

**Emerging Science for Environmental Health Decisions - Meeting #9**

# **Mixtures and Cumulative Risk Assessment**

**Moiz Mumtaz**

Division of Toxicology and Environmental Medicine,  
Computational Toxicology and Methods Development Lab  
ATSDR, Atlanta, GA

**Regulatory Implications Panel**

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Office of the Director

Division of Toxicology and Environmental Medicine

# ATSDR Chemical Mixtures Program

## **Mixtures of Interest:**

Binary, ternary, and quaternary  
TCE, PERC, TCA & DCA  
Biomonitoring NHANES data

## **Assessment Activities:**

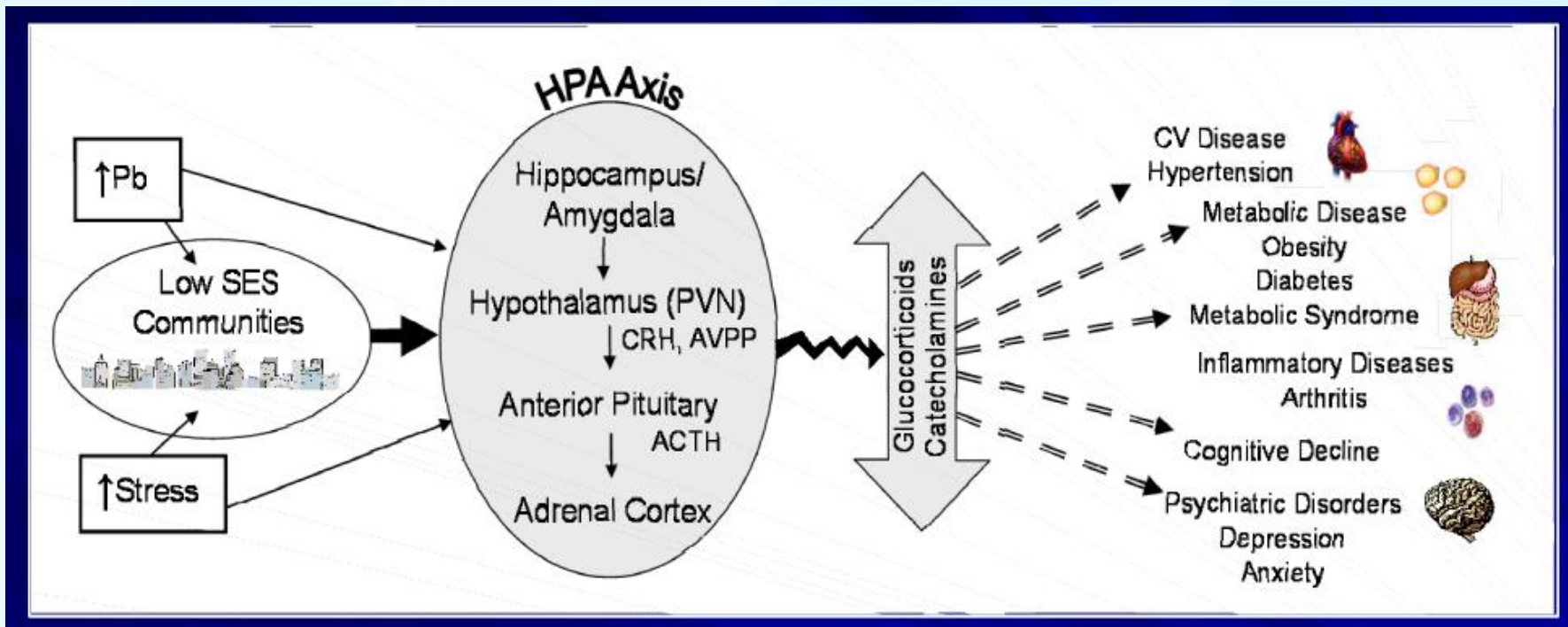
Guidance for Chemical Mixtures Assessment  
Interaction Profiles

## **Research Activities:**

To fill data gaps and develop new methods  
experimental research funded under cooperative  
agreement programs

# What is stress ?

- hard to define
  - means different things to different people
  - BUT: clearly a negative feeling
- occurs when one gets overly stimulated due to the challenges experienced on a daily basis
- results in depleted energy level
- may disrupt homeostasis



