

EOH 2504- Exposure Assessment Lecture 3, **Uses of Human Exposure Data; Relationship of Exposure Assessment to the Risk Assessment Paradigm; and Exposure and Dose Defined (1)**

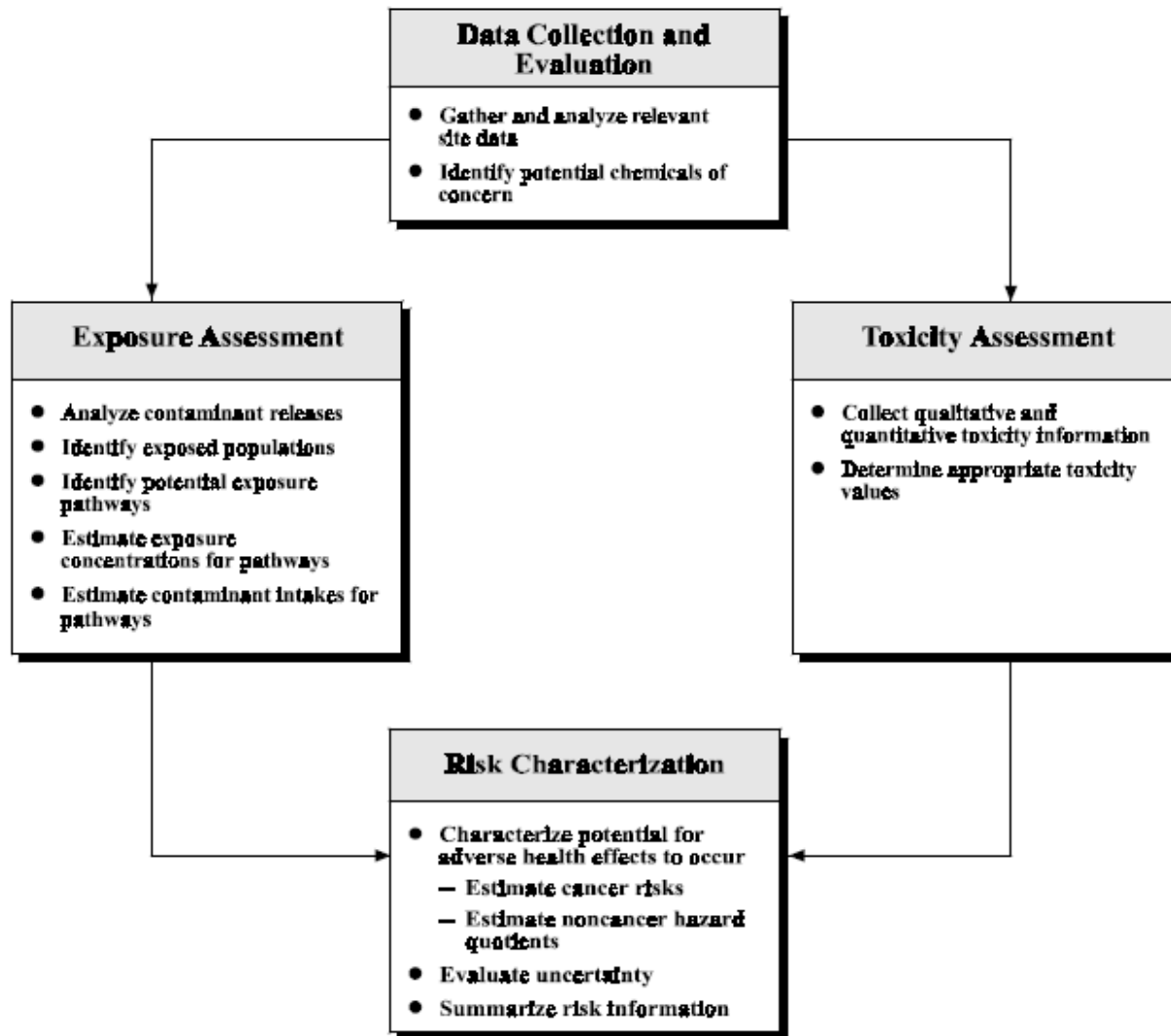
