
Health and Environmental Sciences Institute (HESI) RISK21 Program

*Beyond Science and
Decisions: From Problem
Formulation to Dose-
Response*

- May 29, 2013

Tim Pastoor, PhD, DABT

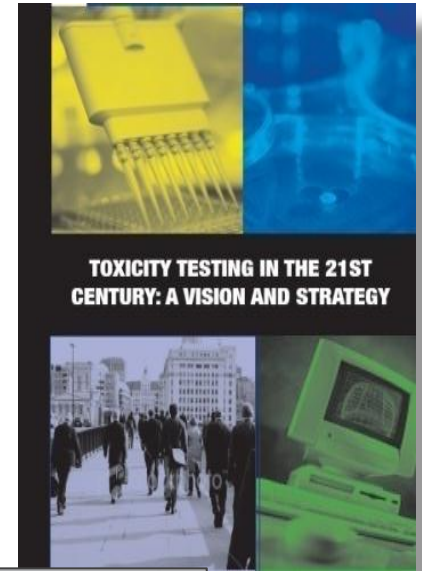
The Stimulus for RISK21: NAS Reports

Toxicity Testing In The 21st Century

“...new methods in computational biology and a comprehensive array of in vitro tests based on human biology.”

Science and Decisions: Advancing Risk Assessment

- Design of risk assessment
- Uncertainty and variability
- A unified approach to dose-response assessment

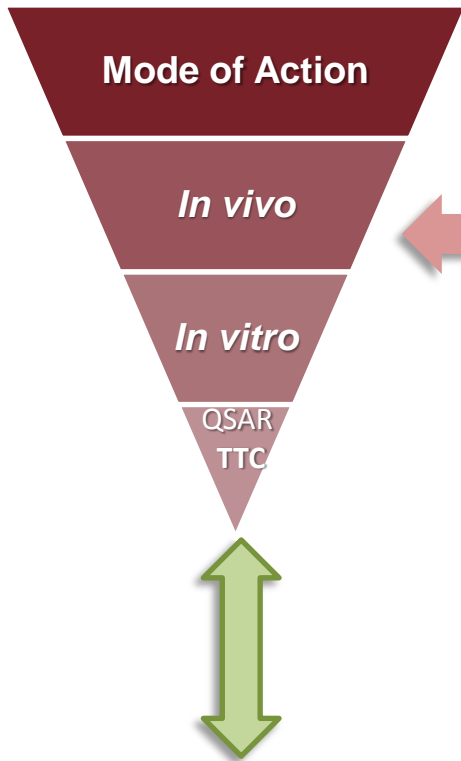


RISK21 Principles



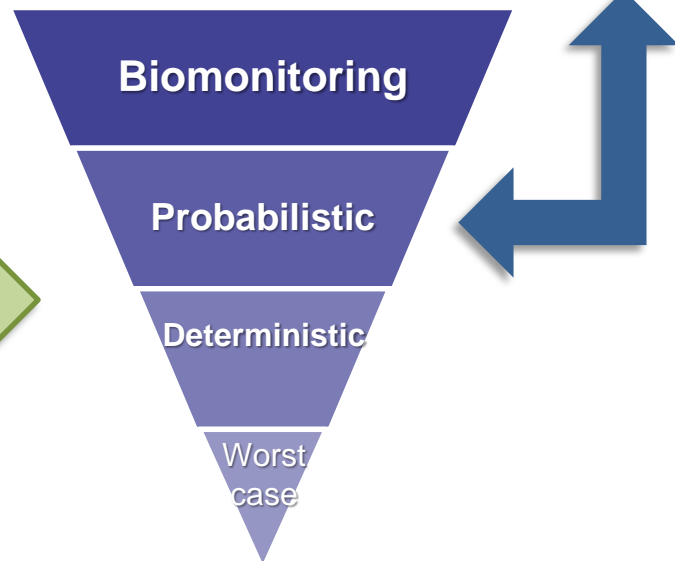
- Start with **problem formulation**
 - Begin with **exposure** estimates rather than toxicity
 - Use **prior knowledge**
 - Seek enough **precision** to make a **decision**
-

The RISK21 Roadmap

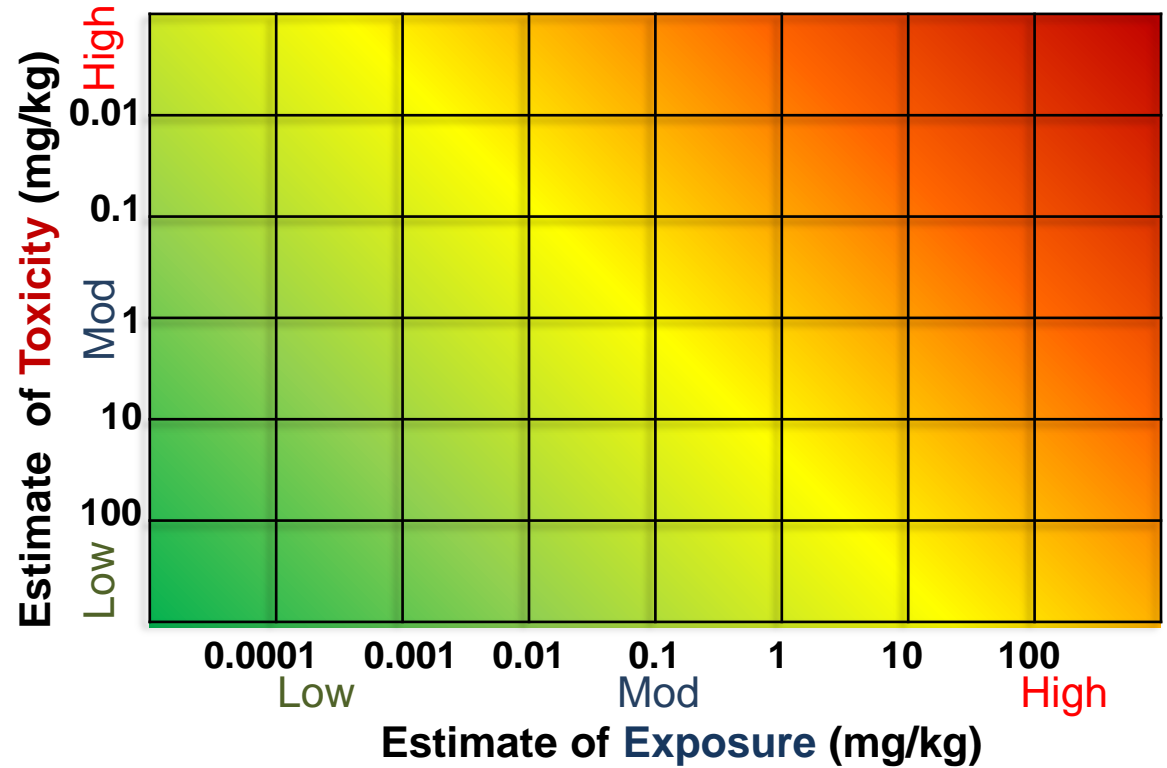


Problem Formulation:

- What is it?
- Where used?
- How used?
- How much?
- What do we already know?



