What are the combinations of chemicals to which we are exposed, how can we identify the relevant combinations, and why is this important?

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Advancing Research on Mixtures:
New Perspectives and Approaches for Predicting Adverse Human Health Effects
NIEHS
September 26, 2011

Workshop goals

- Identify key issues that present challenges in mixtures research
- Obtain advice on integrating multidisciplinary capabilities to address critical topics in mixtures research
- Provide recommendations for research
- Inform research agenda

Challenges in assessing risks from mixtures

- Whole mixture testing
  - Permutations
  - Temporal variation
- At the mercy of the component with the poorest toxicity data
  - 78 compound detected: RfDs for 30
- Testing under the lamppost
  - High dose testing of mixtures
  - Low dose exposures

Missing component data

- Toxicology is changing
  - TTC is being extended
  - New tools for MoA-based Read Across
  - Biological Pathway Altering Dose (BPADs)
- Exposure-based strategy to direct toxicity
  1. Use TTC/Read Across/BPAD
  2. Use additive models
  3. If chemical with missing data is not a driver – Stop!
  4. If it is a driver then focus toxicity studies

Toxicity testing under the lamppost

- Almost all testing of chemical interactions is performed at doses well above the POD for chronic health standards (Frank Effect Levels)
- These mixtures exposures would not be permitted because of single chemical toxicity concerns (components are above their RfDs)
- Reason for this is lack of sensitivity in whole animal studies
- Mixture work needs to focus on *in vitro* HTS data
  - Focus on predicting the threshold of interaction (supra additivity) and can it be lower than the threshold of the effects of a mixtures compnent?

Permutations

When I consider the short duration of my life, the little space I fill, and even can see, engulfed in the infinite immensity of number of chemical combinations of which I am ignorant, I am frightened.

Blaise Pascal (adapted)

n	Pairs	Trios
2	1	-
3	3	1
5	10	10
10	45	120
50	1,225	19,600
100	4,950	161,700
10,000	49,995,000	166,616,670,000

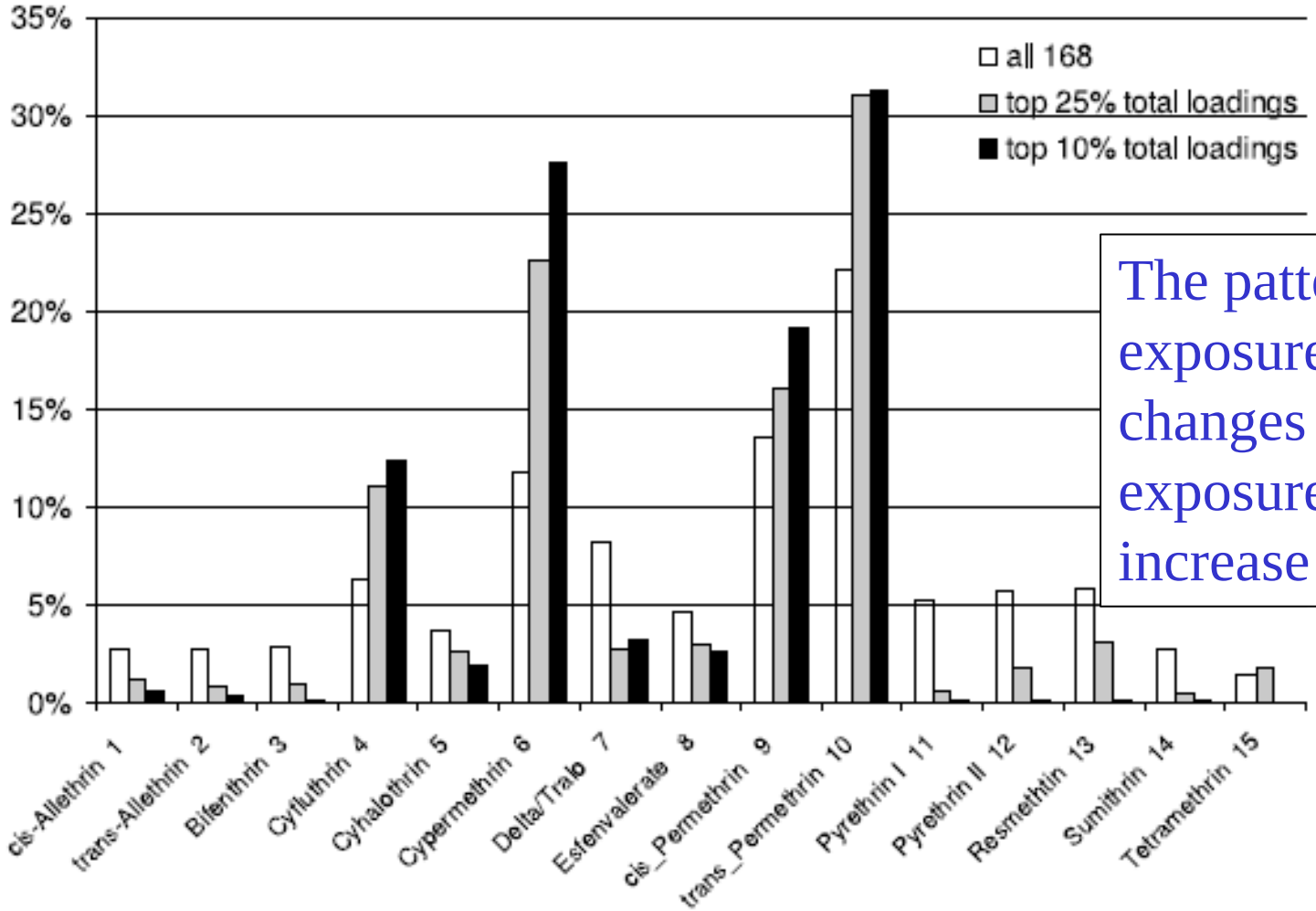
Exposure information can help!

