Risk Assessment Syllabus Series

• A service to SOT Members by the Risk Assessment Specialty Section (RASS)

• An opportunity to enhance understanding of essential concepts and contemporary topics in the risk assessment sciences
  o Seeks to expand upon aspects not typically covered in educational programs (i.e., toxicology, exposure sciences or epidemiology)
  o Inform consideration of career options in Risk Assessment

• Designed for both current trainees and post-graduate professionals
  o Fundamental concepts of risk assessment sciences
  o Knowledge on applying these concepts to health risk evaluations
Prior Events

• June 9, 2021: Introduction to Human Health Risk Assessment
  Speakers: Laura Carlson, PhD and George Woodall, PhD

• June 7, 2022: Animal Toxicology in Risk Assessment—Study Design and Evaluation Considerations
  Speaker: Margaret Pratt, PhD

• November 15, 2022: Evaluations of Epidemiology and Human Studies for Risk Assessment
  Speakers: Rachel Shaffer, PhD, and Rebecca Nachman, PhD
Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
(Past President of SOT 2004 – 2005)
Scientist Emeritus (2019-present) and Former Director (2009-2019), NIEHS and NTP
Scholar in Residence, Nicholas School of the Environment, Duke University
Adjunct Professor:
• Integrated Toxicology Program, Duke University (1995-present)
• Toxicology Curriculum and Department of Environmental Science and Engineering, University of North Carolina (1981-present)
• Department of Environmental Health Sciences, Yale School of Public Health (2021-present)
National Academy of Medicine (2010-present)
AAAS Fellow (2022-present)
Collegium Ramazzini (2010-present)
NC Governor’s Award (2016)
Wife (1967-present), mother (1972-present), grandmother (2001-present)
Cantor at Judea Reform, 1994-2014
Education
• PhD in Microbiology, University of Illinois, Urbana Champaign, 1972
• Damon Runyon Postdoctoral Fellowship, University of Massachusetts, 1972-74
Daniel A. Vallero, Ph.D.

Senior Research Physical Scientist in the Center for Computational Toxicology & Exposure, Office of Research & Development, RTP, NC

- Dan Vallero has devoted decades to conducting research, teaching, and mentoring future scientists and engineers.
- He is currently developing tools and models to predict potential exposures to chemicals in consumer products.
- In addition to his 46 years with EPA, he has served on the science staff of the U.S. House of Representatives and is a full adjunct professor of civil and environmental engineering at Duke University’s Pratt School of Engineering.
- He has authored about 70 peer-reviewed journal articles, more than 100 book chapters, and 20 books on various environmental topics.
  - His latest two books address environmental physics and will be published later this year.
- Dr. Vallero received a Ph.D. from Duke University, master’s degrees from the University of Kansas and Southern Illinois University, and a bachelors degree from SIU.
Nicolle Tulve, Ph.D.

Research Physical Scientist in the Center for Public Health and Environmental Assessment (CPHEA), Office of Research and Development (ORD), U.S. EPA.

- Expertise: Children’s environmental health
- Areas of focus include aggregate and cumulative exposures, the interrelationships between chemical and non-chemical stressors, time activity patterns, exposure factors, cumulative impact assessments
- Chair: RAF Exposure Oversight Committee, Guidelines for Human Exposure Assessment Technical Panel; Co-Chair: ORD’s Cumulative Impacts Workgroup, Soil ingestion Exposure Factors Workgroup; Currently serving on the Multi-Year Plan of Work Exposure Science Committee

Education:
- B.S. Biology (1992; SUNY Oswego)
- M.S. Environmental Health and Toxicology (1994; Albany State)
- Ph.D. Environmental Engineering (2000; Clarkson University)

Guest lectures for colleagues at various universities and mentors both postdoctoral researchers and students

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Paul Price, PhD
Risk Sciences International

- Dr. Price is starting his 45th year in the field of exposure assessment. He is an associate expert with RSI and an adjunct professor at the University of Iowa. He has been employed by USEPA, Dow Chemical, American Petroleum Institute, and the nonprofit LifeLine group.

- He is primary author of 40 peer reviewed publications and coauthor of an additional 60 papers and book chapters. His work has received multiple best paper awards from RASS and the Biological Modeling Specialty Section.

- He has worked on probabilistic exposure models such as FACET, CARES, LifeLine, and CHEM.

