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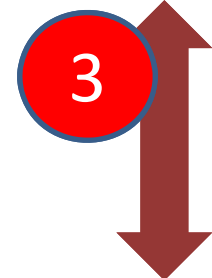
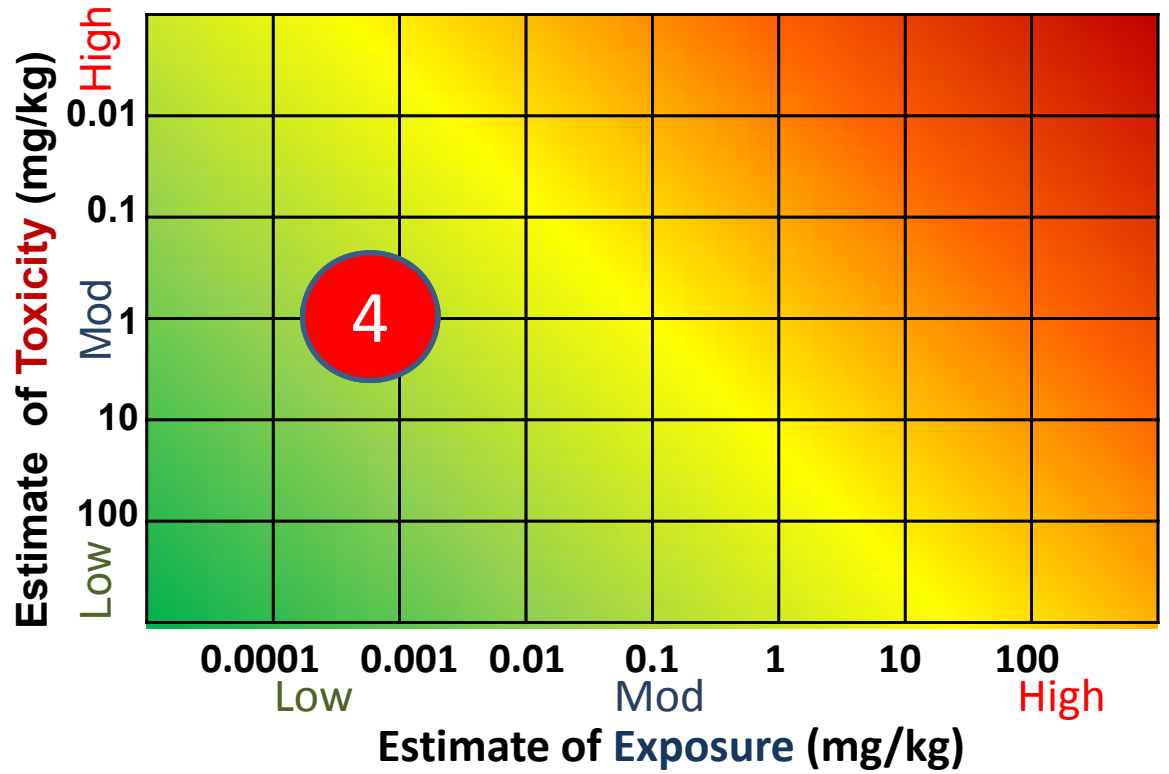
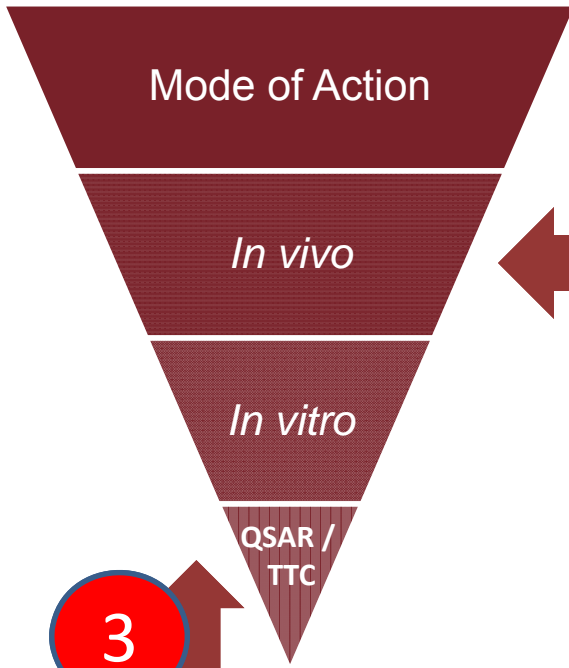
# RISK21 Case Studies

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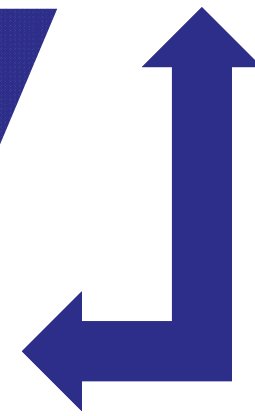
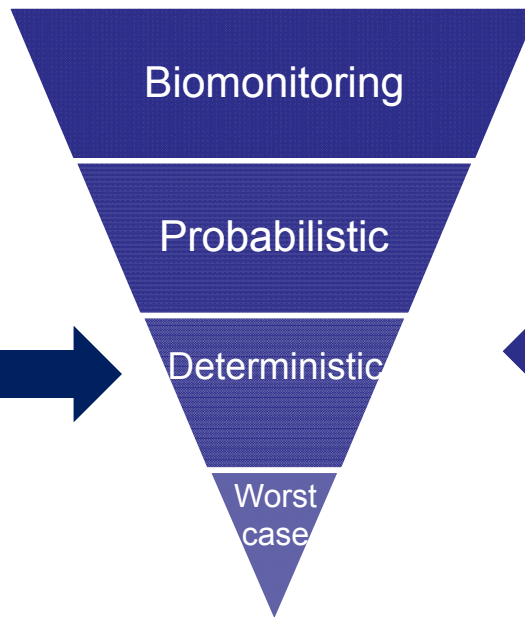
1. “Pseudomethrin”
2. 133 Chemicals in Drinking Water

# The RISK21 Roadmap



**Problem Formulation:**

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



# Case Study to Test the Approach: “Pseudomethrin”

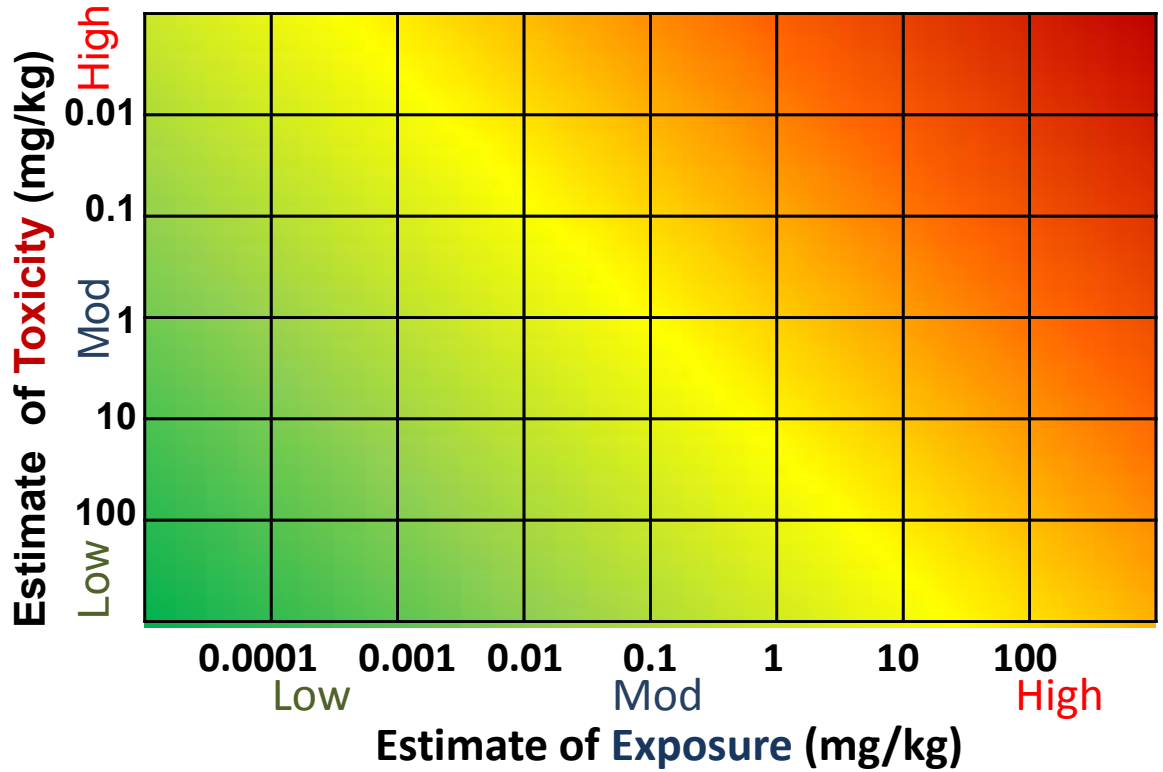
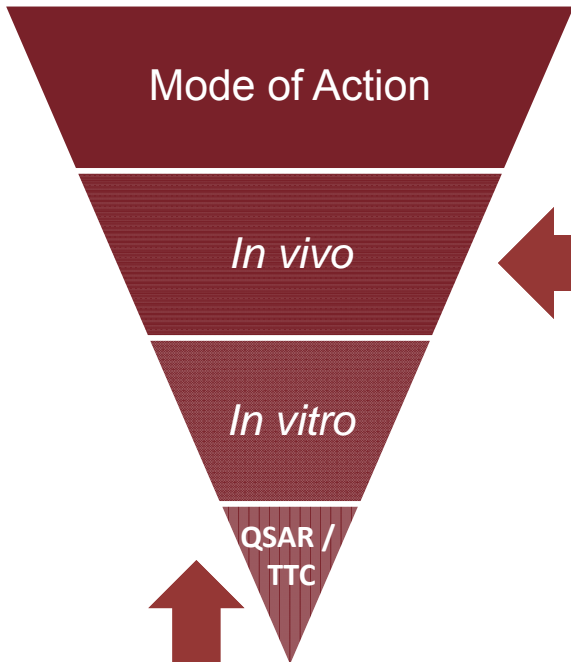
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## Problem Formulation

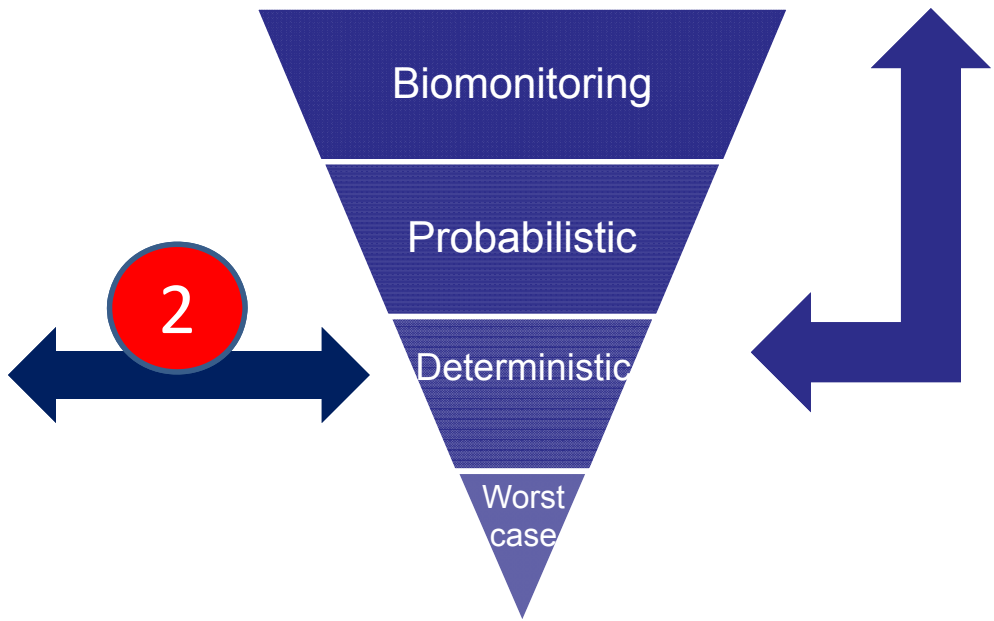
- Can “Pseudomethrin” be used on bed nets to protect against mosquito bites?
- 11<sup>th</sup> pyrethroid
- Determine reasonable certainty of no harm for...
  - Bed-net dipping
  - Sleeping under treated net
- Use no more than 50 animals

