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Health Effects of Mixtures: It is Important. Is it Hopeless?

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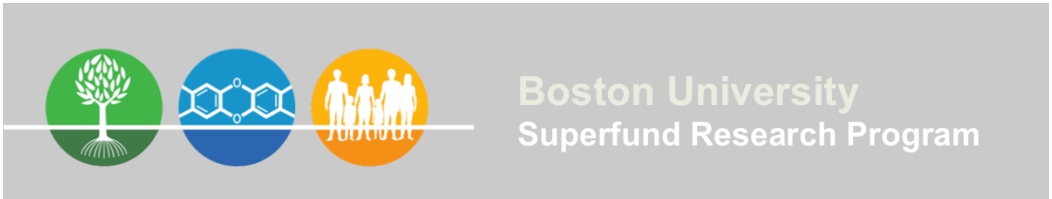
"New Methods in 21st Century Exposure Science"
USEPA STAR Grants Kick Off Meeting
3-4 February 2015

Boston University School of Public Health
Department of Environmental Health

BU



"Findings from epidemiological studies reveal associations between exposures to chemicals and observed health effects. These effects, however, are not always predicted by traditional toxicity tests, many of which are foundational to EPA's chemical evaluation and assessment strategies…"

Good final exam question!

Some traditional answers:

- **Tox: species, dose**
- **Epi: bias, confounding**

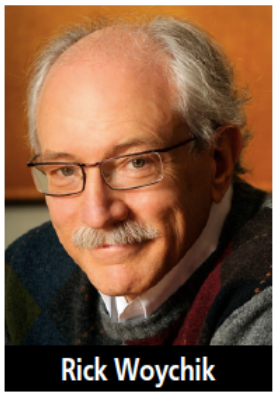
Mixtures are an important issue for environmental health & risk assessment

"Traditionally, toxicological studies and human health risk assessments* have focused primarily on single chemicals. However, people are exposed to a myriad of chemical and nonchemical stressors every day and throughout their lifetime…

It is imperative to develop methods to assess the health effects associated with complex exposures in order to minimize their impact on the development of disease."


Danielle J. Carlin


Cynthia V. Rider


Rick Woychik


Linda S. Birnbaum

Carlin DJ, Rider CV, Woychik R, Birnbaum LS. Unraveling the Health Effects of Environmental Mixtures: An NIEHS Priority. *Environ Health Perspect* 2013; 121: A6-A8.

*** and environmental epidemiology studies**

Is the mixtures problem hopeless?

"There are at least 75,000 chemicals in commerce today [2001]. Roughly 1,000 new chemicals are put on the market each year. Almost none of the 75,000 chemicals have been adequately analyzed for their full impact on the environment and human health, and most have not even received basic toxicological testing."

Estabrook & Tickner, 2001

Is the mixtures problem hopeless?

"Using current methods, laboratory tests for additive, synergistic, and cumulative effects, however, are impractical …*Testing just one dose of just the top 1,000 high volume chemicals in three-way combinations would require 166 million different experiments."*