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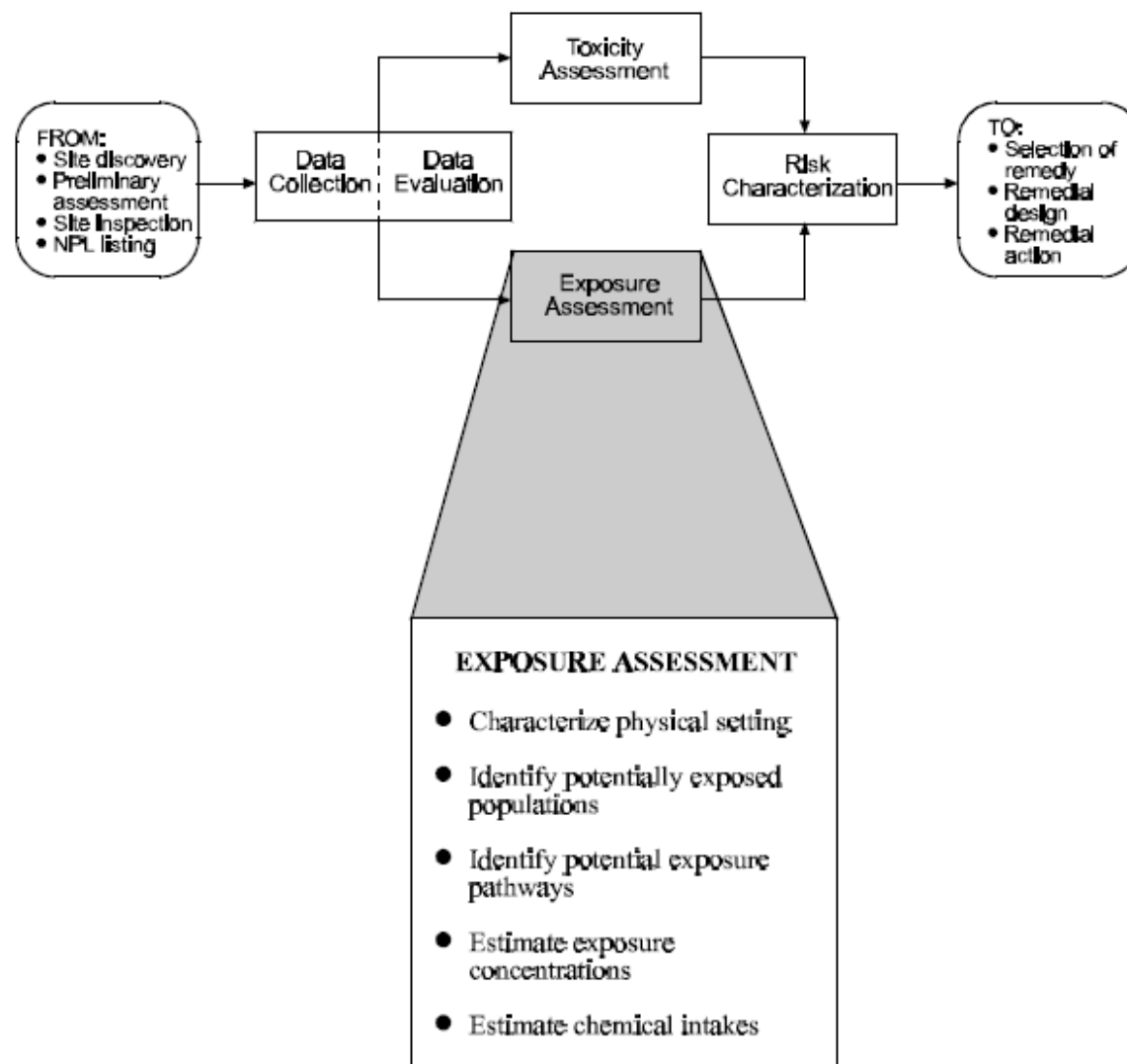
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Where Does Exposure Assessment Fit Into the Risk Assessment Paradigm?

