Introducing HESI's RISK21 Project

Cumulative risk

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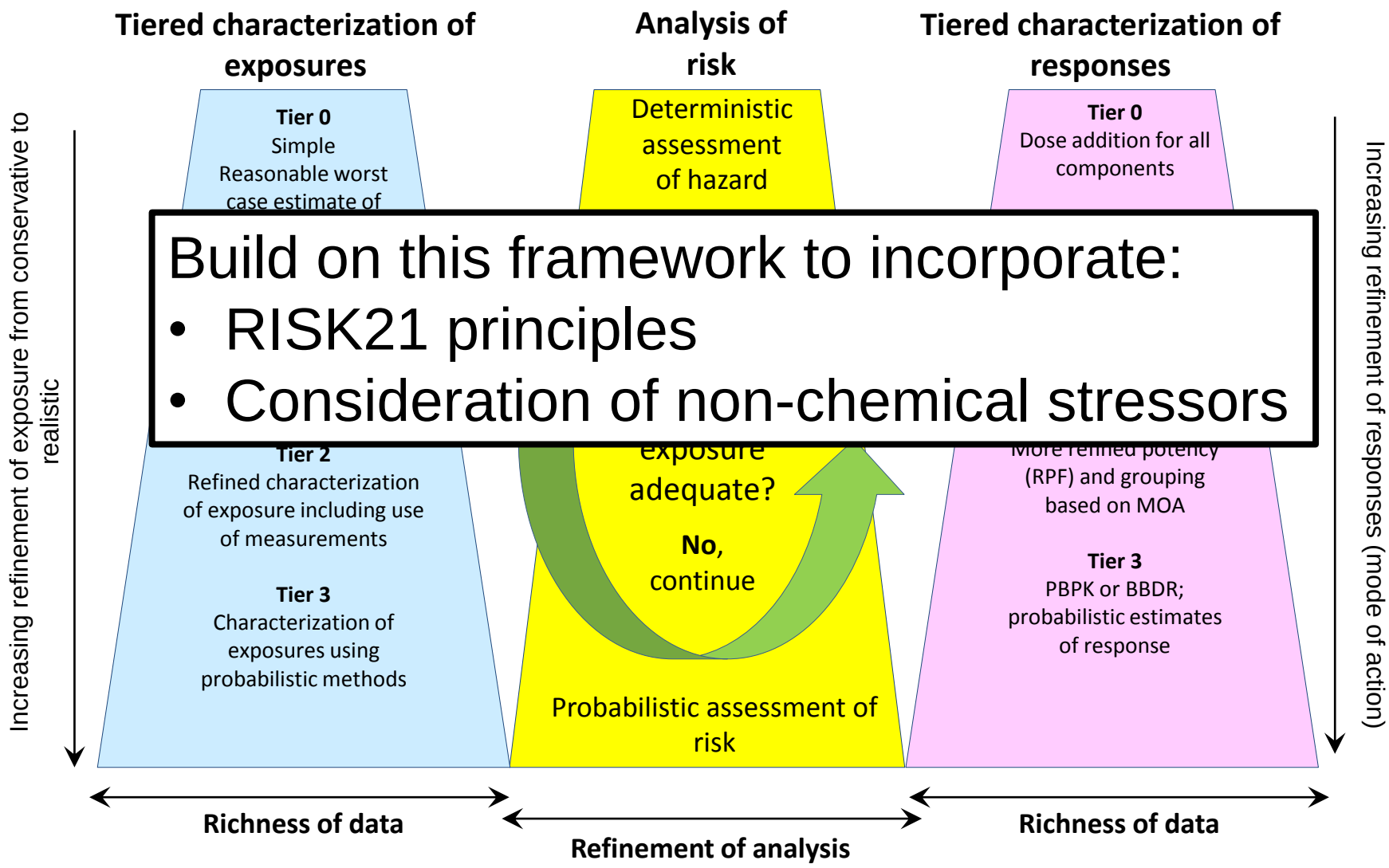
Cumulative Risk: Drivers for Change

- The need for a uniform approach to cumulative risk assessment is growing:
  - Existing statutes (e.g., FQPA, Regulation (EC) No 1107/2009)
  - Regulatory programs (e.g., Superfund)
  - NAS/NRC report Science and Decisions advocates a cumulative approach to risk assessment as do several EU reports (e.g. DG Environment).
- There are different approaches to cumulative risk:
  - Restricted groups of chemicals mode or mechanism of action
  - A broad groups approach that clusters based on target organ
  - What stressors should be combined in a cumulative risk assessment?
    - anthropogenic stressors only (*e.g.* chemicals ± radiation ± noise)?
    - endogenous and other (*e.g.,* dietary ± microbial) agents?