- He is currently the past president of the Mixtures Specialty Section.
Panelist

Ruthann Rudel, M.S.
Director of Research, Silent Spring Institute

- Leads Silent Spring Institute’s exposure and toxicology research
- Applies key characteristics approaches to integrate mechanistic and in vivo evidence to highlight chemicals that likely increase breast cancer risk
- Uses biomonitoring, metabolomics, and environmental monitoring approaches to understand personal exposures to endocrine disruptors and breast carcinogens
- Sifts through risk-related research to prioritize chemicals for exposure reduction and further study
- Has coauthored > 87 original peer-reviewed research articles with more than 13,000 citations
- B.A. Chemistry, Neuroscience (Oberlin); M.S. Environmental Science (Tufts Engineering)
- Silent Spring Institute conducts independent environmental health research to identify opportunities to prevent breast cancer and other adverse outcomes that affect women

rudel@silentspring.org
Sharada Balakrishnan, Ph.D., D.A.B.T.
Staff Toxicologist, Department of Toxic Substances Control (DTSC) - California EPA

• Current work – Risk assessment - Site mitigation and restoration program – Military sites
• Previous positions
  o Associate Toxicologist, Office of Environmental Health Hazard Assessment (OEHHA), Cal EPA
  o Consultant for 10+ years for Product Safety, Personal Care Products
  o Scientist, Central Product Safety group, Procter and Gamble
• Education:
  o B.Sc. Zoology (Stella Maris College, Chennai)
  o M.Sc. Environmental Toxicology (University of Madras, Chennai)
  o Ph.D. Environmental Toxicology (University of California, Riverside)

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General Concepts in Exposure Assessment
(EXA 401 & EXA 402 Combined)

Disclaimer:
The views expressed are those of the speakers and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.
Learning Objectives

By the end of this module, you will understand:

• How exposure assessment relates to human health risk assessment
• Relationship between exposure and dose
• Different routes of exposure and how to calculate exposure for each
• Important elements of exposure assessment
• Important considerations when developing an exposure assessment
• Different methods for quantifying exposure and dose
EPA’s Guidelines for Human Exposure Assessment


  - Chapter 1: Introduction
  - Chapter 2: Principles of Exposure Science and Exposure Assessment
  - Chapter 3: Planning and Scoping and Problem Formulation for Exposure Assessments
  - Chapter 4: Consideration of Lifestages, Vulnerable Groups, and Populations of Concern in Exposure Assessments
  - Chapter 5: Data for Exposure Assessments
  - Chapter 6: Computational Modeling for Exposure Assessments
  - Chapter 7: Planning and Implementing an Observational Human Exposure Measurement Study
  - Chapter 8: Uncertainty and Variability for Exposure Assessments
  - Chapter 9: Developing a Communication Plan and Presenting Results for Exposure Assessments
INTRODUCTION AND BACKGROUND CONCEPTS
The Overall Risk Assessment Process

Communications: Internal and External Stakeholder Input

Risk Assessment

- Hazard Identification
- Dose Response Assessment
- Exposure Assessment
- Risk Characterization

Risk Management

- Decision Making
  - Policy
  - Risk Reduction Actions

Feasibility Considerations

Planning and Scoping and Problem Formulation

Economic, Regulatory, Political, Social, and Other Factors

Adapted from NRC (2009)
Feasibility Considerations

Planning and Scoping
- Exposure Assessment Goals and Scope
- Overarching Considerations
- Stakeholder Involvement
- EPA's Tribal Program and Networks
- Peer Review

Problem Formulation
- Individuals, Lifestages, Groups, Populations
- Conceptual Model

Exposure Assessment Analysis Plan
- Data Sources, Gaps, Limitations and Quality Objectives
- Exposure Scenarios

Feasibility
- Science
- Cost
- Time
- Assessment constraints
- Sampling capabilities
• **Pollutant source**: Where are the pollutants coming from, at what rate, and where are they going?

• **Exposure pathways**: Connection between pollutant source and exposure including exposure media and route of exposure.

• **Contaminants of concern**: Specific contaminants of concern for human health associated with the exposure pathway

• **Receptor**: The individual or population that is exposed
Source-to-Effect Continuum

Note: PBPK = physiologically based pharmacokinetic
Adapted from NRC (1983); NRC (1997)
What is Exposure Science?