- Step 1, Hazard Identification (Toxicology and Epidemiology)
- Step 2, Dose-Response Assessment (Generally Toxicology and Environmental Epidemiology)
- Step 3, Exposure Assessment (Exposure Assessment Scientists - Assessors)
- Step 4, Risk Characterization (Risk Assessors)
- Step 5, Risk Communication

EXHIBIT 1-2
PART A: BASELINE RISK ASSESSMENT







Occupational/Environmental Exposure Definition

- Exposure is defined as contact over time and space between a
 - person and one or more biological, chemical or physical agents (US NRC, 1991a).
 - an ecological receptor and one or more biological, chemical or physical agents.

Exposure Assessment

- Combines elements of industrial hygiene, health physics, epidemiology and relies on aspects of toxicology, biostatistics, atmospheric sciences, geology, analytical chemistry, food sciences, physiology, and environmental modeling.
- Describes the nature and size of various populations exposed to an agent and the magnitude and duration of the exposure.
- Determine the degree of contact that a person has with an agent and estimate the magnitude of the absorbed dose.

Liroy et al., Journal of Exposure Analysis and Environmental Epidemiology (2005) 15, 463.

- An Exposure is defined as the event when a person comes into contact with a toxic material. Coming into contact with a toxic material is a highly dynamic process that varies from person to person (depending on behavior, location, and life style) and from one toxic substance to another.
- The goal of Exposure Science is to identify and characterize 'real world' contacts with and uptake in the body of toxic materials that can cause acute or chronic health effects.

Differences Between Exposure and Dose

- The term exposure refers to the concentration of an agent at the boundary between an individual and the environment as well as the duration of contact between the two, but dose refers to the amount actually deposited or absorbed in the body over a given time period (Hatch and Thomas, Measurement Issues in Environmental Epidemiology).

Measurement Issues in Environmental Epidemiology

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This paper deals with the area of environmental epidemiology where measurement of exposure and dose, health outcomes, and important confounding and modifying variables (including genotype and psychosocial factors). Using examples, we discuss strategies for increasing the accuracy of exposure and dose measurement that include dosimetry algorithms, pharmacokinetic models, biologic markers, and use of multiple measures. Some limitations of these methods are described and suggestions are made about where formal evaluation might be helpful. We go on to discuss methods for increasing the accuracy of dose measurement, including toxicologic analysis and validation studies. In relation to measurement of health outcomes, we discuss some methodologic issues and cover, among other topics, biological markers and other early indicators of disease. Research measurement error in epidemiology is also important, we consider the limitations in measurement of common confounders and effect modifiers. Finally, we discuss some general methodologic research needs. — *Environ Health Perspect* 102(Suppl 4):49-57 (1998)

Key Words: Biologic markers, dose, environment, exposure, mathematical modeling, measurement error, psychosocial factors, sensitivity analysis, susceptibility

Measuring Environmental Exposure and Dose

Concepts

Environmental exposures can occur as a result of contact with a variety of elements (air, water, soil) that, in turn, influence the pathways for exposure (inhalation, ingestion). Generally, individuals' interactions with these elements are complex, and therefore it is not surprising that exposure assessment and dose estimation are formidable challenges to those investigating the health effects of environmental agents.

The concepts of exposure and dose have been elaborated in a series of recent publications issued by the Board on Environmental Studies and Toxicology of the National Academy of Sciences (1,2). The term exposure refers to the concentration of an agent at the boundary between an individual and the environment as well as the duration of contact between the two, but dose refers to the amount actually deposited or absorbed in the body over a given time period. Although internal dose is the ideal measure from the scientific standpoint, regulation can deal only with external exposures, and therefore one may want to measure both exposure and dose.