# The RISK21 Roadmap



**Problem Formulation:**

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



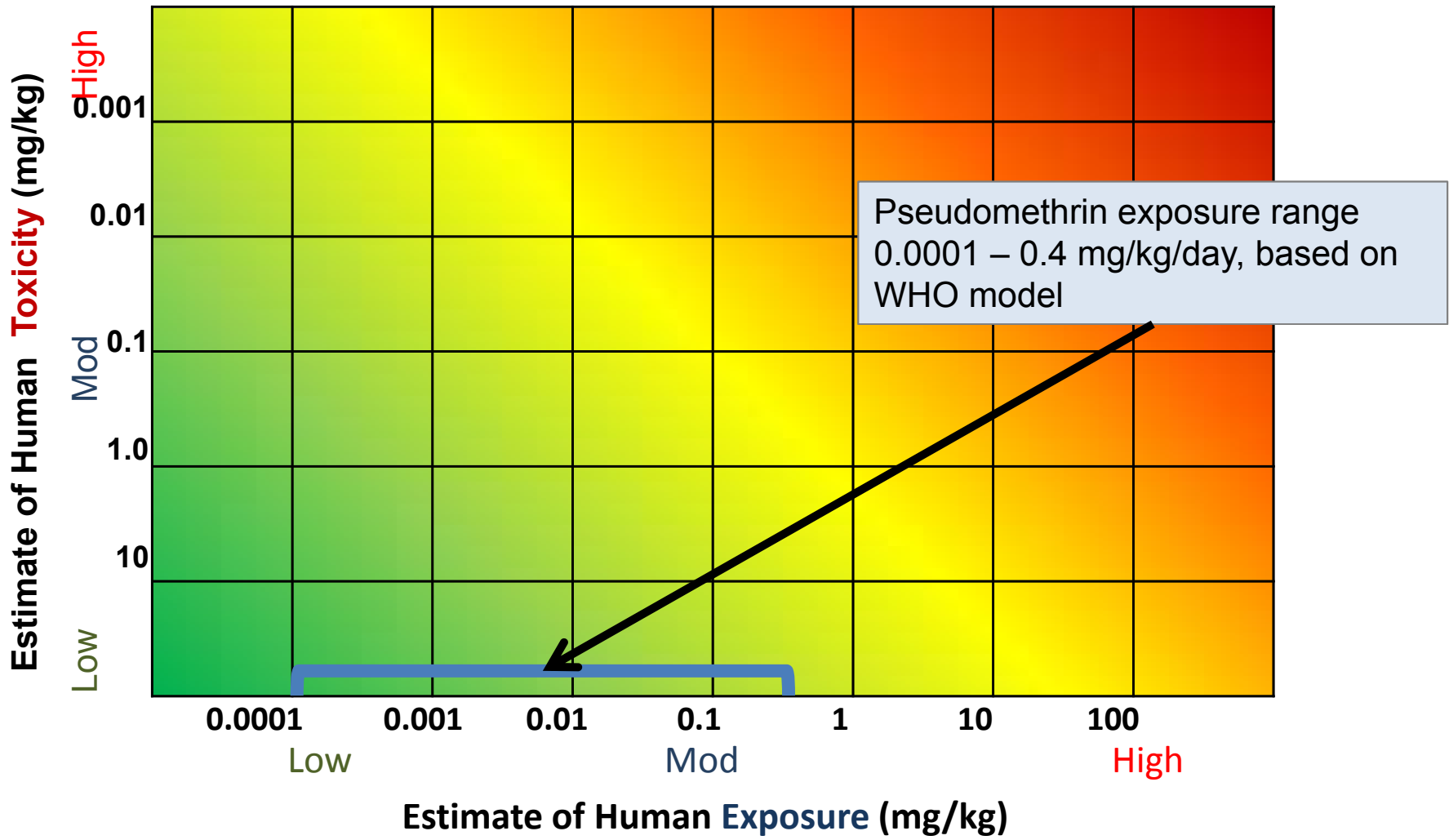
# Tier 0 Exposure

- Phys/Chem: Low volatility; therefore, inhalation negligible.
- Sub-chronic to chronic duration
- WHO Model: Overall = 0.0001 – 0.443 mg/kg/day

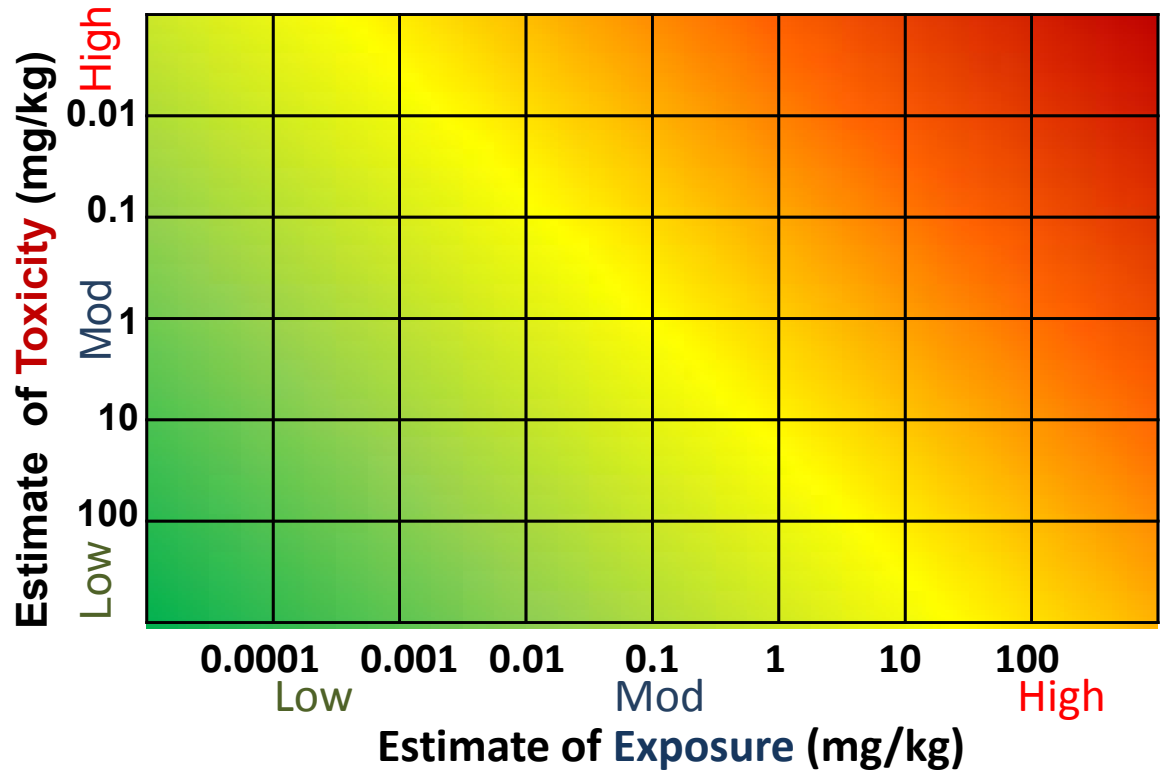
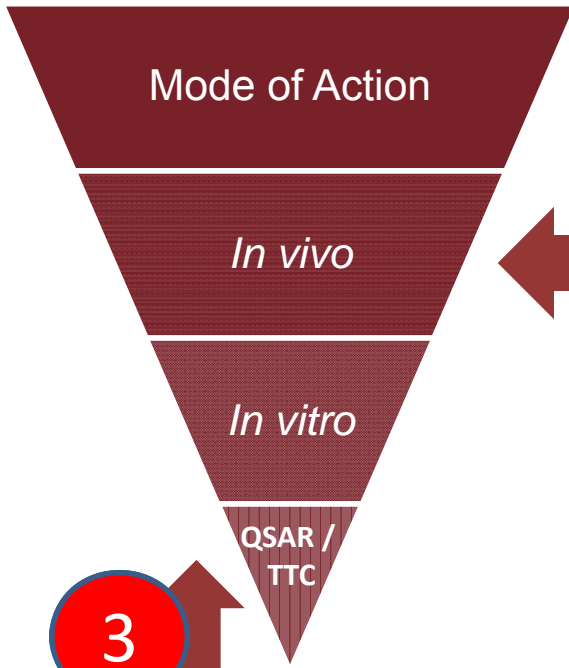
	Adult	Child	Infant
Dermal (mg/kg/day)	0.0002 – 0.16	0.00010 – 0.080	0.00050 – 0.400
Oral (mg/kg/day)	--	0.000002 – 0.006	0.000007 – 0.003
Aggregate	0.0002 – 0.16	0.0001 – 0.086	0.0106 – 0.443

WHO (2004): A generic risk assessment model for insecticide treatment and subsequent use of mosquito nets”

# Sleeping under net: Tier 0

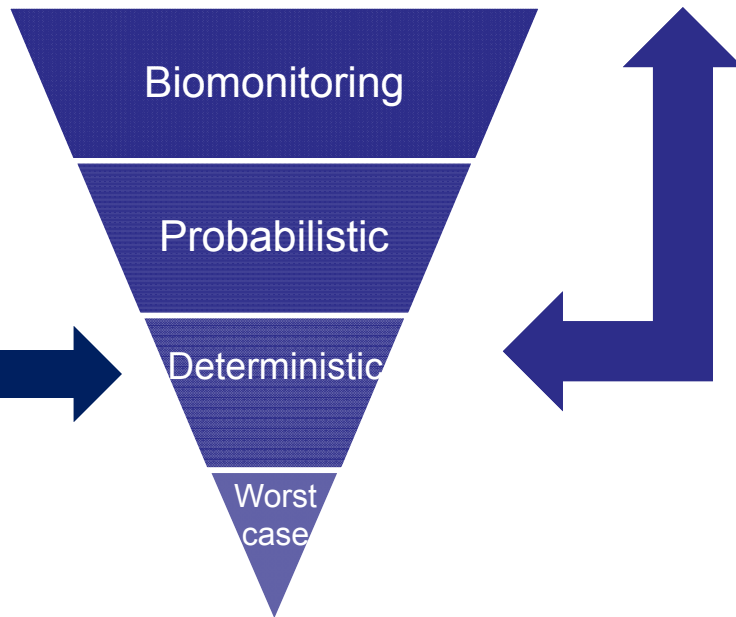


# The RISK21 Roadmap



3

- Problem Formulation:**
- What is it?
  - Where used?
  - How used?
  - How much?
  - What do we already know?

