



# SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

## Why a New Approach is Needed

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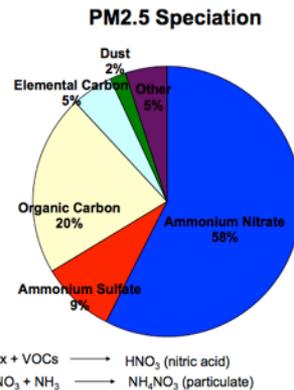
# Conflict of Interest Statement

- The speaker has no actual or potential conflicts of interest in relation to this presentation.



# Why Concern about Mixtures?

- Real life exposure scenario—mixtures
  - Humans exposed simultaneously to large numbers of compounds from various sources
    - Air, water, soil, food
  - Most relevant to all populations
- Superfund sites are mixtures
- Food is a mixture
- Risk assessment of mixtures is a reality...and a challenge



Average levels of detected contaminants in Indy's water from 2010-2015, in parts per billion.

**Averages exceeding health guideline shown in red.**

Contaminant	Health guideline	2010	2011	2012	2013	2014	2015**
Arsenic	0.004	ND	ND	0.263	0.292	ND	0.112
Atrazine	0.15	0.203	0.479	0.549	0.358	0.422	0.186
Bromodichloromethane	0.4	7.21	7.82	8.59	7.94	8.01	7.72
Chlorate	2.0	N/A	N/A	N/A	N/A	N/A	492.9
Chloroform	1	17.9	20.3	20.8	21.3	21.9	19
Chromium (HEX)***	0.02	N/A	N/A	N/A	N/A	N/A	0.08
Dibromodichloromethane	0.07	2.43	2.58	2.72	2.57	2.31	2.43
THMS	0.8	41	44.4	47.6	48	47.9	55

Note: Numbers are in parts per billion.

\*\* 2015 was the first year that Chlorate and Chromium (HEX) were recorded.

\*\*\* Hexavalent Chromium, or Chromium-6, made notorious by the film "Erin Brockovich" is a carcinogen – for which there are no federal regulations – that was detected in the drinking water supplies serving 250 million Americans in all 50 states.

Data analysis: Sarah Bowman / IndyStar

Source: Environmental Working Group

Michael Campbell / IndyStar



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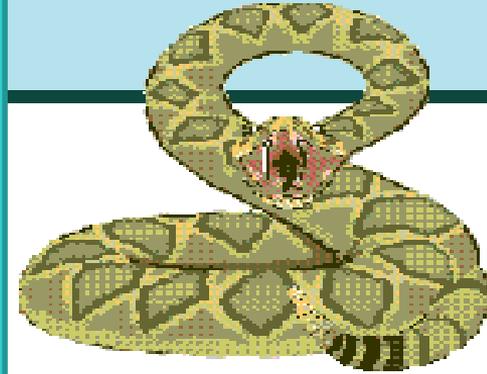
R = Risk