Cumulative Risk: Many Definitions…

- USEPA 2003: "The combined risks from aggregate exposures to multiple agents or stressors."
- NAS / NRC 2009: "The combination of risks posed by aggregate exposure to multiple agents or stressors in which *aggregate exposure* is exposure by all routes and pathways and from all sources of each given agent or stressor."
- WHO/IPCS 2011: Utilized the term, "Combined exposure to multiple chemicals" to delineate their described tiered approach.
- EFSA 2009: "Combined risk assessment to exposures from pesticide residues in food that could arise from plant protection products".

WHO/IPCS Framework



RISK21 & Cumulative Risk

- An appraisal – quantitative to the extent practicable – of the adverse health effects from combined exposure to multiple **chemical and non-chemical** stressors
- To make the problem **manageable**, start with chemical stressors and address non-chemical stressors as modulating factors as necessary

- A unified approach / framework:
  - The information you have in-hand determines where you start, what additional information you need, and what specific methodologies are applied
  - An iterative process that includes reassessment and higher tier evaluation of “initial/preliminary” evidence supporting inclusion into assessment groups

Other chemical and non-chemical stressors: **Modulating Factors** (MFs)

- "Biological, environmental, and individual factors, including control mechanisms or host factors, that can modulate the response to chemical stressors".
  - Alter the probability or magnitude of the adverse outcome
- Modulating factors include:
  - Host factors
  - Lifestyle factors
  - Environmental factors
- **Vulnerability, susceptibility, and sensitivity are captured and broken down into simple modulating factors**

Other chemical and non-chemical stressors: **Modulating Factors** (MF) *[non exhaustive list]*

Category	Sub-category	Aspects
Host Factors	Genetic Variation	Polymorphisms
	Disease/Illness	Chronic
		Acute
	Defense mechanisms	Immune responsiveness
		DNA repair
		Cell proliferation
		Cell death
	Physiology	Gender
		Life stage
		ADME
		Hormonal status
Life Style Factors	Diet	Calories
		Fat content
	Tobacco	Usage
	Alcohol	Usage
	Exercise	Frequency
		Intensity
	Pharmaceuticals	Usage
	Illegal drugs	Usage
	Dietary supplements	Vitamins
		Anti-oxidants
Environmental Factors	Occupation	Duration
	Exposures	Air
		Water
		Food
		Dust
		Other media

From RISK21 Dose-Response Project

Problem Formulation for Cumulative Risk

Initial "gatekeeper" step	Sufficient initial evidence to support a CRA?
Planning & scoping	Define purpose, endpoints, approach, and depth
Consideration of multiple stressor issues	Temporal relationships, relevant modulating factors
Conceptual Models	Exposure and effects
Plan for Analysis	Development of risk hypotheses, specification of data needs and characterization approach

Problem Formulation for Cumulative Risk

When is a Cumulative Risk Assessment Necessary?