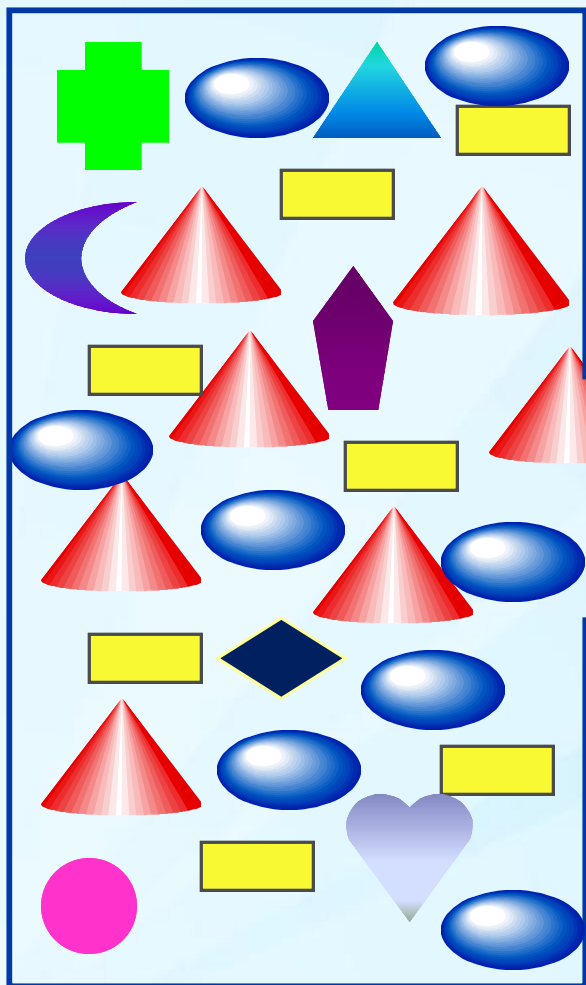
Copied from:

<http://www.epa.gov/ncer/events/calendar/2010/mar17/presentations/cory-slechta.pdf>

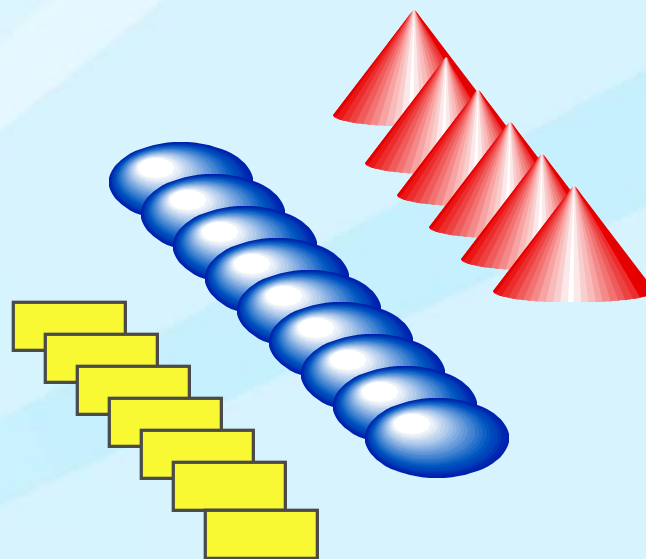
# Caveats to use of MOA

- There is usually more than one MOA
- A given MOA cannot describe population variability
- Different MOAs may occur at high vs low doses
- Different MOAs may occur at different Life Stages
- Mixtures are the reality

