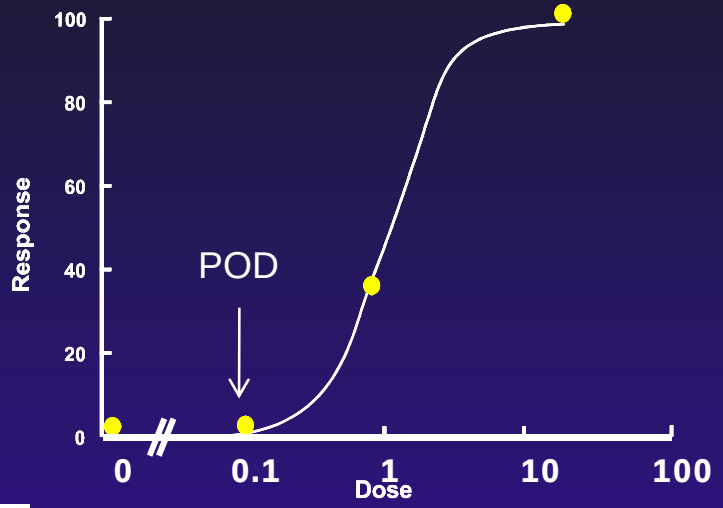

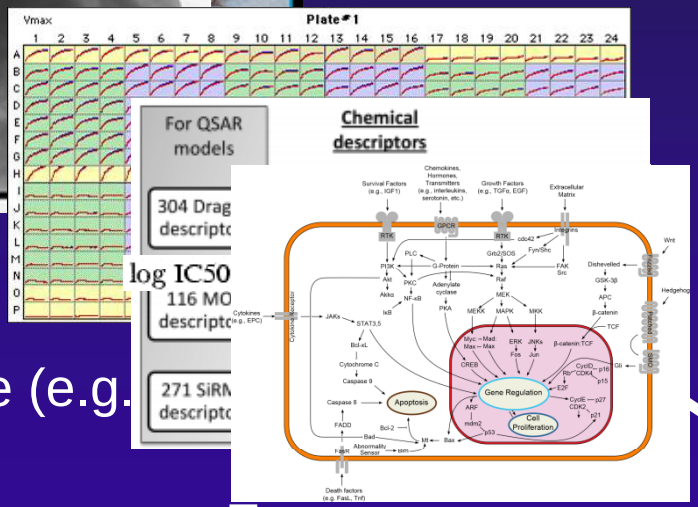

Reference value (e.g.
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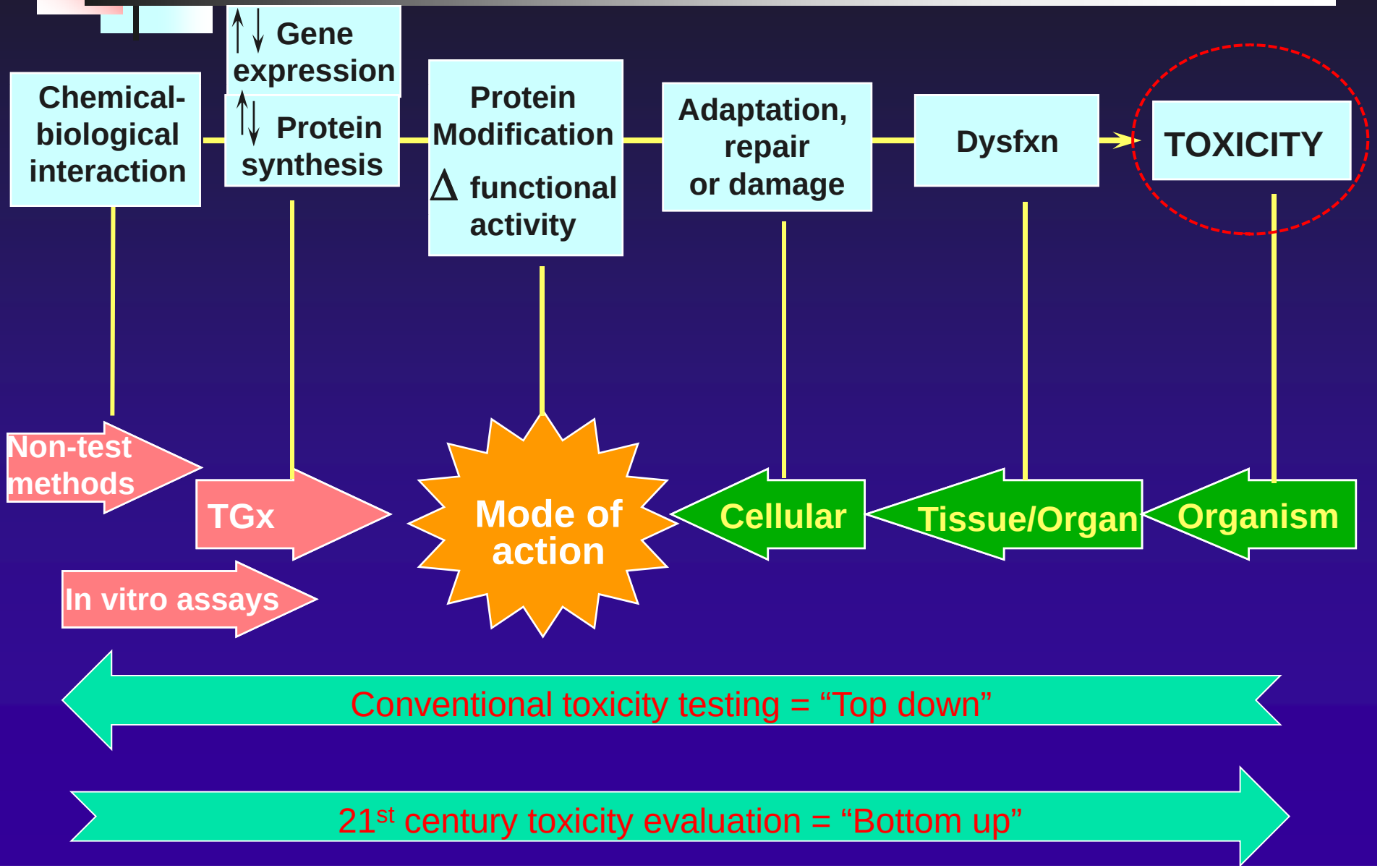
Risk characterisation

MOE = POD/Exposure

Use of the MOA concept



Some challenges in achieving a paradigm shift in toxicity testing

- Adequacy of (Epigenetics AND toxic* = 202 hits 7 <2005; first 1994 ce?
  - Knowledge
- Reliability of extrapolation from effects on *in vitro* toxicity pathways to biologically relevant hazard?
  - Cell models
  - Exposure duration
- Establishing fitness-for-purpose of new methods (who and how)
  - Use of human-derived cell systems
  - Toxicological anchoring to data from laboratory species?
- Quantitative accuracy of *in vitro* – *in vivo* extrapolations
- Domain of applicability