$$\binom{1000}{3} \sim 1.7x10^{8}$$

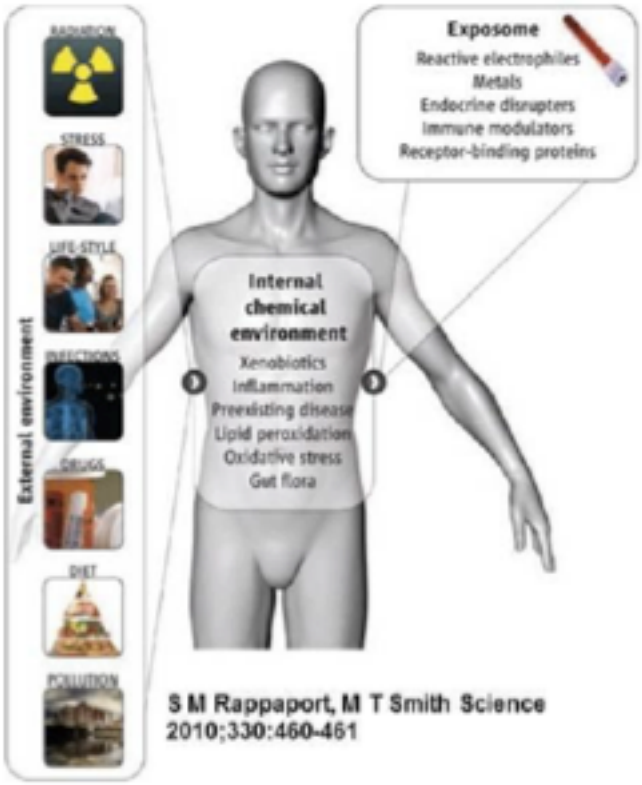
Estabrook & Tickner, 2001

BUT

1. Exposure science, chemistry (& environmental epidemiology) can yield important insights by studying real world exposures.

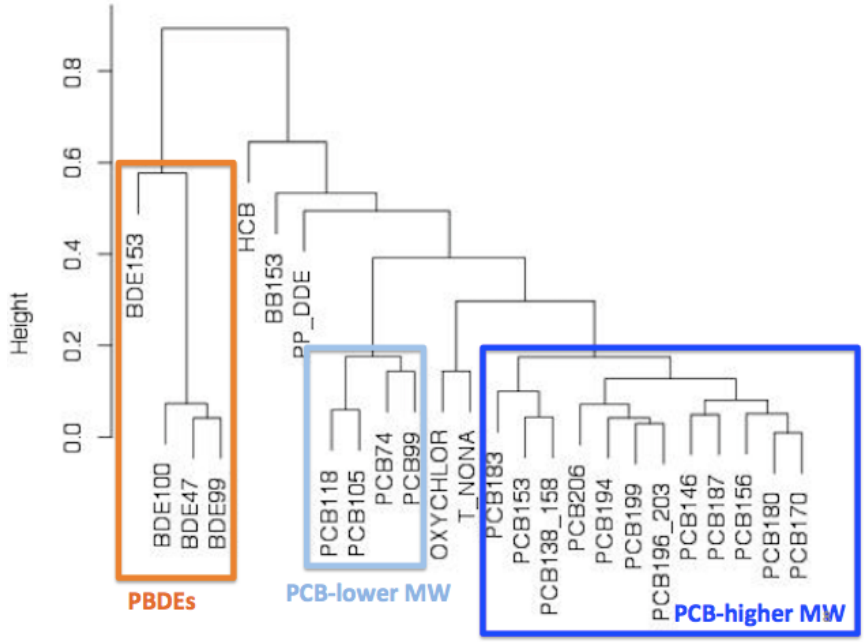
- **Not all possible mixtures occur.**

What else are we exposed to? (besides what we usually look for)



-> Non-targeted analysis

What are the patterns of coexposure? On what do they depend?