- Understanding patterns of exposure
- Modeling and monitoring
- Using exposure data to prioritize toxicity research for mixtures

Not all combinations are equally probable

- All combinations of chemicals are not equally likely
  - Combinations are driven by usage patterns
  - Common fate and transport properties
- As a result only a small fraction of possible combinations actually occur

Pyrethroids in daycare centers



The patterns of exposure changes as exposures increase

Rogelio Tornero-Velez et al., 2011

Not all combinations are equally probable

- All combinations of chemicals are not equally likely
  - Combinations are driven by usage patterns
  - Common fate and transport properties
- As a result only a small fraction of possible combinations actually occur
- The pattern of combinations often changes with total toxicity
- The goal of exposure assessment for mixtures is to determine when and which compounds co-occur

Modeling co-occurrence

- Process for modeling co-exposures
  - Begin with need/purpose for a chemical being present
  - Human behavior
  - Relevant environment
  - Fate and transport
- Use monitoring data as a part of modeling
  - To build model and to evaluate results
- Modeling allows the leveraging of monitoring

Historically, model development

- Has been expensive to develop
- Hamstrung by too little data and too many assumptions
- Difficult to evaluate results
- Limited by the lack of computer power (somewhat)
- Misused
  - Sold as decision making tools (the model says the correct answer is….) rather than tools for analysis that guide research

Models are best used to integrate or leverage data to answer questions that can't be addressed by direct measurement.

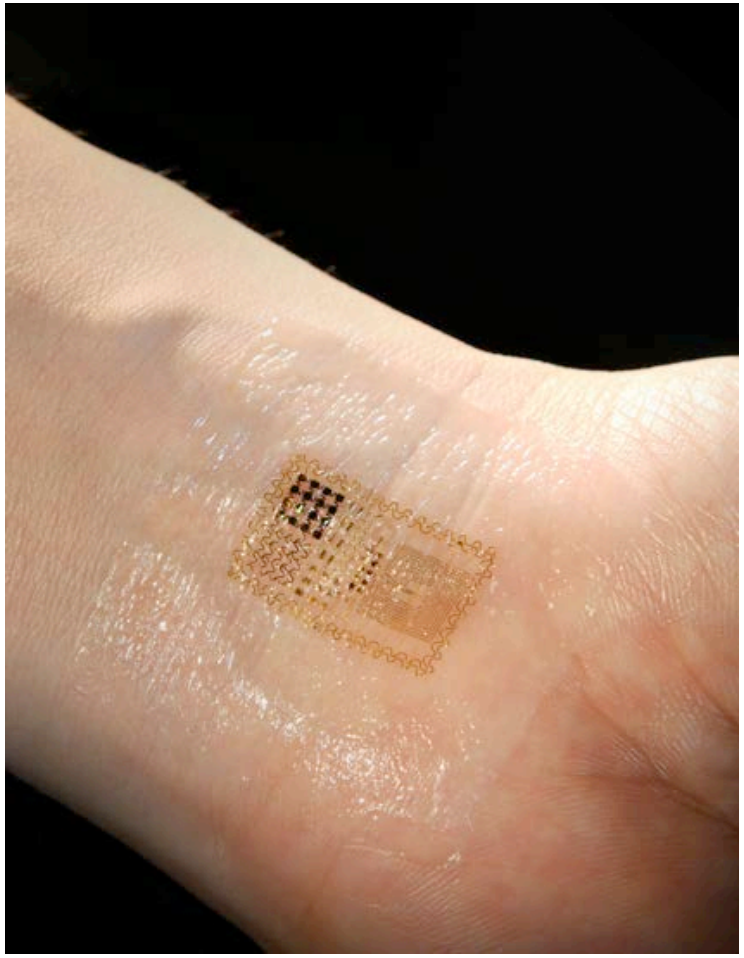
Measuring chemical exposure?

Yeah there's an app for that….