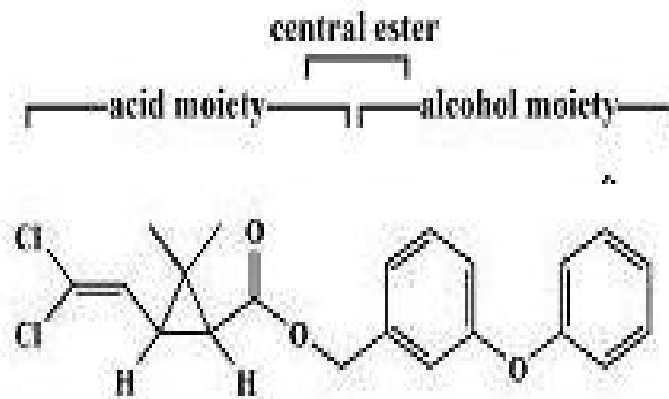


# Pyrethroid Neurotoxicity

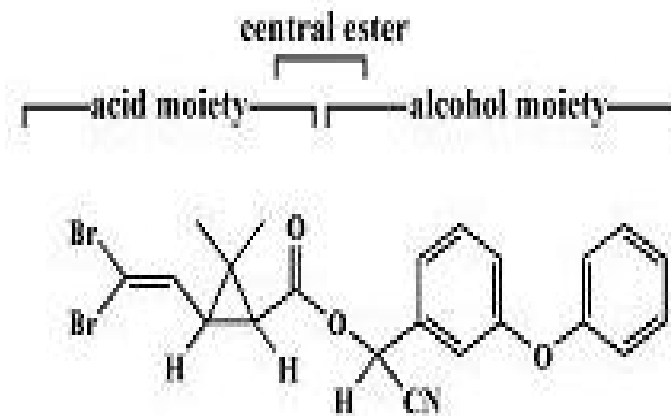


Administration to test animals and insects has identified two distinct poisoning syndromes:

- Type I: Aggressive sparring, increased sensitivity to external stimuli, fine tremors progressing to whole body tremors
- Type II: Pawing and burrowing, profuse salivation, coarse tremors progressing to seizures
- Mixed: some pyrethroids cause signs of both syndromes



Permethrin (1)



Deltamethrin (9)



# Structure Based Groups



Pyrethroid	Structure
Allethrin	Non-Cyano
Bifenthrin	Non-Cyano
Permethrin	Non-Cyano
Resmethrin	Non-Cyano
Tefluthrin	Non-Cyano
Pyrethrins	Non-Cyano
Esfenvalerate	Cyano
Fenpropathrin	Cyano
Cyfluthrin	Cyano
Cyhalothrin	Cyano
Cypermethrin	Cyano
Deltamethrin	Cyano

Type I

Mixed

Type II

# Toxicity Values for Pyrethroids



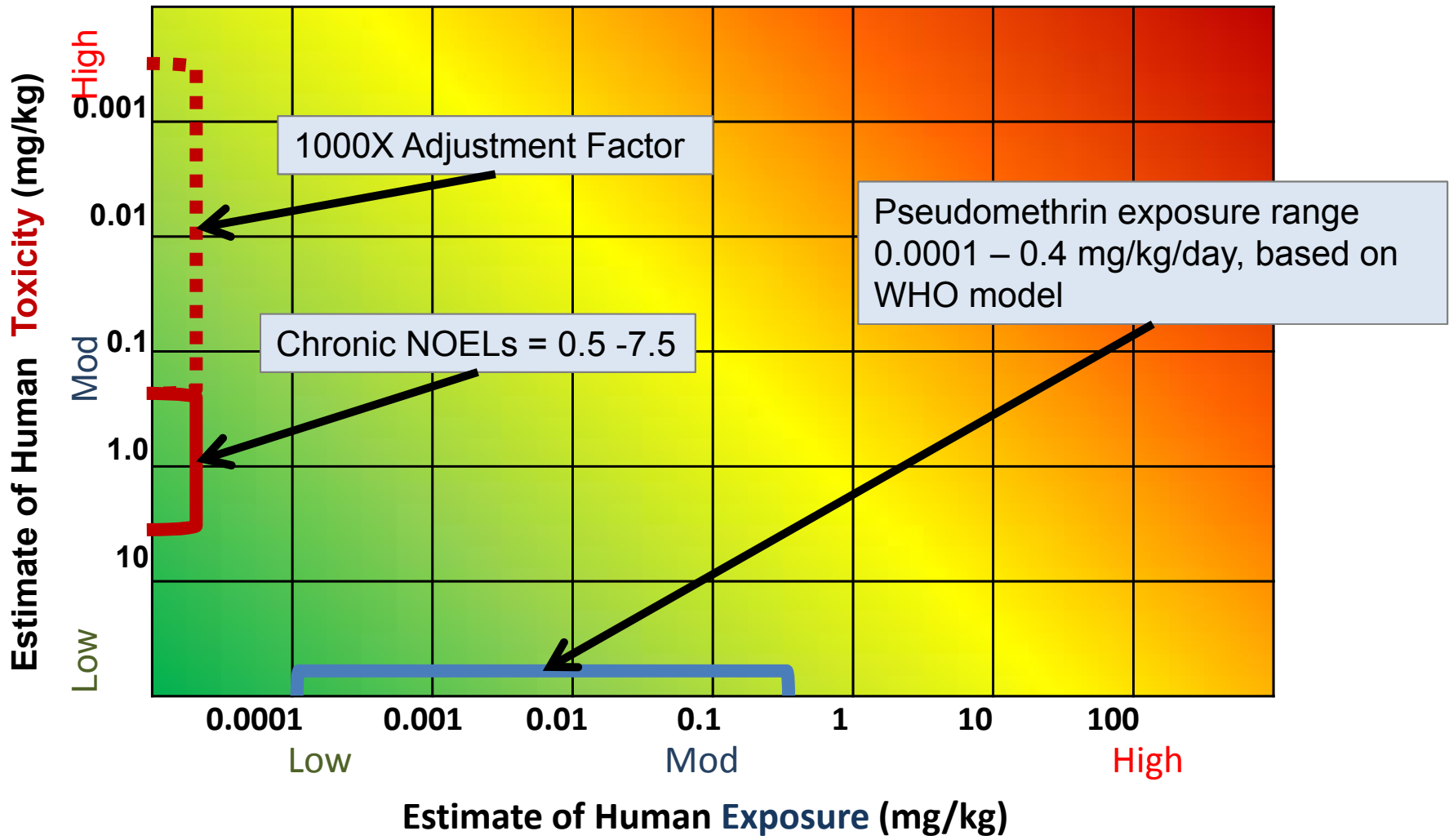
Type I non-cyano

Type II alpha-cyano

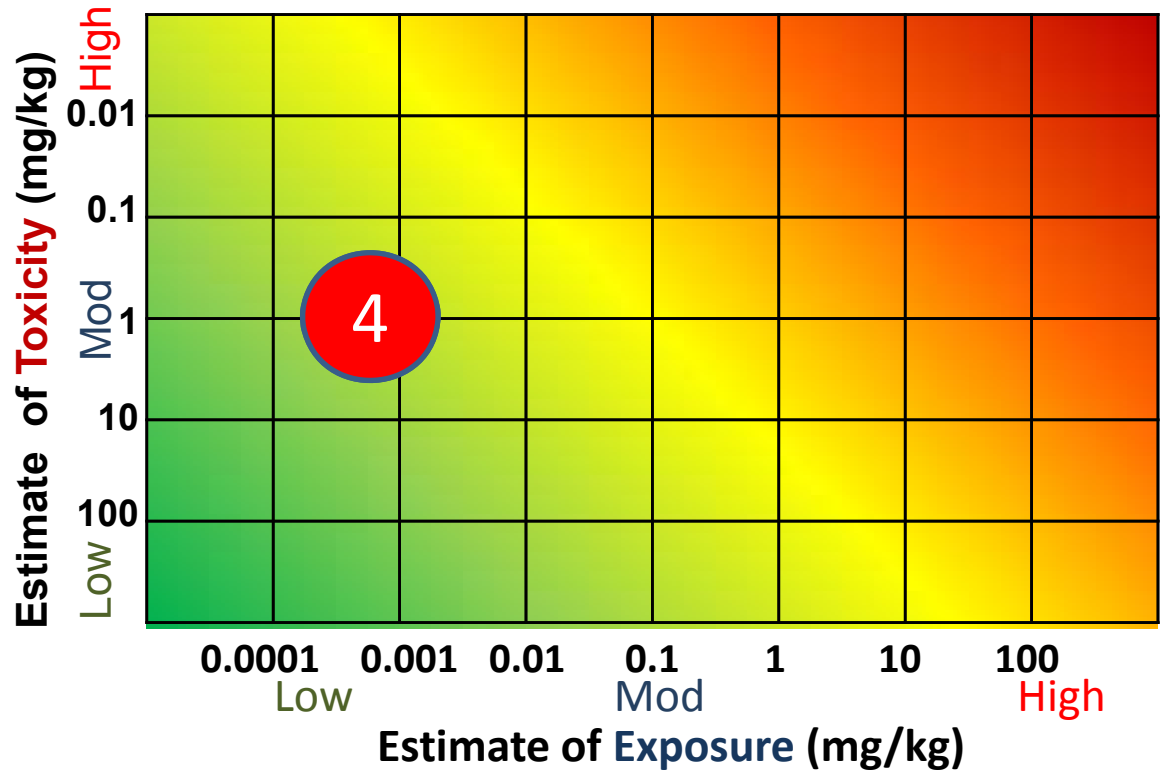
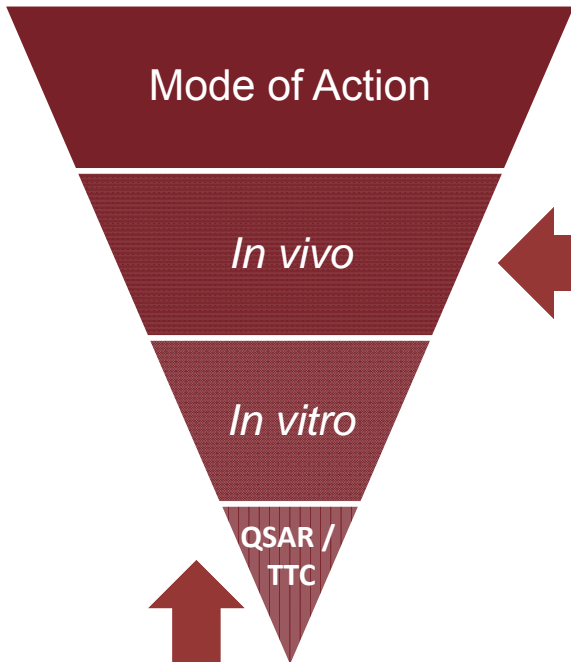
		<i>Permethrin</i>	<i>Bifenthrin</i>	<i>Resmethrin</i>	<i>S-Bioallethrin</i>	<i>Cyfluthrin</i>	<i>Cypermethrin</i>	<i>Deltamethrin</i>	<i>Esfenvalerate</i>	<i>Fenpropathrin</i>	<i>lambda-Cyhalothrin</i>
Short-term/ Acute	BMD20 (Single Dose)	156	14.3	<b>291</b>	135	12.6	76	14.5	40.5	35	<b>8.9</b>
Intermed	Ref 90d NOEL	5	2.5	<b>80</b>	20	1.3	12.5	1	7.5	7	<b>0.5</b>
Long-Term/ Chronic	Ref Chron NOEL	5	1.5	3	<b>14</b>	6.2	7.5	1	2	3	<b>0.5</b>