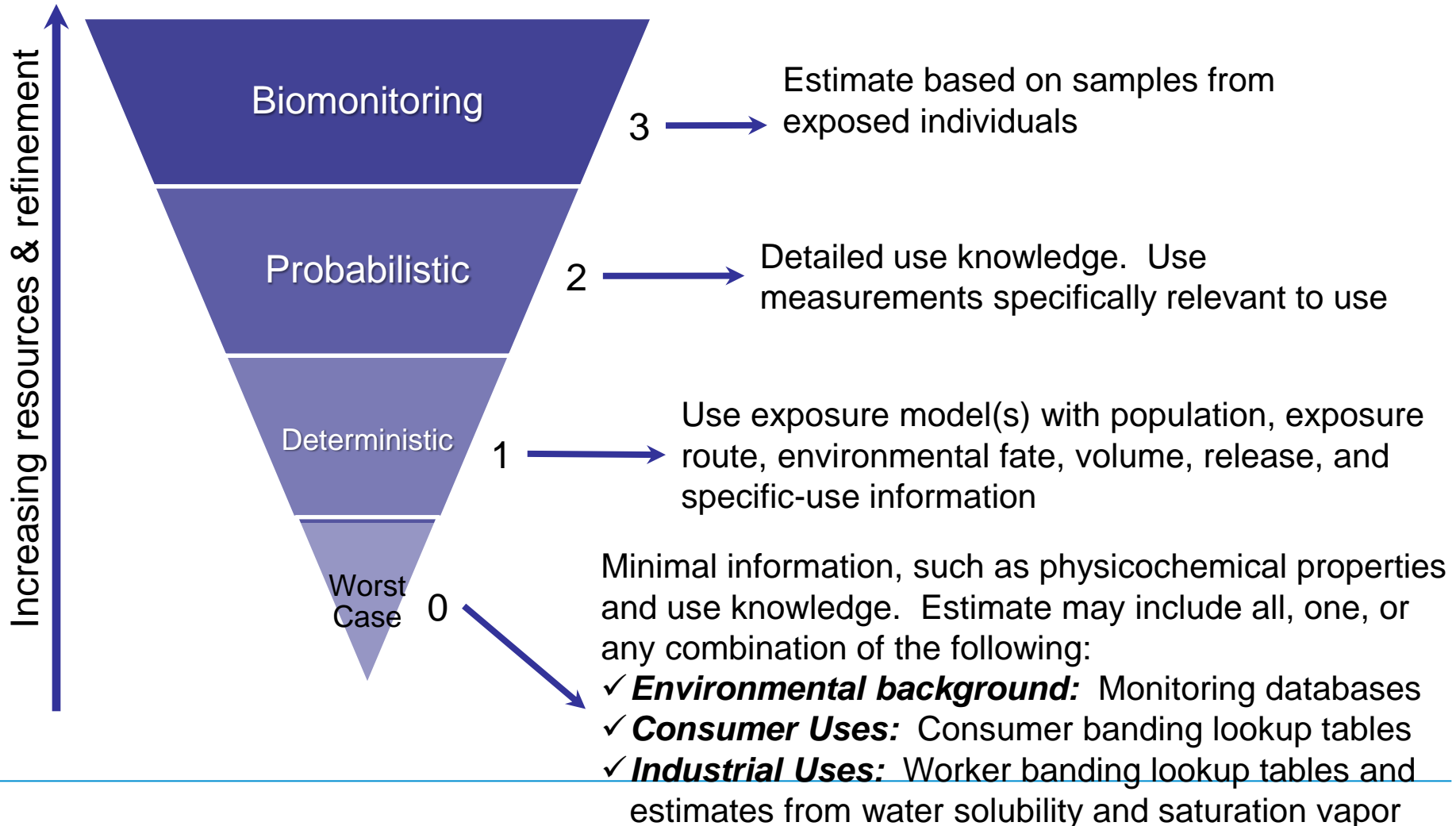
The Matrix



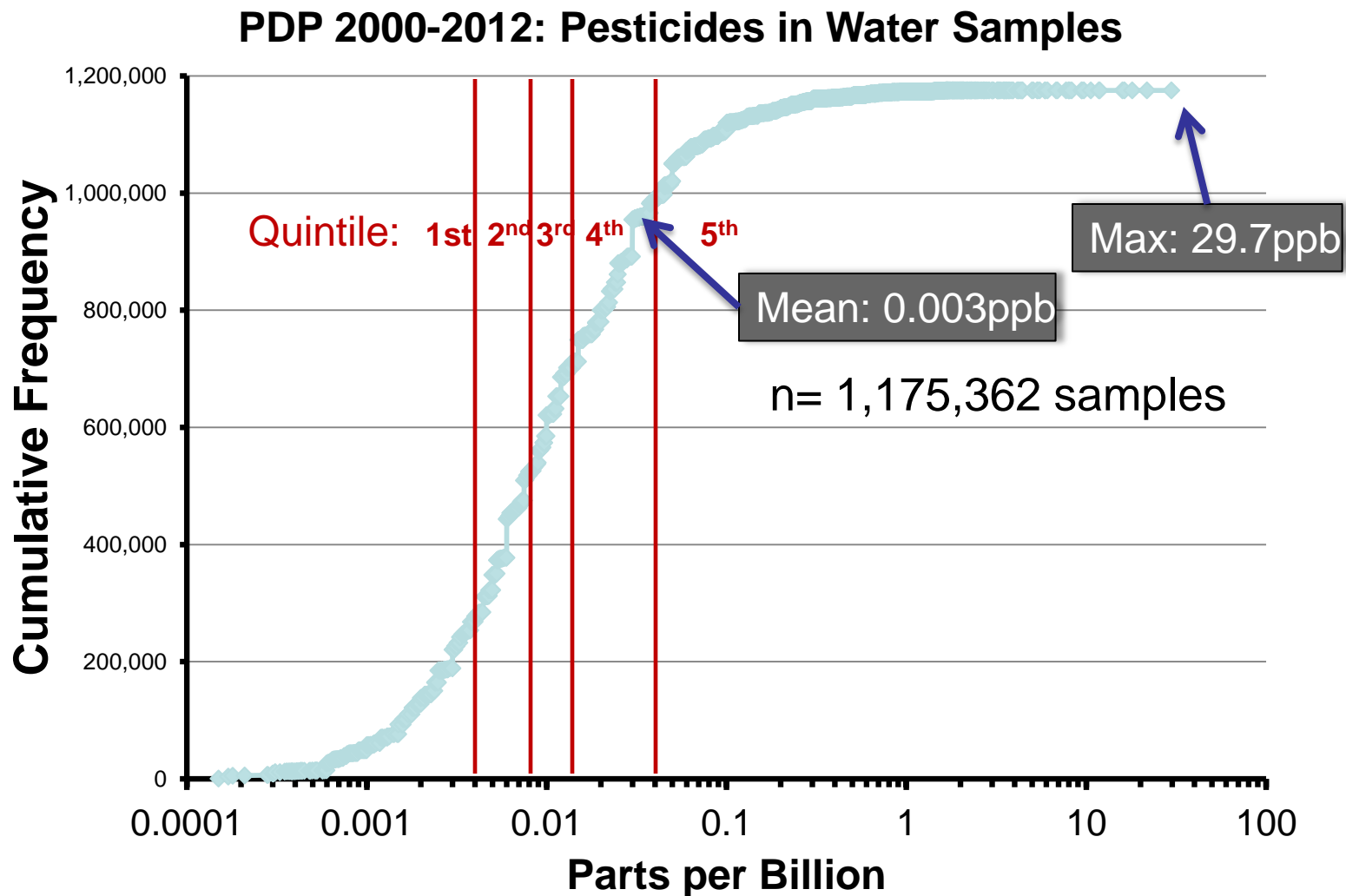
Tiered Approach for Exposure Assessment



- **Purpose:** Creation of a tiered system for