The Importance of Background in Considering Cumulative Risk

Gary Ginsberg

CT Dept of Public Health

March 17 2010

Strenthening EJ Workshop, Washington DC

SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT

National Research Council
Committee on Improving Risk Analysis Approaches Used by EPA
Board on Environmental Studies and Toxicology

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Factors that Contribute to Risk

Community Factors

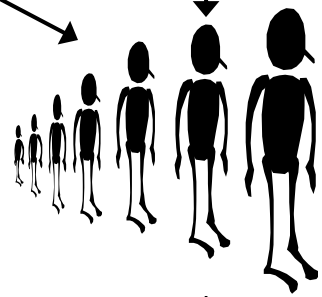
Housing
Medical Care
Education
Stress

Host Factors

Genetics, Age
Lifestyle, Disease

Chemical Exp

Air, water, soil,
consumer prod, food



Disease??

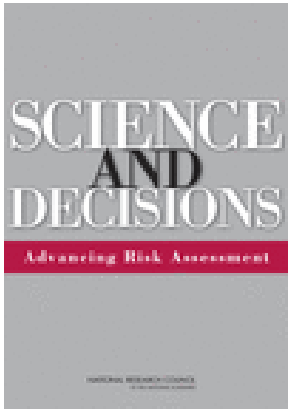
Toxic Chemicals May Interact with Disease Process

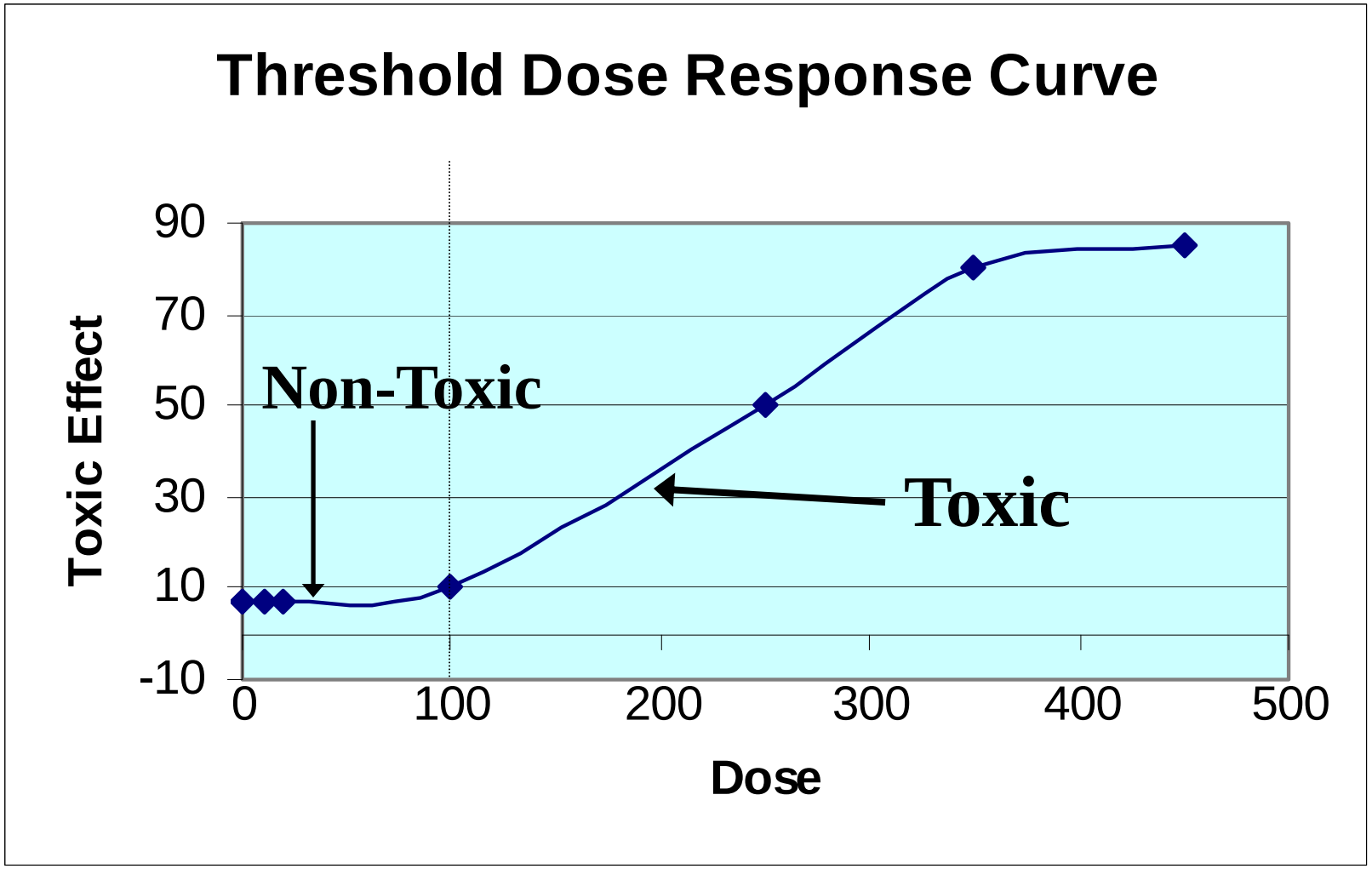
Carcinogens →	Cancer
PM →	CardioPulm Dx
Mercury →	CV disease
TCE →	Autoimmune Dx
Arsenic →	Diabetes
Early Estrogens →	Obesity
Ozone →	Asthma