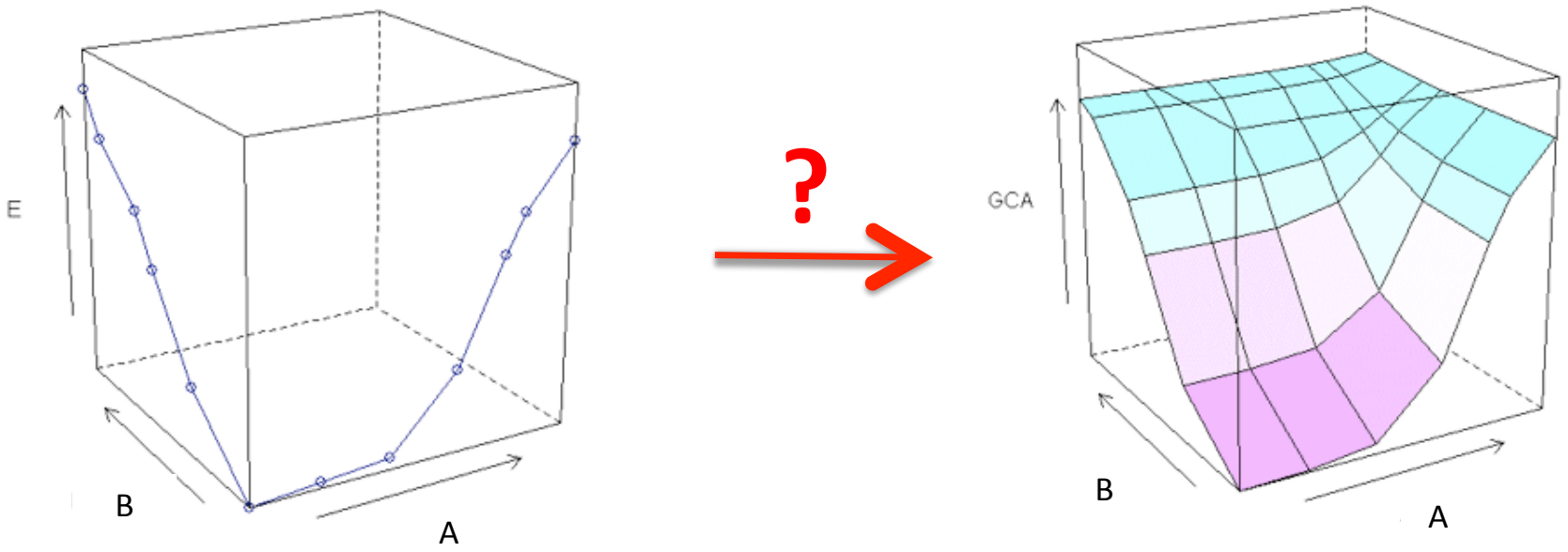
Clustering of POPs in serum

AND

2. Pharmacology & toxicology have developed very useful approaches.

Important insights into mixtures via understanding of mechanism & modeling.

When & how can we predict the dose response of a mixture from: 1) dose response of its components, 2) mechanistic information?



