# Toxicity of Air Toxics

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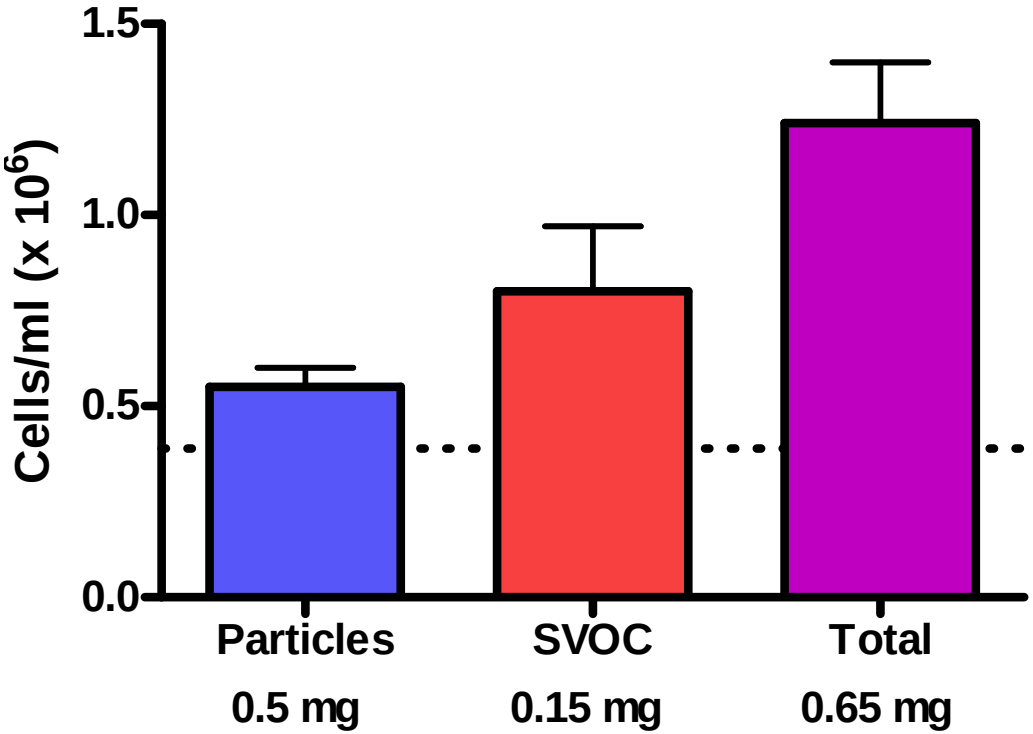
- **Historically**
  - **We have assessed the toxicity of single compounds**
    - **In the environment: 6 criteria pollutants**
    - **In the workplace: various occupational compounds**
- **Now**
  - **We are faced with assessing the toxicity of 188 air toxics (33 are the "dirty thirty").**
  - **Some listings, such as polycyclic organic matter, include hundreds of possible compounds.**

# Can Health Effects Be Caused by Air Toxics?

**Example: Semi-volatile organic compounds (SVOC) in traffic tunnel samples (Seagrave *et al., Toxicologist 60*: 192, 2001)**

1. **PM and vapor-phase SVOC collected from traffic tunnel and instilled into rat lungs**
2. **Measured inflammatory cells in airway fluid 24 hr later**




**SVOC caused most of the effect**

**(4x more toxic per unit of mass than PM)**

# We already have information on some compounds because of occupational concerns

- Benzene
- Butadiene
- Metals
- Some aldehydes
- Acrolein
- Hexane
- Phosgene
- Toluene
- Vinyl chloride
- Lead

# Traditional Approaches are Designed for Single Compounds

- **Hazard Identification**
  - **What toxicities can be caused by the agent?**
- **Dose/Response**
  - **How much of the agent is required to cause the toxicities?**
- **This information is used along with exposure assessments to complete risk characterization.**