Benign?? / Contributory?? / Causative??

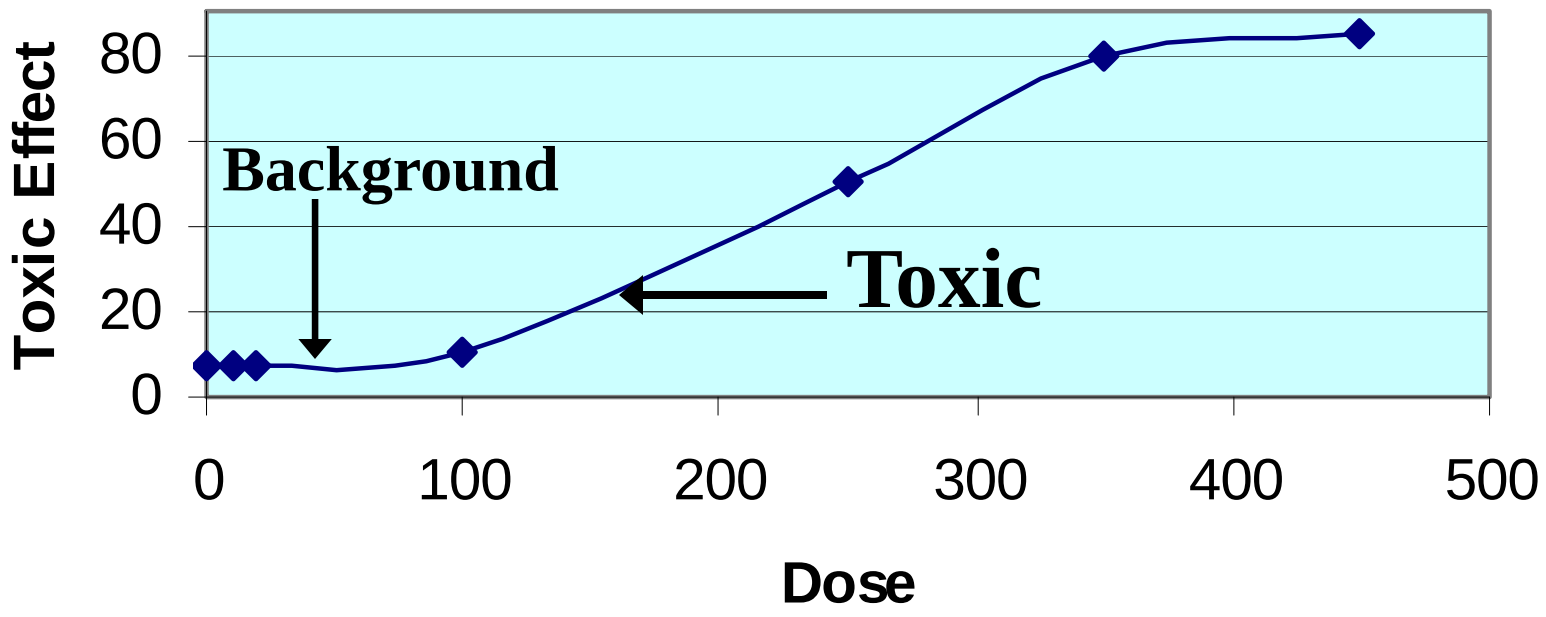
➢Background exposures and underlying disease processes contribute to population background risk

→ can lead to linearity at the population doses of concern




Threshold Dose Response Curve
Toxic Effect
90
70
50
30
10
-10
Non-Toxic
Toxic
0
100
200
300
400
500
Dose

Non-Threshold Dose Response Curve



Background Created by

- Exposures to similarly acting chemicals
  - Add chemical exposures – together they may surpass a threshold
- Ongoing aging and disease processes
  - Decreased functional reserve
  - Decreased defenses
  - Degenerative processes are a toxic response
    - Lipid peroxidation, inflammation, cell death

