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Understanding, Managing and Communicating Risk™

The Hazard Index at thirty-seven

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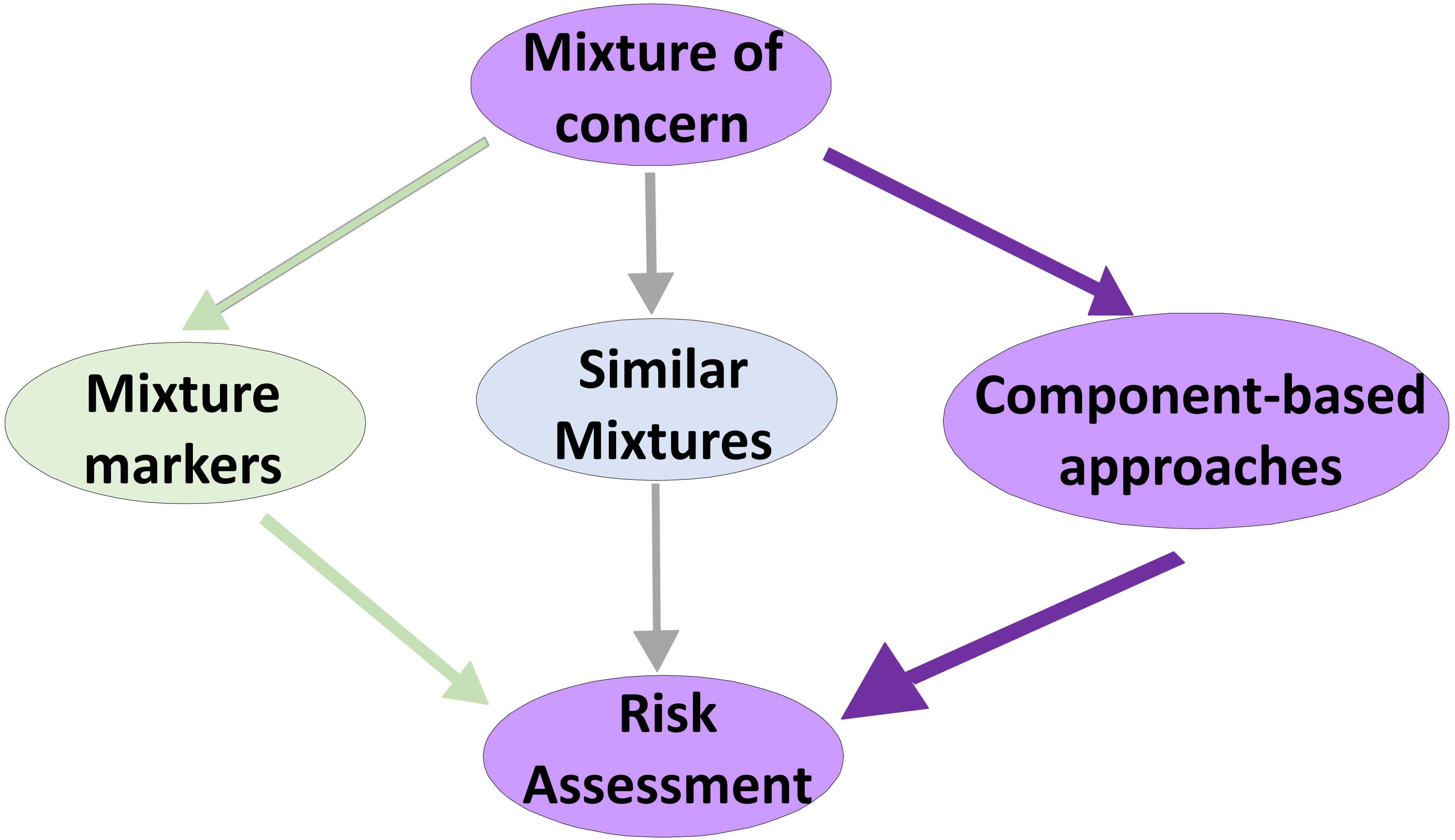
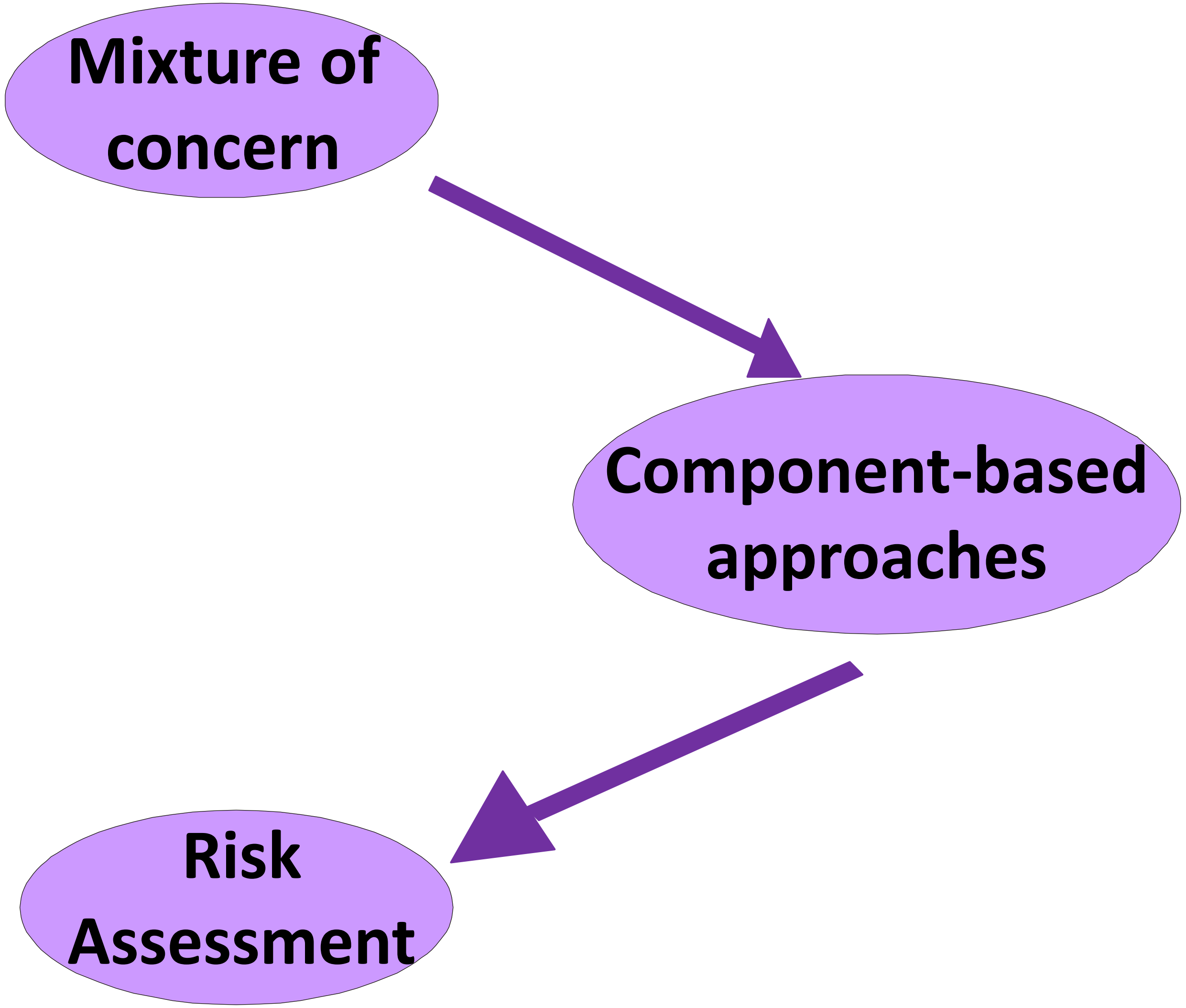
Mixture risk assessment approaches