Individuals' exposures may be modified by factors such as activity patterns, which determine encounters with various sources of exposure; bioavailability of the agent in time and place; and the rate at which exposure occurs (e.g., a relatively constant rate versus a variable rate). Even in a given exposure, a person's resultant dose will depend on host characteristics, such as age, sex, and metabolism. It also will reflect the susceptibility or target tissue at the time of exposure; any shielding provided by the body (e.g., the placenta, the blood-brain barrier); or modulation by buildings that attenuate exposure to electric fields and gamma radiation; but can be a source of exposure to radon; and the effect of concurrent exposures such as cigarette smoking or medication. In addition, only particular components of the dose may be relevant to health effects. For calculating dose response relationships, the biologically effective dose is what ought to be quantified. But in many instances it may be difficult to define what the biologically effective dose is, much less measure it. In any event, the definition is time dependent and subject to change along with the state of scientific knowledge; just as measurement capabilities change with new technology. Epidemiologists undoubtedly need to prepare for a new generation of studies in which measurement of variables will involve not only the level of the gene. A reassessment of resources, such as talent and funding, could improve the state of the art in exposure and dose assessment and potentially yield better estimation of exposure response

relationships and more effective measures of cardiovascular protection.

In the past, the methods used to assign exposures in environmental health studies were quite crude, and in some cases they still are (e.g., pesticide usage patterns, residence near a point source of pollution). Even in studies where disease has been ascertained at the individual level, exposure assessments may be ecological in nature and based on average levels for a group. When the group is defined in geographic terms, exposure levels might be estimated from values recorded by environmental sampling in a subject's general vicinity. However, recent research has shown that conditions sometimes are weak between readings from area monitors and subjects' exposures measured using personal monitors (3), which are presumed to reflect more closely to the true dose. Discrepancies between readings from personal and area-wide samples can result from heterogeneity of exposures, from poor placement of monitors (e.g., air monitors at elevations well above the breathing zone), or from failure to take account of human activity patterns and other sources of exposure.

Exposure monitoring systems can be and are being improved, however. Newer approaches include sampling the microenvironment where exposure principally occurs, including indoor environments (e.g., bedrooms and living rooms in studies of radon and electric and magnetic fields), as well as total exposure monitoring in which all potentially relevant microenvironments are

*The authors would like to thank the participants of the Board on Environmental Studies and Toxicology of the National Academy of Sciences (1,2). The term exposure refers to the concentration of an agent at the boundary between an individual and the environment as well as the duration of contact between the two, but dose refers to the amount actually deposited or absorbed in the body over a given time period. Although internal dose is the ideal measure from the scientific standpoint, regulation can deal only with external exposures, and therefore one may want to measure both exposure and dose.