human exposure estimates (“Exposure Profiles”) to estimate the range of likely exposure to a given chemical.



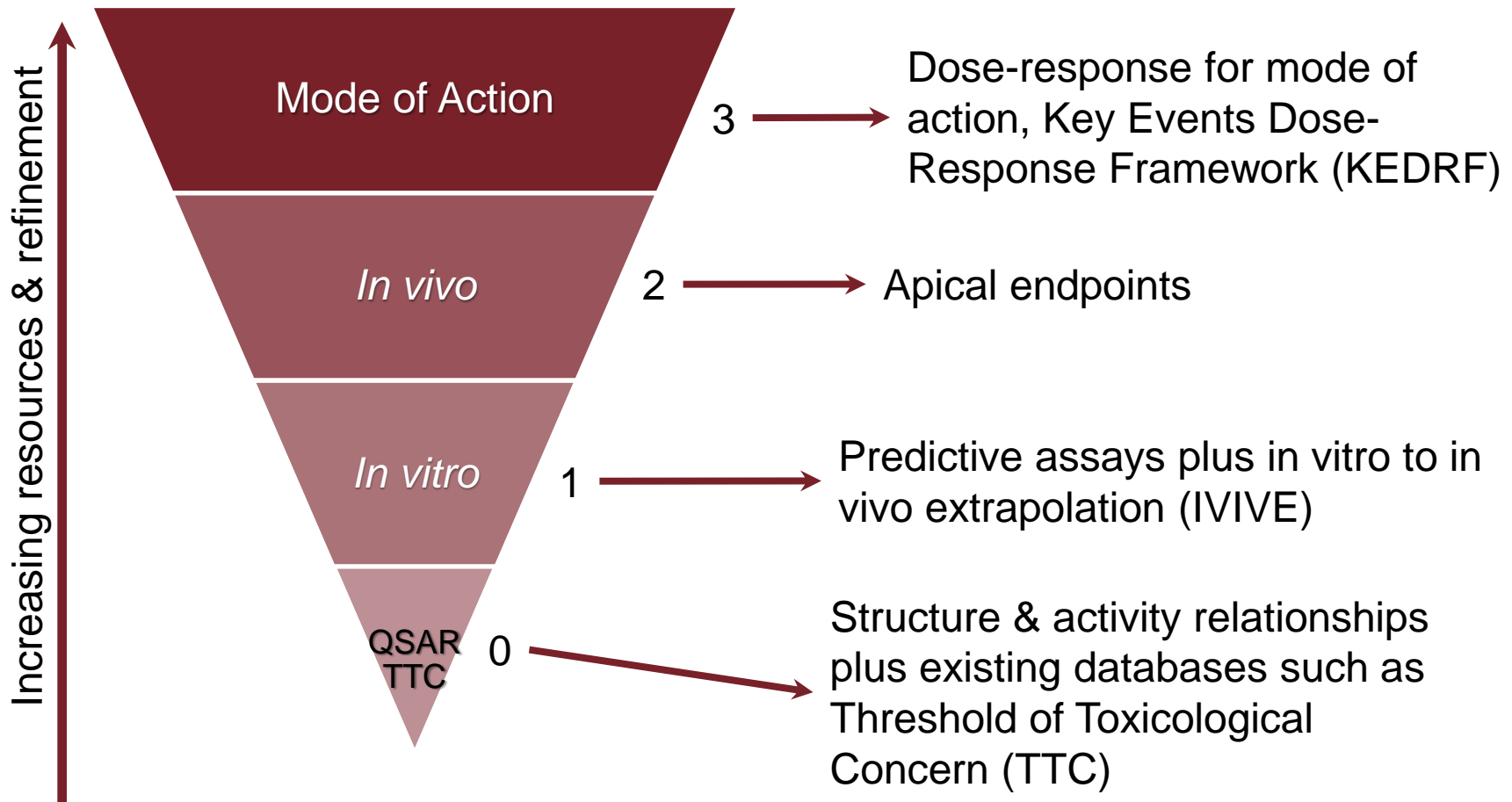
USDA Pesticide Data Program (PDP)