Demchuk et al. 2007, EHP 115: 231-234

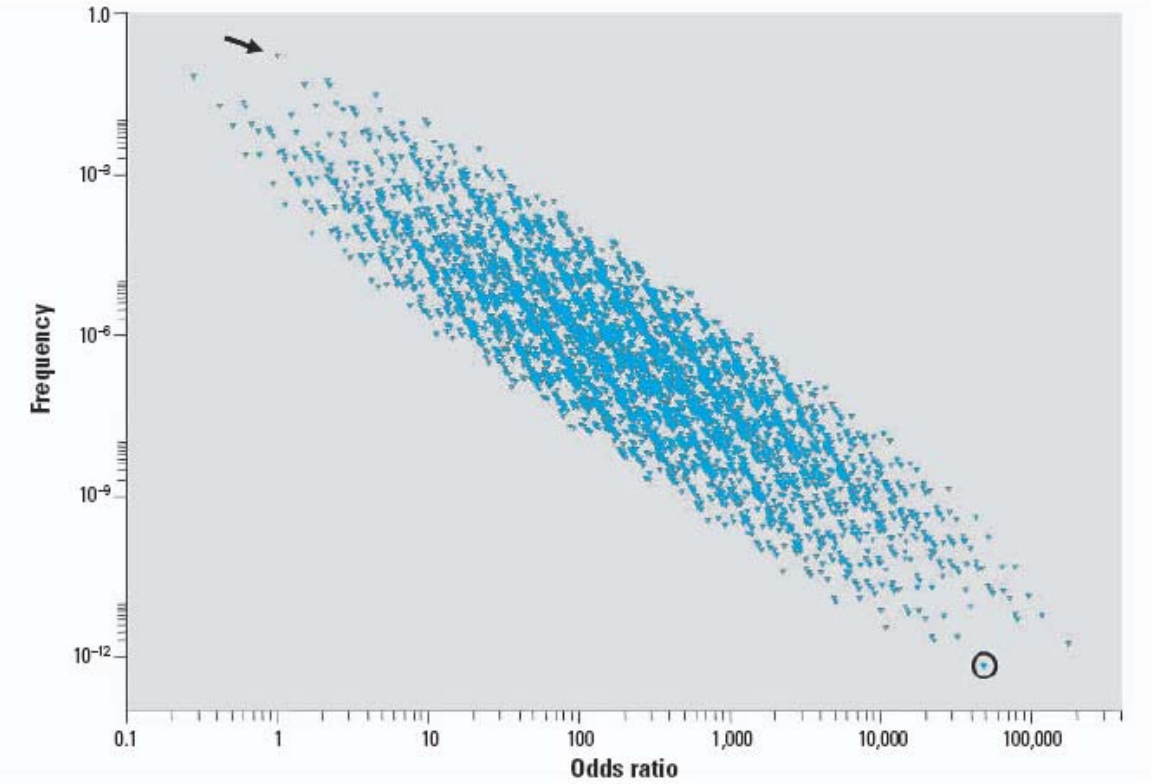


Figure 1. Frequencies and ORs of genotypes in a control population calculated using 16 gene variants listed in Table 1. Each point represents a unique genotype combination. Referent genotype profile is identified by the arrow (OR = 1). Genotypic profile composed of all minor variants is identified by the circle.