• Exposure science characterizes and predicts the intersection of an agent and receptor in both space and time. It provides information to develop exposure assessments and the most effective strategies to reduce human health risk through mitigating exposure.

• The processes important for exposure science begin with a contaminant entering the environment and end with dose characterization.
Exposure is contact between an agent and the external boundary of a receptor (exposed surface) for a specific duration

- Exposure can be described in terms of
  - Magnitude
  - Route (e.g., ingestion, inhalation, dermal)
  - Frequency
  - Duration
  - Timing (e.g., lifestage considerations)

(Adapted from WHO 2004; Zartarian et al. 2005).
Demographics: Who Are the Receptors?

Human Receptor: Any biological entity (e.g., a human, human population, lifestage within a human population) that receives an exposure.

EPA’s Guidelines for Human Exposure Assessment, 2019

Ecological or Wildlife Receptor: The ecological entity exposed to the stressor. May refer to tissues, organisms, populations, communities, and ecosystems.

EPA’s Guidelines for Ecological Risk Assessment, 1998

Susceptibility: An increased likelihood of an adverse effect, often discussed in terms of relationship to a factor that can be used to describe a human population (e.g., lifestage, demographic feature, or genetic characteristic)

EPA’s Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, 2005

Examples:

- Highly exposed populations
  - Individuals who eat fish or produce that is contaminated by the stressor
  - People who are occupationally exposed
  - Certain product uses

- Potentially susceptible populations
  - Children and the elderly
  - Women of child-bearing age
  - People with compromised immune systems
**Stressor:** Any chemical, physical, social or biological entity that induces a change (either positive, negative, or neutral) in health or well-being (either now or into the future).

EPA's Guidelines for Human Exposure Assessment, 2019; Tulve et al., 2016

- Radiological Stressors
- Socioeconomic Stressors
- Other Non-Chemical Stressors
- Physical Stressors
- Biological Stressors
- Single Stressor (chemical or non-chemical)
- Multiple Stressors (combinations of stressors – both chemical and non-chemical)
**Dose** is the amount of an agent that enters a receptor after crossing an external exposure surface.

- **Potential dose** is the amount of agent ingested, inhaled, or applied to skin, not all of which will be absorbed.
- **Applied dose** is the amount of agent at an absorption barrier (e.g., skin, respiratory tract, gut).
- **Absorbed/Internal dose** is the amount of agent that enters a receptor by crossing an absorption barrier.
- **Biologically effective dose** is the amount of agent that reaches the target internal organ, tissue, or toxicity pathway.
The Relationship Between Exposure and Dose

• Dose profiles over time depend on:
  
  o The factors affecting exposure mentioned previously
    ▪ Magnitude
    ▪ Route (e.g., oral, dermal, nasal)
    ▪ Frequency
    ▪ Duration
    ▪ Timing (e.g., lifestage considerations)

  o Kinetic Parameters (ADME)
    ▪ Absorption into the body
    ▪ Distribution throughout the body
    ▪ Metabolism by various tissues within the body
    ▪ Elimination from the body

• Thus, the duration of the dose is always equal to or longer than the duration of exposure.
Aggregate Exposure:
• Exposure to a **single chemical** from multiple sources and exposure pathways

Cumulative Exposure:
• Exposure to **multiple chemicals** from multiple exposure pathways
EXPOSURE ROUTES:
INGESTION, INHALATION, DERMAL
• Exposure occurs via **ingestion**, **inhalation**, and **dermal** routes.

• Each route can lead to different intake and uptake rates, different doses, and different consequences.

• A chemical can cross the boundary of the body in two ways:
  - **Intake**: where the chemical crosses an exposure surface without passing an absorption barrier (e.g., food into the mouth)
  - **Uptake**: where the chemical crosses a biological barrier and results in an internal dose (e.g., absorption and transport through the stomach lining to the blood)
Ingestion Route

Exposure → Potential dose → Applied dose → Internal dose → Organ → Effect

Chemical

Mouth → Intake

G.I. Tract → Uptake

**Ingestion Exposure Equation:**

\[ E_{ing} = C_{ing} \times IR \]

\( E_{ing} \) = ingestion exposure (mass per time)

\( C_{ing} \) = concentration of the chemical in food or other exposure media (mass of chemical per mass or volume of medium)