I = is equal to

T = Toxicity ~~X~~

E = Exposure

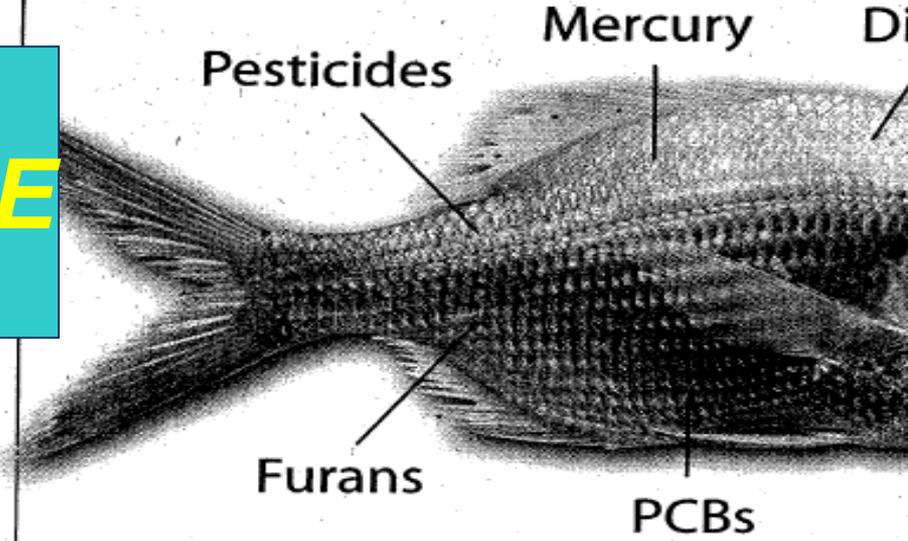
**RITE**



Federal Page, 5/18/04 Washington Post

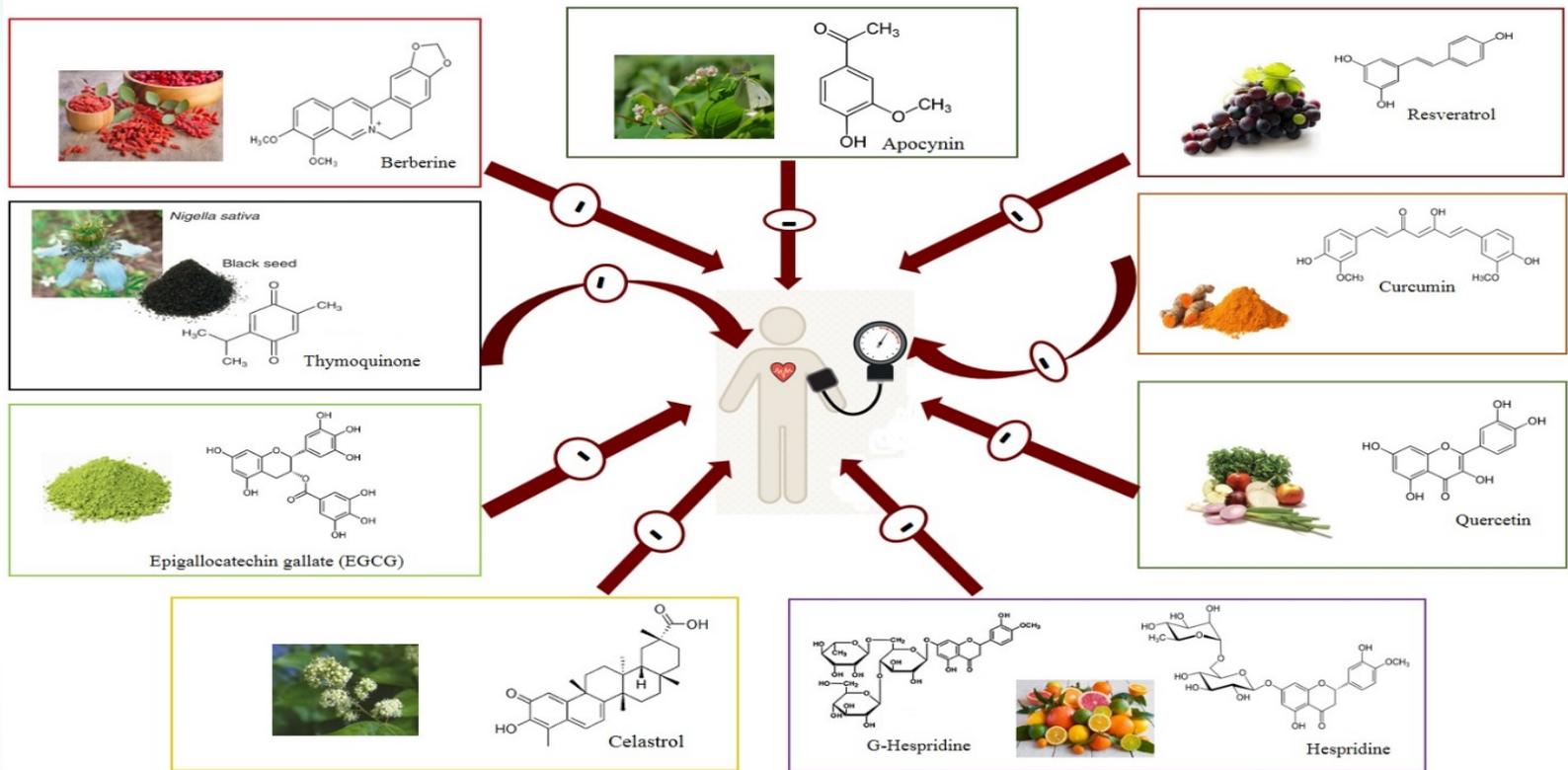
# Brane Fude?

$$R = H \times E$$



Mercury is such a potent ne





Chemical structure of apocynin, berberine, thymoquinone, epigallocatechin gallate, celastrol, resveratrol, curcumin, quercetin, hesperidin and G-hesperidin. These compounds can be effective on hypertension through NADPH oxidase inhibition.

# Key Definitions

- **Aggregate Risk** – involves consideration of exposures to a single compound from multiple pathways (food, drinking water, residential or occupational sources)
- **Cumulative Risk** - is an analysis, characterization, and possible quantification of **combined risks** to human health or environment from **multiple agents or stressors**. [EPA Framework For Cumulative Risk Assessment (2003)]
- **Multiple exposures**, to the same or different compound, may interact in a way that generates risk different from those when assessed individually
  - It is how real-life works
  - Characterization of significant sources of similar risk may be important for risk management
    - Still a question of how to use cumulative risk information



# Chemical Mixture Interactions

- o **Additive**: effect is equal to individual effects added together.  $2 + 2 = 4$
- o **Synergistic**: combined effect of exposure to two or more chemicals is greater than the sum of their individual effects.  $2 + 2 = 10$
- o **Antagonistic**: two chemicals when administered together interfere with each other's actions or one interferes with the actions of the other, e.g., Calcium blocking Tetracycline absorption.  $2 + 2 = 1$
- o **Potentiation**: non-toxic chemical causes a toxic chemical to become more toxic or more active (adjuvants).  $0 + 2 = 7$
- o **Coalitive**: several agents that have no known toxic effects interact to produce a toxic effect.  $0 + 0 + 0 = 8$



# Standardized Framework

- Assessment of Complete Chemistry of Botanical
  - Sufficient data demonstrating safety for intended application in the target population
- Characterization
  - Can compounds of concern [?] be identified for this botanical and its relevant preparation
- Compounds of concern
  - Is there relevant data available to assess safety of these compounds in botanical preparation at level of intended use in intended population
- No—refrain from use
- Yes—safe use or continue to monitor compounds of concern



# Can Alternatives Inform the Risk Assessments of Mixtures in Food?

- Can High Thru-put Assays/Tox 21 Inform the Process?
  - Michael J. DeVito, NTP, Research Triangle Park, NC
- Proposed *In Silico* Approach for Botanical Mixtures
  - Catherine Mahoney, Procter & Gamble Technical Centres Ltd, Surrey, UK
- Non-mammalian *In Vivo* models: *C. elegans* as a Model System to Inform Hazard Identification
  - Piper Reid Hunt, US FDA, Laurel, MD
- Extrapolating New Approaches into a Tiered Approach to Mixtures Risk Assessment
  - Mike Dourson, TERA, Cincinnati, OH
- Roundtable Discussion
  - Moderator: A. Wallace Hayes
  - All speakers