Highest and lowest values for each row are **bolded**

# Sleeping under net: Tier 0

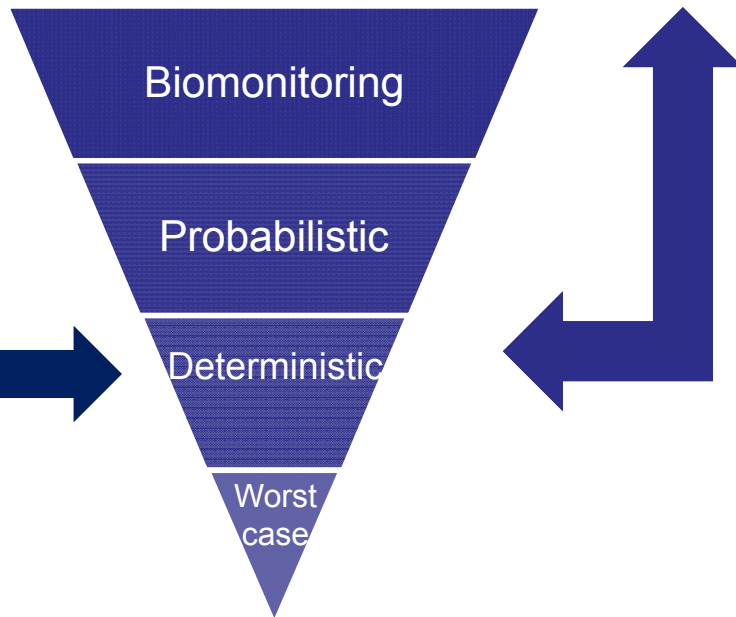


# The RISK21 Roadmap

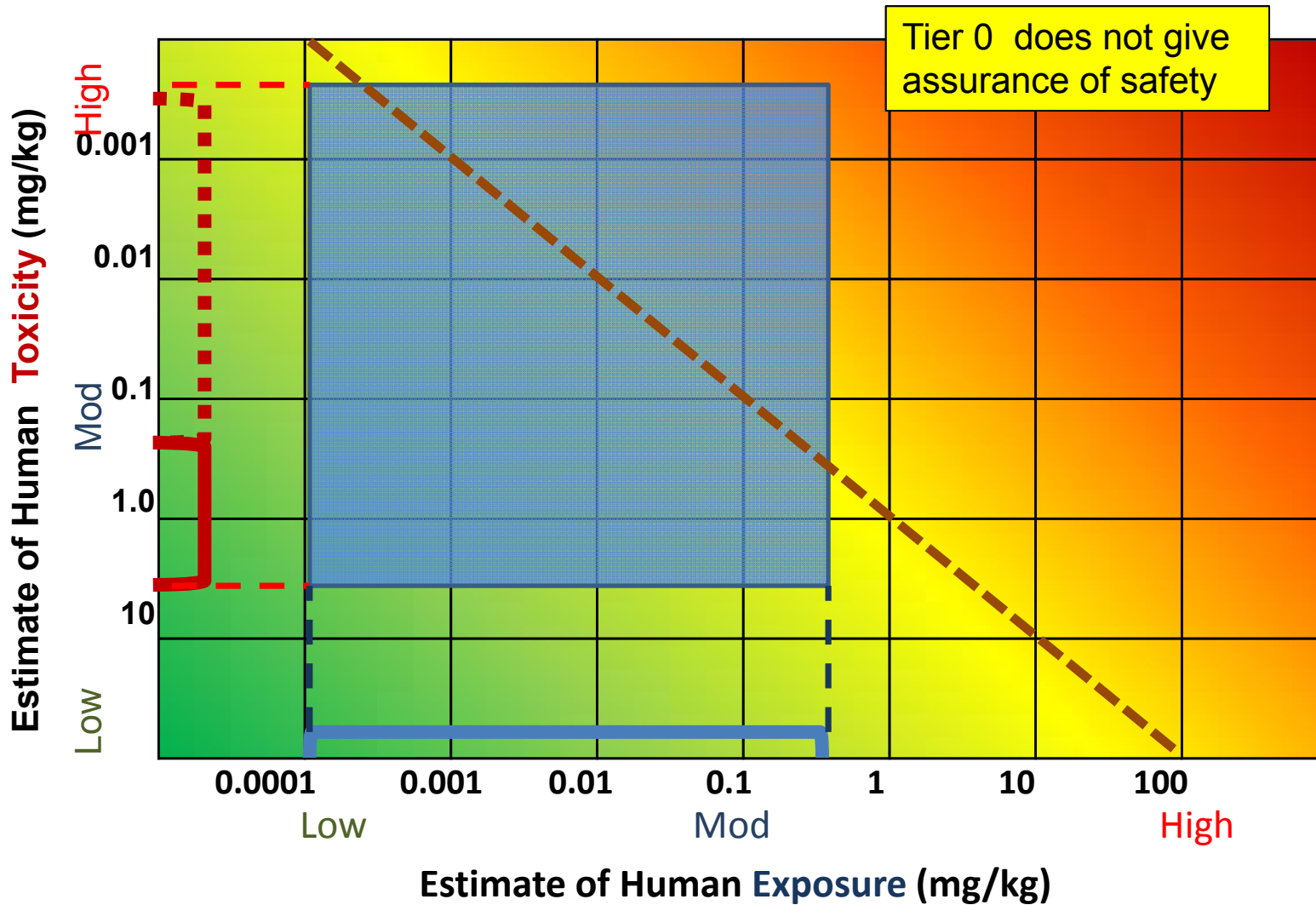


**Problem Formulation:**

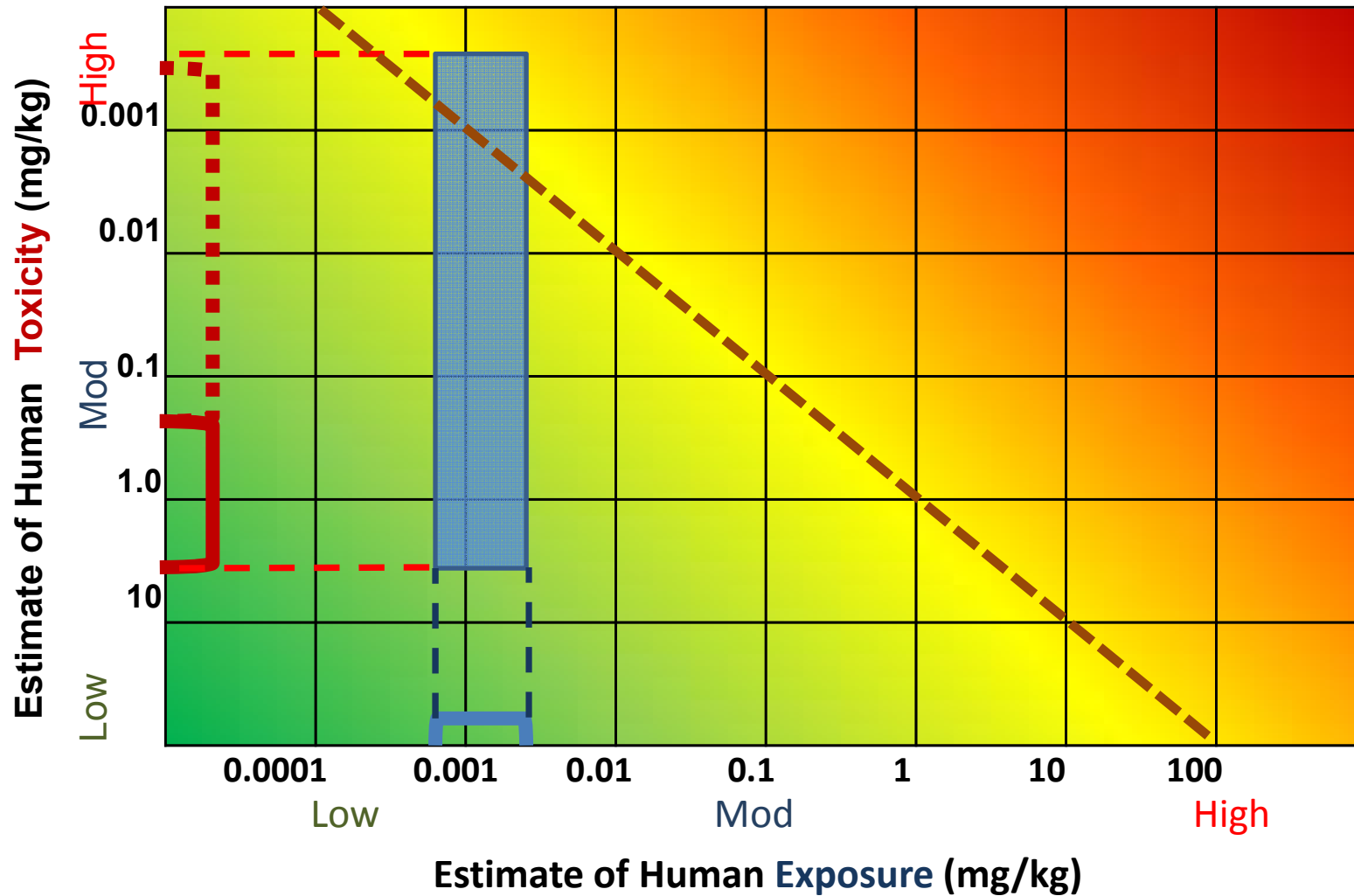
- What is it?
- Where used?
- How used?
- How much?
- What do we already know?