- Detects ammonia, chlorine, and methane
- Size of a postage stamp
- Plugged in to an iPhone to process and transmit sensor data to a computer via telephone communication network or Wi-Fi

http://www.nasa.gov/centers/ames/news/features/2009/cell_phone_sensors.html

Real time monitoring of chemical exposures



Patch monitor for heart rate, temperature, blood pressure.
"Tattoo" monitor for glucose and sodium levels in blood

http://news.cnet.com/8301-27083_3-20091454-247/tattoo-like-patch-may-be-future-of-health-monitoring/

http://www.technologyreview.com/computing/38065/?mod=related

It is the pattern of the exposures that determines the importance of performing a cumulative assessment

not just the toxicology

Hazard Quotients and Indices

- Hazard Quotient (HQ) = Dose/Permitted Dose
- Hazard Index (HI)= Sum of Hazard Quotients
- HI <1 low concern
- HI >1 higher concern
- Revising HI based on MoA –only sum when the MoA indicates a common target

Two cumulative exposures

Consider two individuals:

- Each individual is exposed to 5 chemicals
- Each individual has a Tier 1 hazard index of 3.5 (unacceptable)

The hazard quotients for individual 1 are:

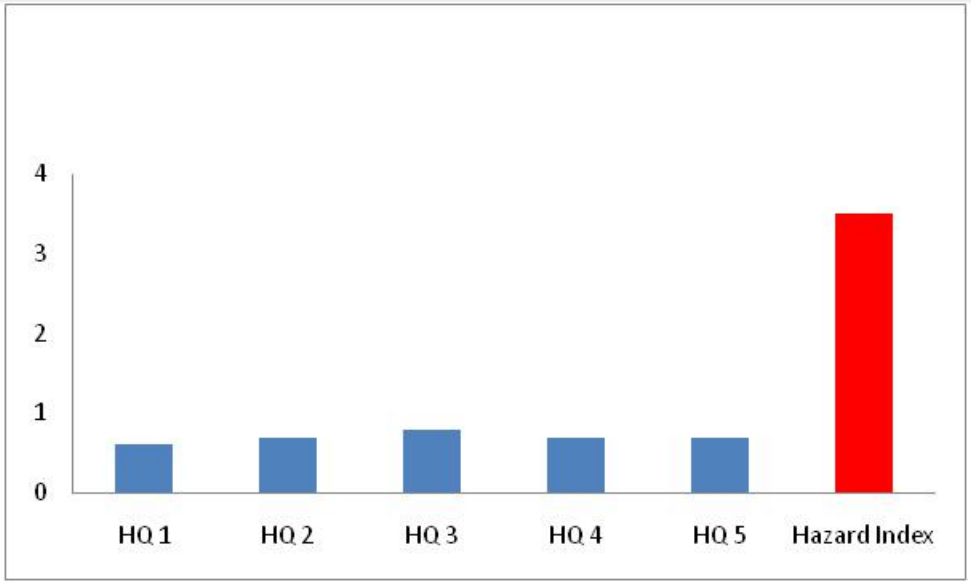
- 0.6, 0.7, 0.8, 0.7, 0.7

The hazard quotients for individual 2 are:

- 3.2, 0.25, 0.04, 0.009, 0.001

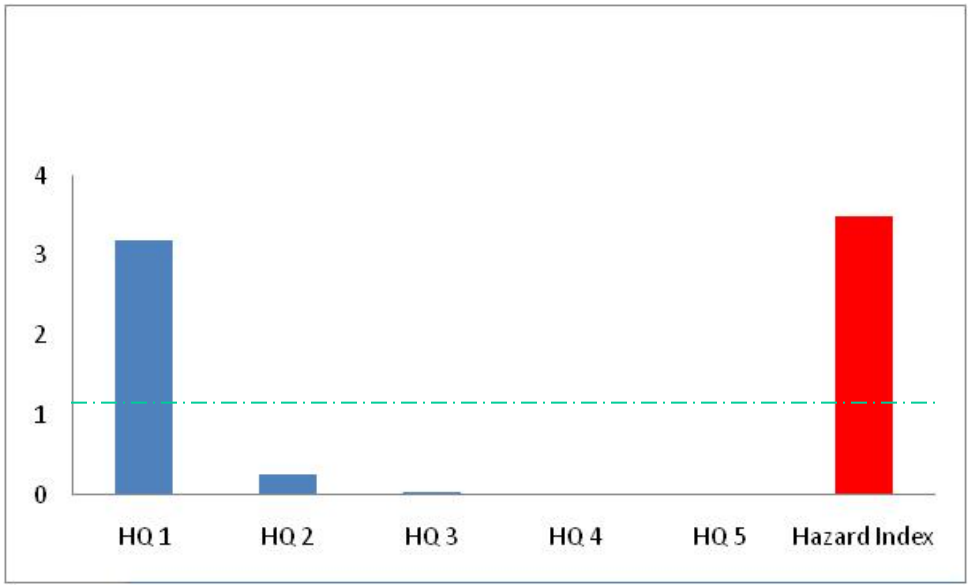
The two individuals present very different risk management challenges

A cumulative assessment was required for the first individual



A cumulative assessment was not required for the second individual:

- Chemical 1 was the problem
- A chemical-by-chemical based approach would have found the risk
- Addressing chemical 1 would control the individual's cumulative risk



Key questions

1. What do real world mixtures look like?
   - Individual 1 (Cumulative assessment is required)
   - Individual 2 (Cumulative assessment is not required)
2. How often will we miss a cumulative toxicity of concern (HI > 1) if we evaluate exposures based on a chemical-by-chemical basis?
3. How big is the “missed toxicity”?
   - Is the HI underestimated by 1.5X? 2X? 5X? 10X?