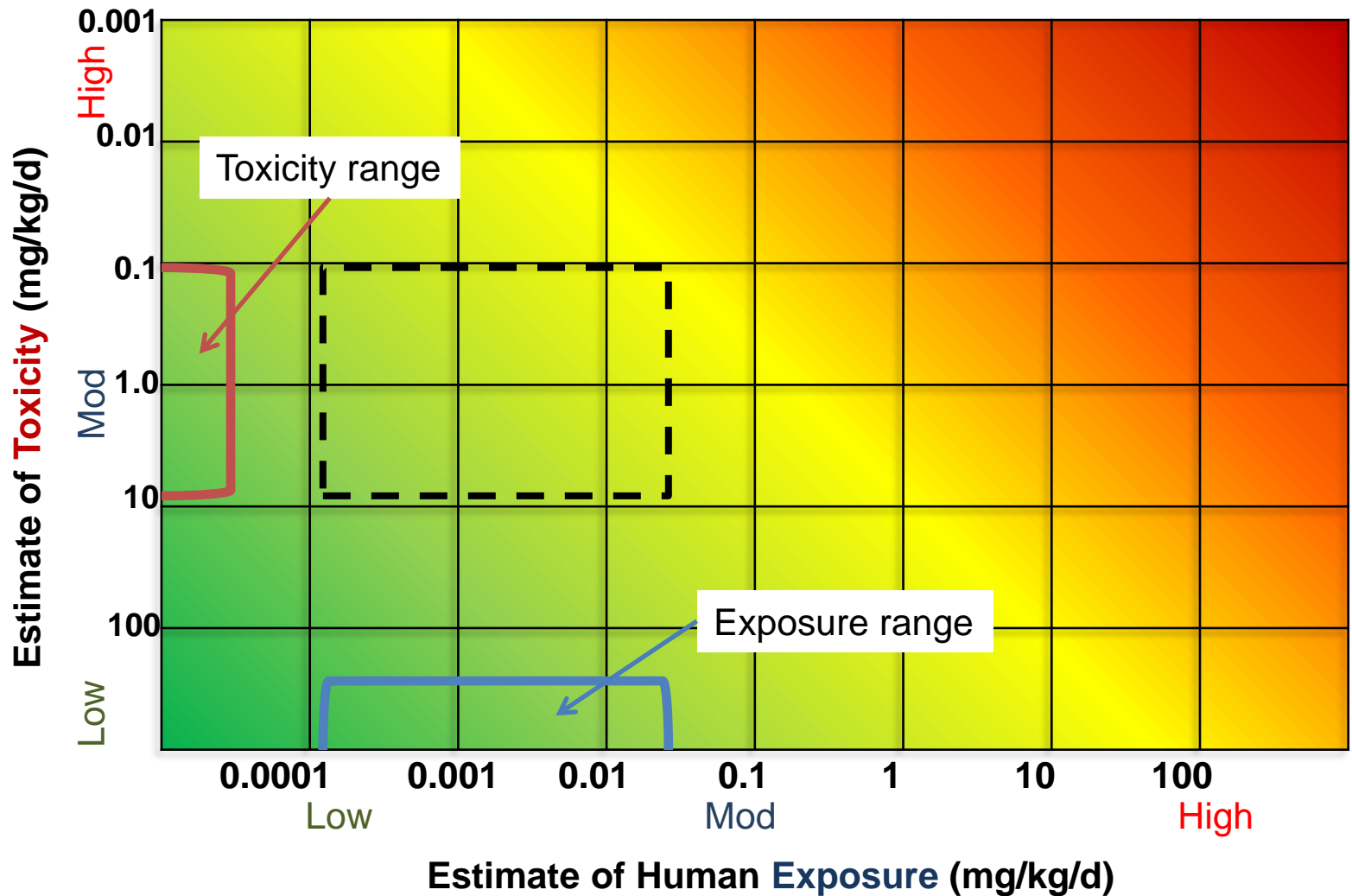
Tiered Approach for Toxicity Estimate



- **Purpose:** Creation of a tiered system for human toxicity estimates (“Toxicity Profiles”) to estimate the range of likely PODs/RVs for a given chemical.