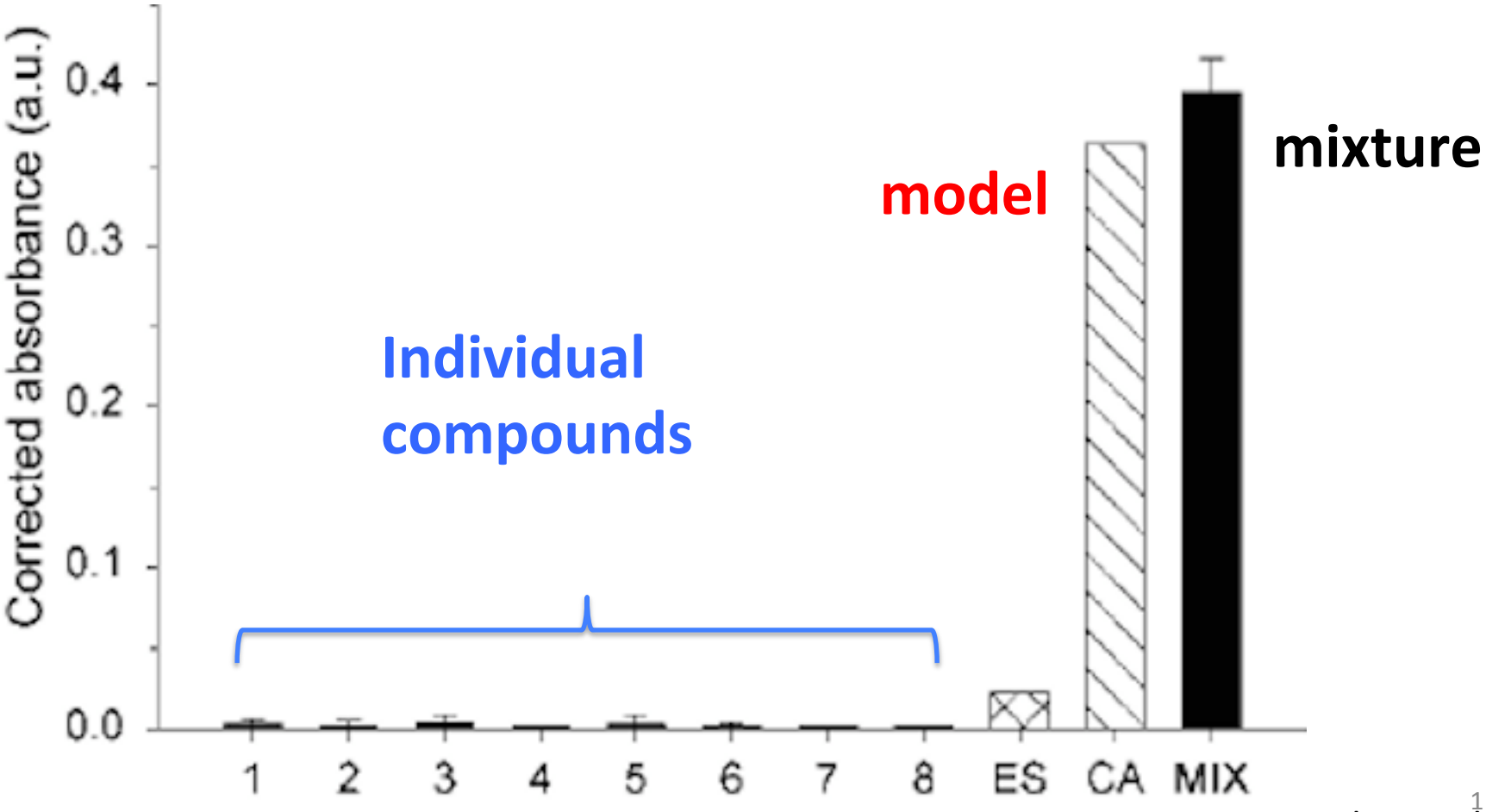
Individual dose response curves

Joint dose response surface

2D example

E.g.: "Something from Nothing" Eight Weak Estrogenic Chemicals Combined at Concentrations below NOECs Produce Significant Mixture Effects

(Can be effectively modeled here)

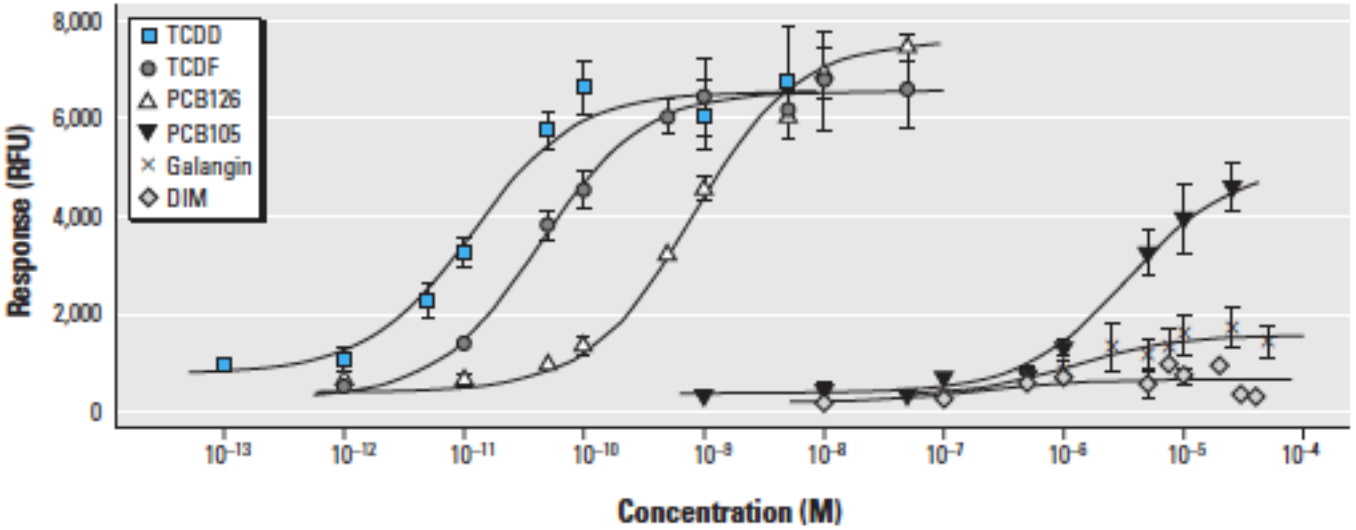


Silva et al. 2002

What about compounds that have the "same" mechanism of action but differ in their efficacy (maximal effect), not just potency?