Large genetic variability in sensitivity to asthma

Its All About Background

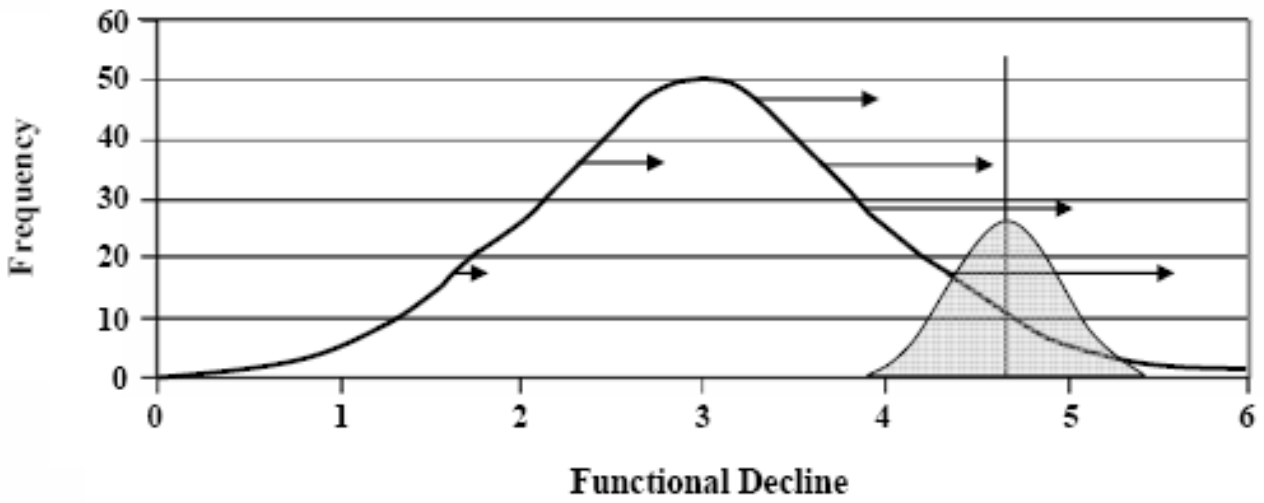


FIGURE 5-9 Population vulnerability distribution. Arrows represent hypothetical response to same toxicant dose for people at given level of functional decline unrelated to any particular toxicant. Vertical line represents presumed threshold between overt adverse and nonadverse effect in median person. Shaded area straddling line represents distribution of thresholds in population.

Background Contribution is Source of Variability

- Risk assessment approaches to variability
  - Cancer - avg person
  - Non-cancer –10 fold more sensitive than avg
    - Still a bright line that's safe for everyone
- New thinking – everyone has a different threshold
  - Population level – no threshold – low doses may cause risk if there is additivity to backgrnd

