The Maximum Cumulative Ratio (MCR), a tool that uses both exposure and toxicity data to determine when cumulative assessments are most necessary.

Paul Price and Xianglu Han
The Dow Chemical Company
1. The concern for cumulative exposures
2. Cumulative risk case study:
   – Assessing cumulative risks to human and ecological receptors based on NAWQA dataset
3. MCR approach – a tool to evaluate the value of performing a cumulative risk assessment
4. Application of MCR to NHANES biomonitoring data
5. Conclusions
THE CONCERN FOR CUMULATIVE EXPOSURES
The importance of cumulative exposures

Cumulative assessments address the concern that:

– Even if exposure to each chemical in isolation is safe, the combination of the chemicals’ effects will be a concern; therefore,
– Programs that look at chemical risks on a chemical-by-chemical basis may not be sufficiently protective

The key questions:

– How much toxicity is “missed” when a chemical-by-chemical approach is used to assess an individual’s exposures?
– When is the “missing” toxicity large? When is it small?
Two cumulative exposures

Consider two individuals (or environmental receptors):

– Each individual is exposed to 5 chemicals
– Each individual has a 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 to determine that the first individual’s exposures were a concern

A cumulative assessment was not required for the second individual to identify the concern:

- 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)?

3. How big is the “missed toxicity”? 
CUMULATIVE RISK CASE STUDY
WHO tiered approach to cumulative risk

**Tiered Exposure Assessments**

- **Tier 0**: Simple semi-quantitative estimates of exposure
- **Tier 1**: Generic exposure scenarios using conservative point estimates
- **Tier 2**: Refined exposure assessment, increased use of actual measured data
- **Tier 3**: Probabilistic exposure estimates

**Tiered Hazard Assessments**

- **Tier 0**: Default dose addition for all components
- **Tier 1**: Refined potency based on individual POD, refinement of POD
- **Tier 2**: More refined potency (RFP) and grouping based on MOA
- **Tier 3**: PEPK or BEDR; probabilistic estimates of risk

**Decision Points**

- **Yes, no further action required**
- **No, continue with iterative refinement as needed i.e. more complex exposure & hazard models**
The NAWQA program

• A national U.S. survey
  – 4,380 water samples collected and analyzed
  – Up to 83 Plant Protection Products (PPPs) analyzed in each sample
  – 51 water sheds
  – Number of PPPs detected in a given sample ranged from 0 to 29

• Assessment focused on the ~3,000 samples with 5 or more detected PPPs
  – Mean number of detected PPPs in these samples is 9
  – Data evaluated in this example are old (collected in 1992-2001) and reflect past practices no longer supported in the U.S.
  – Surface waters often were smaller streams near treated fields or urban locations (may not be appropriate supplies for drinking water systems or fish habitat)
Tier 1 assessments

• Performed two cumulative assessments
  – Human health and impacts on fish
• Human health assessment
  – Chronic toxicity standards taken from U.S.EPA pesticide standards (cPAD or cRfD)
  – Assume untreated water is used as a long-term drinking water supply (conservative)
• Assessment of impacts on fish
  – Based on chronic fish Aquatic Life Benchmarks
    http://www.epa.gov/oppefed1/ecorisk_ders/aquatic_life_benchmark.htm
  – Assume concentrations remain constant over long periods of time (conservative)
Tier 1 assessment

• Values of HI were determined for each water sample assuming additivity for PPPs
• Impacts of non detects were evaluated
  – Significant impacts on HI values for samples with low values of HI did not affect samples with HI values >1.0
• Samples were categorized into three groups:
  – HI <1 (low concern)
  – All HQ <1 and HI > 1 (fails cumulative assessment)
  – One or more HQ>1 (fails chemical by chemical assessment)
Human Health: 3,099 mixtures
5 to 29 chemicals in each mixture

3,036 Samples HI <1

63 Samples HI >1

12 Samples
No HQ >1

51 Samples where one or more chemicals have HQs >1

HI values range from 1.0-2.0
Mean value 1.3

HI values range from 1.1-57.2
Mean value 5.4
Fish: 2,957 surface water mixtures
5 to 23 chemicals in each mixture

2887 Samples
HI <1

9 Samples
No HQ >1
HI values range from 1.02-2.46
Mean value 1.36

70 Samples HI>1

61 Samples
One or more HQs>1
HI values range from 1.03-9.84
Mean value 2.65

14
Cumulative risks from the NAWQA data are modest

- Most samples (97-98%) have a low concern for cumulative risk
- Mixtures of concern:
  - 63 mixtures human health
  - 70 mixtures for fish
- Under the WHO these samples would be passed on to the tier 2 and 3
Mixtures of concern

• The majority of the mixtures that are a concern for cumulative risk are a concern on a chemical-by-chemical basis
  – 80% of human health – 85% for fish
• The mixtures with the highest concern (HI>2.5) always have at least one HQ>1

• Why are so few mixtures like individual 1?
• Is this a general pattern for cumulative exposures?