Plotting exposure and toxicity information on the RISK21 matrix using ranges



“Pseudomethrin” case study

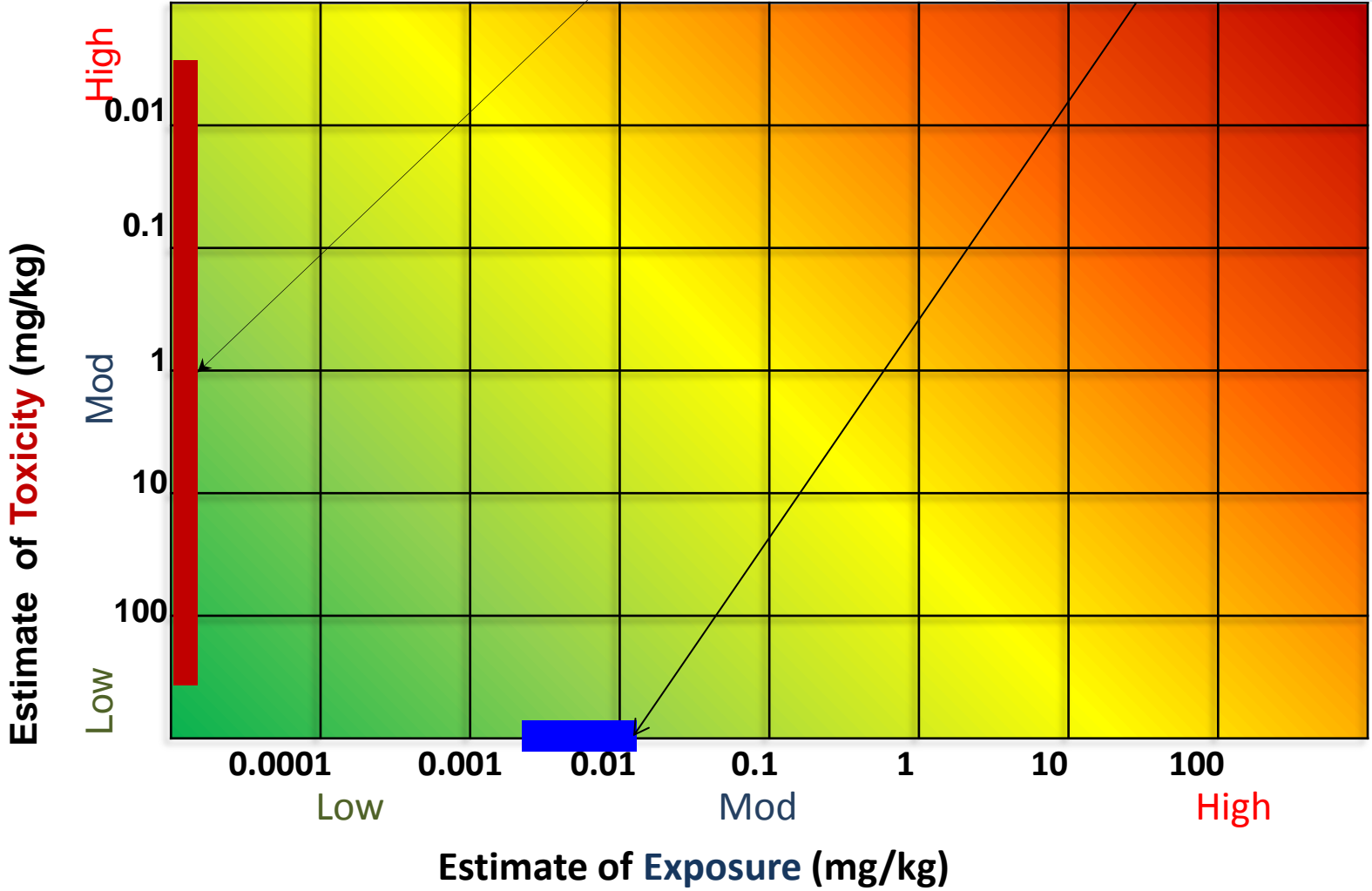
Problem Formulation

- ❖ Use pyrethroid-impregnated bed nets to protect against mosquito bites
- ❖ Pseudomethrin is a candidate pyrethroid for this use
- ❖ 11 pyrethroids registered
- ❖ Determine reasonable certainty of no harm for...
 - ✓ Bed-net dipping
 - ✓ Sleeping under treated net

Sleeping scenario:
Tier 0

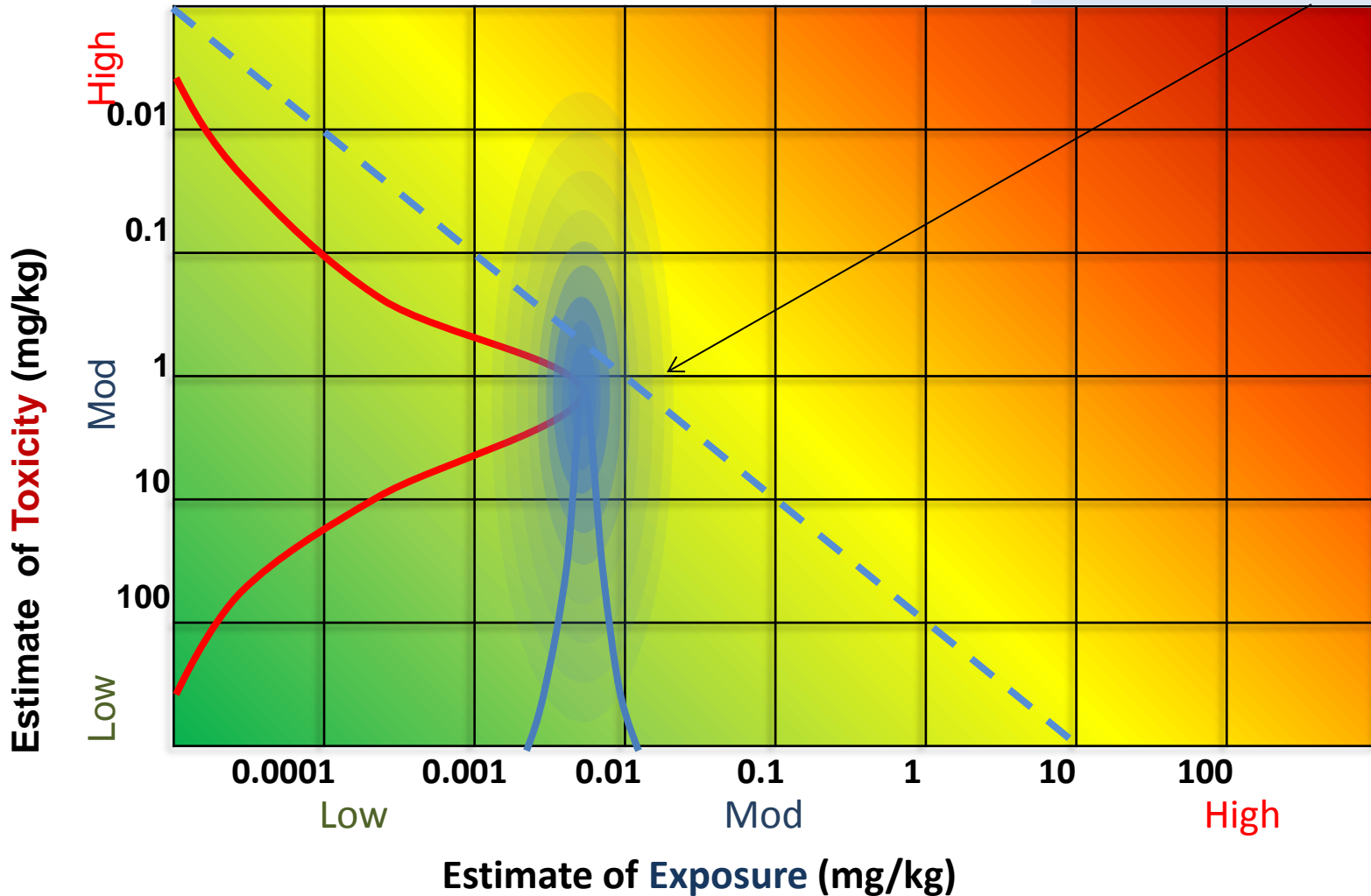
Pseudomethrin tox range
based on Cramer class III

Pseudomethrin exposure
range of 0.003– 0.02 mg/kg
based on WHO model for
sleeping