The Hazard Index is a component-based approach



The Hazard Index (HI) was proposed by the USEPA in 1986

- As a quantitative tool for characterizing the safety of combined exposures to multiple chemicals.
- Similar to earlier approaches used by American Council of Governmental and Industrial Hygienists for occupational exposures and proposed by the National Academy of Sciences for mixtures in drinking water.
- Mathematically equivalent to “Toxicity Equivalents” or “Relative Potency Factor” approaches.
- Related to the Cumulative Margin of Exposure.

The Hazard Index is a measure of safety not risk

- Intended to assure that adverse effects do not occur
- Interactions are a concern when they result in effects at lower doses than the separate effects of chemicals.
- Interactions of concern include:
  - Dose addition
  - Response addition (sum of the residual risks that occur at or below the individual RfDs)
  - Synergy and potentiation

Requirements for use of the Hazard Index

- Chemical must reach a common individual
- Exposures must be sufficiently close in time that the effects of doses are cumulative at some point in time
- Chemicals must fall into a common assessment groups
  - Chemicals cause a common adverse outcome
  - The outcome occurs by a common mechanism of action
  - Chemicals follow dose addition at doses ten- and twenty-fold below NOAELs
  - There is a concordance of effects between the test animal and humans for all chemicals
  - The “sensitive individual” is sensitive to every chemical in an assessment

Hazard Index

$$Hazard\ Quotient\ of\ i^{th}\ chemical = \frac{Dose_i}{Permited\ dose_i}$$

$$Hazard\ Index = \sum Hazard\ Quotient_i$$

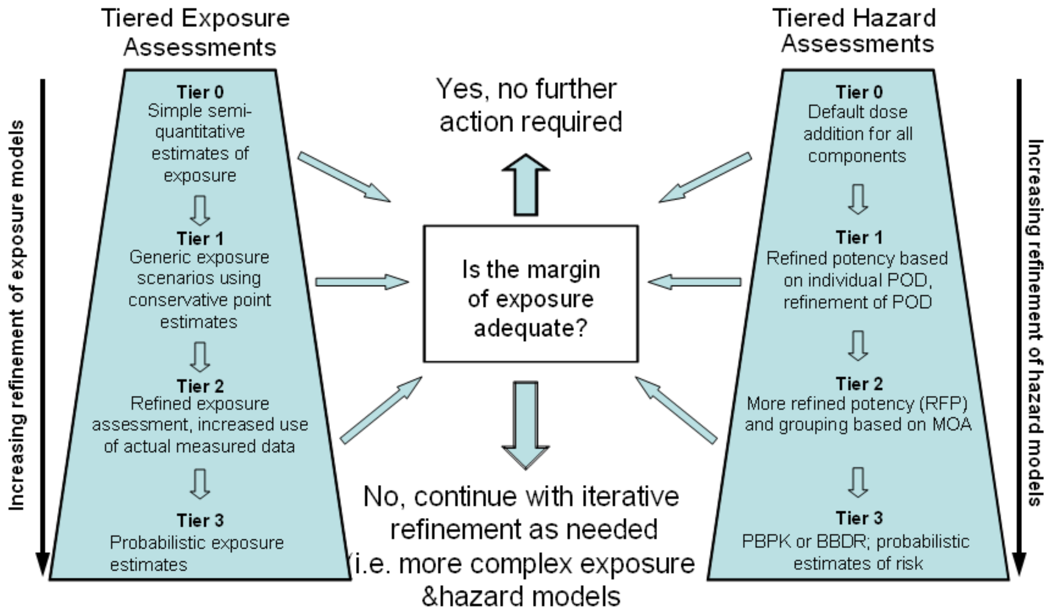
A Hazard Index of <1 implies that:

- The risk posed by concurrent exposure to multiple chemicals will be no higher than the risk that would occur if the exposures to the chemicals occurred separately.
- The sums of residual risk (response addition) would also be minimized

Chemical	Dose	Permitted dose	Hazard Quotient
X1	300	600	0.5
X2	100	300	0.33
X3	30	150	0.2
X4	15	150	0.1
X5	10	200	0.05
X6	8	200	0.04
X7	5	166	0.03
X8	3	100	0.03
X9	2	200	0.01
X10	1	100	0.01
		Hazard Index	1.3

Relaxing the requirements

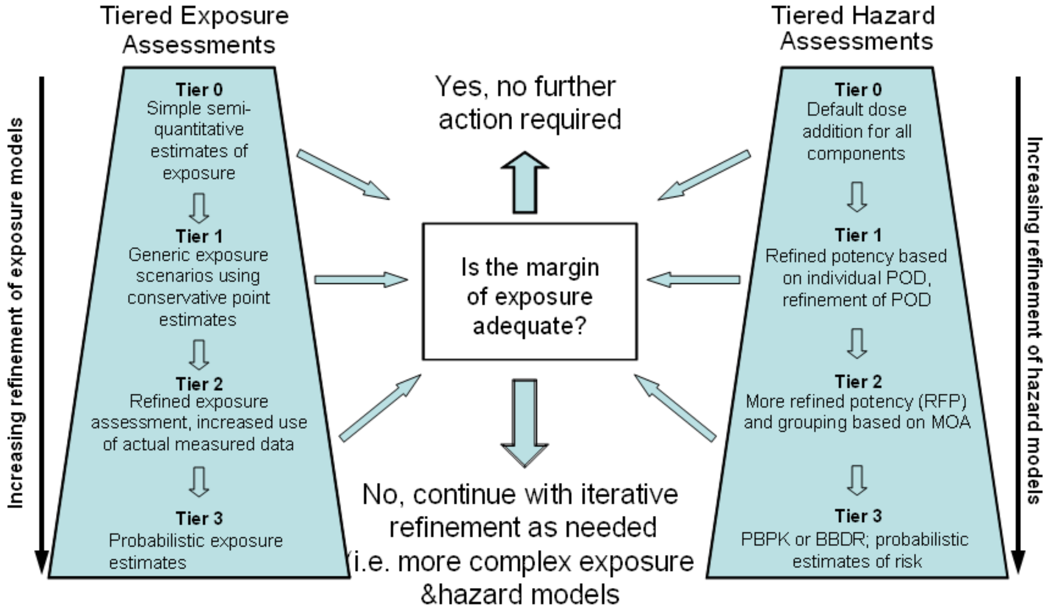
- Relaxing the toxicity requirements
  - All chemicals causing a specific endpoint even if the mechanism varies or is unknown
  - All chemicals affecting a common organ/system/tissue
  - All chemicals causing any systemic effect
- Relaxing exposure requirements
  - Chemicals reach an individual at different points in time
  - Chemicals reach a member of a population at some point in time
  - Upper bounds of chemical exposures that reach a common population occur to the same individual at the same time
- Tiered approaches for determining mixture risks (Meek et al., 2011)
  - Low tiers – very relaxed requirements - less data required
  - High tiers – require that key assumptions are met – large amounts of data



Meek et al., 2011

Relaxing the requirements does not mean the such exposures follow dose addition

- Relaxing the requirements has the impact of overestimating the probability of having an HI value greater than one.
- As a result, HI values from lower tiers are useful screens for mixture risks.