Chemicals

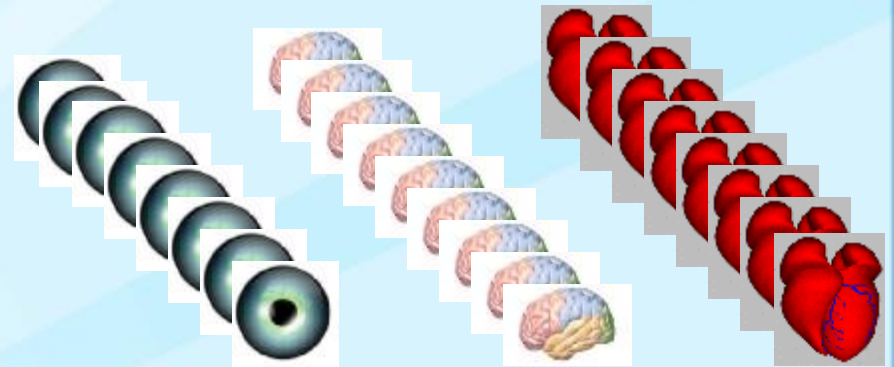
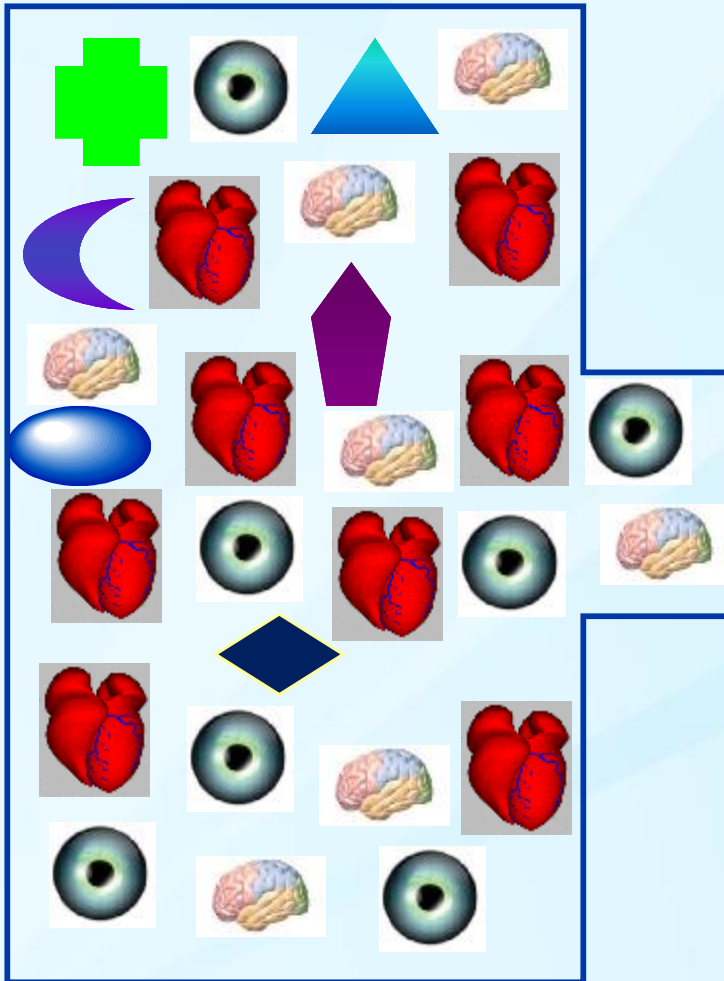