Some challenges in achieving a paradigm shift in toxicity testing

- Adequacy of coverage of toxicological/biological space?
  - Knowledge gap?
- Reliability of extrapolation from effects on *in vitro* toxicity pathways to biologically relevant hazard?
  - Cell models
  - Exposure duration
- Establishing fitness-for-purpose of new methods (who and how)
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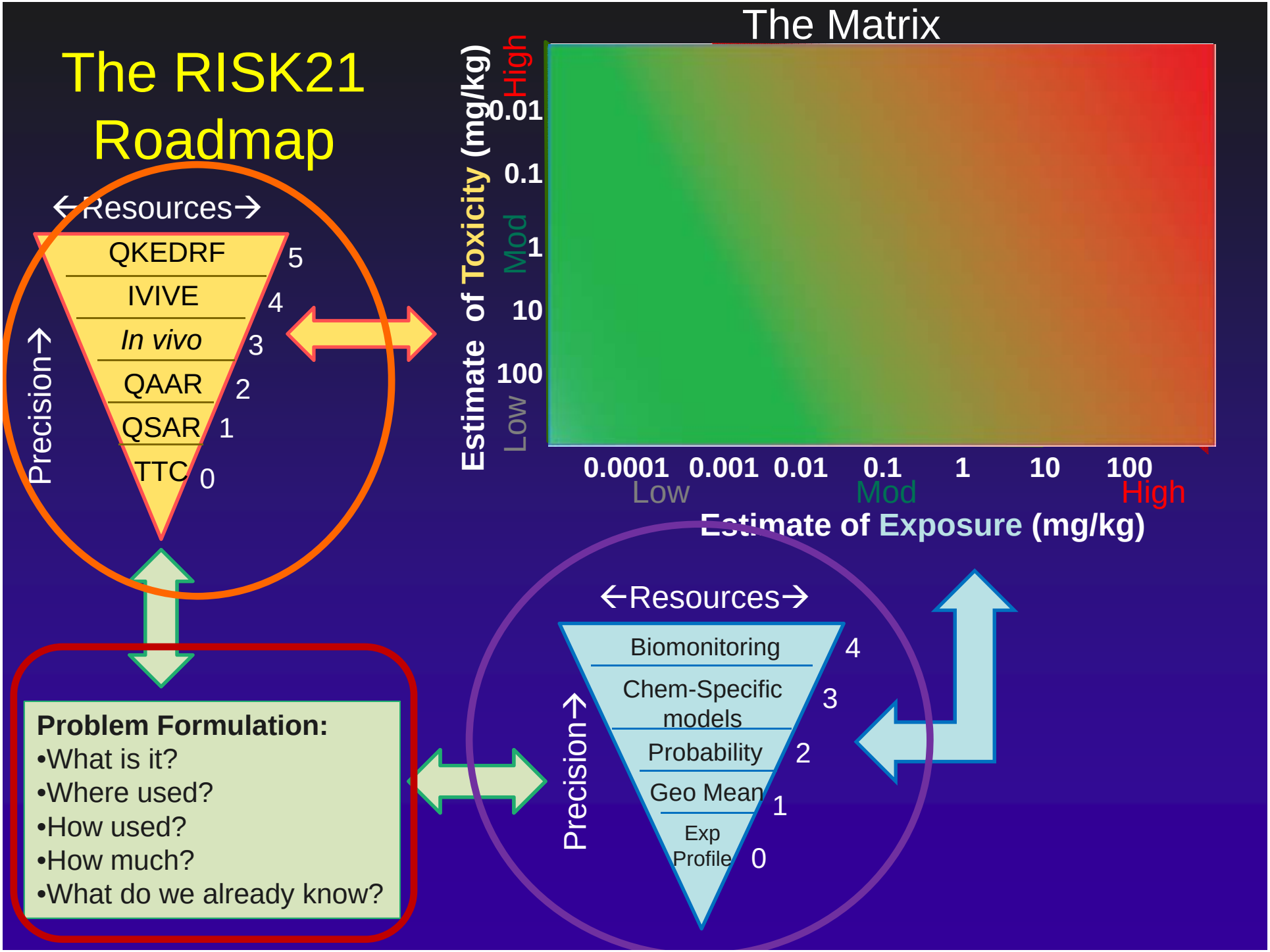
A change in philosophy is needed