Maximum Cumulative Ratio (MCR)

Is a characteristic of an individual (or local population of ecological receptors)

Defined as:

$$\text{MCR} = \frac{\text{Cumulative Toxicity}}{\text{Maximum Toxicity from One Chemical}}$$

MCR is calculated using the same data that determines the Hazard Index/Quotients

$$\text{MCR} = \frac{\text{Hazard Index}}{\text{Largest Hazard Quotient}}$$

Price and Han, 2011

MCR for Individual 1 is:

MCR =

3.5/0.8 = **4.4**

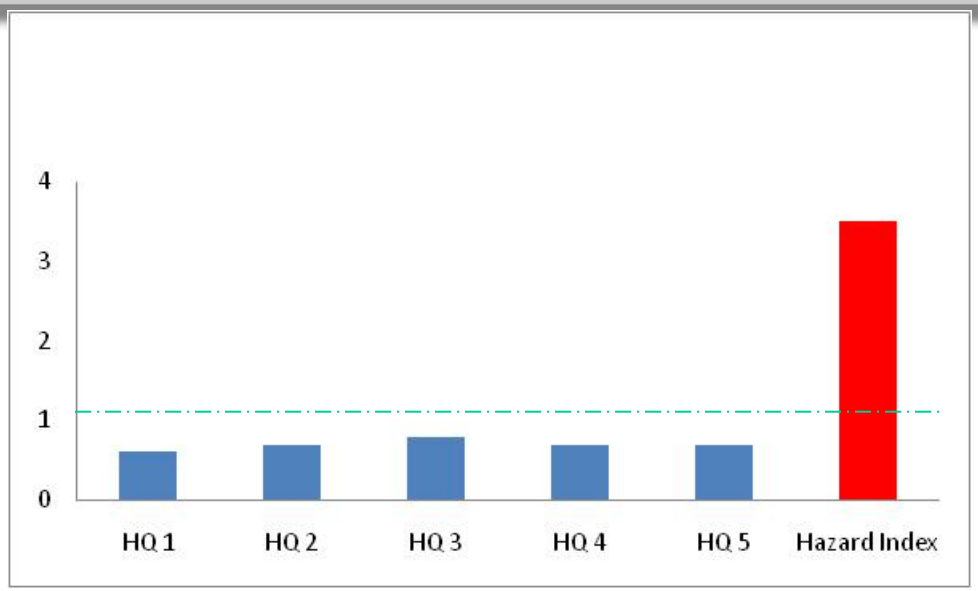
MCR for Individual 2 is:

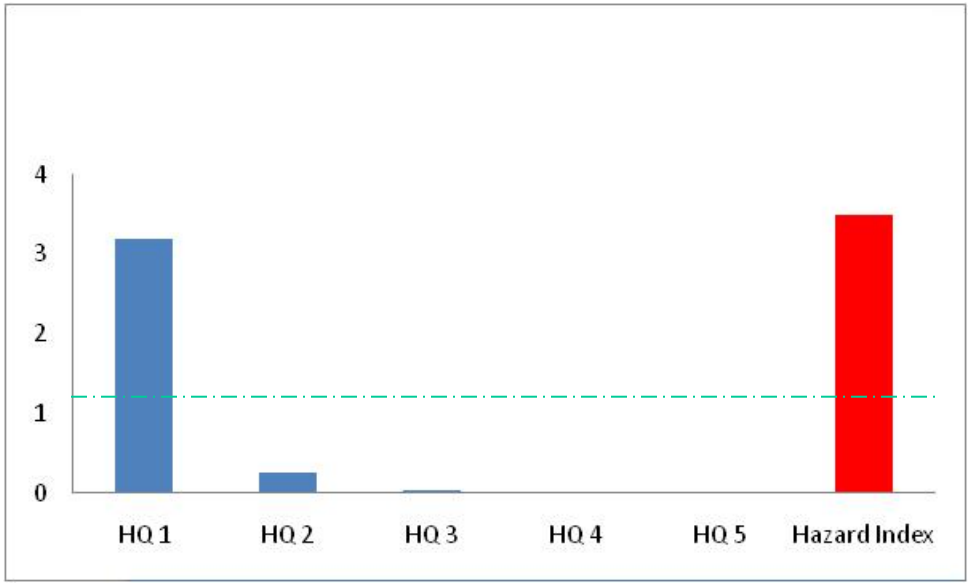
MCR =

3.5/3.2 = **1.1**

When MCR is close to 1.0 there is little need for a cumulative risk assessment

The need for a cumulative risk assessment increases when MCR is larger



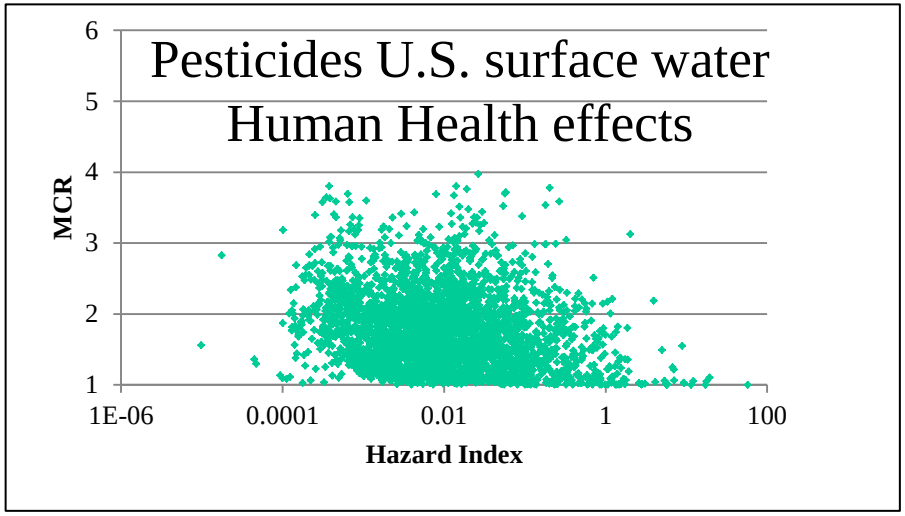


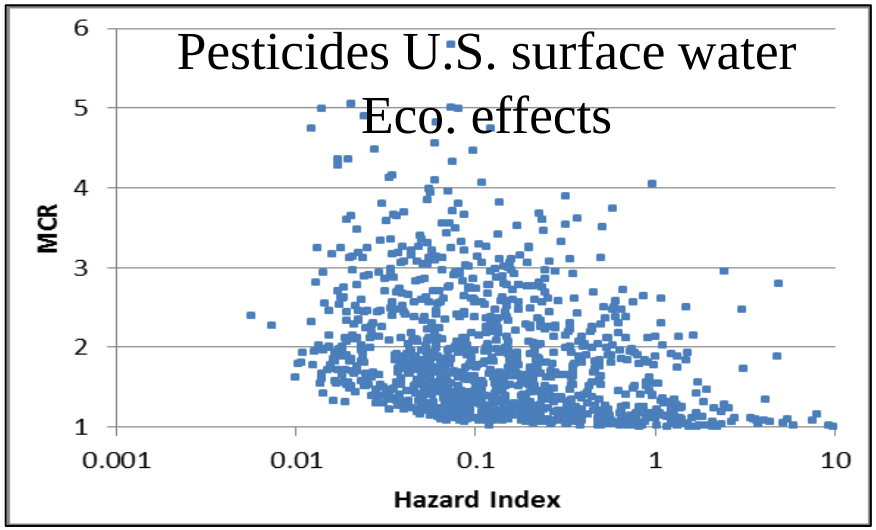
Properties of MCR

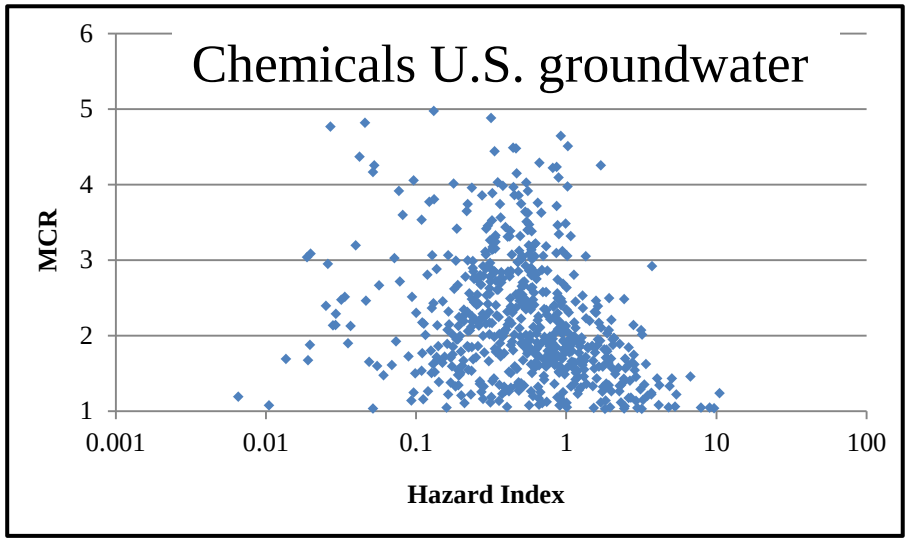
- MCR is the measure of the largest fraction of toxicity that comes from a single component
  - A value of 2 indicates one chemical is providing 50% of the individual's toxicity
  - A value of 1.1 indicates one chemical is providing 90% of the individual's toxicity
- MCR and Perato principle
  - When there are multiple of sources of an agent the majority of the agent comes from a minority of sources
    - "80/20 rule" - in sales 80% of your sales come from 20% of your clients
  - A mixture follows the Perato principle if MCR is closer to 1 than n (the number of chemicals in a mixture)