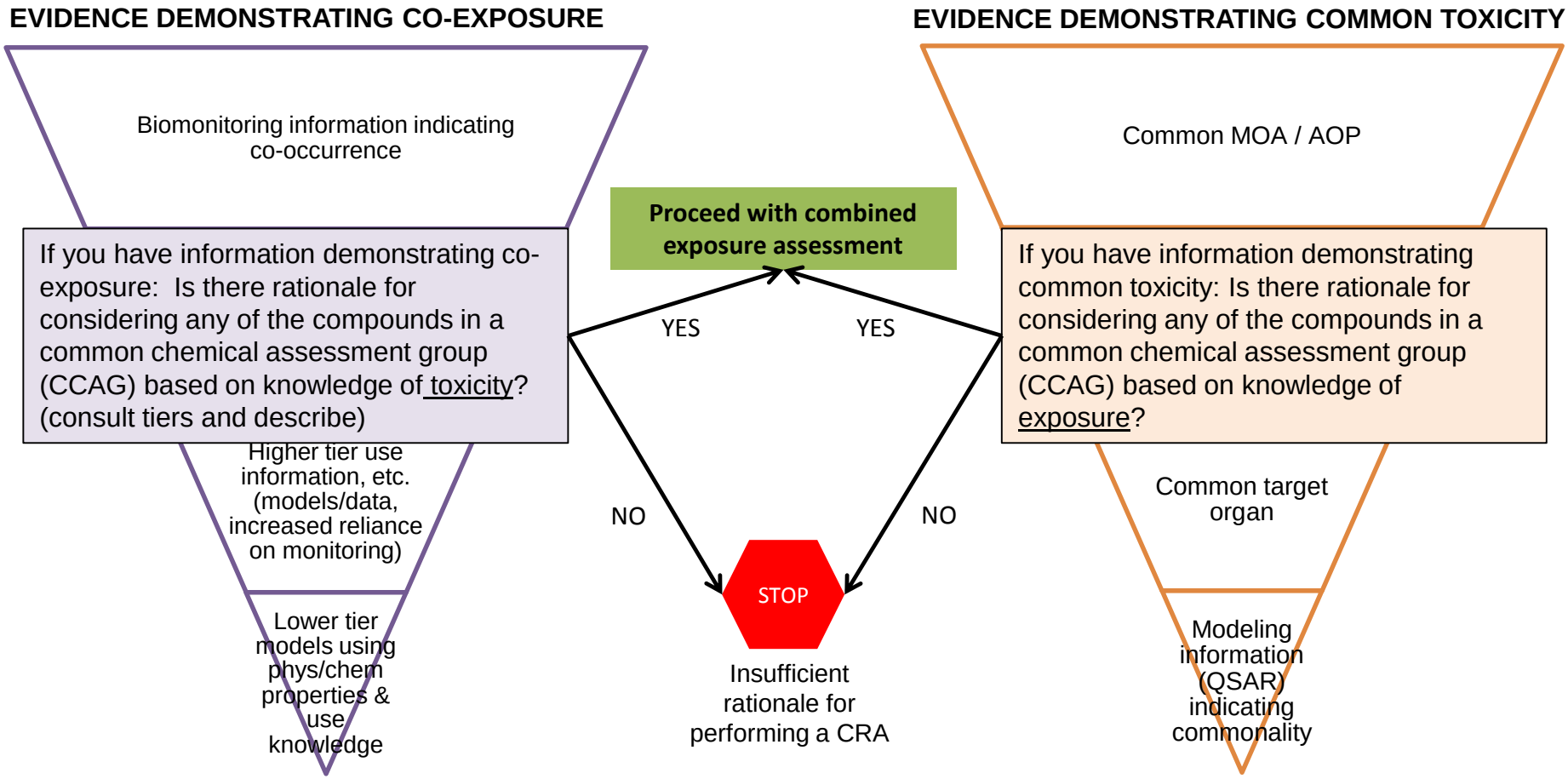
Scientific evidence

- Indicates a likelihood of co-exposure **AND** common toxicity;
- Determines inclusion into a common chemical assessment group (CCAG)

  – **Co-exposure**: evidence based on models, detection in environmental or biological samples [includes considerations of context & temporality]

  – **Common toxicity**: evidence based on QSAR (or other) models, common target organ, common apical effect, common MOA/AOP; in the absence of information use dose-addition as lowest/screening tier