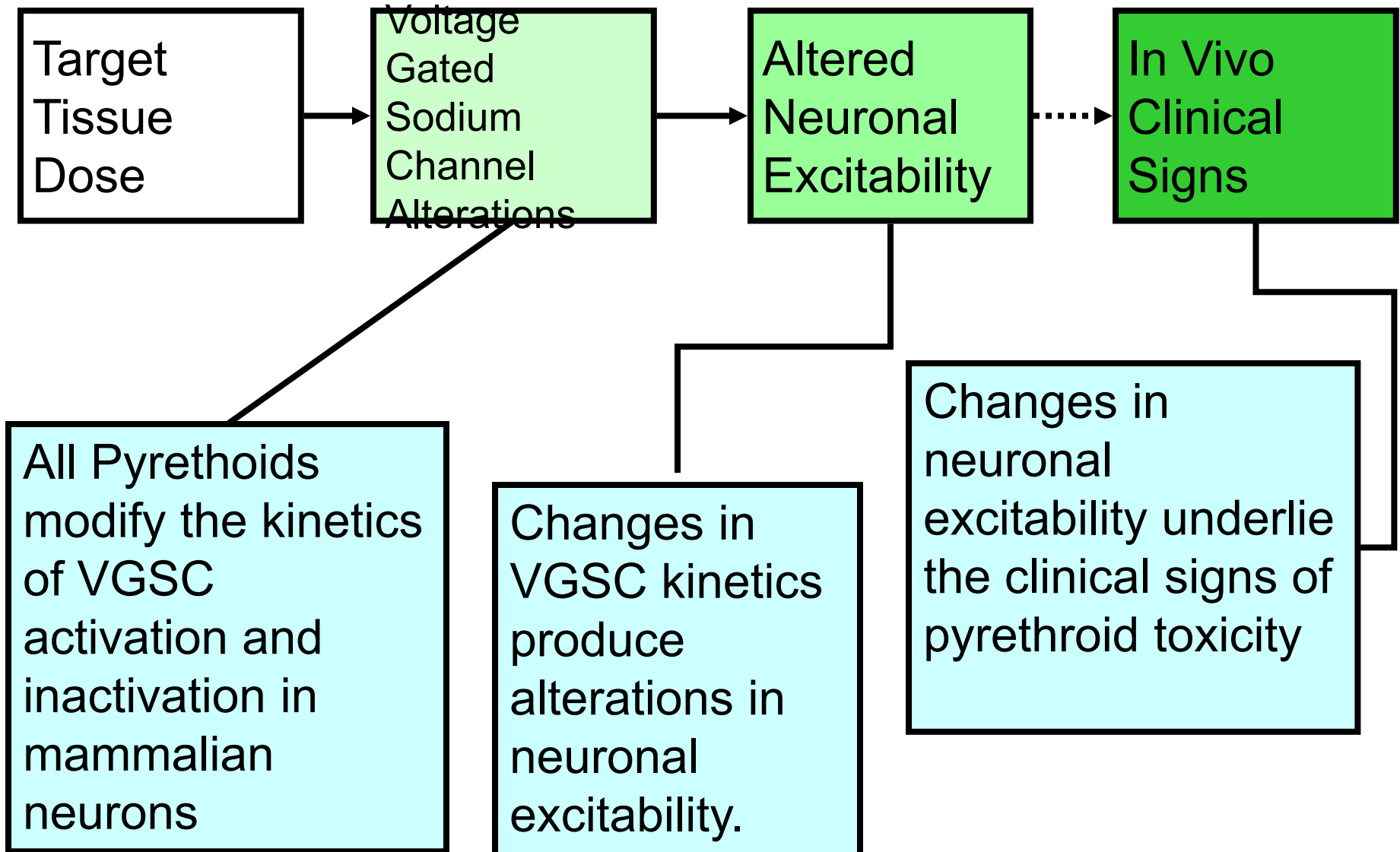
# Sleeping under net: Tier 0



# Sleeping under net: Exposure refinement



# Common Mechanism of Toxicity



# Toxicity Values for Pyrethroids



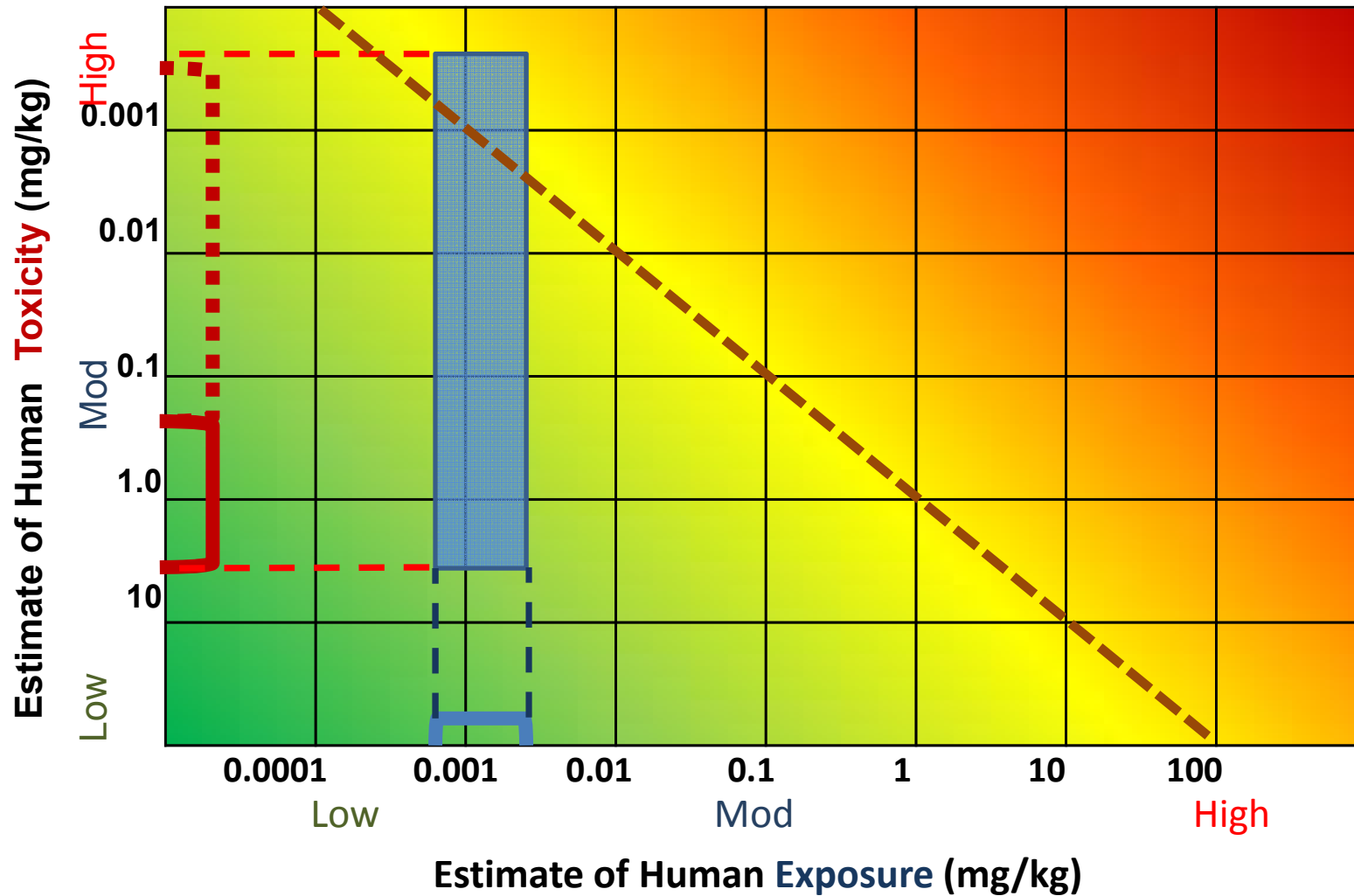
Type I non-cyano

Type II alpha-cyano

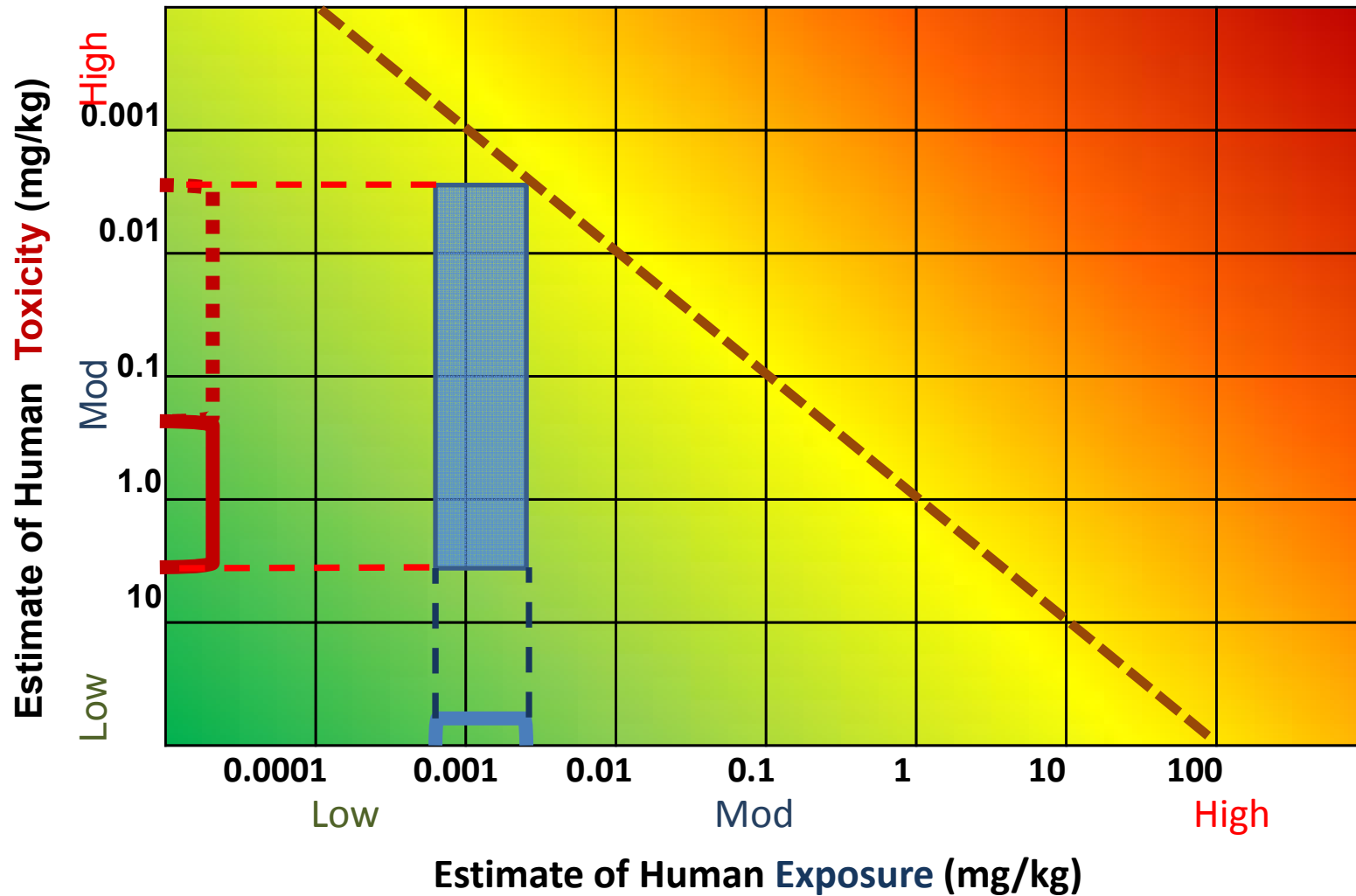
	<i>Permethrin</i>	<i>Bifenthrin</i>	<i>Resmethrin</i>	<i>S-Bioallethrin</i>	<i>Cyfluthrin</i>	<i>Cypermethrin</i>	<i>Deltamethrin</i>	<i>Esfenvalerate</i>	<i>Fenpropathrin</i>	<i>lambda-Cyhalothrin</i>
BMD20	156	14.3	<b>291</b>	135	12.6	76	14.5	40.5	35	<b>8.9</b>
Ref 90d NOEL	5	2.5	<b>80</b>	20	1.3	12.5	1	7.5	7	<b>0.5</b>
Ref Chron NOEL	5	1.5	3	<b>14</b>	6.2	7.5	1	2	3	<b>0.5</b>
MEA IC50	719	439	<b>1685</b>	1525	305	181	175	809	1518	<b>25</b>



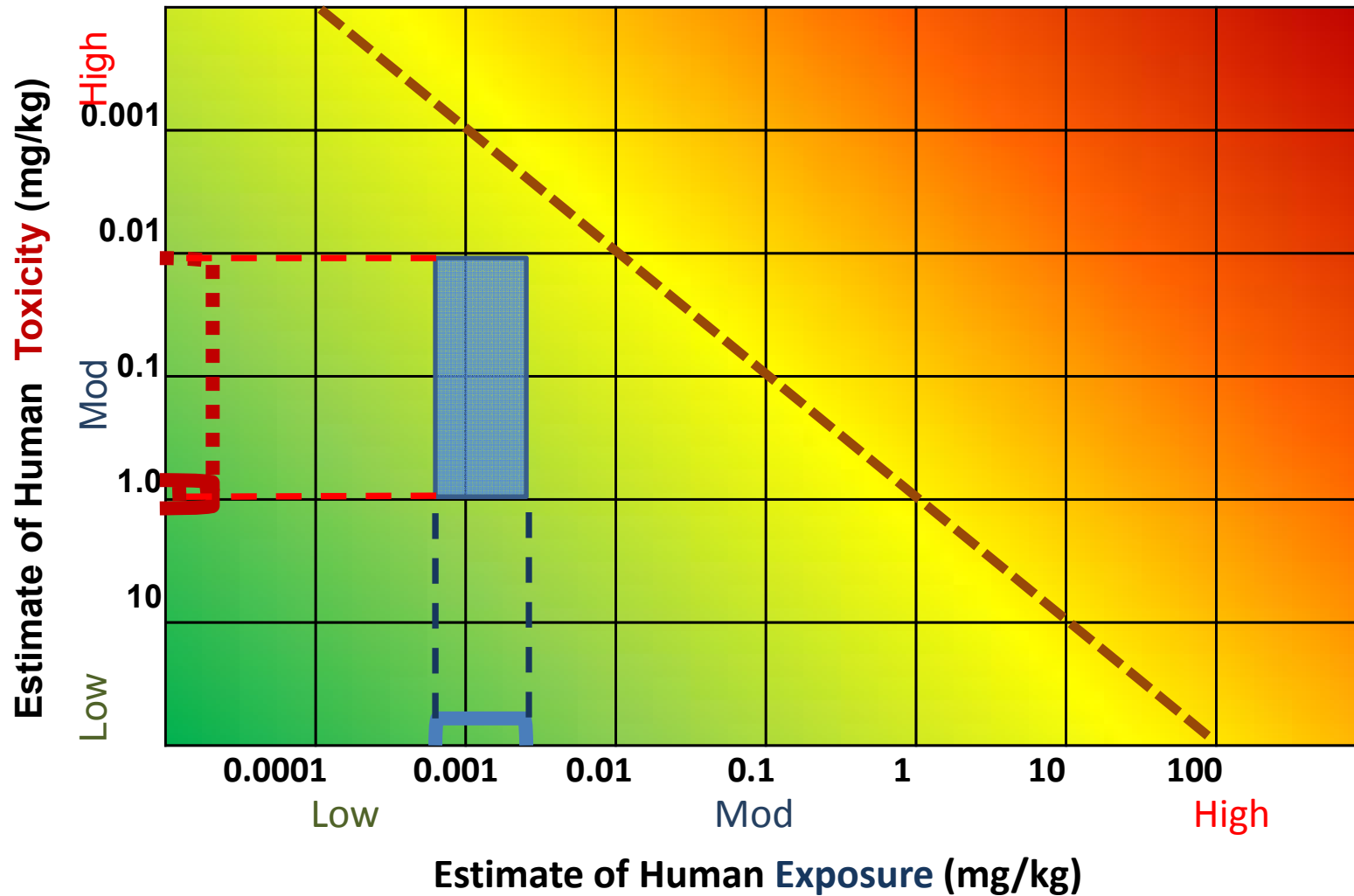
# Sleeping under net: Exposure refinement



# Sleeping under net: 2<sup>nd</sup> Assessment



# Sleeping under net: 3<sup>rd</sup> Assessment



# Is this what Tox21 is asking?

	Full Regulatory Studies Package	Risk 21 Stepwise Assessment
Lead Effect	Neurotoxicity	Neurotoxicity
Other Effects	None significant; from full package	None significant; from ToxCast assays
Short term relevant NOEL	1mg/kg from dog study	1mg/kg from dog study
Long term relevant NOEL	1mg/kg from dog study	1mg/kg from dog study
Number of animals used	2000+	24