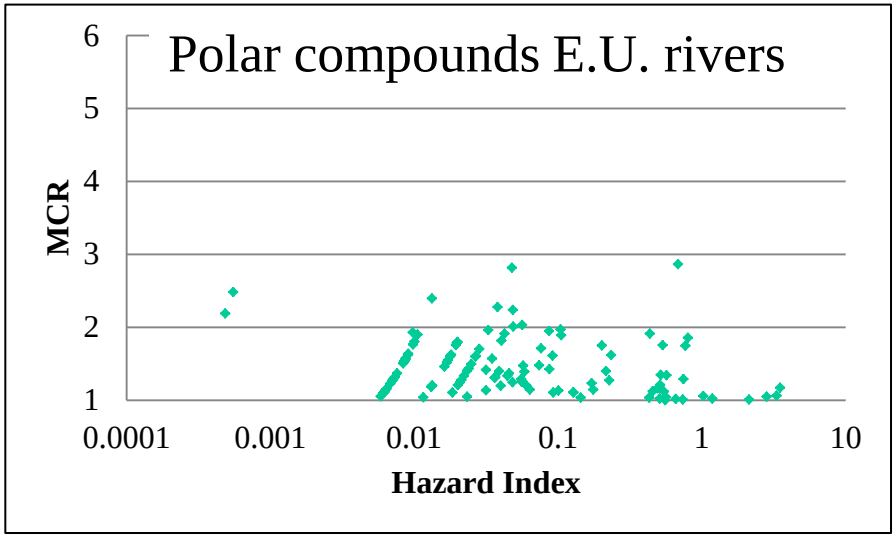
Hazard Index and MCR combine to provide guidance on the need for cumulative risk assessments

	Hazard Index < 1	**Hazard Index > 1**
MCR > 2	Cumulative toxicity is driven by multiple chemicals - but is of low concern.	Cumulative toxicity is a concern and is being driven by exposures to multiple chemicals.
MCR < 2	Cumulative toxicity is of low concern and is primarily due to exposure to one compound.	Cumulative toxicity is a concern - but the toxicity is being driven by one compound. Further action should focus on this dominant chemical.