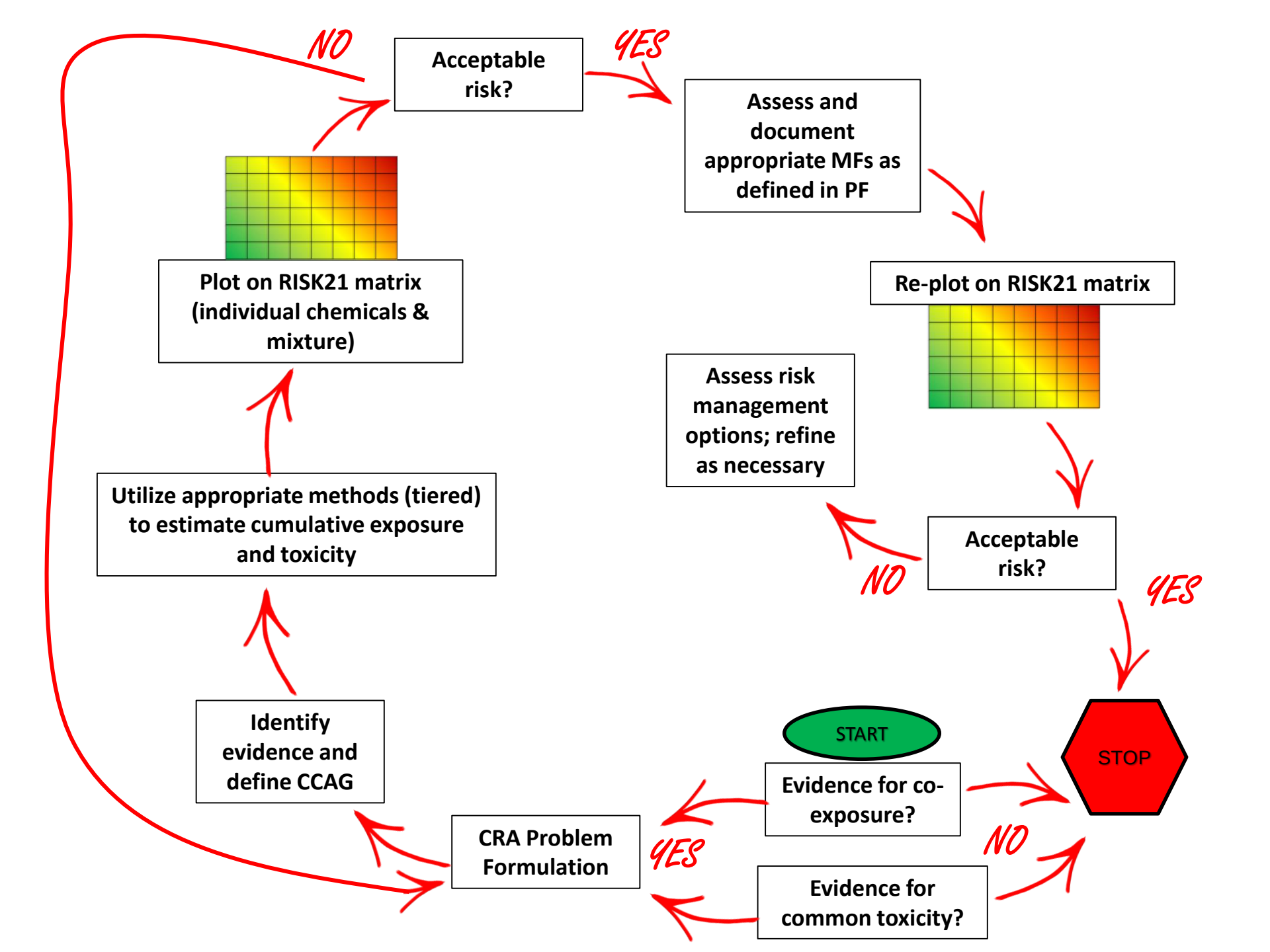
Problem Formulation for CRA: Initial Step



Tables to Evaluate CRA Evidence

CHEMICAL	EVIDENCE TO SUPPORT COMBINED EXPOSURE (CO-EXPOSURE)							
	Lower tier models		Higher tier models		Env. Monitoring data		Biol. Monitoring data	
	Description	Strength	Description	Strength	Description	Strength	Description	Strength
1								
2								
3								