- TEFs (and concentration addition) theoretically don't work
- mixtures of full and partial agonists for receptors are very common

e.g., ligands for AhR



Different maximal effects

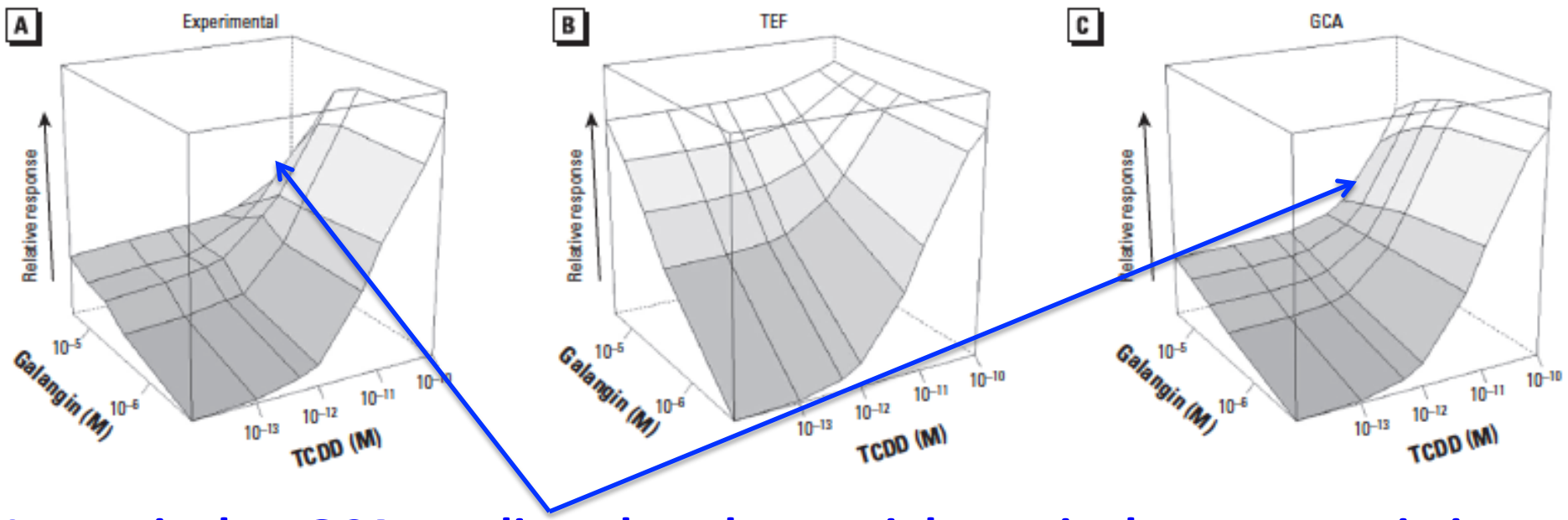
Howard et al 2010

Empirical data: e.g., AhR ligands TCDD + galangin

Effect = AhR reporter assay

GCA prediction fits empirical data better than alternative TEF model (& others)

Experimental **TEF model** **GCA model**



In particular, GCA predicts that the partial agonist has antagonistic effects at higher doses (above the maximal effect level)

Howard et al 2010

And other examples, e.g., ligands for PPARγ = “master regulator of adipogenesis”

Mixtures analysis via combinations of exposure science, chemistry & toxicology (with applications in epi as well)

e.g., effect directed analysis (EDA)

with Mingliang Fang, Heather Stapleton (Duke)

Many environmental epi studies examine one exposure at a time, or closely related ones (often based on feasibility)