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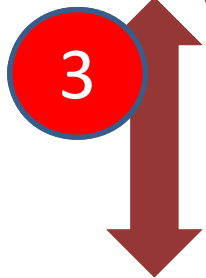
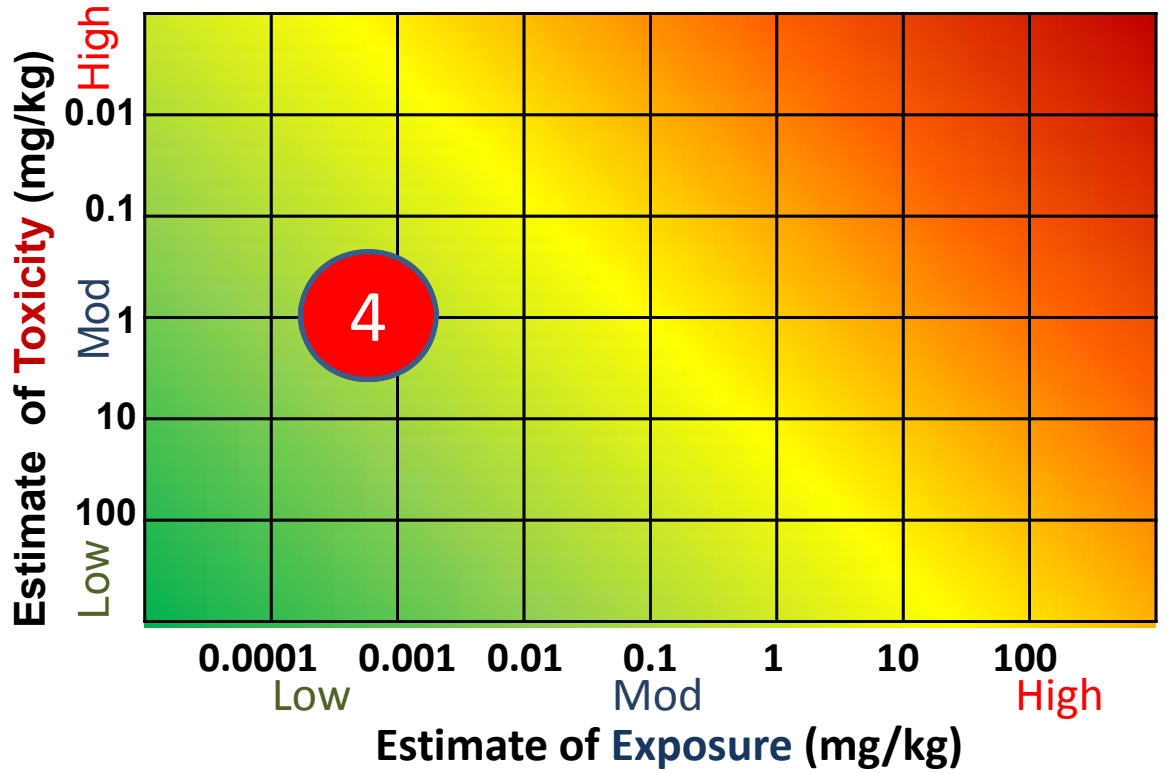
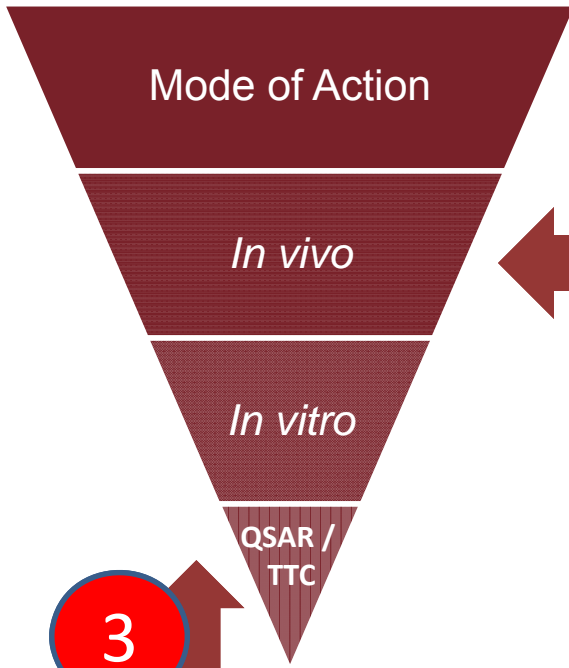
# RISK21 Case Studies

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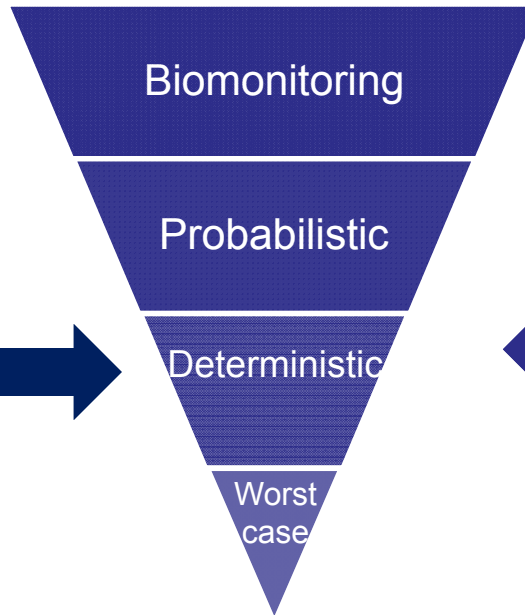
1. “Pseudomethrin”
2. 133 Chemicals in Drinking Water

# The RISK21 Roadmap



**Problem Formulation:**

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



# Case Study to Test the Approach: Water

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## **Problem Formulation**

- A regulatory agency has identified 20 chemicals that have been detected in surface 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 as potential drinking water contaminants.
- Maximize use of existing knowledge

# Water Case Study: General Approach

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- Tier 0: Utilize solubility as a worst-case exposure estimate and compare to TTC
- Tier 1: Utilize Tier 1 exposure model estimates and compare to TTC
- Tier 2: Utilize Tier 1 exposure model estimates and compare to existing chronic toxicity values