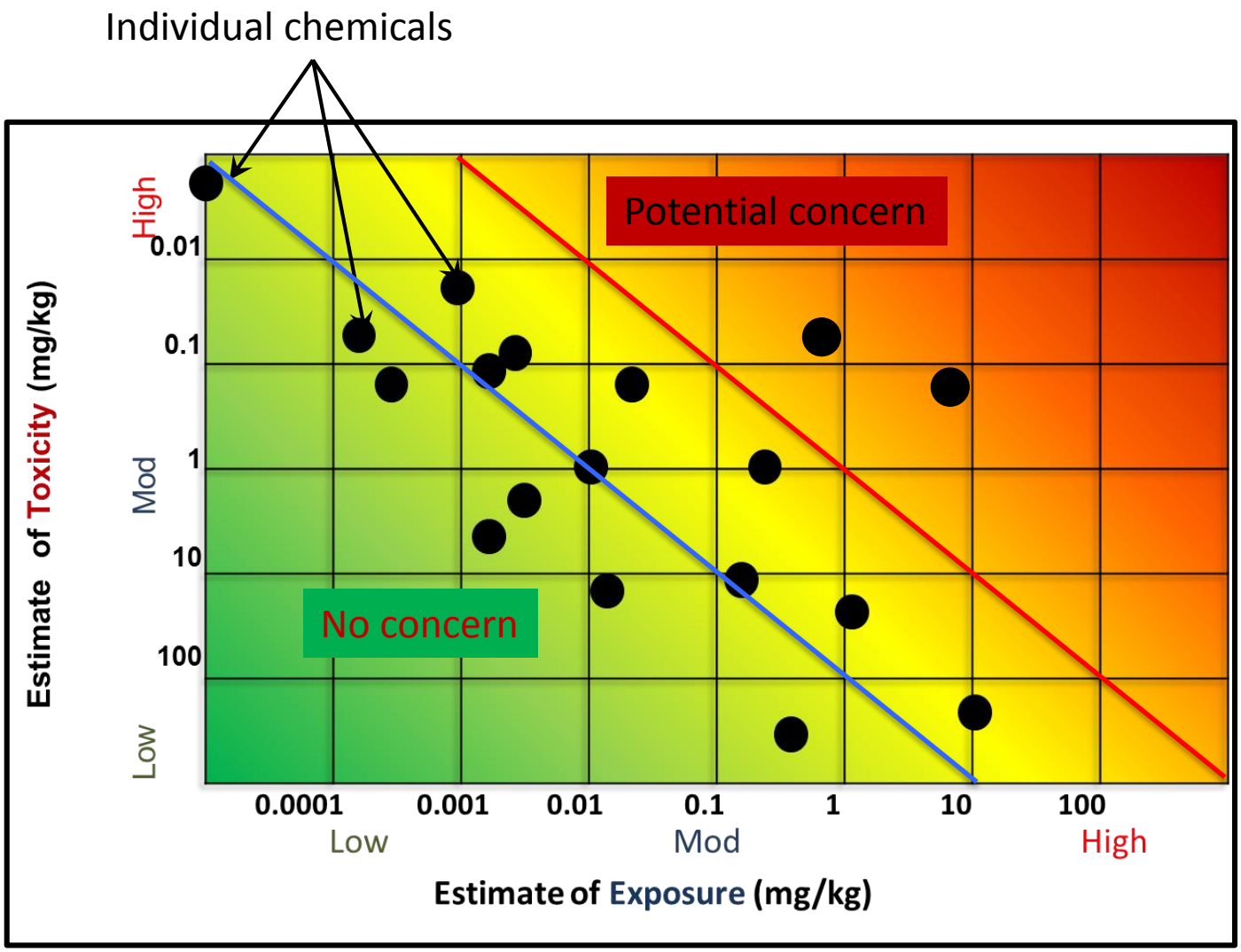
CHEMICAL	EVIDENCE TO SUPPORT COMBINED TOXICITY (COMMON-TOXICITY)							
	Model alerts		Common target organ		Common apical endpoint		Common MOA / AOP	
	Description	Strength	Description	Strength	Description	Strength	Description	Strength
1								
2								
3								


START
Evidence for co-exposure?
Evidence for common toxicity?
YES
NO
STOP
CRA Problem Formulation
Identify evidence and define CCAG
Utilize appropriate methods (tiered) to estimate cumulative exposure and toxicity
Plot on RISK21 matrix (individual chemicals & mixture)
Acceptable risk?
NO
YES
Assess and document appropriate MFs as defined in PF
Re-plot on RISK21 matrix
Assess risk management options; refine as necessary
Acceptable risk?
NO
YES