\( IR \) = ingestion rate (mass of medium ingested during the exposure per time)
Inhalation Exposure Equation:

\[ E_{inh} = C_a \times IR \]

- \( E_{inh} \) = inhalation exposure (mass per time)
- \( C_a \) = airborne concentration of the chemical contacted by the exposed individual (mass of chemical per volume of air in breathing zone)
- \( IR \) = inhalation rate (volume of air breathed per unit time)
Dermal Exposure Equation:

\[ E_{derm} = MR_{medium} \times C \times SA \]

- \( E_{derm} \) = dermal exposure (mass per time)
- \( MR_{medium} \) = mass of medium contacting the skin per time (mass of medium per skin surface area per time)
- \( C \) = average concentration in medium (mass of chemical per mass of medium)
- \( SA \) = skin surface area available for contact (area)
EXPOSURE ASSESSMENT: EXAMPLES OF EXPOSURE
Exposure Example 1: Ingestion

• Eating produce without washing it first, leading to ingestion of pesticide residues
Exposure Example 1: Ingestion

Exposure

Potential dose

Applied dose

Internal dose

Biologically effective dose

Chemical

Metabolism

Mouth

Intake

G.I. Tract

Uptake

Organ

Effect

Amount of pesticide residue on produce

Amount of pesticide residue that crosses the stomach barrier into the bloodstream

Amount of pesticide residue ingested

Potential dose

Applied dose

Internal dose

Assessment of dose and effect
• Using a gas stove to cook in a poorly-ventilated area, resulting in inhalation of NO$_2$
Exposure Example 2: Inhalation

- **Amount of NO₂ in air**
- **Amount of NO₂ that crosses the lung barrier into the bloodstream**

**Chemical**
- **Exposure**
- **Metabolism**
- **Applied dose**
- **Internal dose**
- **Biologically effective dose**
- **Organ**
- **Effect**

**Intake**
- **Mouth/nose**
- **Lung**

**Uptake**
- **Amount of NO₂ inhaled**
Exposure Example 3: Dermal Exposure

- Children playing at the playground where the soil is contaminated with lead, resulting in dermal exposure
Exposure Example 3: Dermal Exposure

Exposure

Potential dose

Applied dose

Amount of lead that contacts skin

Internal dose

Biologically effective dose

Organ

Effect

Chemical

Skin

Metabolism

Amount of lead that crosses the skin barrier into the bloodstream

Amount of lead in the soil

Amount of lead that contacts skin

Uptake
EXPOSURE CONSIDERATIONS
Exposure frequency and duration are important to consider when conducting exposure assessments

- **Acute**: Exposure by the oral, dermal, or inhalation route for 24 hours or less

- **Short-term**: Repeated exposure by the oral, dermal, or inhalation route for more than 24 hours, up to 30 days

- **Longer-term (Sub-chronic)**: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10% of the life span in humans

- **Chronic**: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans

The Relationship Between Everyday Exposure and Exposure Estimates
• Exposure assessments are usually conducted for populations or groups

• **Exposure factors** account for variability in populations, and allow for assessment of the risks to those populations
  - Ingestion rates
  - Inhalation rates
  - Skin exposure factors
  - Population behaviors
  - Other factors relevant to scenario
  - Body weight
  - Life expectancy
Use of Statistical Descriptors to Describe Measurements

- **Statistical descriptors** are estimates of specific points on the distribution of measurements
  - Based on selected parameter values
  - May be for individual or population estimates
  - Help assessors communicate with risk managers and others
  - May be developed to support regulatory decisions

![Diagram showing typical percentiles of exposure]

- 50%
- 90%
- 95%
- 98%
- 99%
- 99.9%

Central tendency estimate

High-end estimates

Bounding estimate

Typical percentiles of exposure
**Variability** refers to heterogeneity or diversity

- Known
- Characterize by collecting more or better data
- Inherent property of a population & cannot be reduced or eliminated, only described
- Examples of sources of variability in exposure:
  - Location
  - Occupation
  - Activities within a location
  - Socioeconomic status
  - Consumer preferences
  - Dietary habits