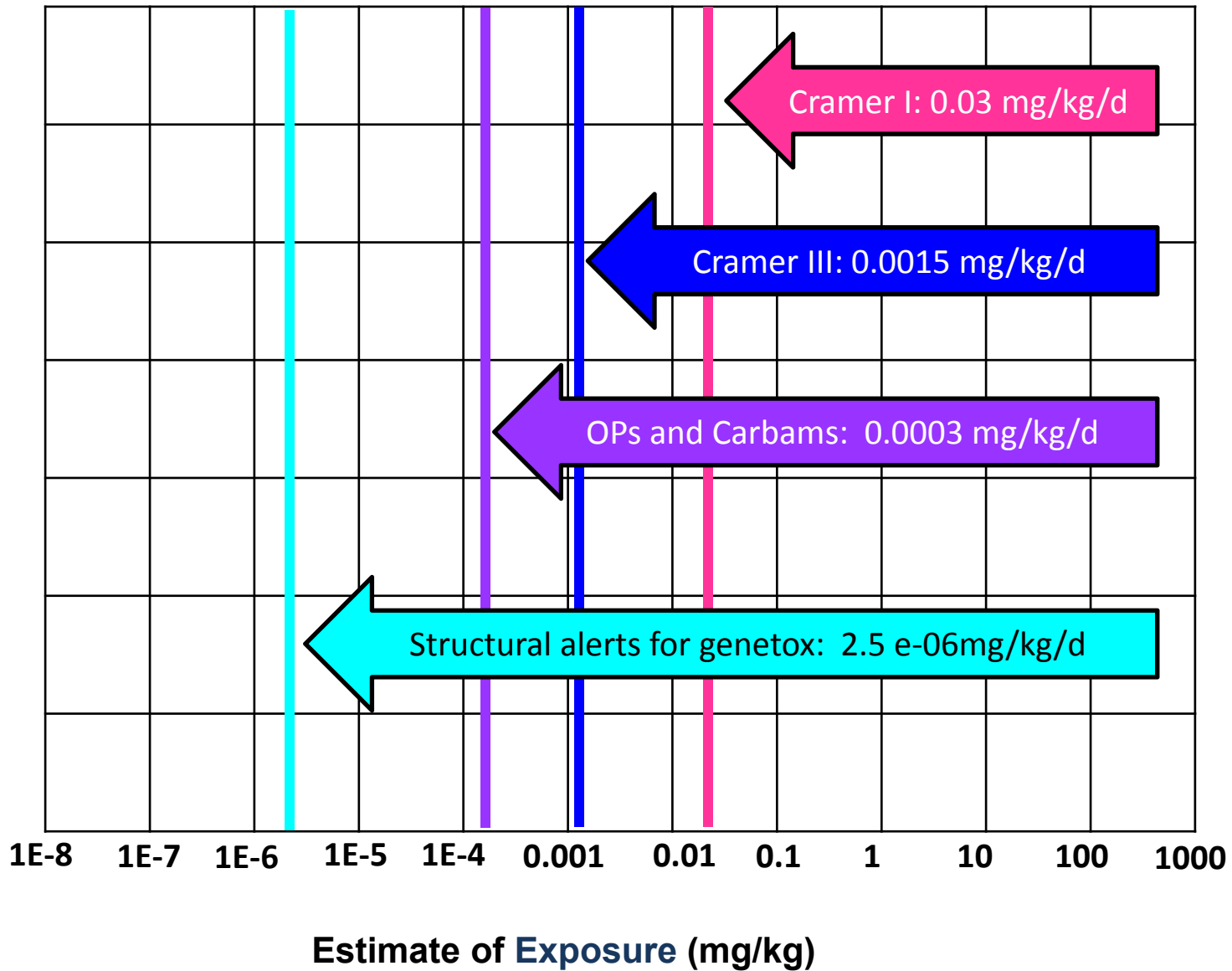


# 20 Selected Chemicals: Tier 0 Information

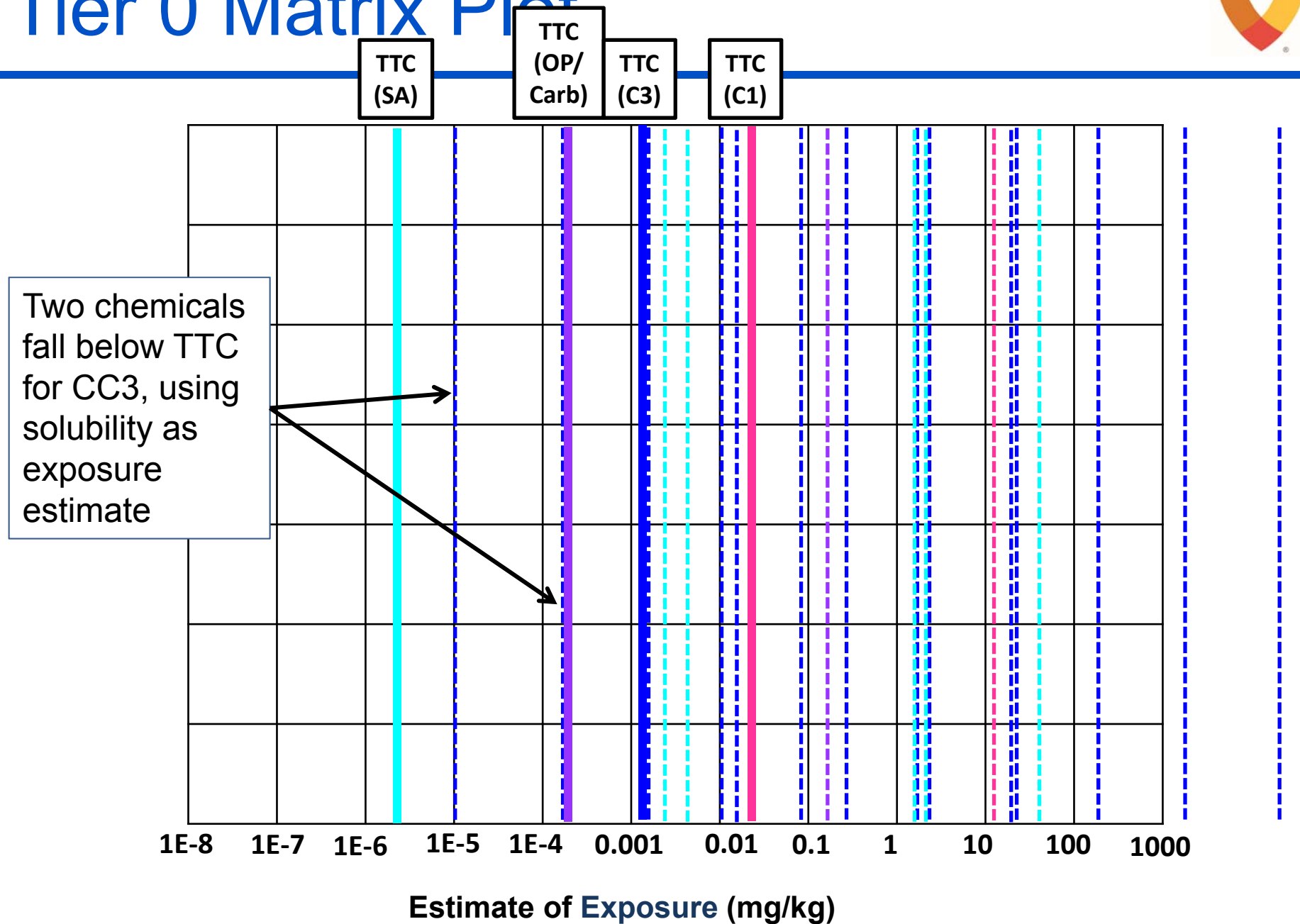


CHEMICAL	Water Solubility (mg/L)	Exposure value (based on solubility) (mg/kg bw/d)	Cramer Class	TTC (mg/kg/d)
Styrene	310	10.33	1	0.03
Chlorobenzene	498	16.6	3	0.0015
1,4-Dioxane	1000000	33333	3	0.0015
Hexachlorobenzene	0.0062	2E-04	3	0.0015
Methyl tert-butyl ether	51000	1700	3	0.0015
Toluene diisocyanate	37.57	1.252	SA	0.0000025
1,2-Dibromo-3-chloropropane (DBCP)	1230	41	SA	0.0000025
Heptachlor epoxide	0.2	0.007	SA	0.0000025
Picloram	430	14.33	3	0.0015
Oxyfluorfen	0.116	0.004	SA	0.0000025
Dimethipin	4600	153.3	3	0.0015
Chlordane	0.056	0.002	3	0.0015
Fenarimol	14	0.467	3	0.0015
Fenoxycarb	6	0.2	OP/Carbam	0.0003
Fenoxaprop-P-ethyl	0.9	0.03	3	0.0015
alpha-Hexachlorocyclohexane	7.3	0.243	3	0.0015
Toxaphene	0.0003224	1E-05	3	0.0015
2,4,5-TP (Silvex)	71	2.367	3	0.0015
Quizalofop-P-ethyl	0.3	0.01	3	0.0015
Fomesafen sodium	50	1.667	SA	0.0000025

# TTC Values and the RISK21 Matrix



# Tier 0 Matrix Plot

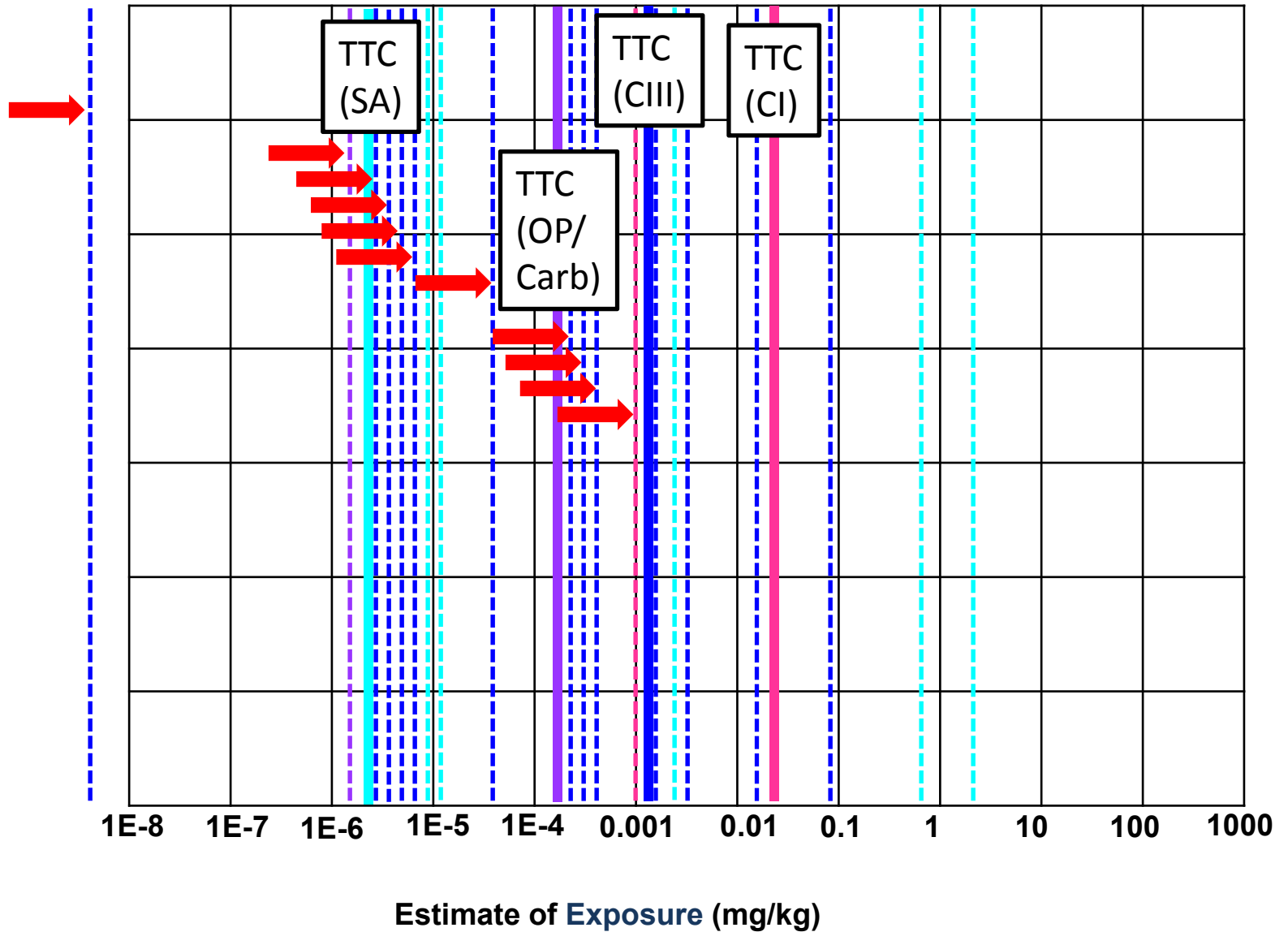


# Tier 1: Exposure refinement of 18 chemicals

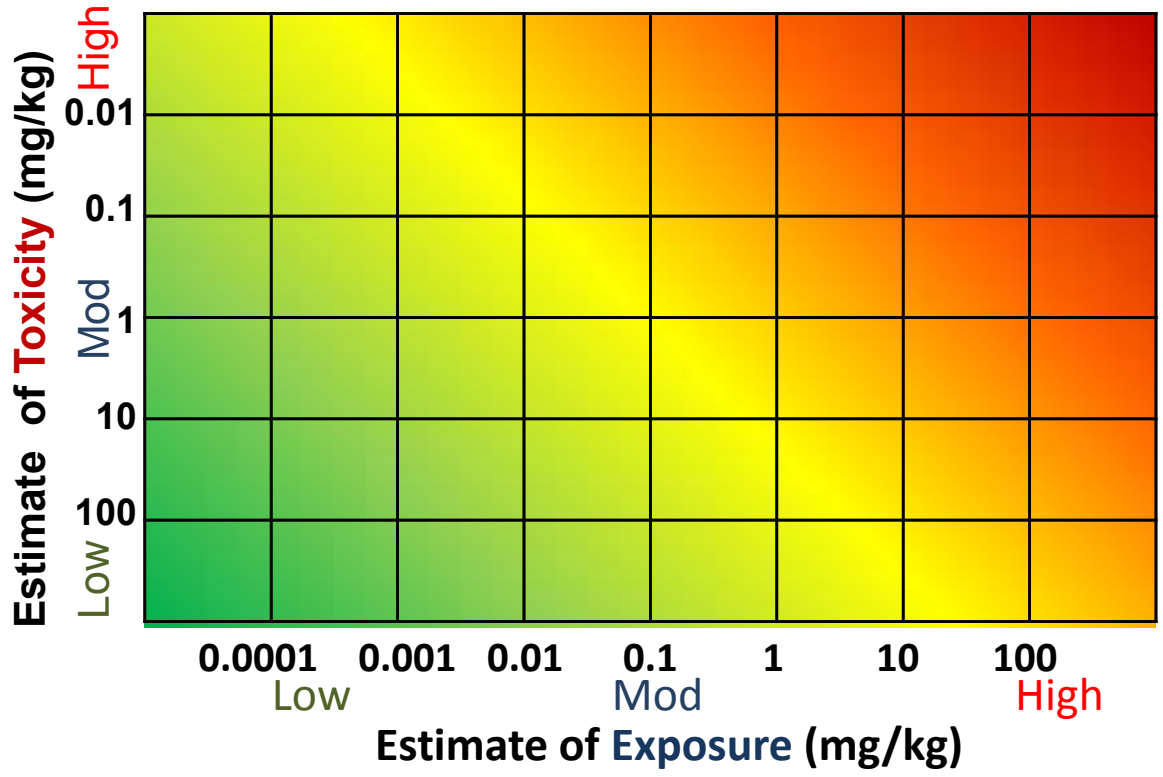
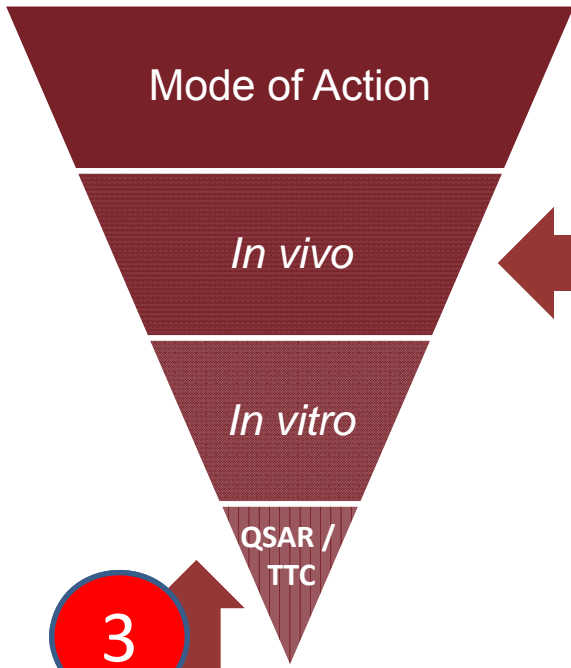


CHEMICAL	Water Solubility (mg/L)	Exposure value (based on solubility) (mg/kg bw/d)	Refined Exposure value (mg/kg bw/d)
Styrene	310	10.33	1E-03
Chlorobenzene	498	16.6	3E-02
1,4-Dioxane	1000000	33333	3E-03
Methyl tert-butyl ether	51000	1700	0.767
Toluene diisocyanate	37.57	1.252	0.8
1,2-Dibromo-3-chloropropane (DBCP)	1230	41	1.3E-05
Heptachlor epoxide	0.2	0.007	1E-05
Picloram	430	14.33	5.4E-03
Oxyfluorfen	0.116	0.004	2.4E-04
Dimethipin	4600	153.3	2.4E-04
Chlordane	0.056	0.002	3.3E-06
Fenarimol	14	0.467	8E-06
Fenoxycarb	6	0.2	2.2E-06
Fenoxaprop-P-ethyl	0.9	0.03	7E-06
alpha-Hexachlorocyclohexane	7.3	0.243	1E-09
2,4,5-TP (Silvex)	71	2.367	2.9E-06
Quizalofop-P-ethyl	0.3	0.01	6.6E-05
Fomesafen sodium	50	1.667	3E-04

# Tier 1: 11 chemicals below TTC

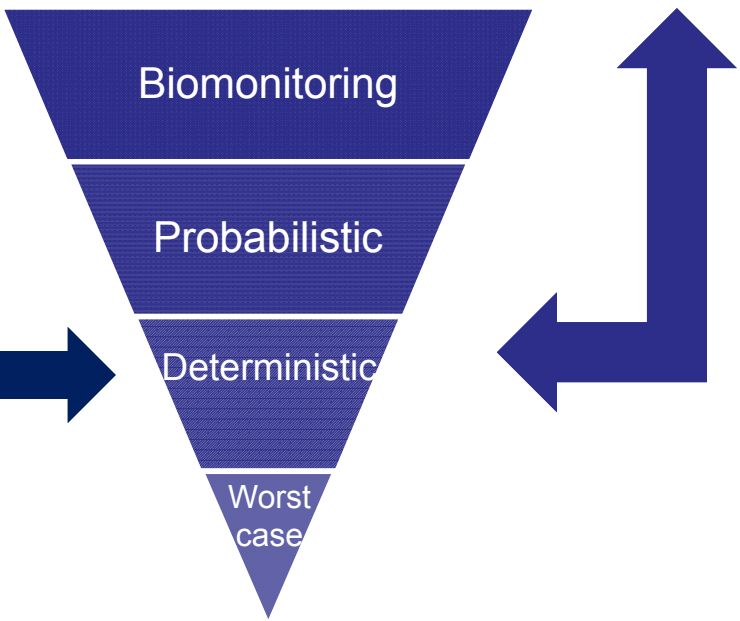


# The RISK21 Roadmap



3

- Problem Formulation:**
- What is it?
  - Where used?
  - How used?
  - How much?
  - What do we already know?