For studies of general populations, I think this will need to change

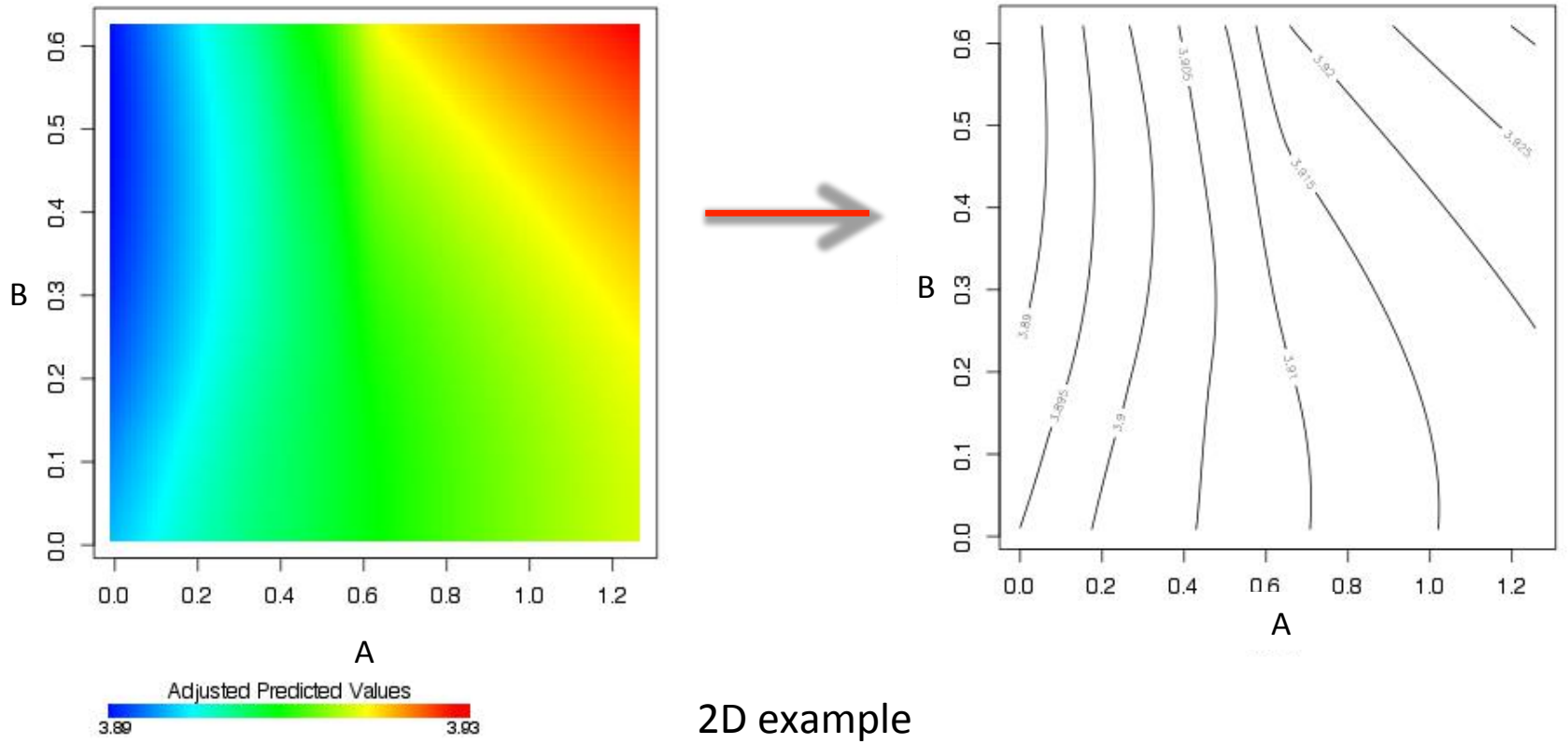
- **Expand the range of target exposures.**
- **Add non-targeted analysis.**
- **New methods needed**

Outline of one novel method:

- **borrows from spatial epidemiology & toxicology**

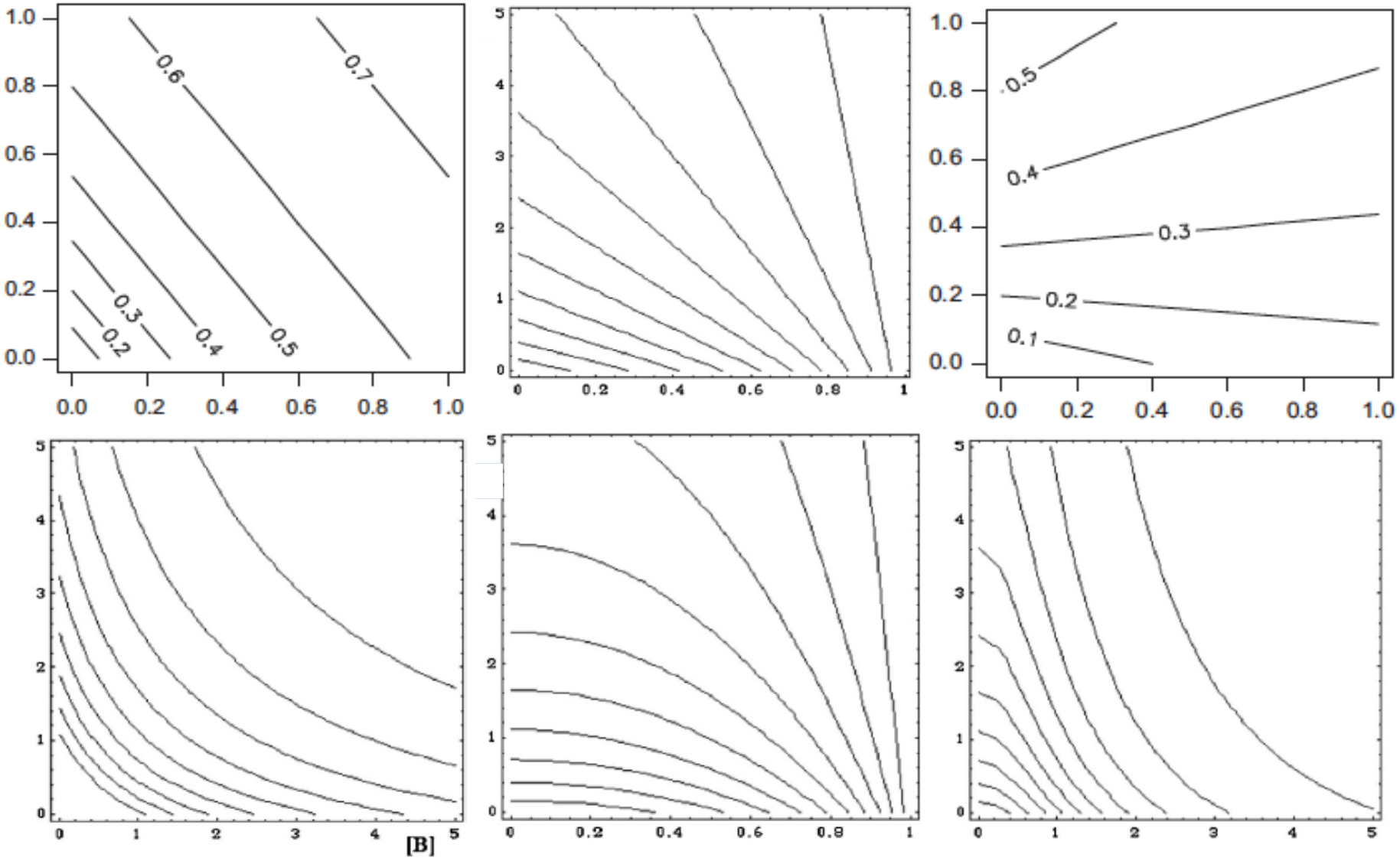
"Map" of outcome in exposure space (X1 vs. X2 vs. X3…)

Contours = equal effect levels (isoboles in toxicology)