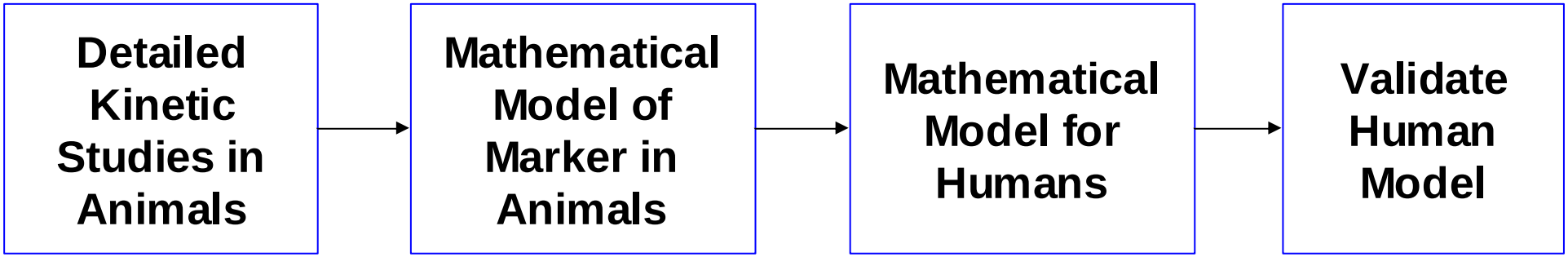
# Hazard Identification

- **Epidemiology**
  - **Human data always best if available.**
  - **Confounding factors make interpretation difficult.**
  - **Epi studies can only show associations; causality may be difficult to demonstrate.**
- **Animal studies**
  - **Well controlled.**
  - **Require extrapolation to human situation.**
  - **Require high dose to detect statistically valid response.**
- **In vitro studies**
  - **Valuable for mechanistic studies.**
  - **Are difficult to extrapolate to human situations.**

# Dose/Response

- Dose makes the poison
  - Mechanisms of toxicity vary with dose
- Dosimetry of inhaled pollutants must be assessed
  - Total inhaled
  - Total absorbed
  - Dose to target tissue
- Most often studied in animals

# Use of Animal Data to Predict Kinetics and Dosimetry of Inhaled Pollutants in Humans




- Percent Absorbed
- $T_{1/2}$ to Steady State
- $T_{1/2}$ for Clearance
- Effect of
  - Exposure concentration
  - Exposure rate
  - Repeated exposures
  - Route of exposures

- Animal Toxicokinetic Data
- Animal Physiological Data

- Human Physiological Data
- Human Metabolic Data *In Vitro*

- Limited Human Data

# Health Effects Observed

**For noncancer health effects, conduct studies to determine:**

- **No-observed-adverse-effect-level (NOAEL)**
- **Lowest-observed-adverse-effect level (LOAEL)**
- **Shape of exposure/response curve for use in benchmark dose (concentration) modeling**

# For Carcinogens

- **Use epidemiology data, if available (usually only available from occupational settings).**
- **Animal models can only detect ~10% response.**
  - **Must use high doses, where mechanism of action may be totally different from mechanisms at low exposures of interest. Price = 3 years and $3M.**
- **Use linear, no-threshold model for extrapolation to responses at lower concentrations.**
- **Mechanistic information is required to determine nonlinearity at low doses.**

# Advantages of Assessing Toxicity of Single Compounds

- **Large data base available.**
- **Standard tests are established.**
- **Appropriate when there are relatively few compounds of concern, such as criteria pollutants or major occupational compounds.**

# Disadvantages of Single Compound Approach

- Time
  - We have spent decades on the six criteria pollutants.
  - How long will it take to get the information we need for 188 air toxics?

- Reality
  - People inhale mixtures, not single compounds.