The MCR is proposed as a tool for investigating this issue.
Maximum Cumulative Ratio (MCR)

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

Defined as:

\[
MCR = \frac{\text{Cumulative Toxicity (Stress)}}{\text{Maximum Toxicity (Stress) from One Chemical}}
\]

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

\[
MCR = \frac{\text{Hazard Index}}{\text{Largest Hazard Quotient}}
\]
MCR for Individual 1 is:
MCR =
3.5/0.8 = 4.4

MCR for Individual 2 is:
MCR =
3.5/3.2 = 1.1

The need for a cumulative risk assessment increases with the size of MCR. When MCR approaches 1.0, there is little need for a cumulative risk assessment.
MCR

• Can be applied to human and ecological endpoints
• Can be determined if you have data that supports:
  – Hazard Index-based approaches for an individual
  – TEQ-based approaches
• Is consistent with WHO tiered approach
  – MCR values can be determined at different tiers of a cumulative risk assessment
Values of MCR are constrained

• Values can approach 1 (when one chemical completely dominates the toxicity to an individual)
• Values can approach “n”, where “n” is the number of chemicals to which an individual is exposed
  – This occurs when each chemical is present in “equitoxic” concentrations
• Thus the MCR value of cumulative exposure to 30 chemicals will fall in a range from 1 to 30
Properties of MCR

- MCR is the measure of the fraction of toxicity that comes from the most toxic component
  - A value of 2 indicates one chemical is providing 50% of the mixture’s toxicity
  - A value of 1.1 indicates one chemical is providing 90% of the mixture’s toxicity

- MCR values indicate the amount of an individual’s cumulative risk that are missed by not doing a cumulative risk assessment

\[
\text{Fraction of Risk Missed} = 1 - \frac{1}{\text{MCR}}
\]

- A value of 4 indicates that a chemical-by-chemical approach would underestimate the toxicity of a mixture by a factor of 75%
- A value of 1.1 indicates that 10% of the toxicity would be missed
MCR and the Perato Principle

- **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

- **MCR and Perato principle**
  - A mixture fits the Perato principle if MCR is closer to 1 then n (the number of chemicals in a mixture)
MCR values for chronic human health

MCR values were closer to 1 than “n” (Perato Principle holds!)

- Up to 29 chemicals present
- Values of MCR ranged from 1 - 4
- Most samples had MCR levels of <2

MCR declined with predicted toxicity:

- Average for mixtures with HI values <1 is 1.8
- Average value for mixtures with HI values >1 is 1.3
- Implies one chemical is driving the mixtures
MCR values decline with toxicity

This is potentially a very important finding

- It implies that cumulative toxicity for most individuals is driven by multiple chemicals, but
- Individuals with extremely high toxicity (top 1%) occur because one or two chemicals occur at extremely high levels not because many chemicals are present at above average levels

If MCR values decline then individuals most at risk are more likely to be found by the chemical-by-chemical approach
MCR values for chronic effect in fish

MCR closer to 1 than n:
- Most values of MCR ranged from 1 – 3
- MCR declined with toxicity:
  - Average for mixtures with HI values <1 is 1.6
  - Average value for mixtures with HI values >1 is 1.2
The original question: *When are chemical-by-chemical approaches insufficient and by how much?*

• **How much toxicity would missed for mixtures?**
  – Ranges of MCR values were 1 – 4 (human health) and 1 – 5 (fish)
  – Means for higher toxicity mixtures (HI>1) of 1.3 and 1.2
  – Chemical-by chemical on average missed 25 to 16.7% of toxicity

• **Identifying samples of concern (HI >1)**
  – Most exceeded the HI because one or more HQ exceed 1 (81% of human and 87% for fish endpoints)
  – 19% and 13% would have been missed (cumulative would be required)
Conclusions

• MCR can be used to characterize the impact of cumulative risk

• MCR values in the NAWQA data:
  – Closer to 1 than n (supports Perato Principle)
  – Declined with hazard

• As a result:
  – Mixtures were a concern when they contained one or more chemicals that pose a concern
Applying MCR approach to biomonitoring data

• Value of biomonitoring data:
  – Gives a snapshot of internal doses at a point in time for an organism
  – Integrates exposures from multiple routes
  – Can integrate exposures over time (depending on persistence of compound)

• Limitations
  – Biomonitoring data are not equivalent to dose and more difficult to evaluate (BE’s may change this!)
  – Short lived compounds are difficult to measure (reflect only recent exposures)
Applying MCR approach to biomonitoring data