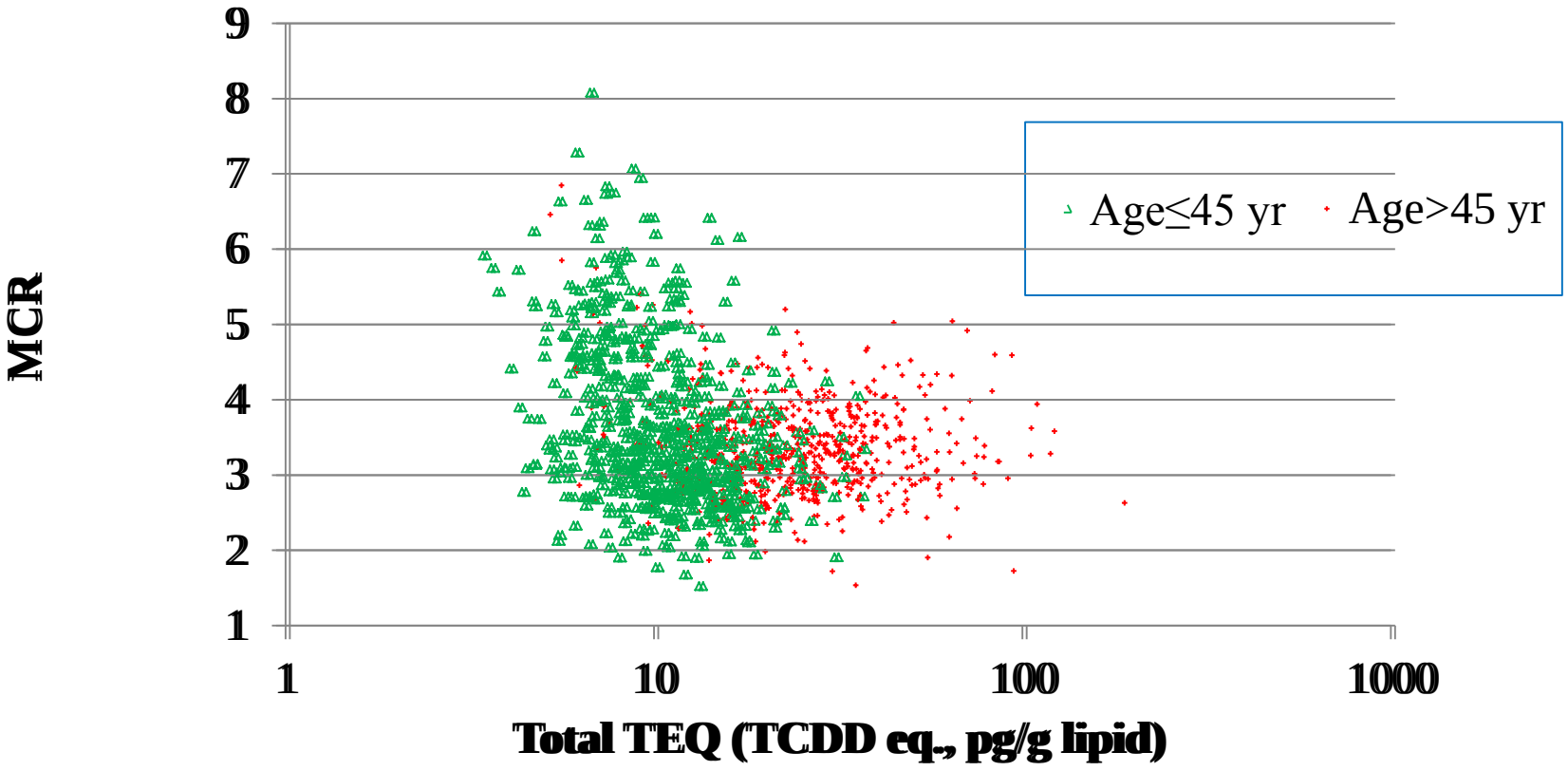

Pesticides U.S. surface water
Human Health effects
MCR
6
5
4
3
2
1
1E-06
0.0001
0.01
1
100
Hazard Index


Pesticides U.S. surface water
Eco. effects
MCR
6
5
4
3
2
1
0.001
0.01
0.1
1
10
Hazard Index


Chemicals U.S. groundwater
MCR
6
5
4
3
2
1
0.001
0.01
0.1
1
10
100
Hazard Index


Polar compounds E.U. rivers
MCR
6
5
4
3
2
1
0.0001
0.001
0.01
0.1
1
10
Hazard Index

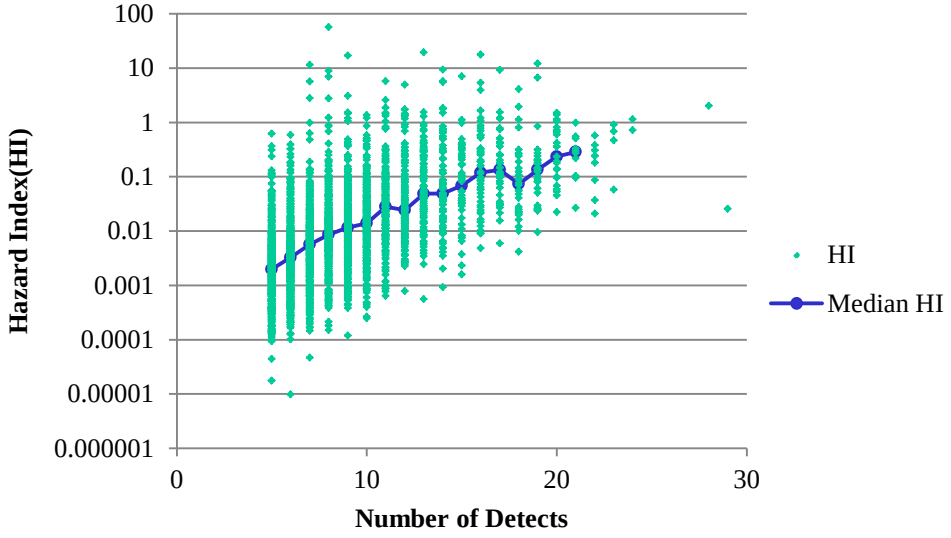
MCR Values NHANES Serum Adjusted levels of Dioxins Furans and PCBs