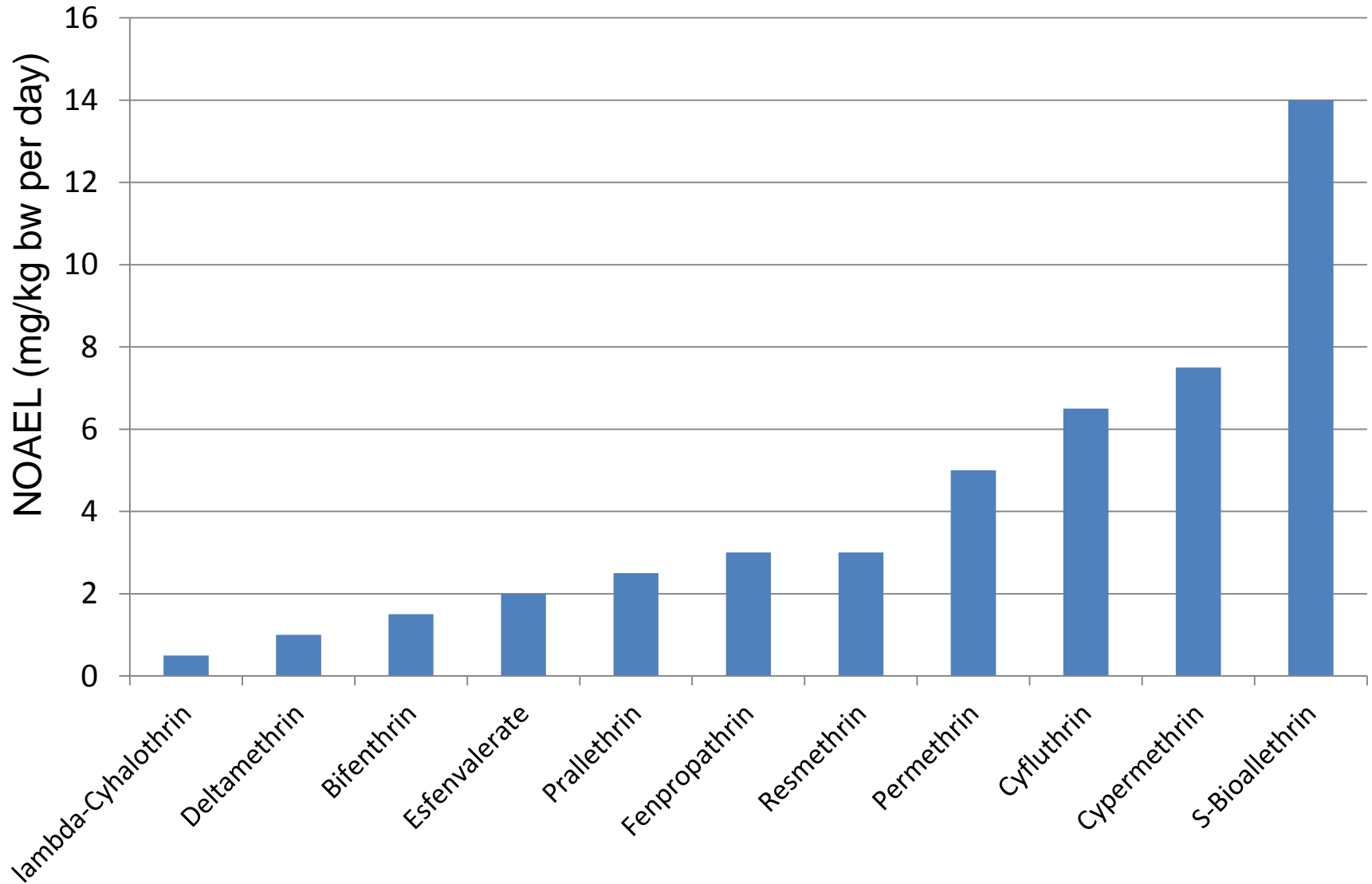
Sleeping scenario: Tier 0

“Mix” of toxicity and exposure probability estimates indicating position of the situation



Tier 0 does not give assurance of safety; shape of probability mix indicates refinement of toxicity would be more relevant for Tier 1