Responses to ozone are increased in obese mice

Shore et al. J Appl Phys 95: 938-945 2003

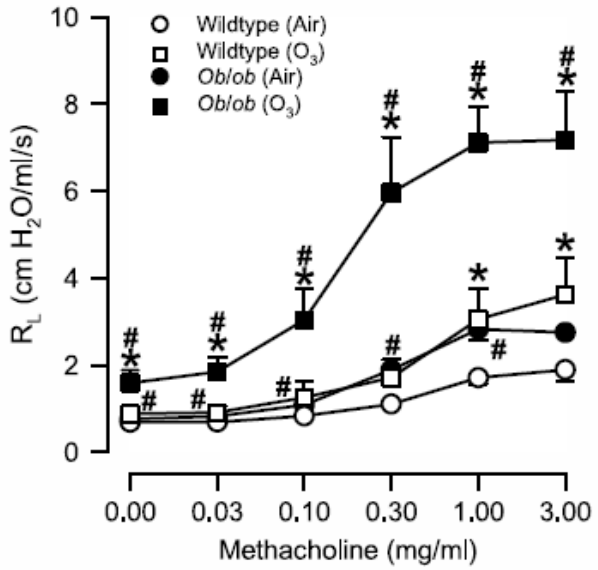
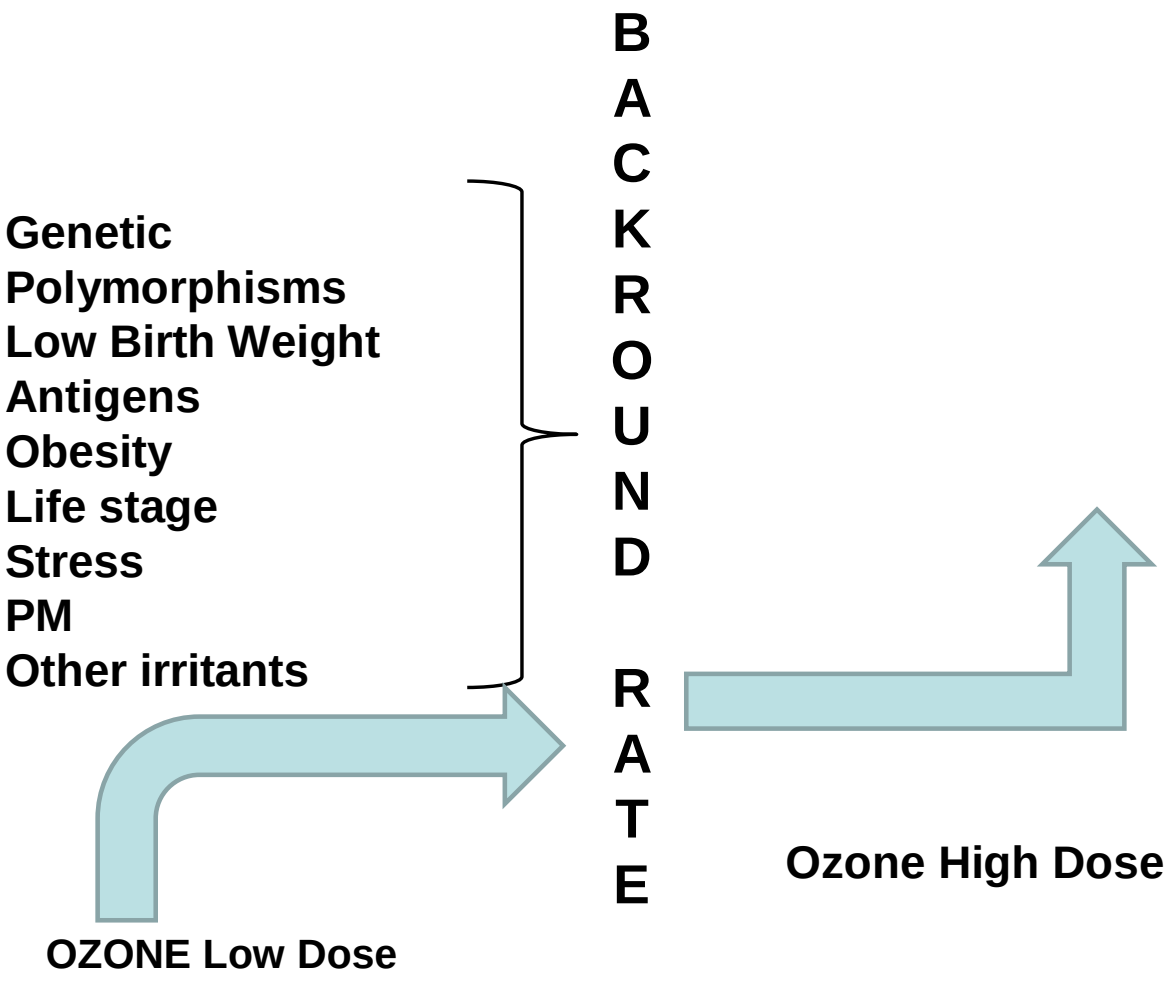
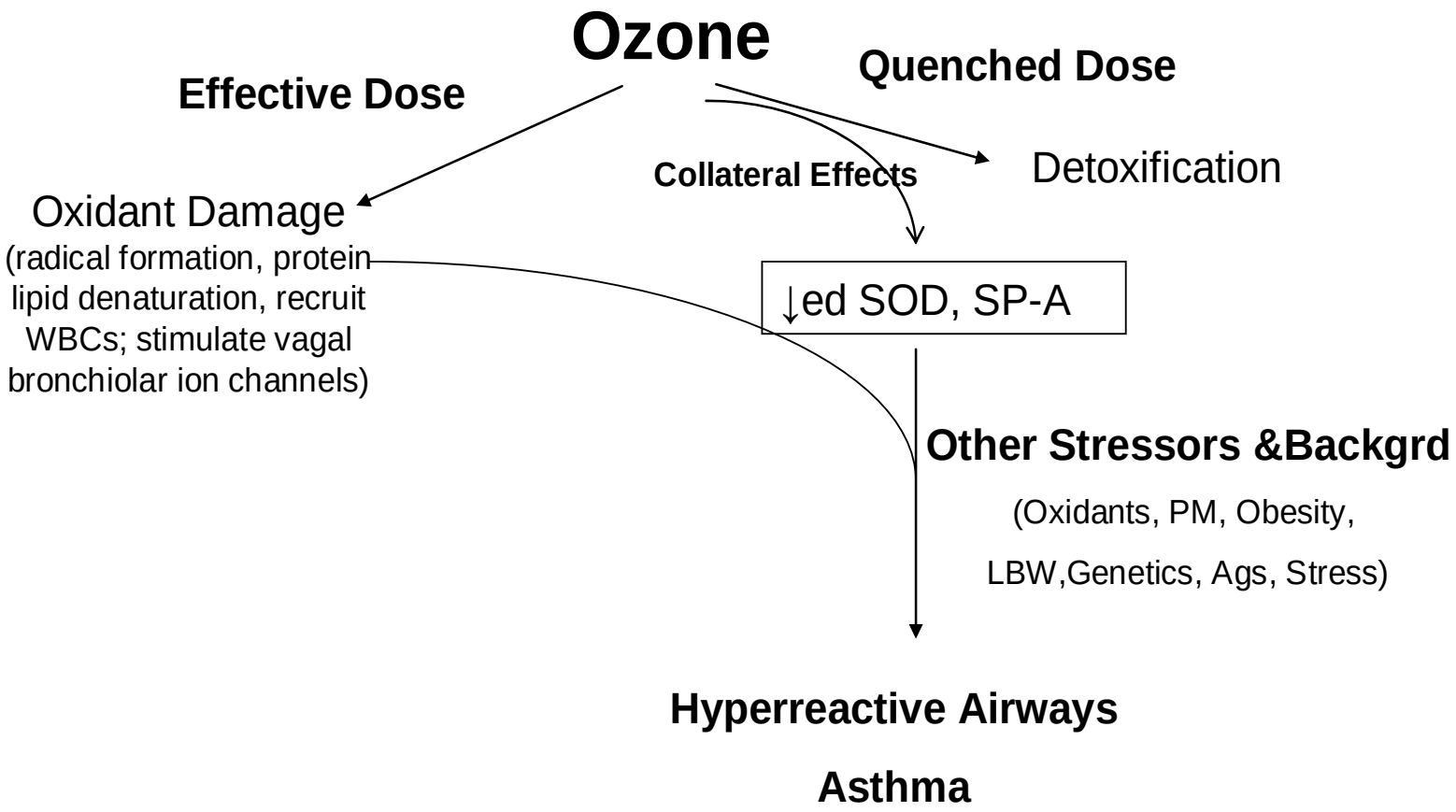