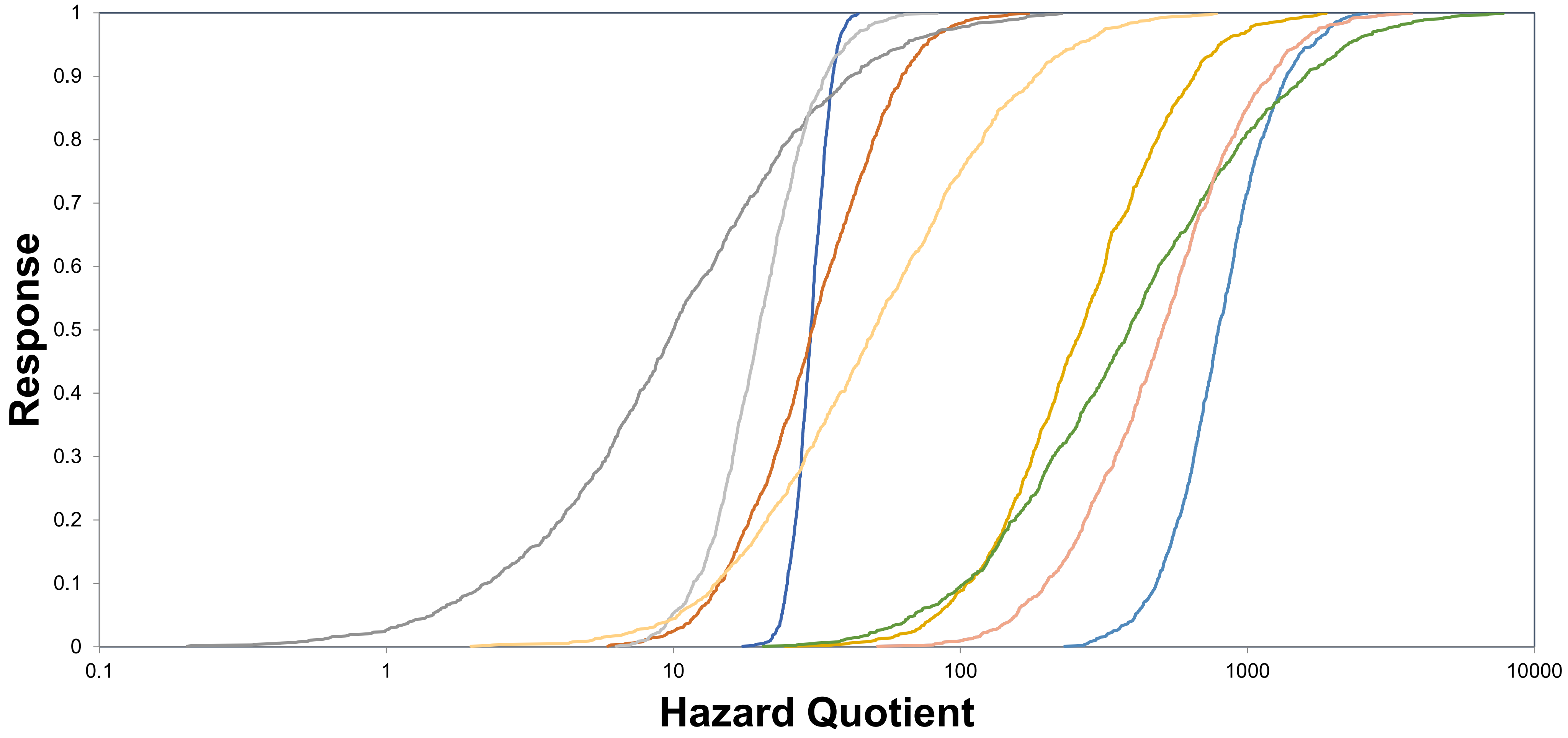


Meek et al., 2011

Problems with the Hazard Index

- The approach cannot be applied when the dose and toxicity of mixture components are unknown (data gaps).
  - Problem with data gaps increases with the number of chemicals included in the assessment
  - HI is therefore of more use for assessing small numbers of well-studied chemicals (pesticides) than complex exposures to many chemicals (the chemical exposome)
- Unless there are data to proceed to a higher tier assessment, the HI becomes a trap where decisions based on lower tier assessments could result in the regulation of non-risks.
- HI may not be protective if synergy or potentiation occurs.
  - Potentiation is a greater concern since any chemical could potentiate another chemical’s effects
- The HI is not a quantitative predictor of risk because the RfD is not a quantitative predictor of risk

Response curves for Hazard Quotients greater than 1 that are consistent with an uncertainty factor of 100



What has changed over the last 37 years?

- The HI is still being used
- The methodology is largely unchanged
- But changes are coming

NAMS and the HI

- NAMS are a way of filling the data gaps required by HI
  - Toxicity findings
    - Higher throughput *in vivo* testing (EPA Transcriptomic Assessment Products, USEPA, 2023)
    - *In vitro* assays
    - QSAR based estimates
      - Threshold of Toxicological Concern (TTC) and the Conditional Toxicity Value (CTV) (Wignall et al., 2018)
  - High throughput exposure assessments predicting combined exposures
    - SHEDS HT (Isaacs et al., 2014)
    - EAS-E Suite (Li et al., 2018).
    - Consumer exposure model (ConsExpo)
    - Probabilistic Aggregate Consumer Exposure Model (PACEM)
- Non-targeted analyses to identify unknown chemicals
- Conservative estimates for chemicals' toxicity and exposure that are not drivers of cumulative risk do not impact HI values