**Uncertainty** refers to a lack of knowledge

- Unknown
- Reduce by collecting more or better data
- Compensate for uncertainty with approximations and assumptions
- Examples of uncertainty:
  - Incomplete data
  - Incomplete understanding of processes
  - Unknown information about the geographic extent of the population exposed
  - Other exposure information for the population
THREE APPROACHES FOR ESTIMATING EXPOSURE
Approaches for Estimating Exposure

Exposure occurs

Measurement
- Direct (Point-of-Contact)
- Indirect (Scenario Evaluation)
- Biomonitoring

Problem Formulation

Analysis
- Point-of-Contact
- Scenario Evaluation
- Exposure Reconstruction

Risk Characterization
POINT-OF-CONTACT (DIRECT MEASUREMENTS) FOR EXPOSURE ASSESSMENT
Point-of-Contact (Direct Measurement) Methods

Point-of-contact methods measure the contact of the person with the chemical concentration in the exposure medium over an identified period.

**Examples:**
- Dosimeters
- Personal inhalation monitoring (breathing zone)
- Personal dermal monitoring
- Food and beverage consumption

EPA’s Guidelines for Human Exposure Assessment, 2019
Point-of-Contact Methods: Strengths and Weaknesses

**Strengths:**
- Measures exposures directly
- Representative of individual exposures
- Most accurate method for quantifying exposure

**Weaknesses:**
- Expensive
- Not source-specific
- Not available for all chemicals
- Relies on accuracy of the device, the person operating it and the strength of analytical methods
Direct Measurements of Inhalation Exposure

- Monitors are typically compact and located close to the breathing zone of the individual
  - Passive monitoring:
    - Uses sorption method
    - More appropriate for long-term exposure
  - Active monitoring:
    - Small air pump draws air through a filter, packed tube or similar device.
    - Requires power (either battery or electricity)
Direct Measurements of Dermal Exposure

• Wide range of methods and devices for measuring dermal exposure
  ▪ Patches – used for pesticides, metals, dusts
  ▪ Whole-body dosimeters – radiation badges, coveralls, full-length cotton underwear
  ▪ Removal – rinsing, wiping, and tape strips to collect contaminants from skin
  ▪ Optical methods – fluorescent tracers
Direct Measurements of Ingestion

• Duplicate diet collection
  ▪ Individuals collect duplicate samples of all foods consumed in a given period
  ▪ Samples are analyzed to measure concentrations of chemicals of interest
  ▪ Provide information on:
    • Concentration of chemical in food
    • Intake rate of chemicals of interest, per bodyweight of participant
SCENARIO EVALUATION (INDIRECT) FOR EXPOSURE ASSESSMENT
**Scenario Evaluation (Indirect) for Exposure Assessment**

- **Scenario evaluation** estimates exposure by developing an exposure scenario to combine information on chemical concentration, time-of-contact information, and data on exposed persons.

- **Exposure scenario**: A set of facts, assumptions, and inferences about how exposure takes place that aids the exposure assessor in evaluating, estimating, or quantifying exposure.
  
  - Characterized by:
    - Setting
    - Chemical characteristics and sources
    - Exposure pathways and routes
    - Environmental and exposure media
    - Intake and uptake rates
    - Characteristics of exposed population

- Will be discussed in detail in EXA 403.
Key Questions in Model Selection

What do you need to consider when selecting your model?

• Objectives of assessment
• Appropriateness for your scenario
• Data needs
• Previous uses and outcome predictions
• Logistics of using the model (appropriate expertise)
• Peer review
• Regulatory considerations that may influence choice of model
# EXAMPLES: Types of Models Used

<table>
<thead>
<tr>
<th>Models</th>
<th>Inputs</th>
<th>Output</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Fate and Transport | • Emission rates  
• Fate and transport properties | • Pollutant concentrations (mg/m³, mg/L, or mg/kg) in environmental media | • AERMOD  
• EXAMS  
• CMAQ |
| Exposure        | • Concentrations in environments and microenvironments  
• Exposure factors  
• Time activity patterns | • Predicted exposures or doses (mg/m³ or mg/kg-day) | • APEX  
• DEEM  
• SHEDS |
| Linked          | • Population characteristics  
• Dietary exposure  
• Fate and Transport  
• Home Chemical Usage | • Population distribution of exposure  
• Model to measurement comparison | • SHEDS + IEUBK |
Scenario Evaluation: Strengths and Weaknesses

Strengths:
• Can be economical, depending on the scale of the study
• Well-suited to evaluating proposed actions
• Can be done with limited data

Weaknesses:
• Simplification of the exposure scenario leads to less accuracy
• Limited data needed for approach means more uncertainty
EXPOSURE RECONSTRUCTION FOR EXPOSURE ASSESSMENT
Exposure reconstruction uses pharmacokinetic (PK) models to estimate exposure from biomonitoring data (e.g., blood, urine).