Original equation (risk based):
\[
MCR = \frac{\text{Hazard Index}}{\text{Largest Hazard Quotient}}
\]

Revised equation (exposure based):
\[
MCR = \frac{\text{Total TEQ}}{\text{Maximum TEQ}} = \frac{\sum (\text{Conc.} \times \text{TEF})}{\text{Max (Conc.} \times \text{TEF})}
\]

TEQ: Toxicity equivalents
TEF: Toxicity equivalent factors
Two groups of chemicals investigated

- Dioxins/Furans/Coplanar PCBs (D/F/P) 26 chemical in the group
  - Serum levels available for 1,848 individuals
  - Number of chemicals detected in one sample ranged from 1 - 24 with a mean of 13
  - WHO TEFs used

- Select estrogenic compounds: phytoestrogens and three phenols (PE) 9 chemicals in this group
  - Urine levels were available for 1,881 individuals
  - All 9 compounds detected in each sample
  - TEFs developed based on 17β-estradiol as the index chemical
### TEQs for chemicals in PE group

<table>
<thead>
<tr>
<th>Chemical</th>
<th>TEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daidzein</td>
<td>0.001</td>
</tr>
<tr>
<td>o-desmethylangolensin</td>
<td>0.005</td>
</tr>
<tr>
<td>Equol</td>
<td>0.085</td>
</tr>
<tr>
<td>Enterodiol</td>
<td>0.01</td>
</tr>
<tr>
<td>Enterolactone</td>
<td>0.01</td>
</tr>
<tr>
<td>Genistein</td>
<td>0.05</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>0.005</td>
</tr>
<tr>
<td>4-tert octylphenol</td>
<td>0.00036</td>
</tr>
<tr>
<td>2,5-dichlorophenol</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Results

![Graph showing the relationship between MCR and Total TEQ Level in Urine or Serum. The x-axis represents the Total TEQ Level in Urine or Serum, ranging from 0.001 to 10, while the y-axis represents MCR, ranging from 1 to 8. The data points are scattered across the graph, indicating a correlation between the two variables.](image-url)
Results

Total TEQ Level in Urine or Serum

MCR

D/F/P

PE
Mean Values of MCR for Typical and Highly Exposed Individuals

Percentile of total TEQ

MCR (95% CI)

D/F/P

PE
Implications

• MCR values closer to 1 than “n” (Perato principle again)
• MCR values differed for the two groups of chemicals
  – Values are greater for D/F/P than PE
  – Values decline with total body burden (more important for PE than D/F/P)
• Findings suggest that D/F/P have a greater need for cumulative risk assessments than PE
Implications of the MCR for cumulative risk programs

• MCR provides a tool for investigating data on cumulative exposures to human and ecological receptors
  – Existing data on concurrent exposures should be investigated using MCR
  – Additional targeted surveys should be considered to determine MCR values for chemicals and sources of interest

• Goal of such efforts will be to identify when:
  – MCR values are large
  – Are certain chemicals associated with large MCR values

• Such finding could direct the management of cumulative risks
Implication of case study findings

• MCR values varied across individuals (1-7)
• MCR values typically decline with increasing cumulative exposure or cumulative risk
  – Do not assume that MCR values for typical individuals will apply to highly exposed individuals
• Mean values of MCR in highly exposed populations are generally less than 2 (with the exception of D/F/P)
• D/F/P have a greater need of cumulative risk assessments than PE
Implications for programs that use chemical-by-chemical approaches

• The limited data do not suggest that substantial levels of risk are missed by not performing cumulative risk assessments
  – MCR values are closer to 1 than “n”
  – MCR values decrease with toxicity and at higher toxicities are often <2
  – Over 80% of water samples would have been found by a chemical-by-chemical approach
• But data analyzed so far are limited!
• Additional work is required to determine:
  – When will MCR levels will be large for highly exposed individuals (e.g., D/F/P)
  – How to predict MCR values for chemicals not yet on the market
On-going work at Dow

• Applying MCR to new data sets (D/F/Ps in workers, polar chemicals in surface water, and anthropogenic compounds in surface water)

• Investigating how MCR values are influenced by:
  – Statistical properties of distributions of doses and toxicity of chemicals
  – Correlations between doses of different chemicals on MCR values
  – Missing chemicals (what is the impact of unmeasured chemicals)

• Look at MCR values at higher tiers of WHO assessments impact of
  – Setting up assessment groups
  – Probabilistic analyses
Summary

• The MCR is a simple tool applicable to a wide range of data and endpoints (both ecological and human)
• Identify instances where cumulative risk assessments are most needed
• Can be integrated into tiered approaches to assess mixtures
• Preliminary analyses suggest chemical-by-chemical approaches will identify much, but not all cumulative risk
Questions!