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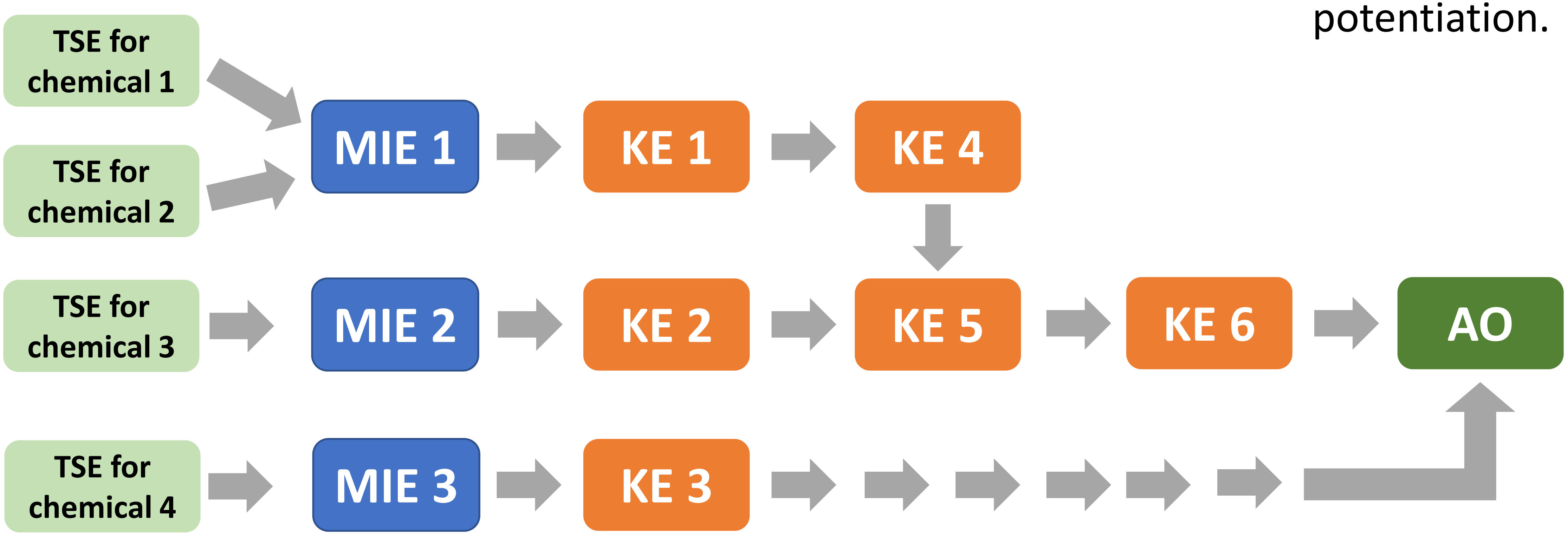
Implications of the AOP for the HI

The concept of the Adverse Outcome Pathway introduced the concept of the Molecular Initiation Event (MIE).

Different AOPs that have common key events form networks

AOP networks describe the toxicodynamic interactions between chemicals causing a common AO. The interactions could result in dose additivity, synergy, or potentiation.



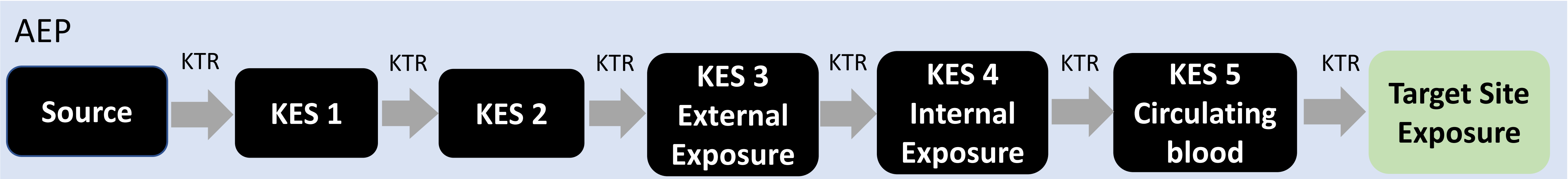
Adapted from C. Ryder

Implications for the Hazard Index

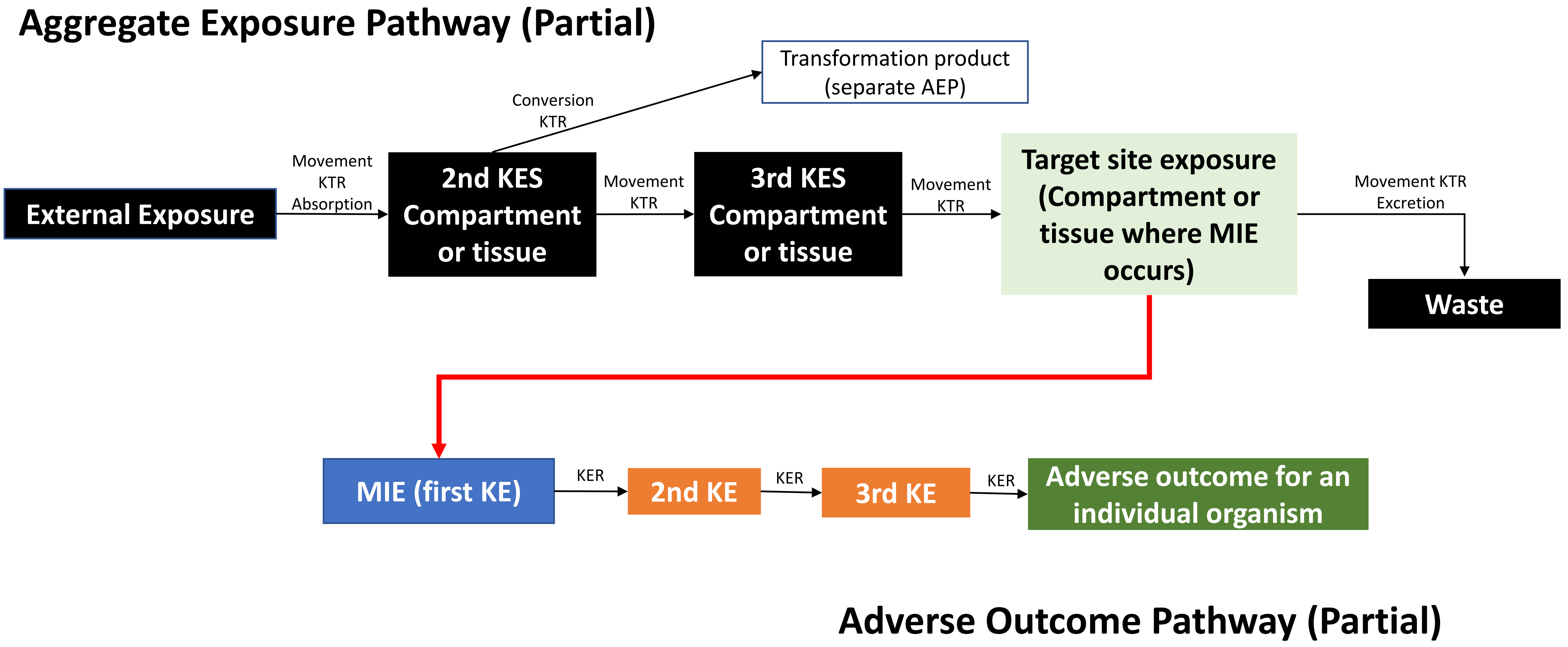
- If one or more of the key event relationships (KERs) are dose dependent, the MIE may occur at a dose that is smaller than the dose that causes an adverse outcome.
- This suggests that doses below the NOAEL can cause perturbations of normal biological functions that could provide a basis for synergy or potentiation.
- Synergy and potentiation could cause adverse effects to occur when HI values are less than 1.