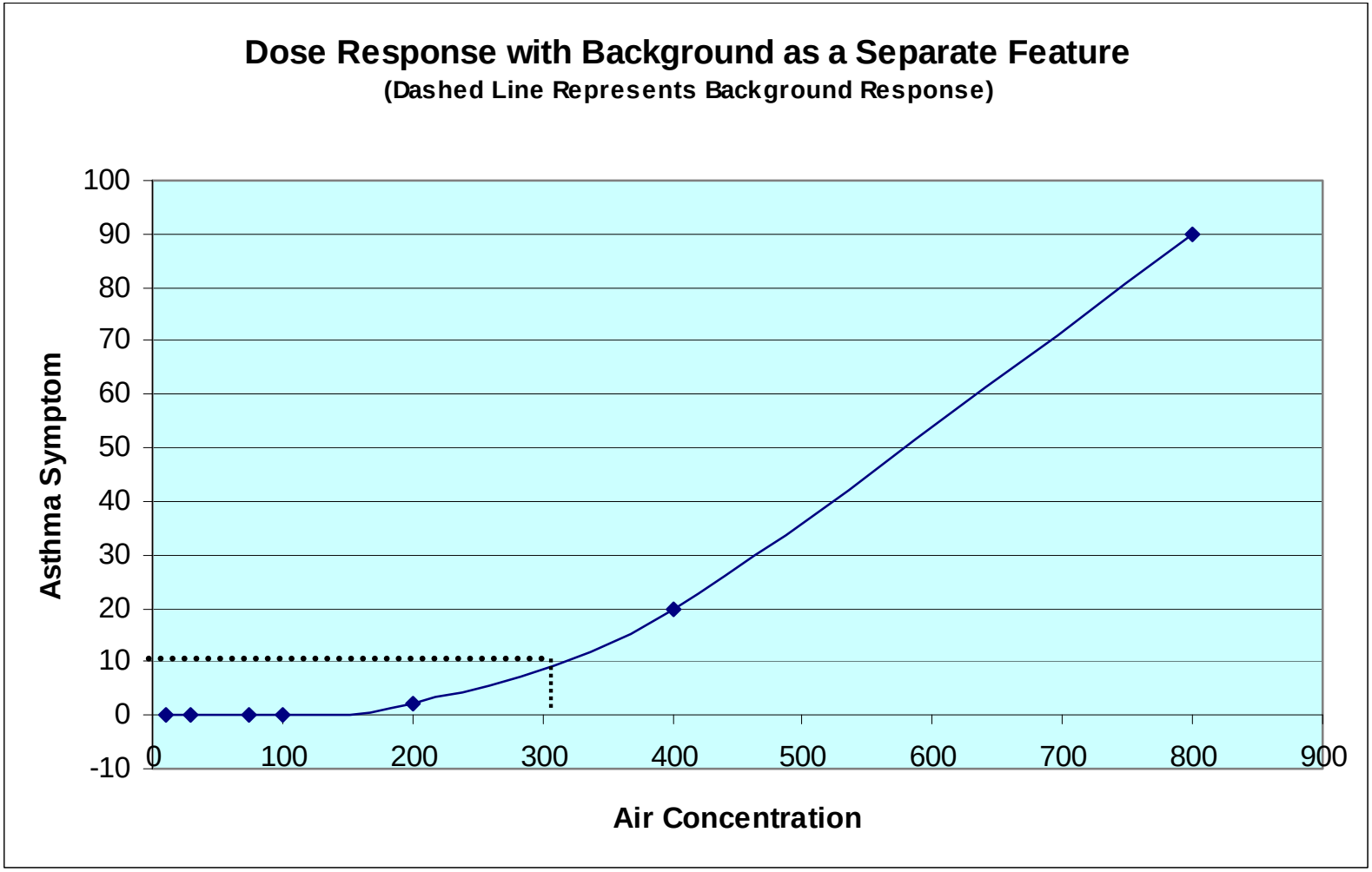
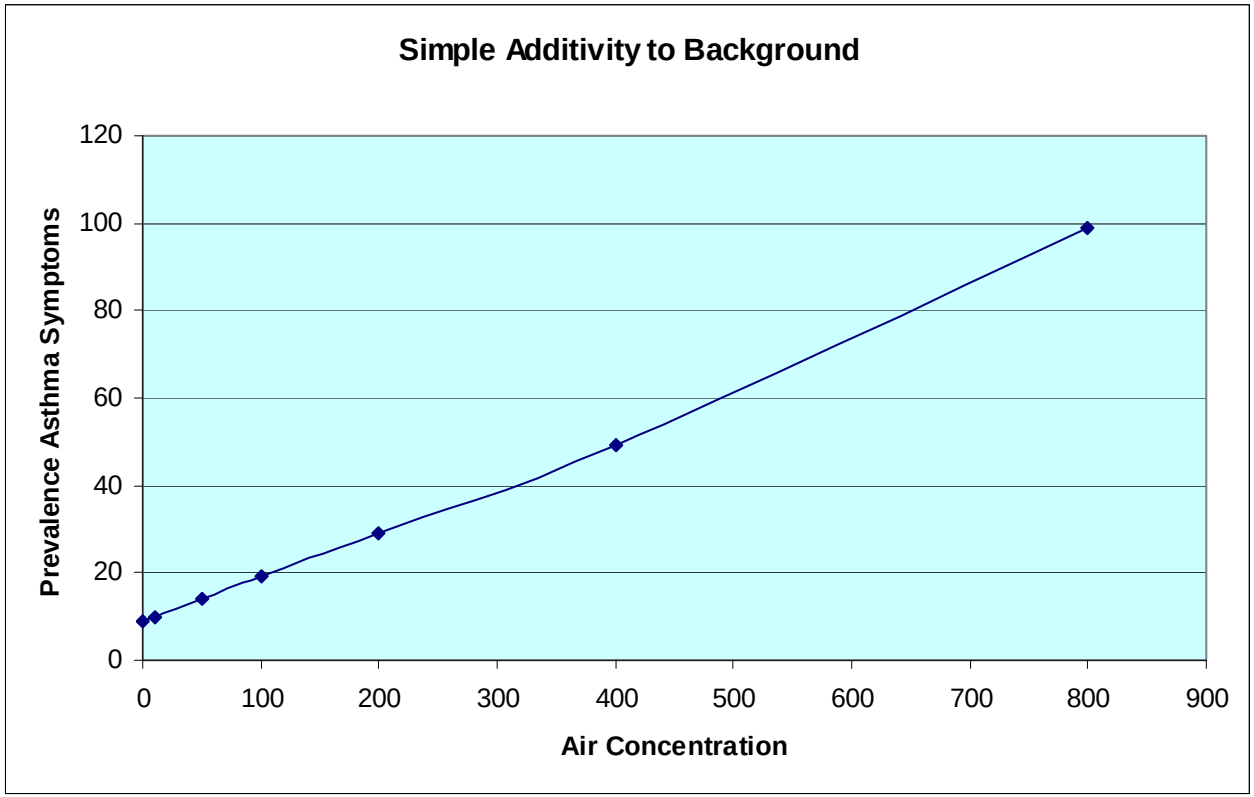