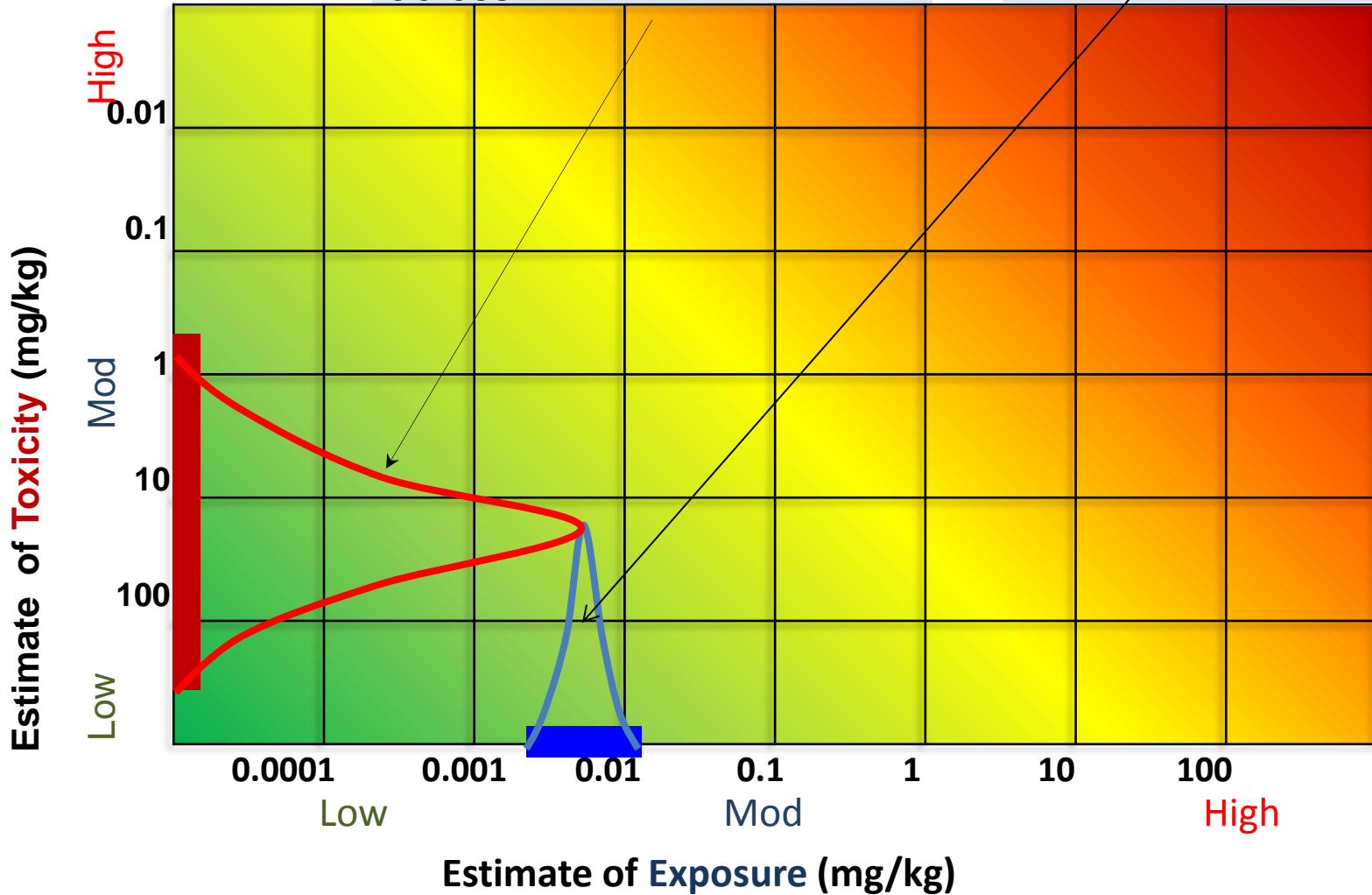
Pyrethroid Chronic NOELs



Sleeping scenario:
Tier 1

Pseudomethrin tox
probability range of 0.5 –
500 mg/kg based on “read
across” +

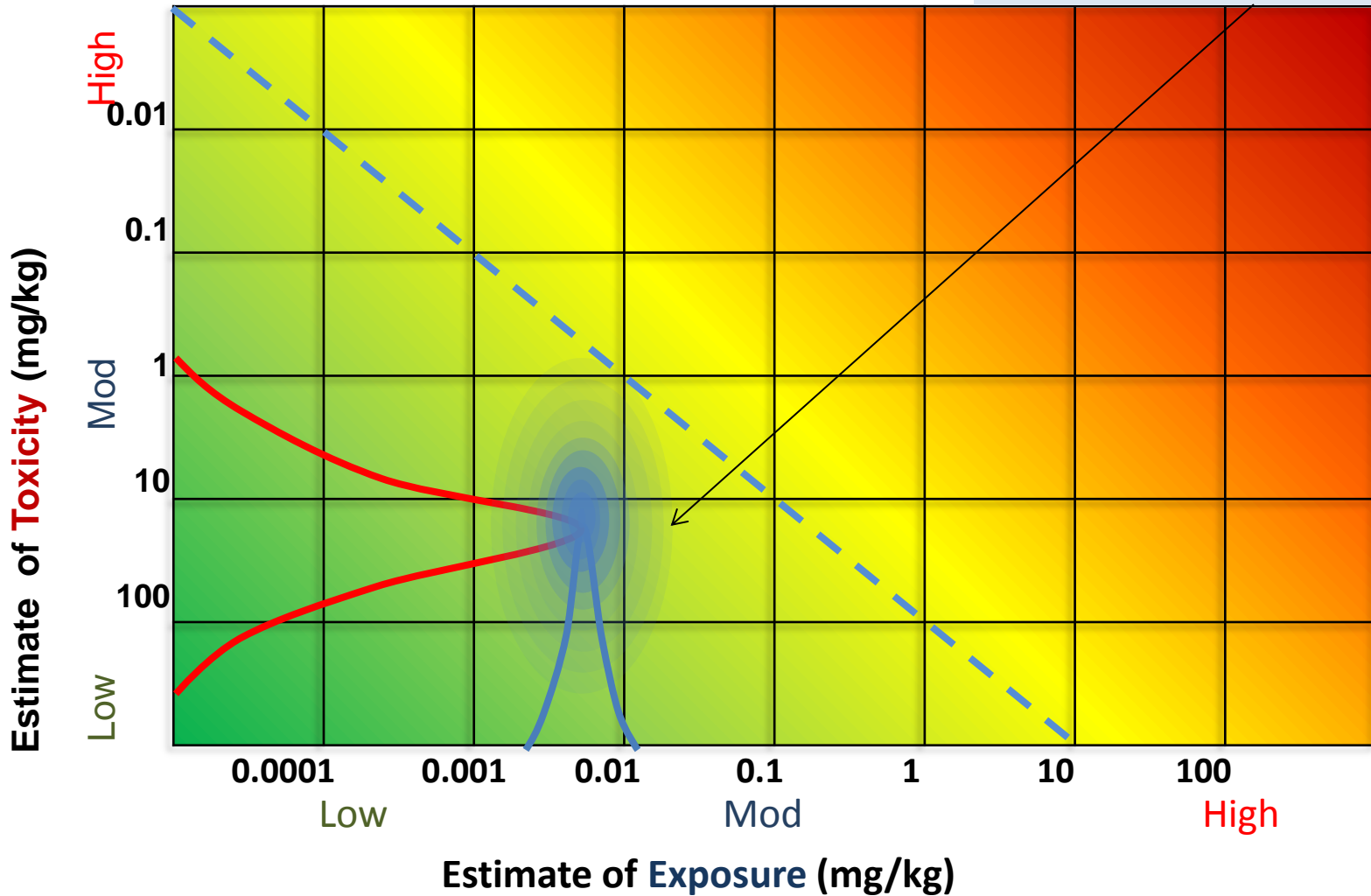
Pseudomethrin exposure
probability range of 0.003–
0.02 mg/kg based on WHO
model