Aggregate Exposure Pathway

- AEPs cover:
  - “Conceptual Site Model” (source, release, transport, environmental fate, and exposure)
  - Toxicokinetics (adsorption, distribution, metabolism, and excretion)
- AEPs are chemical-specific
- Deal with two processes mass transport and chemical reaction
- Begins with a source of exposure and ends with the Target Site Exposure (TSE) corresponding to the chemical’s MIE – Key Event States (KESs) and Key Transitional Relationships (KTRs)

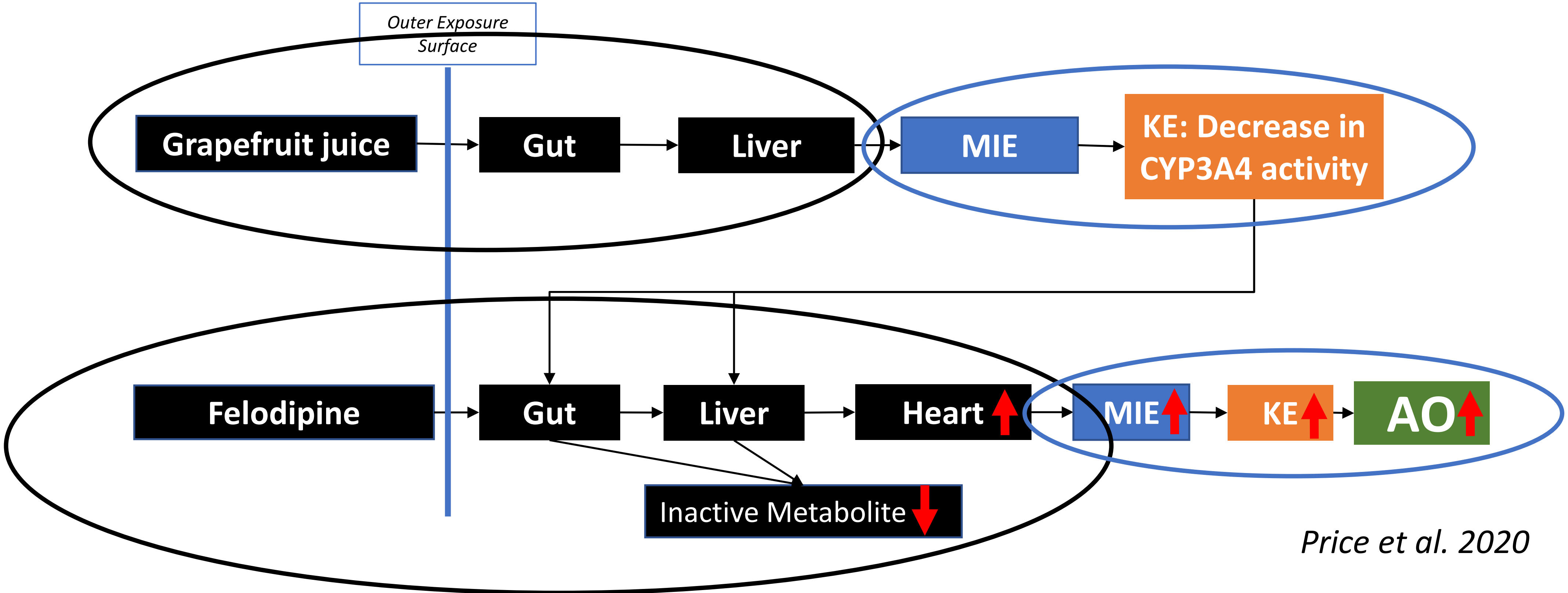


Modeling dose response requires both an AOP and AEP



Combined AEP-AOP networks are required to describe toxicokinetic interactions

Grapefruit juice and drug metabolism:
A KE in the AOP of a chemical in grapefruit juice affects the KTR in Felodipine's AEP (detoxification) leading to potentiation



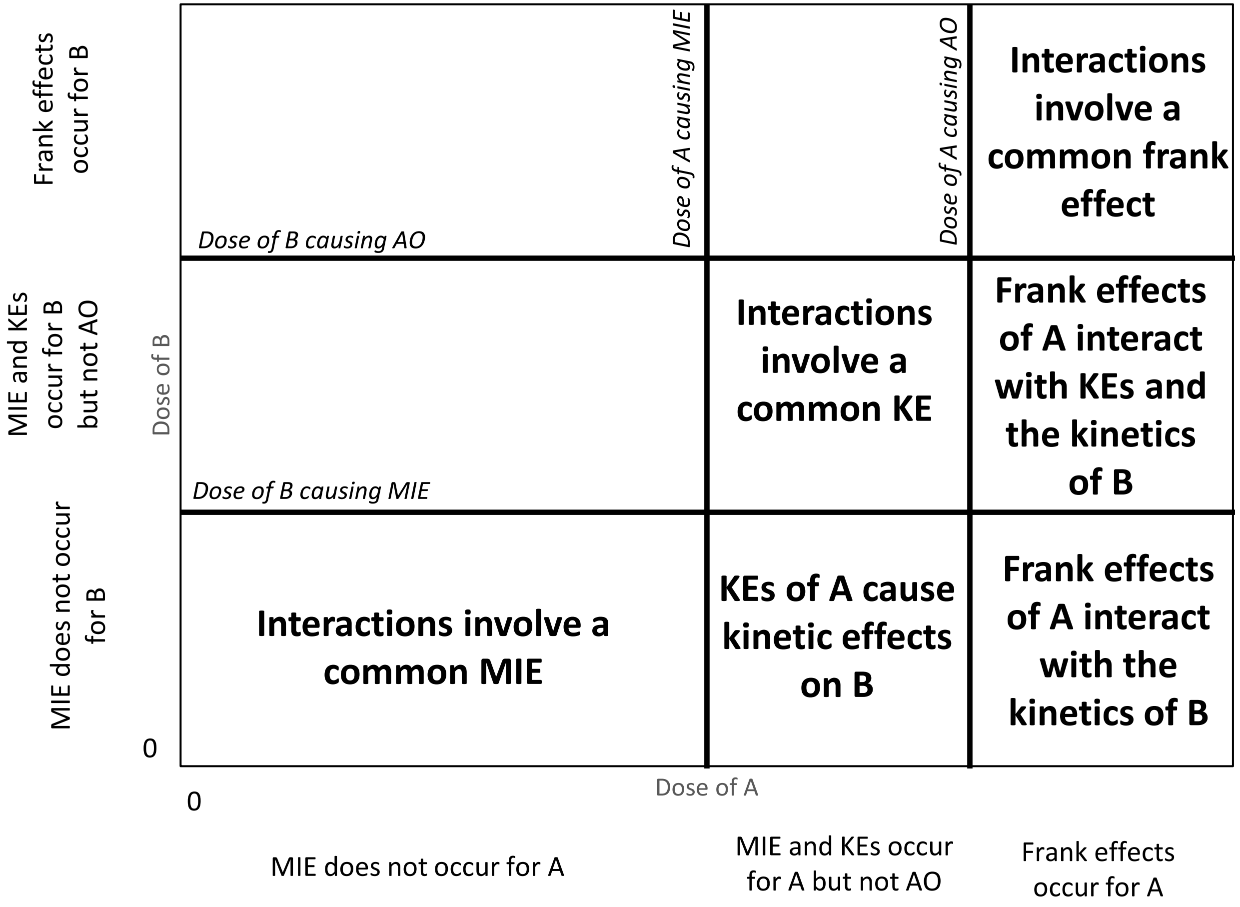
Price et al. 2020

Interactions permitted in different dose ranges

Unpublished

Interactions permitted in different dose ranges

- The MIE conceptually defines a dose range where only dose additive effects can occur.
- At doses that are greater than that needed to cause the MIE other interactions can occur. But these interactions have thresholds.
  - Kinetic interactions must have at least one chemical with a dose greater than the MIE.
  - Dynamic interactions must have at least two chemicals with dose greater than the MIE.