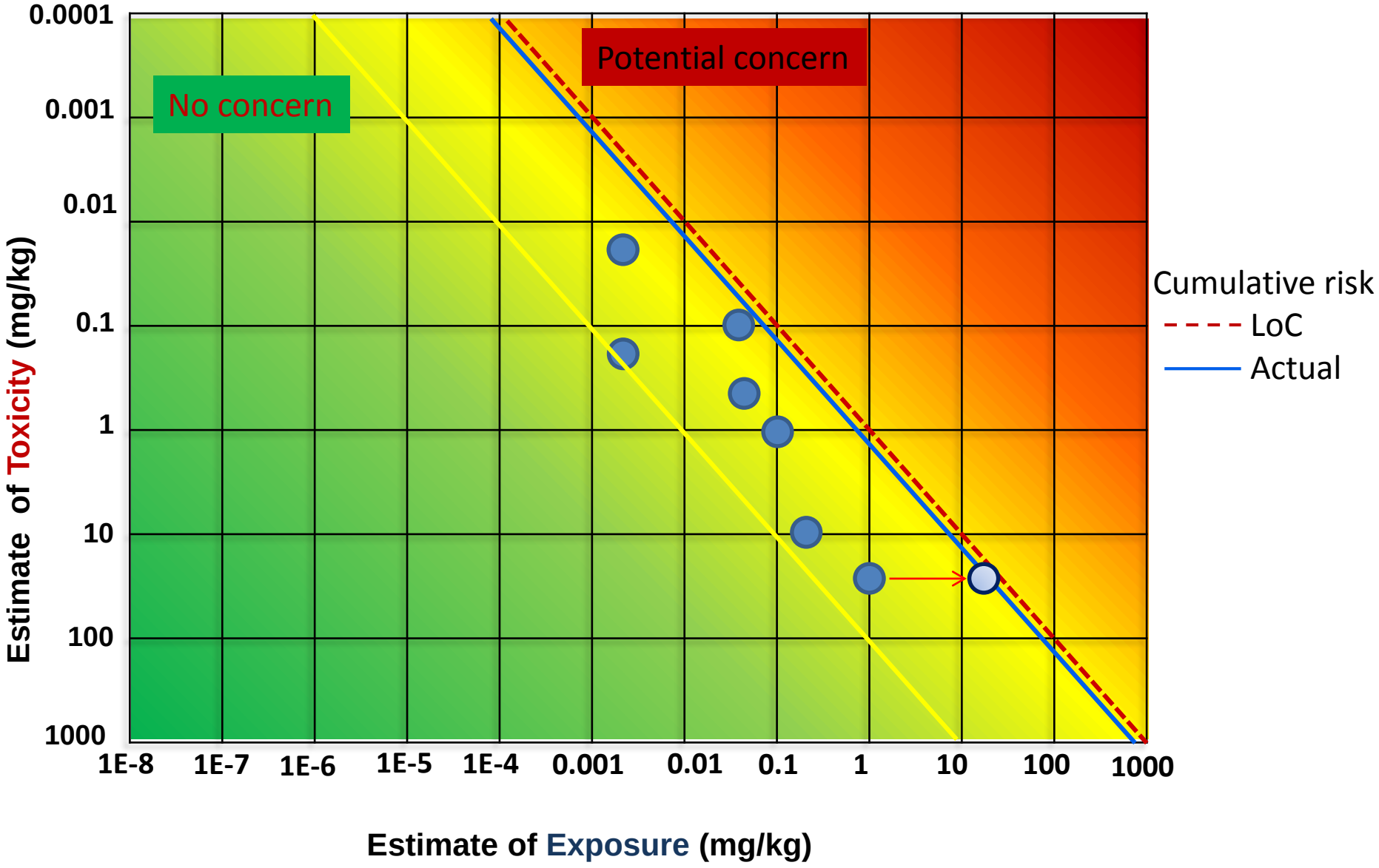
Examples of Available Methods for CRA

Method	Explanation	Evaluation
Hazard Index (HI)	Sum of the Hazard Quotients, i.e. the ratio between exposure and the RV of each component	HI<1: risk is considered acceptable
Adjusted Hazard Index (aHI)	Sum of the adjusted Hazard Quotients, i.e. the ratio between exposure and the derived reference value of each component for the specific effect for CAG. This is applied when the effect relevant for CAG has a NOAEL higher than the critical NOAEL (i.e. that used to set the RV)	aHI<1: risk is considered acceptable
Cumulative Risk Index (CRI)	Reciprocal of the sum of HQ	CRI>1: risk is considered acceptable
Reference Point Index (RfPI)	Sum of the exposures to each compound expressed as a fraction of their respective RfP for the relevant effect	RfPI<1/SF: risk is considered acceptable
Combined Margin of Exposure (MOET)	Reciprocal of the sum of the reciprocals of the individual MOEs. Where MOE is the ratio RfP/exposure	MOET<1 x SF: risk is considered acceptable
Toxic equivalency/potency equivalency/relative potency factors (TEF/PEF/RPF)	Normalization of all components to the potency of an “index compound” (IC). Exposure expressed as “IC-equivalents”. Calculate HQ for the IC-normalized exposure	HQ<1: risk is considered acceptable