**NHANES** data include national biomonitoring data collected by CDC:
- Stratified by age, race, and sex for numerous chemicals.
Biomarkers for Exposure Reconstruction: Strengths and Weaknesses

Strengths:
• Provide confirmation of exposure to an agent
• Important for linking external exposure to internal dose and health outcomes
• One way to characterize total internal dose of agent from multiple sources (aggregate exposure)

Weaknesses:
• Not linked to pathway or source
• Requires pharmacokinetic (PK) model and parameters
• Sampling and evaluation may be expensive
Exposure Reconstruction Example: PFOS

Table 3. Summary of studies measuring general population blood concentrations of five key PFCs measured in the United States (all units = ng/ml; M = male; F = female).

<table>
<thead>
<tr>
<th>Study description</th>
<th>PFOS</th>
<th>PFOA</th>
<th>PFOSA</th>
<th>PFNA</th>
<th>PFHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calafat et al. (2007); n = 2094, NHANES 2003/2004; serum, GM (% detected)</td>
<td>M: 23.6</td>
<td>M: 4.5</td>
<td>0.2 (22%)</td>
<td>M: 1.1</td>
<td>M: 2.2</td>
</tr>
<tr>
<td></td>
<td>F: 18.5</td>
<td>F: 3.5</td>
<td></td>
<td>F: 0.9</td>
<td>F: 1.7</td>
</tr>
<tr>
<td>Calafat et al. (2007); n = 1562, NHANES 1999/2000; serum, median</td>
<td>M: 33.4</td>
<td>M: 5.7</td>
<td>M: 0.4</td>
<td>M: 0.6</td>
<td>M: 2.7</td>
</tr>
<tr>
<td></td>
<td>F: 28.0</td>
<td>F: 4.8</td>
<td>F: 0.2</td>
<td>F: 0.5</td>
<td>F: 1.7</td>
</tr>
</tbody>
</table>

Exposure assessment, relationship between exposure and dose, routes and calculations

Quantify exposures to stressors and potential impacts on receptor populations

Depends on data, resources, exposure of concern, stressors, and receptor populations

Quantification approaches all have strengths and weaknesses, one or multiple might be best, depending on the scenario

- Point-of-contact
- Scenario evaluation
- Exposure reconstruction
Other Key EPA Resources

- Exposure Factors Handbook
- Example Exposure Scenarios
- Risk Assessment Guidance for Superfund (RAGS)
- Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants
- Dermal Exposure Assessment: Principles and Applications
# Exposure Quantification Approaches at a Glance

<table>
<thead>
<tr>
<th>Approach</th>
<th>Key Points</th>
<th>Examples</th>
</tr>
</thead>
</table>
| **Point-of-Contact**      | • Quantifies exposure as it occurs, at the interface between the person and the environment.  
• Representative of individual exposure.  
• Most accurate method of quantifying exposure.  
• Can be expensive; not source-specific; relies on accuracy of the device used for sampling. | • Whole-body radiation dosimeters  
• Patch or tape stripping measurements  
• Duplicate diet collection                                                        |
| **Scenario Evaluation**   | • Combines data on chemical concentration, time-of-contact, and population characteristics.  
• Elements that determine exposure: setting, chemical characteristics, sources, exposure pathways and routes, intake and uptake.  
• Can be economical; well-suited to evaluating proposed actions; can be done with limited data. | • Fate and transport models: AERMOD, EXAMS, CMAQ  
• Exposure models: APEX, DEEM, SHEDS  
• Linked models: SHEDS + IEUBK                                                 |
| **Exposure Reconstruction** | • Estimate exposure using biomarkers.  
• Can provide unambiguous proof of exposure, may give most accurate estimate of external dose.  
• Does not provide exposure pathway, amount, or source. Data not always available, may be expensive. | • Biomarkers of exposure: NHANES                                                                 |

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**General Concepts in Exposure Assessment (EXA 401 and EXA 402 Combined)**  

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