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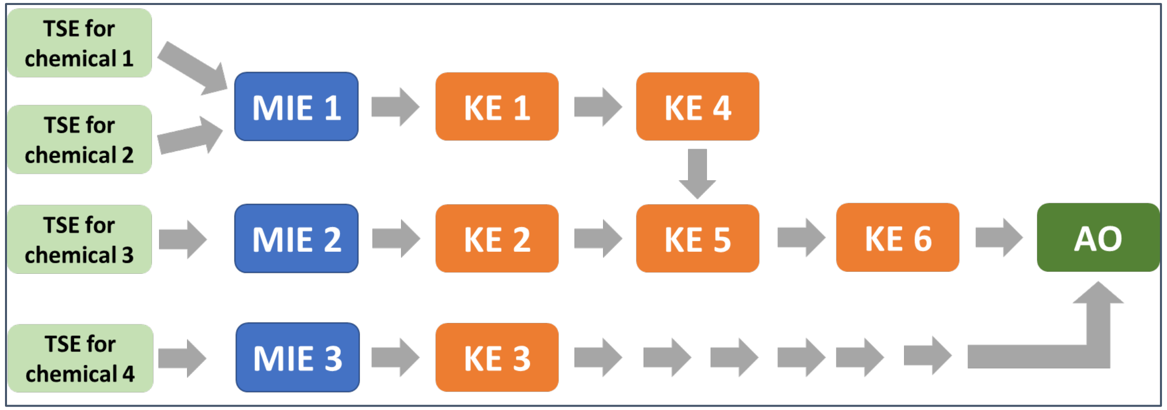
Threshold dose addition occurs when dose addition occurs for Key Events other than the MIE

- If chemicals cause the same MIE then there is no threshold in dose addition.
- If chemicals cause a common key event that occurs later in an AOP network, then dose addition occurs only if the doses of the chemicals are above the levels needed to trigger the common key event.



Chemical	Dose	Permitted dose	HQ no threshold	HQ with threshold
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X4	15	150	0.1	0
X5	10	200	0.05	0
X6	8	200	0.04	0
X7	5	166	0.03	0
X8	3	100	0.03	0
X9	2	200	0.01	0
X10	1	100	0.01	0
		HI	1.3	0.83

Basing the Hazard Index on doses that do not cause MIEs or other early events rather than doses that do not cause Adverse Outcomes

- The assumption of only dose addition is more defensible if the HI was based on doses that protect against the MIE and not the doses that protect against the Adverse Outcome.
- Thresholds of MIE determined in *in vitro* systems can be more accurately characterized than NOAELs in *in vivo* systems.
- Thresholds for MIEs can be set by determining the intensity and duration of the event that is sufficient to trigger the subsequent key event(s) in an AOP
- Variability in response in humans is not captured by measure of MIEs but neither is it captured by *in vivo* models.

Basing the Hazard Index on doses that do not cause MIEs or other early events rather than doses that do not cause Adverse Outcomes

- Assessment groups would be based on causing early key events in AOPs (Eccles et al., 2023)
- Membership in an assessment group could be empirically determined using *in vitro* assays
- Doses that cause MIEs may have less interindividual variation than doses that cause adverse outcomes
- Possible mechanisms of qAOPs could support dose responses other than dose addition providing a mechanism for higher tiered assessments

In the future most chemicals will not have in vivo data and assessments will be based on NAMs. These measurements will determine doses that cause MIEs or other early event in an AOP and not the doses that cause adverse outcomes.

On beyond the Hazard Index: Can quantitative models of mixture risks be generated?

- qAEP-AOPs have been used to predict non-cancer risks (Hinderliter et al., 2011) there is no reason why qAEP-AOP networks could not be used to model risks from cumulative exposure.
- Revise the RfDs
  - Separate uncertainty and variation (lower percentile of the uncertainty distribution of $HD_{M^*}^{I^*}$ (Chui and Slob, 2015)
  - Address concordance (the ability of test models to predict specific adverse effects in humans)
- Develop methods to predict thresholds for interactions in addition to thresholds for toxicity
  - Is there a minimum dose required for the ability of chemicals to change the ADME of other chemicals?
- Can a version of the TTC be developed that is based on the molecular formula of a compound?

Exposure to intentional and variable mixtures

- Intentional mixtures (constant and defined composition over time)
  - Mixtures engineered to produce combined toxicological effects (multi drug therapies and pesticide products with multiple active ingredients)
  - Mixtures engineered to achieve a specific function (consumer products)
- Discrete mixtures generated by a specific process that are variable (but not random) and include unknown or poorly characterized components
  - Botanicals
  - Petroleum products
  - Combustion products
    - Diesel exhaust
    - Wildfire smoke
  - Disinfection byproducts

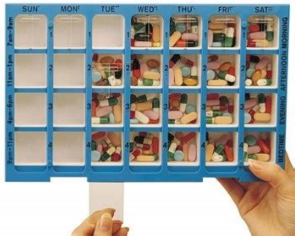





Unintentional (accidental) combined exposures

- Unintentional mixtures in a single media resulting from multiple sources of contamination
  - Indoor air
  - Groundwater contamination
  - Pesticide residues in a food
  - Surface waters/POTW effluents
- Unintentional combined exposures from multiple sources in a single category of human activity
  - Polypharmacy
  - Occupational exposures
  - Exposures from use of multiple consumer products
  - Pesticides/food additives/naturally occurring chemicals in an individual's diet
- The chemical exposome: cumulative chemical exposures from all sources and all routes

Unintended exposures vary across individuals in the exposed population and over time for an individual.