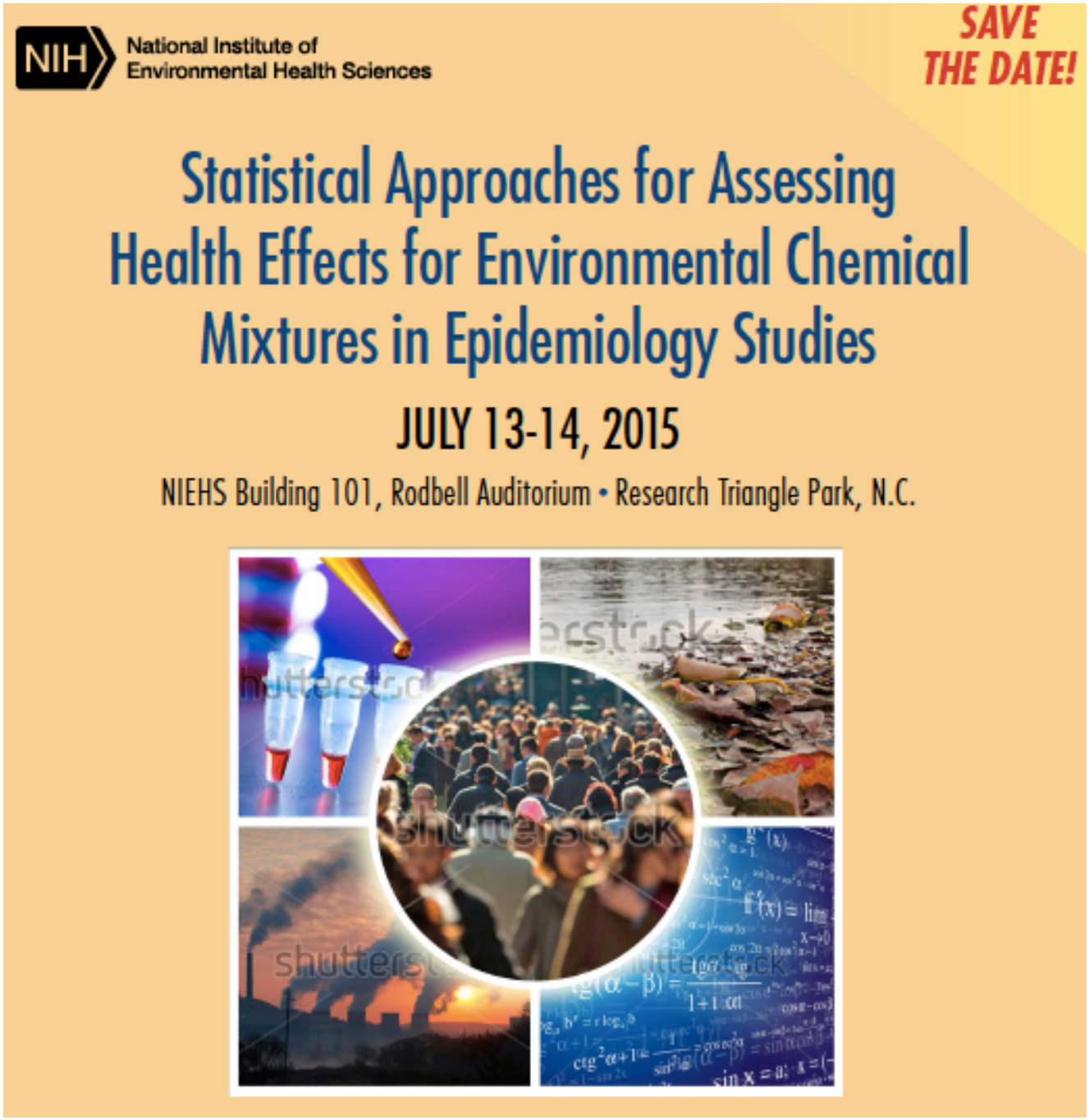


2D example

The shape of isoboles (contours) can be informative about underlying toxicology & modeling



Webster 2013



NIEHS workshop
July 2015

Data analysis competition

- **Synthetic data sets (posted)**
- **Real world data set**

What are the relative strengths & weaknesses of methods?

Is the mixtures problem hopeless?

I don't think so, but it is transdisciplinary

SOT | Society of Toxicology — Mixtures Section

ISEE — International Society for Environmental Epidemiology

International Society of Exposure Science — *Science for Better Environmental Health*

ACS Chemistry for Life®

ASA — American Statistical Association — *Promoting the Practice and Profession of Statistics*

Society for Mathematical Biology

United States Environmental Protection Agency

STAR grants

THANK YOU!

NIH National Institute of Environmental Health Sciences — *Your Environment. Your Health.*

Two aspects of the mixtures problem:

What are the patterns of co-exposure in real populations and on what do they depend?

→ important role for exposure science

What are the health impacts of mixtures (to which we are exposed)?

→Epidemiology and toxicology/pharmacology can learn from each other.

WARNING

Use of the following words—interaction, additive, synergy, antagonism—may lead to severe confusion. Avoid with alcohol. Toxicologists, epidemiologists and statisticians d not mean the same thing by these terms.

Acknowledgments:

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Further reading:

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- **Howard GJ, Webster TF. Contrasting Theories of Interaction in Epidemiology and Toxicology. *Environ Health Perspect* 2013; 121:1–6.**
- **Silva E, Rajapakse N, Kortenkamp A. Something from "nothing"--eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. *Environ Sci Technol*. 2002; 36:1751-6.**
- **Webster TF. Mixtures of endocrine disruptors: How similar must mechanisms be for concentration addition to apply? *Toxicology* 2013; 313: 129– 133.**