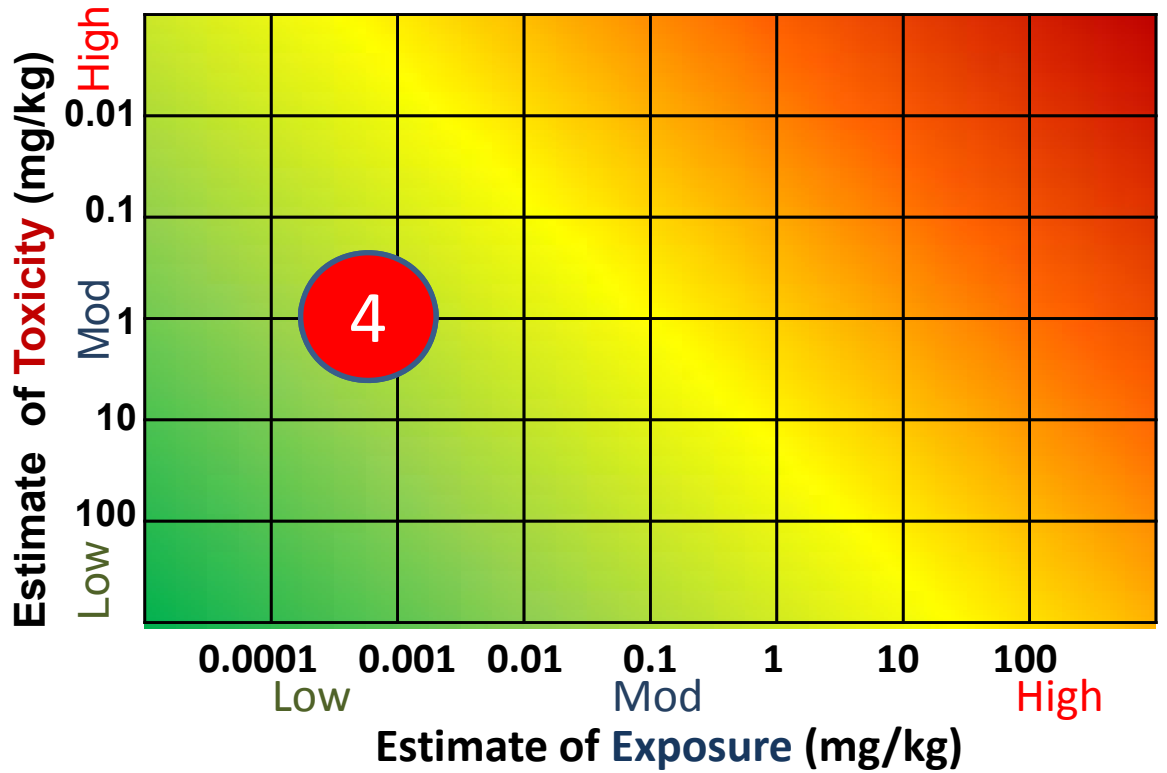
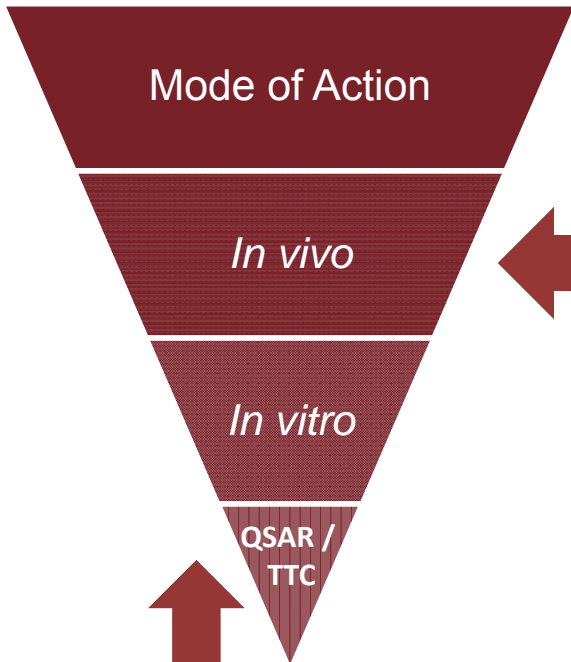


# Tier 2: Toxicity Refinement for 7 chemicals



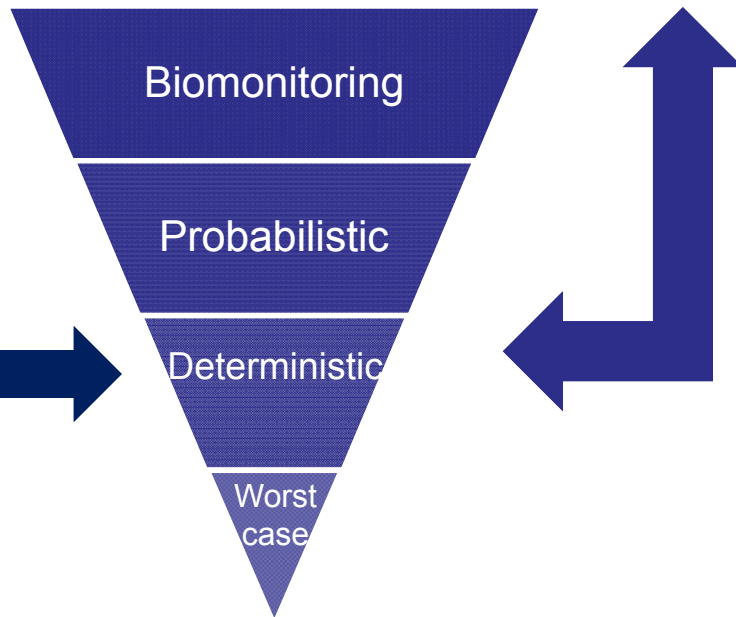
CHEMICAL	Water Solubility (mg/L)	Tier 1 modeled exposure value (mg/kg bw/d)	Toxicity value (mg/kg/d)
Chlorobenzene	498	3E-02	NOAEL = 19
1,4-Dioxane	1000000	3E-03	NOAEL= 9.6
Methyl tert-butyl ether	51000	0.767	NOAEL= 300
Toluene diisocyanate	37.57	0.8	LOAEL = 30
1,2-Dibromo-3-chloropropane (DBCP)	1230	1.3E-05	Oral MRL = 0.002
Heptachlor epoxide	0.2	1E-05	LOAEL = 0.0125
Picloram	430	5.4E-03	NOEL = 7

# The RISK21 Roadmap



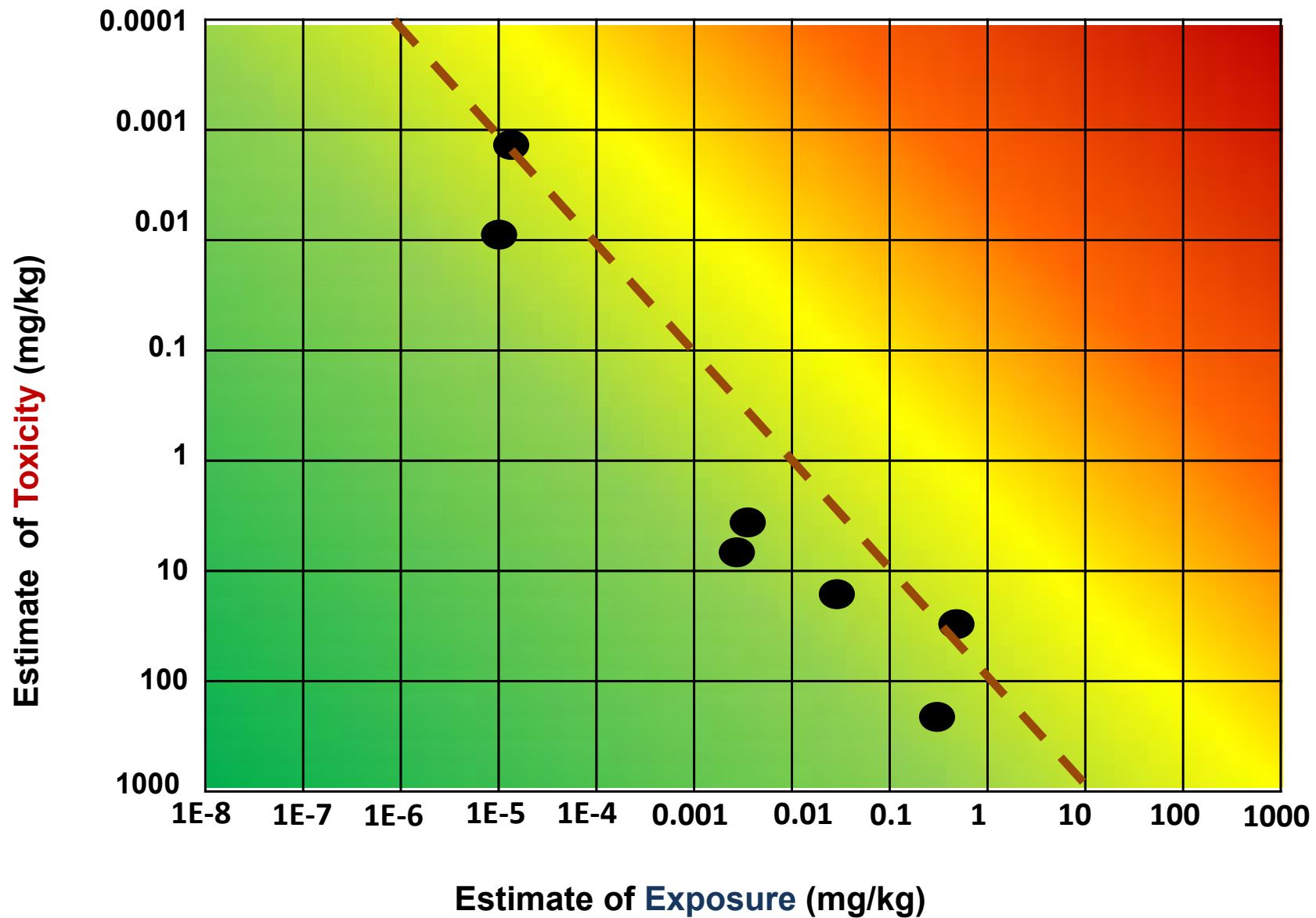
**Problem Formulation:**

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- What do we already know?





# Tier 2 Matrix Plot of 7 Chemicals (point estimates)



# Summary and Next Steps

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## Initial Summary

- Using TTC and exposure information, winnowed down this subset of 20 chemicals by >60% (from 20 to 7) without running ANY toxicity studies

## Next Steps

- For most of the chemicals on the list, there is toxicity information available; need to gather and plot ranges when available
- Using available information on toxicity and exposure the list of chemicals was narrowed and the next iteration of problem formulation can begin.