Group via  
Completed Exposure  
Pathways



Target Organ

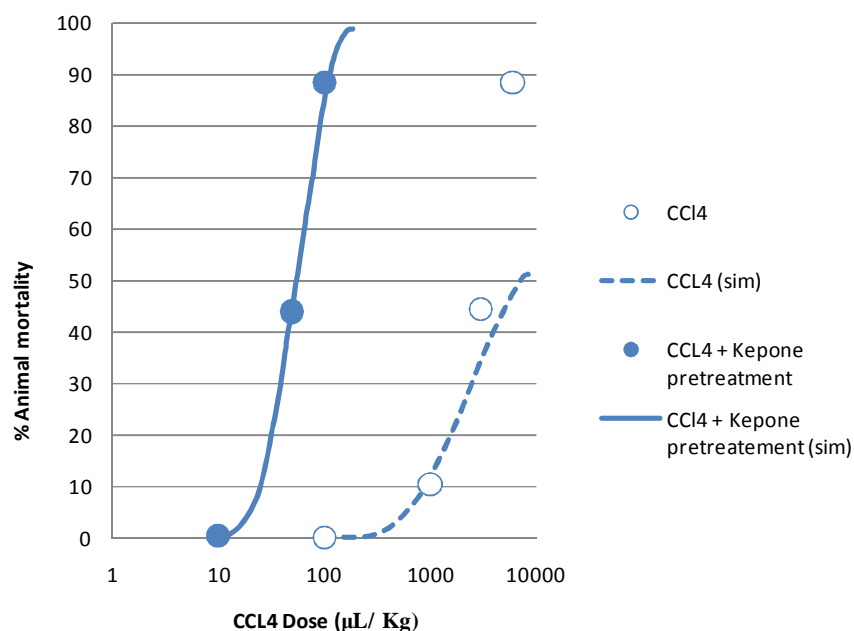
Group via  
Target Effects



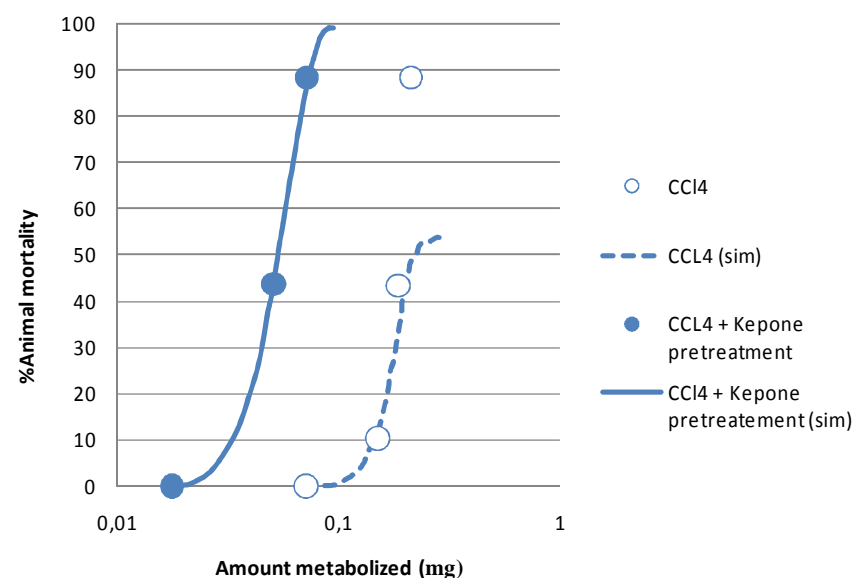
Group via  
Mode of Action

# CCl4 increased liver toxicity by Kepone

Dose-Response based on exposure dose



Dose-Response based on target tissue dose



60- 142 fold increase in cell mortality  
(based on exposure dose)  
•Toxicokinetic + toxicodynamic interactions

4 fold increase in cell mortality (based  
on target tissue dose)  
•Toxicodynamic interactions

# ATSDR PBPK Tool Kit

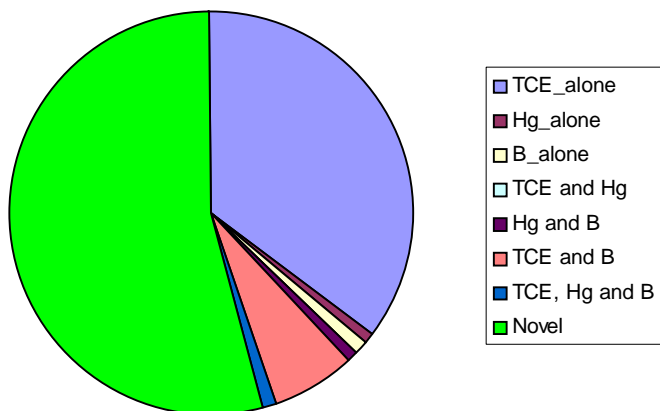
- Develop human PBPK models to encourage their use by public health practitioners
- All the models will be available in a single simulation language configured so that users are required to input minimal information to perform simulations under specific exposure scenarios
- Increase ATSDR capability to assist in public health decision making concerning environmental chemicals