RISK21 Matrix Plot: CRA



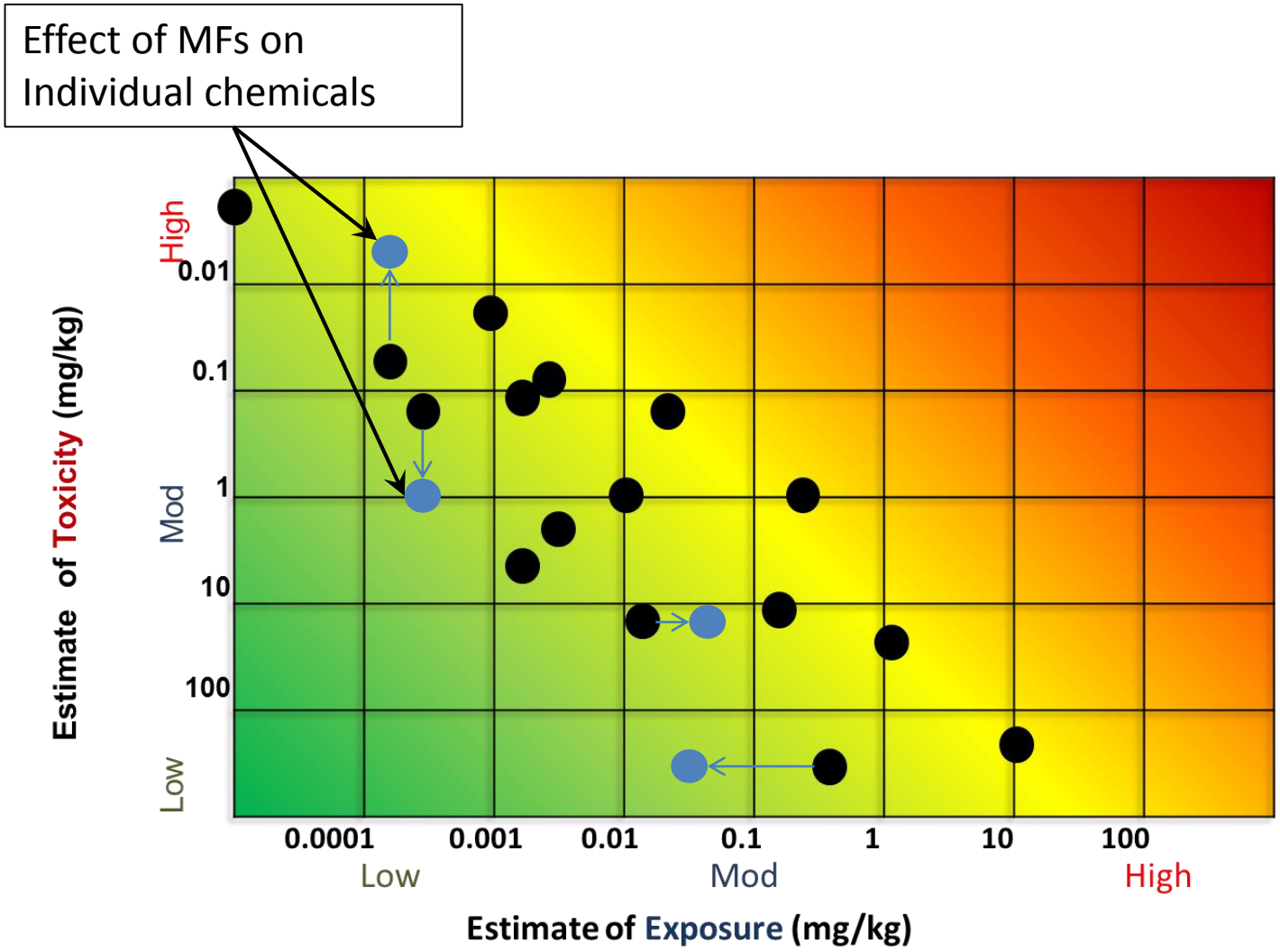
RISK21 Matrix Plot: CRA



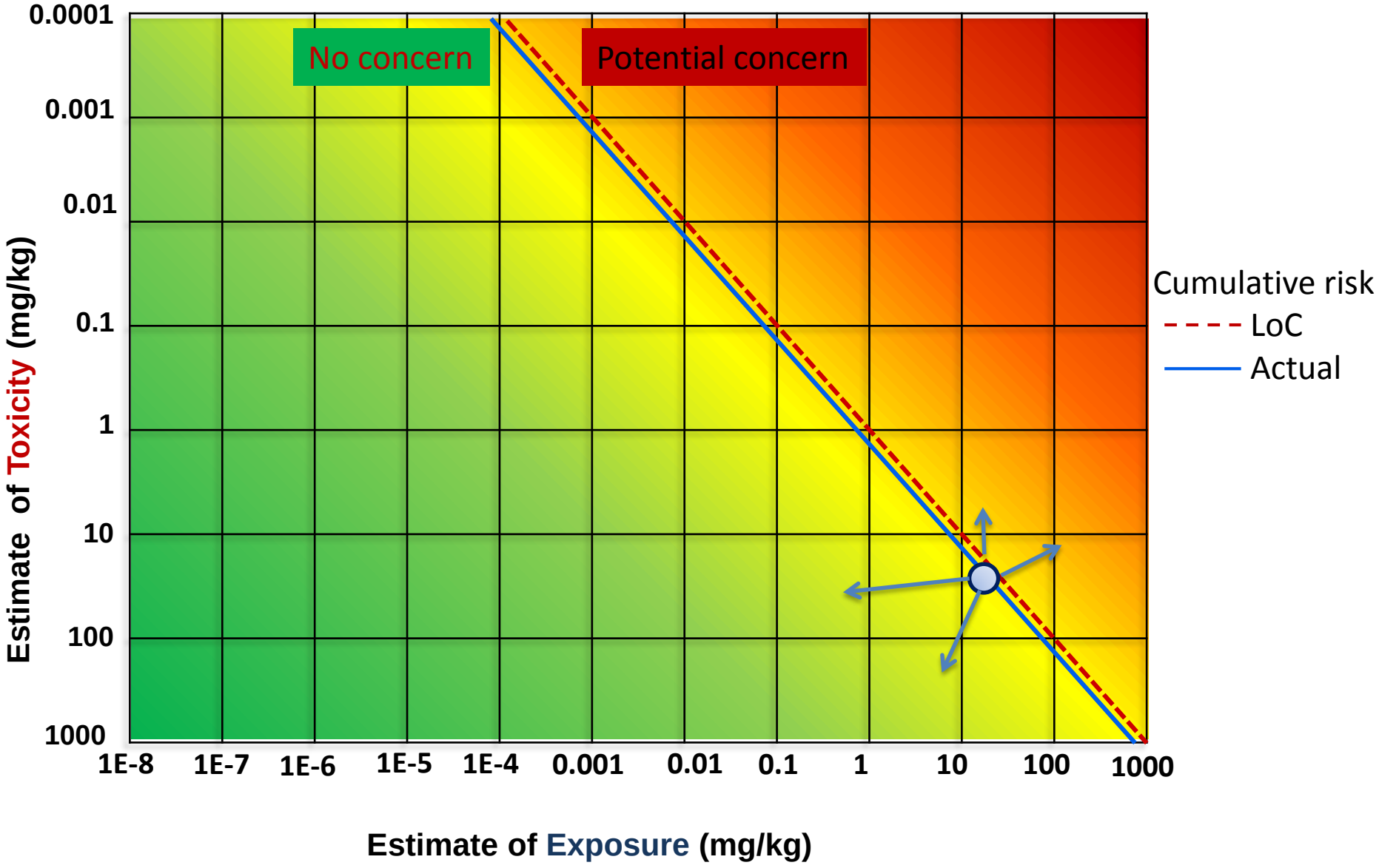
Consideration of Modulating Factors

	Impact on Exposure			Impact on Toxicity		
	Description	Strength +/-	Direction ↑↓	Description	Strength +/-	Direction ↑↓
MF#1						
Chemical 1						
Chemical 2						
Chemical 3						
MF#2						
Chemical 1						
Chemical 2						
Chemical 3						
MF#3						
Chemical 1						
Chemical 2						
Chemical 3						

RISK21 Matrix Plot: Consideration of MFs



RISK21 Matrix Plot: CRA



Conclusions and Next Steps

- Cumulative Risk is a difficult issue
- The RISK21 approach is feasible and transparent:
  - Problem formulation-based
  - Exposure-driven
  - Iterative
  - Introduces modulating factors stepwise
  - Provides transparent and visually “simple” documentation of the process at each step
  - Resource efficient

For More Information

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