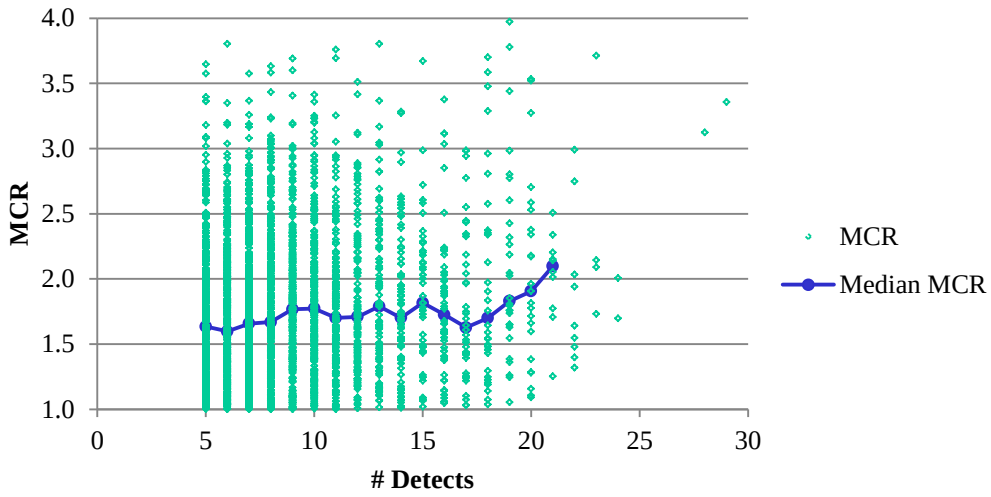


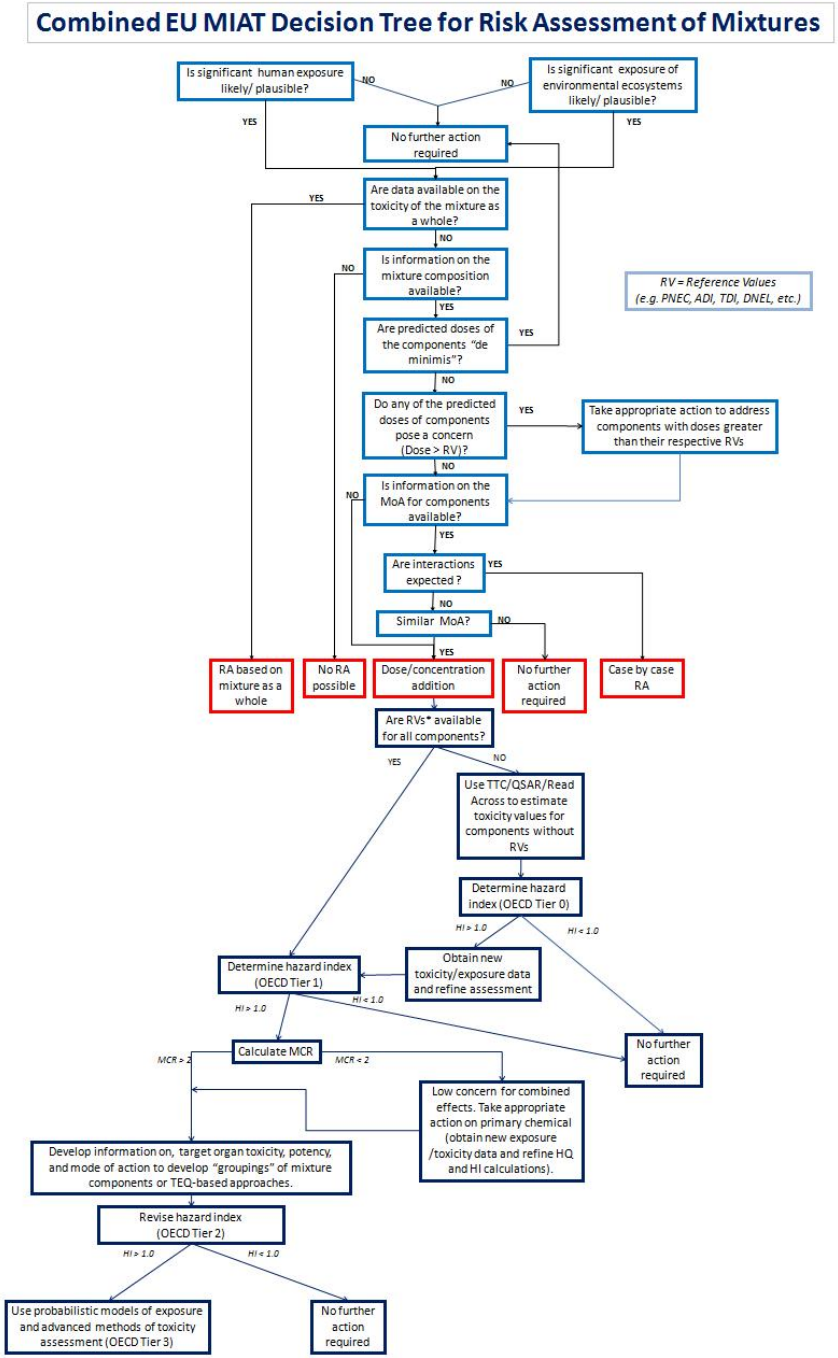
On going research on MCR

- Large MCR values are favored by
  - Multiple chemical make similar sized contributions to toxicity
  - Similar toxicity
  - Similar concentrations
  - Chemical exposures are correlated
- In many instances MCR declines with toxicity
- MCR increases slowly with N

Human toxicity and pesticides in surface waters in the U.S.







- Builds on WHO guidance
- Divides exposures
  - Low concern
  - One or more chemical exceeds a standard
  - Mixture is a concern but individual chemicals are not
- Tiered approach to assessing cumulative risks
- Uses TTC to fill data gaps (BPAD?)
  - When chemical doesn't drive risk of mixture stop
- Identifies which chemicals need MoA data

Summary

- Research is needed on exposure not just toxicity
  - Both monitoring and modeling are worthy areas for research
  - Technological breakthroughs are changing what is possible to be measured
- Integration of exposure and toxicity data is critical to understanding risks posed by mixtures
- MCR and exposure based decision tools can help identify toxicity data most necessary to refine predictions of cumulative toxicity

Thank you

QUESTIONS!