# Toxicity of

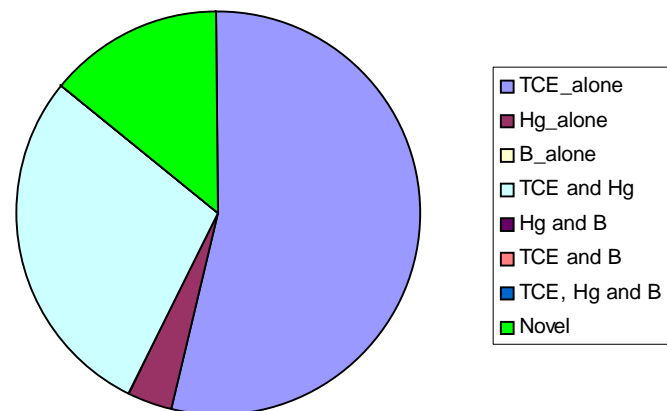
## Effect of

	Atrazine	Simazine	Diazinon	Nitrate
Atrazine		<ul style="list-style-type: none"> <li>· Additive</li> <li>· Reproductive effects</li> <li>· High confidence</li> </ul>	Data Gap	<ul style="list-style-type: none"> <li>· Greater than additive</li> <li>· Cancer effects</li> <li>· Low confidence</li> </ul>
Simazine	<ul style="list-style-type: none"> <li>· Additive</li> <li>· Reproductive effects</li> <li>· High confidence</li> </ul>		Data Gap	<ul style="list-style-type: none"> <li>· Greater than additive</li> <li>· Cancer effects</li> <li>· Low confidence</li> </ul>
Diazinon	<ul style="list-style-type: none"> <li>· Greater than additive</li> <li>· Neurological effects</li> <li>· Medium confidence</li> </ul>	<ul style="list-style-type: none"> <li>· Greater than additive</li> <li>· Neurological effects</li> <li>· Medium confidence</li> </ul>		Data Gap
Nitrate	<ul style="list-style-type: none"> <li>· Greater than additive</li> <li>· Cancer effects</li> <li>· Low confidence</li> </ul>	<ul style="list-style-type: none"> <li>· Greater than additive</li> <li>· Cancer effects</li> <li>· Low confidence</li> </ul>	Data Gap	

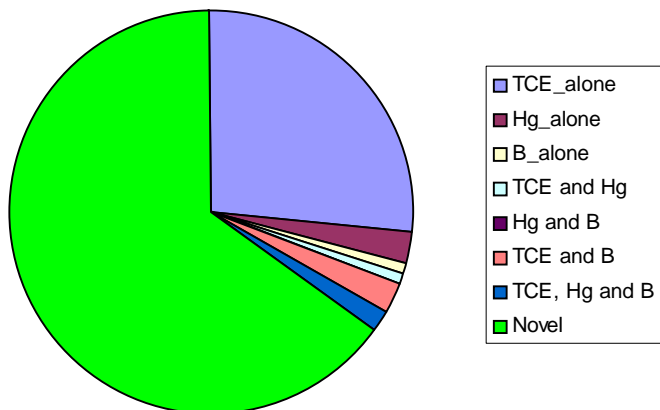
**Liver: upregulated by ternary mixture (n = 105):  
proportions also upregulated by individual compounds**



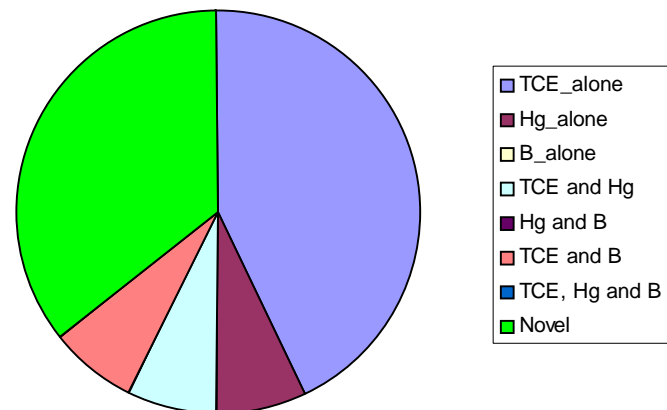
**Kidney: upregulated by ternary mixture (n = 28):  
proportions also upregulated by individual compounds**



**Liver: downregulated by ternary mixture (n = 120):  
proportions also upregulated by individual compounds**



**Kidney: downregulated by ternary mixture (n = 14):  
proportions also downregulated by individual compounds**



# **Focuses on the Use of Mode-of-Action**

“The quality of risk analysis will improve as the quality of input improves. As we learn more about biology, chemistry, physics, and demography, we can make progressively better assessments of the risks involved. Risk assessment evolves continually, with re-evaluation as new models and data become available.”

**“Science and Judgment in Risk Assessment” (National Research Council, 1994)**

# The Future of Cumulative Risk Assessment Data Availability (EHP, 2007)

- Establish state and federal environmental health tracking system
- Creation of linked monitoring systems, databases, and registries
- Availability of specific and sensitive biologic markers of exposure, effects, and susceptibility
- New quantitative tools –Omics
- Development of innovative technologies including environmental sensors (GIS) etc



# Remaining challenges

- A critical need to evaluate effects of toxicants in the context of other extant risk factors with which they share common biological substrates and /or common adverse outcomes
- Current approaches leave us picking the low-hanging fruit
- Using criteria including co-occurrence and shared biological substrates and/or adverse outcomes continues to be the strategy to prioritize and address Complex Exposures problems

Learning is but an adjunct to ourself,  
And where we are, our learning likewise is

**Shakespeare**

Declare the past,  
Diagnose the present,  
Foretell the future

**Hippocrates**  
**460 – 357 BC**

# Complex Exposures