Dominance of a single chemical in unintentional combined exposures

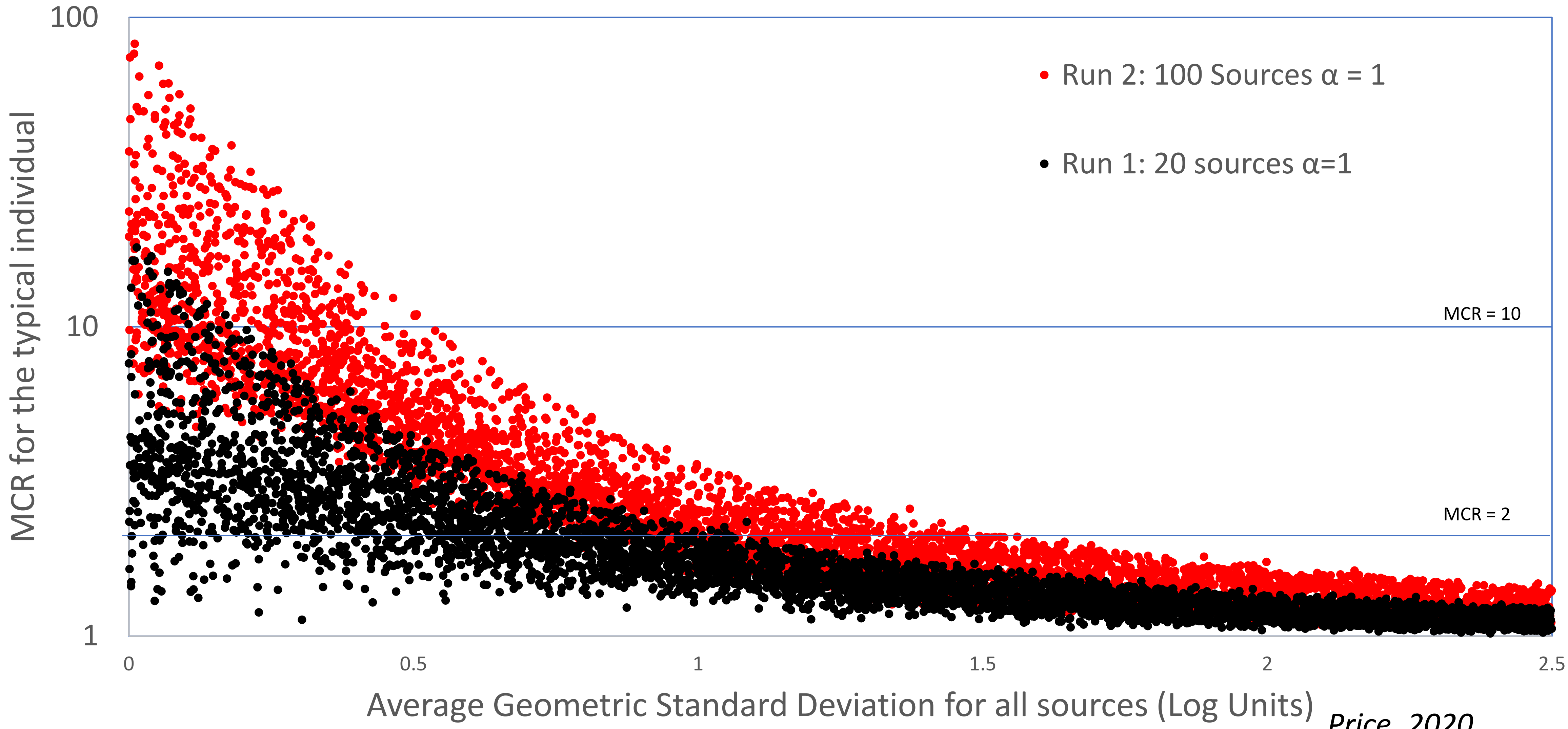
- The Maximum Cumulative Ratio (MCR) is a property of an individual receptor. It is a measure of the safety of combined exposures under the assumptions of dose addition and response addition.
- MCR values close to 1 indicates that:
  - The toxicity of a single chemical dominates the combined risk (Dose addition ≈ Response addition)
  - Mixture toxicity will be similar to the toxicity of the largest chemical
  - Potential for interactions is reduced

$$MCR = \frac{Hazard\ Index}{Maximum\ Hazard\ Quotient}$$

MCR and unintentional complex combined exposures

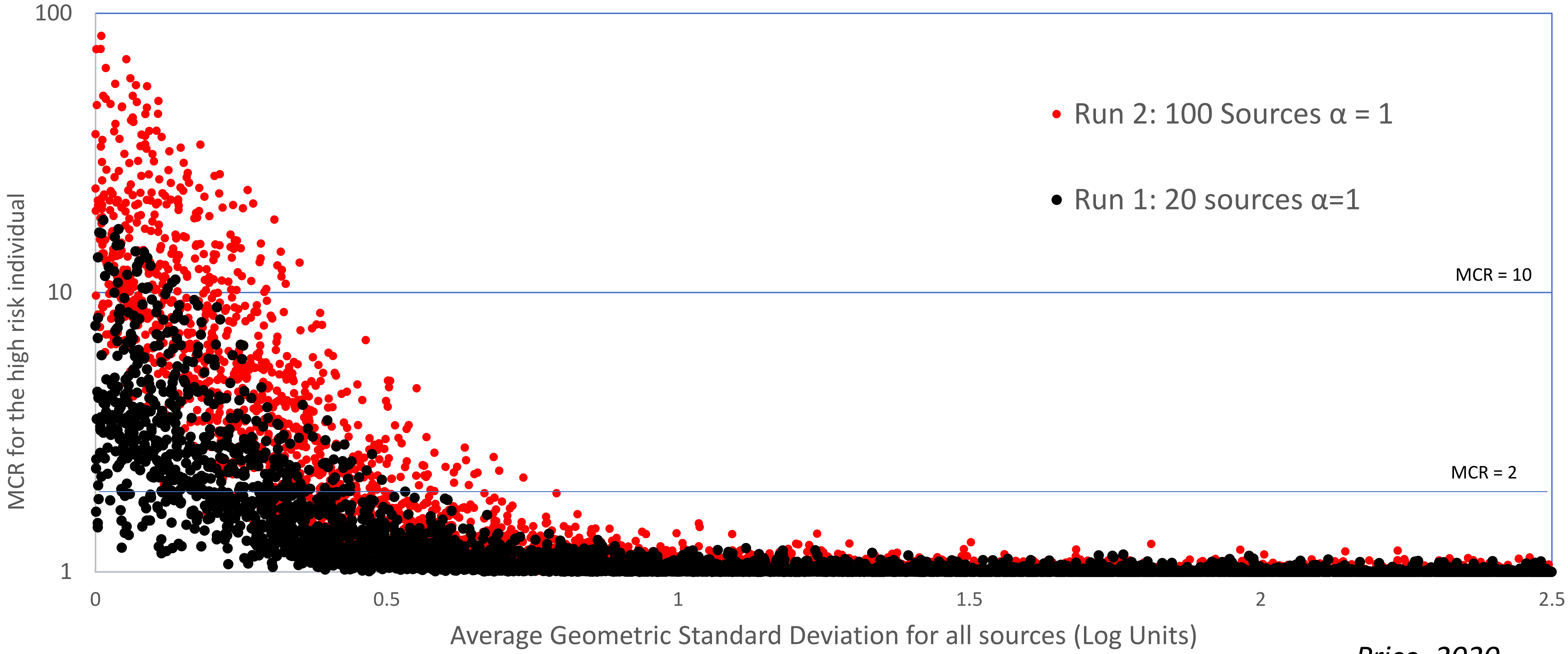
- Assessments of the HI for receptors has found that the majority of risk occurs as a result of a small fraction of the chemicals (drivers of toxicity). This is an example of the Pareto principle or “80 – 20 rule”.
- Studies in interindividual variation in HI in exposed populations found that individuals with the largest combined risk received the majority of their risk from one or two chemicals.
- Simulation modeling demonstrated that this pattern occurs when the interindividual variation in Hazard Quotients of individual chemicals are right skewed with geometric standard deviations that are greater than 0.5.