# CURRENT APPROACH

# REALITY

5466-1

# An Alternative Approach for Environmental Pollutants

- Sources emit mixtures of air pollutants
- Sources can be regulated to reduce emissions
- Test for toxicity of source-specific mixtures

- **Test the toxicity of source-specific mixtures in animal studies.**
- **Regulate based on mixtures rather than specific compounds.**
- **Using multi-variate analyses**
  - **Compare toxicity testing results among the various mixtures to determine which components contribute most to toxicity.**

# What are Major Sources of Air Pollutants in U.S.?

- Mobile sources
  - Diesel engine exhaust
  - Gasoline engine exhaust
- Coal combustion emissions
- Road dust
- Cooking fumes
- Tobacco smoke
- Wood smoke

# Mixture Studies Under Way at Lovelace Respiratory Research Institute

## Strategy

- **For all real-world mixtures:**
  - **Apply identical experimental protocols to test for toxicity.**
  - **Conduct detailed measurement of composition of exposure atmospheres.**
  - **Assess dose-response over plausible human response range.**
  - **Analyze aggregate database to identify associations between classes of compounds and individual contaminants vs. health responses.**

# CREATING THE DATABASE

| | Irritation & Inflammation | Allergies & Asthma | Respiratory Defenses | Respiratory & Cardiac Functions | Cancer |
|---|---|---|---|---|---|
| Diesel Exhaust | – | – | – | – | – |
| Wood Smoke | – | – | – | – | – |
| Gasoline exhaust | – | – | – | – | – |
| Coal emissions | – | – | – | – | – |
| Cooking Fumes | – | – | – | – | – |
| Road dust | – | – | – | – | – |
| Tobacco smoke | – | – | – | – | – |

- Study of each atmosphere creates a "layer" in the combined database
- Multiple animal models address a range of health concerns

  Exposures = 6 hr/day, 7 days/wk for up to 6 months

- 4 exposure levels plus controls allows evaluation of trends & thresholds

# Exposures are Characterized in Detail

## (Hundreds of individual analytes and variables)

**Particles**

- Mass concentration
- Size distribution
- Number counts
- Morphology
- Size-specific chemistry
- Extractable fraction
- Mutagenicity of extracts

**Gases**

- CO
- $CO_2$
- $NO_x$
- $SO_2$
- HC
- $NH_3$

**Particle Extract and SVOC**

- Ammonium
- Sulfate
- Nitrate
- Elements
- n-alkanes, cycloalkanes
- alkenes
- Branched alkanes, alkenes
- Furans, benzofurans
- Terpenes
- Volatile aromatics
- Phenols (+methoxy)
- Carbonyls
- organic acids
- alkaloids
- nitrosamines
- PAHs (+ oxy, nitro)
- Hopanes
- Steranes
- Aliphatic alcohols
- Carbohydrates

# Many Health Outcomes are Measured

**General toxicity in F344/CrlBR rats and A/J mice (after 7 days and 6 months of exposure):**

- Body & organ weights of F344 rats and A/J mice
- Hematology, clinical chemistry, coagulation of F344 rats
- Bronchoalveolar lavage of F344 rats
- Histopathology of all major organs of F344 rats

**Pulmonary immune responses in BALB/C mice:**

- Development of allergic responses (3 wk of exposure)
- Exacerbation of allergic responses (3 d of exposure)

**Resistance to respiratory infection in C57/BL6 mice (after 7 days of exposure):**

- Instilled *Pseudomonas aeruginosa* (test at 18 hrs)
- Instilled Respiratory Syncytial Virus (test at 4 days)

**Cardiac effects in SHR/Crl rats (before, during, and 4 days after 7 day exposure):**

- Heart rate and variability
- ECG Waveform abnormalities
- Heart and vessel histopathology

**Carcinogenic potential in F344 rats and A/J mice:**

- DNA Methylation in F344 rats and A/J mice (after 7 d or 6 mo of exposure)
- Oxidative DNA damage in F344 rats and A/J mice (after 7 d or 6 mo of exposure)
- Micronuclei in A/J mice (after 6 months of exposure)
- Lung tumors in A/J mice (6 mo after end of 6 mo exposure)

**Lung gene microarray in F344 rats** **[www.nercenter.org]**

# Suggested New Approach

- **Screen toxicity of source-specific mixtures.**
- **Overlapping composition should allow determination of most toxic components.**
- **Conduct in-depth toxicity tests only on most toxic compounds.**