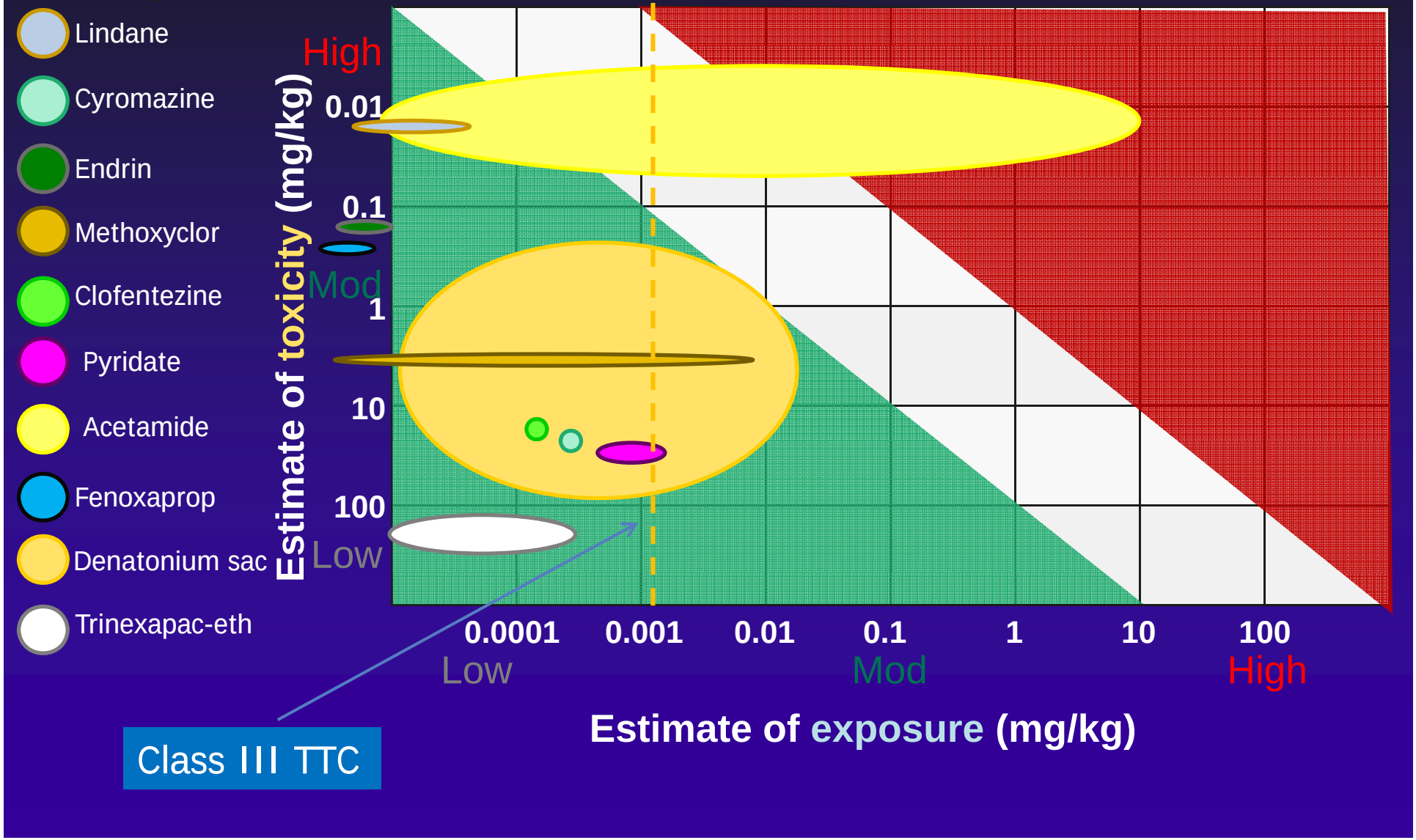
- From…
  - Do all the toxicity testing; then think about the risk assessment. Anything less is second best or even unacceptable
- To…
  - Think about the problem that needs to be addressed; then select sources of information that will be of the most value


The RISK21 Roadmap
←Resources→
Precision→
QKEDRF
IVIVE
In vivo
QAAR
QSAR
TTC
5
4
3
2
1
0
The Matrix
Estimate of Toxicity (mg/kg)
High
Mod
Low
0.01
0.1
1
10
100
0.0001
0.001
0.01
0.1
1
10
100
Low
Mod
High
Estimate of Exposure (mg/kg)
Problem Formulation:
•What is it?
•Where used?
•How used?
•How much?
•What do we already know?
←Resources→
Precision→
Biomonitoring
Chem-Specific models
Probability
Geo Mean
Exp Profile
4
3
2
1
0

Water contaminants case study

- A regulatory agency has identified 133 chemicals that have been detected in surface water and ground water that could potentially appear in drinking water
- You have ONE year to decide whether risk management is required for any or all chemicals on this list as potential drinking water contaminants

Water case study



The future of toxicity prediction

- Four futures, all likely to be quite different from each other
  - The future we would like (“The Vision”)
  - The future we are investing resources in (e.g. ToxCast, SEURAT-1)
  - The future we convince ourselves has been achieved
  - The future we eventually find ourselves in
- We need to recognise which future it is that we are most likely to achieve, based on:
  - Resources committed
  - State of knowledge