Fig. 1. Airway responsiveness to intravenous methacholine in wild-type and *ob/ob* mice exposed to air or ozone (O_3) [2 parts/million (ppm) for 3 h]. Measurements were made 24 h after exposure. Values are means ± SE of data from 6–7 mice in each group. RL, pulmonary resistance. $^{*}P < 0.05$, compared with air-exposed mice in the same group. $^{\#}P < 0.05$, compared with wild-type mice in the same exposure group.


Genetic
Polymorphisms
Low Birth Weight
Antigens
Obesity
Life stage
Stress
PM
Other irritants
BACKROUND
RATE
Ozone High Dose
OZONE Low Dose

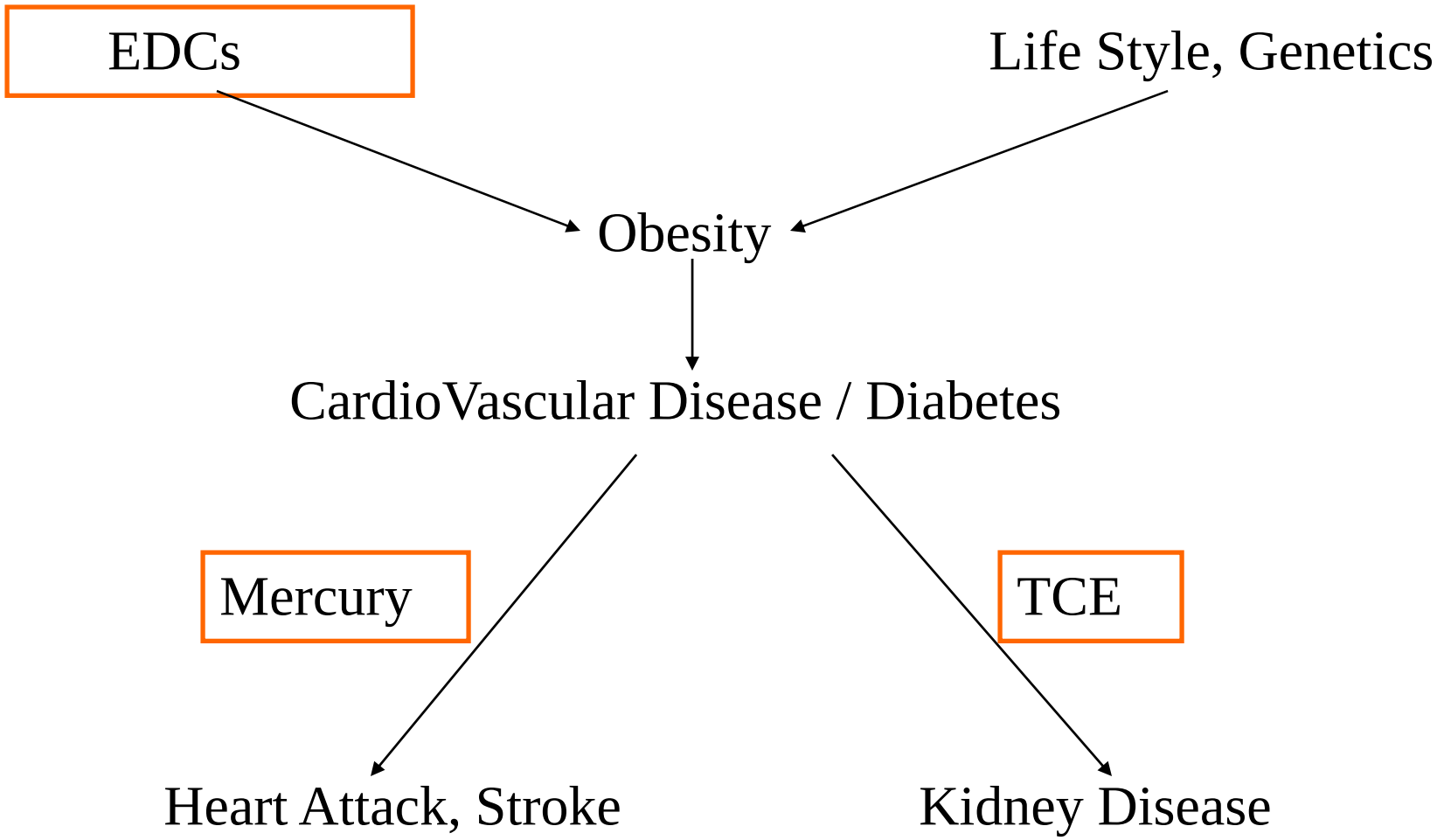

Ozone
Effective Dose
Quenched Dose
Detoxification
Collateral Effects
Oxidant Damage
(radical formation, protein lipid denaturation, recruit WBCs; stimulate vagal bronchiolar ion channels)
↓ed SOD, SP-A
Other Stressors &Backgrd
(Oxidants, PM, Obesity,
LBW,Genetics, Ags, Stress)
Hyperreactive Airways
Asthma


Dose Response with Background as a Separate Feature
(Dashed Line Represents Background Response)
Asthma Symptom
100
90
80
70
60
50
40
30
20
10
0
-10
0
100
200
300
400
500
600
700
800
900
Air Concentration


Simple Additivity to Background
Prevalence Asthma Symptoms
120
100
80
60
40
20
0
0
100
200
300
400
500
600
700
800
900
Air Concentration

Other Sources of Variability

- Childhood (pre- and post-natal)
  - Intake rate, metabolism, clearance, windows of vulnerability
- Nutrition, life style, stress level
- Genetic variation
  - Metabolism
  - DNA repair
  - Host defenses


EDCs
Life Style, Genetics
Obesity
CardioVascular Disease / Diabetes
Mercury
TCE
Heart Attack, Stroke
Kidney Disease

Research Challenges

- Understand how chemicals interact with aging, disease and susceptibility factors
- Understand how chemicals interact – more than just adding risk, but shifting threshold
- Incorporate this into RA to better protect vulnerable populations
  - Modify RfD to mean risk-specific dose
- Keep in mind that current methods may not protect everyone
- Interim default approaches that are reasonably protective & set the stage for more refined models

Colleagues

- Chapter 5 Committee
  - **Lauren Zeise, Jonathan Levy, John Bailar**
- Children's Issues
  - **Melanie Marty**
- USEPA
  - **Bob Sonawane, Kate Guyton**
  - **Brenda Foos, Michael Firestone**
- Clark University
  - **Dale Hattis**