Tier 1: Use read across to estimate toxicity, exposure estimate unchanged

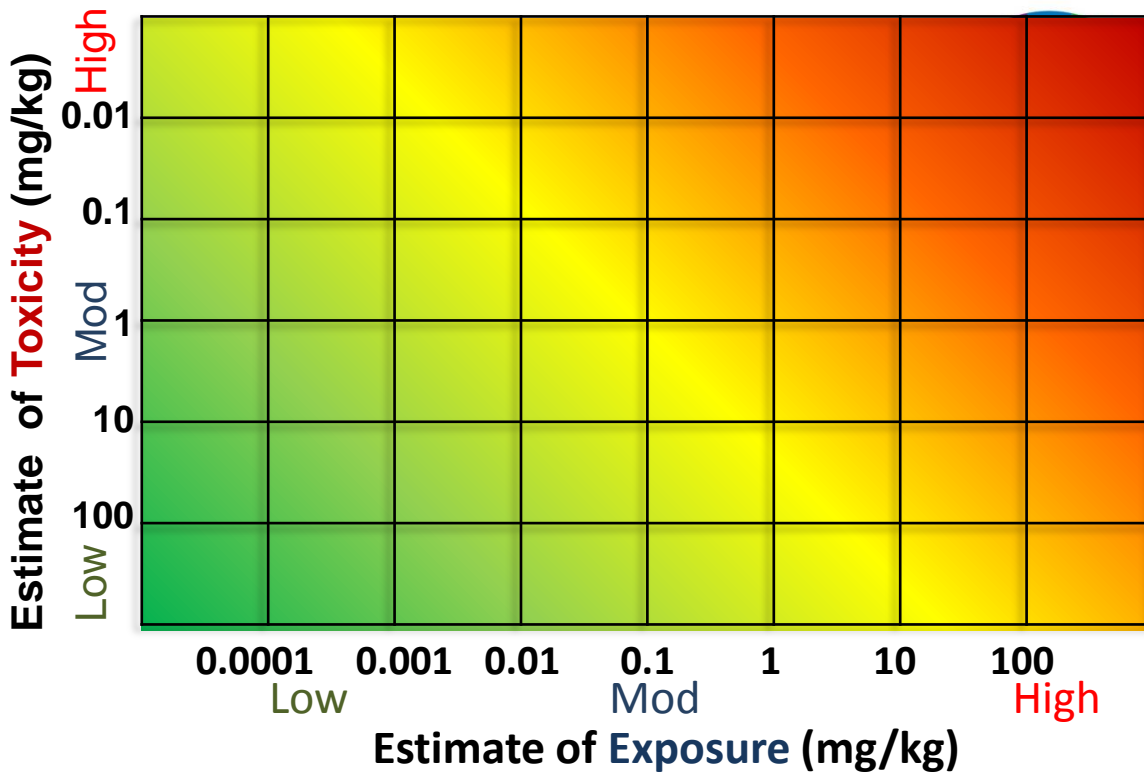
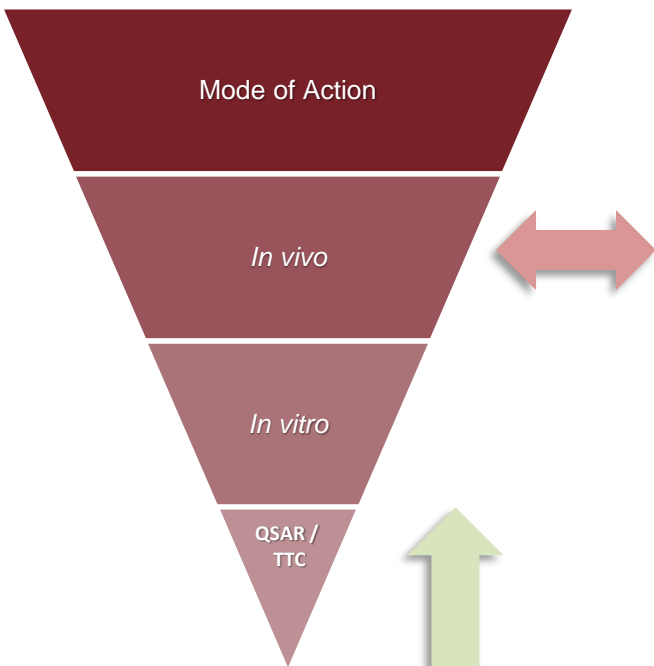
Sleeping scenario: Tier 1

“Mix” of toxicity and exposure probability estimates indicating position of the situation



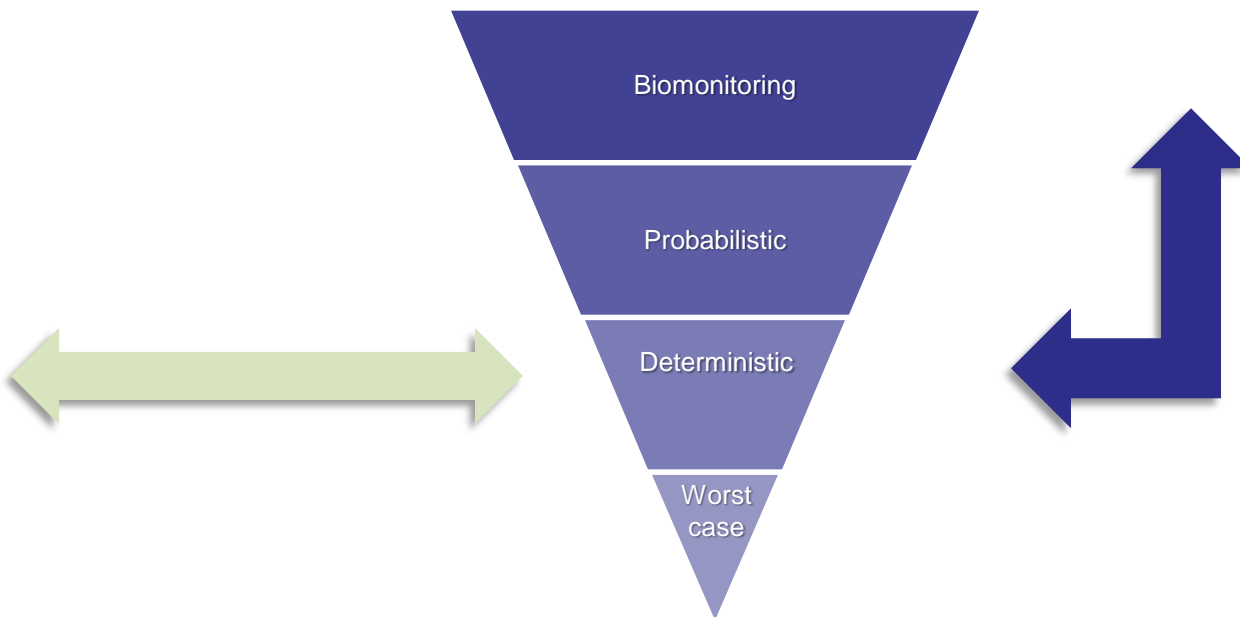
Tier 1: Sleeping scenario acceptable

The RISK21 Roadmap



Problem Formulation:

- What is it?
- Where used?
- How used?
- How much?
- What do we already know?



HESI RISK21

For more information, contact:

Michelle Embry (membry@hesiglobal.org)

Nancy Doerrer (ndoerrer@hesiglobal.org)

Jennifer Young (jyoung@hesiglobal.org)

Alan Boobis (a.boobis@imperial.ac.uk)

Tim Pastoor (tim.pastoor@syngenta.com)

<http://www.hesiglobal.org>