MCR for typical individual vs. interindividual variation in dose from a source



Price, 2020

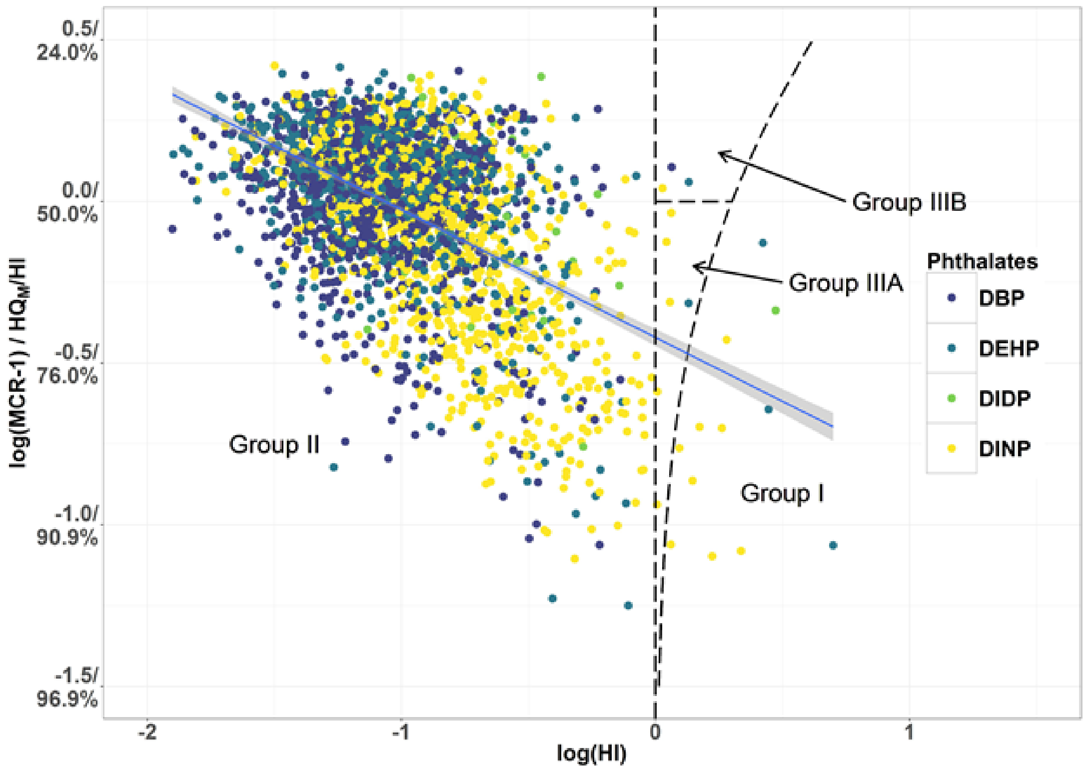
MCR for highly exposed individual vs. interindividual variation in dose from a source



Price, 2020

The dominance of a few compounds suggests that cumulative risks identified by the HI will be small for unintentional mixtures

- Data on complex mixtures with many sources found that the HI did not indicate significantly higher risks then separate chemical assessments of risk (Price and Han, 2011; Reyes and Price, 2018)
- The potential for interactions decreases when only a few chemicals drive risk.
- This suggests that separate assessments of individual chemicals and MCR values could be used as screens to determine cumulative risks for sources that have high variability



Why has the HI lasted so long?

- HI works very well for regulatory programs that deal with small numbers of well-tested chemicals with well-characterized exposures (pesticides in diets).
- It has difficulty with combined exposures from many sources involving large numbers of chemicals (e.g., dietary exposures to natural and manmade chemicals, chemicals in consumer products, the chemical exposome, etc.).
- Risks from highly variable unintentional mixtures are driven by exposures to one or two substances even though the mixture can be complex. The impact of controlling individual chemicals versus controlling individual chemicals plus controlling HI is small for many sources of combined exposures, even when using lower tier assessments of HI.

Conclusions

- Screening level HIs will continue to be used in instances where a single chemical dominates the hazard posed by combined exposures to a receptor
- NAMs can help fill the data gaps for exposure and toxicity to extend
- Research is needed to predict the thresholds for:
  - Molecular initiating events
  - Kinetic interactions
  - TTC based on empirical formulas
- Basis for HI will move from the Adverse Outcome to the Molecular Initiating Event or other early events in AOPs – AOPs will define assessment groups
  - Downsides, upsides, but probably no choice
- Quantitative predictions of risk can be developed based on qAOP-AEP networks or on improved versions of Reference Dose that better separate uncertainty and variation

Looking for candidates for leadership positions in the SOT Mixtures Specialty Section!

References

Chiu, W. A., & Slob, W. (2015). A unified probabilistic framework for dose–response assessment of human health effects. Environmental health perspectives, 123(12), 1241-1254.

Eccles, K. M., Karmaus, A. L., Kleinstreuer, N. C., Parham, F., Rider, C. V., Wambaugh, J. F., & Messier, K. P. (2023). A geospatial modeling approach to quantifying the risk of exposure to environmental chemical mixtures via a common molecular target. Science of The Total Environment, 855, 158905.

Hinderliter, P. M., Price, P. S., Bartels, M. J., Timchalk, C., & Poet, T. S. (2011). Development of a source-to-outcome model for dietary exposures to insecticide residues: an example using chlorpyrifos. Regulatory Toxicology and Pharmacology, 61(1), 82-92.

Isaacs, K. K., Glen, W. G., Egeghy, P., Goldsmith, M. R., Smith, L., Vallero, D., ... & Özkaynak, H. (2014). SHEDS-HT: an integrated probabilistic exposure model for prioritizing exposures to chemicals with near-field and dietary sources. Environmental science & technology, 48(21), 12750-12759.

Li, L., Westgate, J. N., Hughes, L., Zhang, X., Givehchi, B., Toose, L., ... & Arnot, J. A. (2018). A model for risk-based screening and prioritization of human exposure to chemicals from near-field sources. Environmental science & technology, 52(24), 14235-14244.

Meek, M. E., Boobis, A. R., Crofton, K. M., Heinemeyer, G., Van Raaij, M., & Vickers, C. (2011). Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework. Regul Toxicol Pharmacol, 60(2), S1-S14.

Price PS: Interindividual variation in source-specific doses is a determinant of health impacts of combined chemical exposures. Risk Anal 2020, 12:2572–2583.

Price, P. S. (2023). The Hazard Index at thirty-seven: new science new insights. Current Opinion in Toxicology, 100388.

Price, P. S., & Han, X. (2011). Maximum cumulative ratio (MCR) as a tool for assessing the value of performing a cumulative risk assessment. International journal of environmental research and public health, 8(6), 2212-2225.

Price, P. S., Jarabek, A. M., & Burgoon, L. D. (2020). Organizing mechanism-related information on chemical interactions using a framework based on the aggregate exposure and adverse outcome pathways. Environment international, 138, 105673.

Reyes, J. M., & Price, P. S. (2018). An analysis of cumulative risks based on biomonitoring data for six phthalates using the Maximum Cumulative Ratio. Environment international, 112, 77-84.

USEPA: Guidelines for the health risk assessment of chemical mixtures. Fed Regist 1986, 51:34014–34025.

USEPA (2023): Standard Methods for Development of EPA Transcriptomic Assessment Products (ETAPs), External Review Draft EPA/600/X-23/083

Wignall, J. A., Muratov, E., Sedykh, A., Guyton, K. Z., Tropsha, A., Rusyn, I., & Chiu, W. A. (2018). Conditional toxicity value (CTV) predictor: An *in silico* approach for generating quantitative risk estimates for chemicals. Environmental health perspectives, 126(5), 057008.