Exposure and Biomarkers of Exposure, Leading to Disease

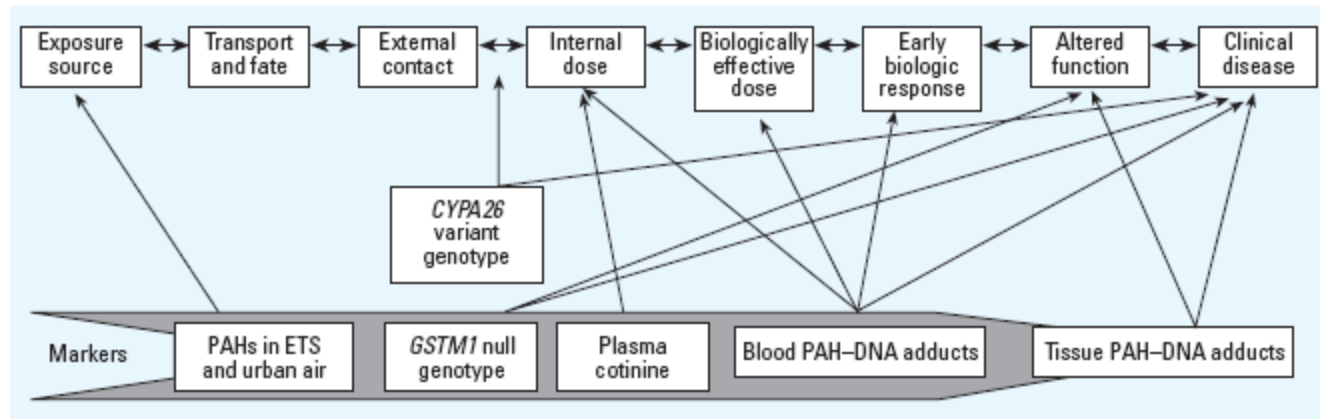


Figure 1. A schematic representation of markers of exposure, response, and susceptibility in the exposure–disease continuum: an example for PAHs and cancer. *CYP2A6*, cytochrome P4502A6 gene; ETS, environmental tobacco smoke; *GSTM1*, glutathione *S*-transferase M1 gene; PAHs, polycyclic aromatic hydrocarbons; Arrows indicate predictability of each marker for exposure or disease in the exposure–disease continuum. Adapted from NRC (1987). PAHs in ETS and urban air are a marker for exposure source. *GSTM1* null genotype and blood PAH–DNA adducts are independent markers of cancer case status (disease) but have a multiplicative effect in combination (Perera et al. 2002; Tang et al. 1995). *GSTM1* null genotype is a predictor of tissue PAH–DNA adducts, which are a marker for altered function (Perera et al. 2002; Rundle et al. 2000; Tang et al. 1995). *CYP2A6* variant is a marker for increased internal dose of nicotine and protective effect on cancer development (Spitz et al. 2005). Plasma cotinine is a marker for internal exposure to ETS but is not correlated with blood PAH–DNA adducts (Mooney et al. 2005). Blood PAH adducts are a marker for PAH/ETS exposure, internal dose, biologically effective dose, early biologic response, and cancer (Mooney et al. 2005; Perera et al. 2002, 2004; Poirier and Beland 1992; Veglia et al. 2003; Whyatt et al. 1998). Tissue PAH–DNA adducts are a marker for altered function and cancer (Rundle et al. 2000).

Personalized Exposure Assessment: Promising Approaches for Human Environmental Health Research Environmental Health Perspectives • VOLUME 113 | NUMBER 7 | July 2005.

Components of Environmental and Occupational Health Exposure Pathways

- Source (s)—Often with unique fingerprint(s).
- Rate(s) of contaminant emissions.
- Transport route(s) through environmental media.
- Route(s) of exposure.
- Exposure concentration(s).

Factors Influencing Human Exposure

- The duration, frequency and intensity of contact with the contaminant.

How Long/Often and Much?

- Identification of individual activity patterns, population distributions and susceptible populations.

Primary Routes of Human Environmental Exposure

- Dust, mist, fume, gas and/or vapor inhalation.
- Dermal contact with contaminated soils or dusts or contaminated water.
- Ingestion of contaminated food, water dusts and/or soil.

Important Terms

- Agent(s) -biological, chemical, physical, single agent, multiple agents, mixtures
- Source(s)- anthropogenic/non-anthropogenic, area/point, stationary/mobile, indoor/outdoor
- Transport/carrier medium- air, water, soil, dust, food, product/item
- Exposure pathways(s)- eating contaminated food, breathing contaminated workplace or ambient air, touching residential/municipal surfaces or bathing in contaminated water.

Important Terms Continued

- Exposure concentration- mg/kg (food), mg/litre (water), $\mu\text{g}/\text{m}^3$ (air), $\mu\text{g}/\text{cm}^2$ contaminated surface), fibres/ m^3 (air), percent by weight or ppm (mg/kg) for contaminated soils.
- Exposure route(s) -inhalation, dermal contact, ingestion, multiple routes.
- Exposure duration- seconds, minutes, hours, days, weeks, months, years, lifetime, population-generational.
- Exposure frequency- continuous, intermittent, cyclic, random, rare.
- Exposure setting(s) -occupational/non-occupational (environmental), residential/non-residential, indoors/outdoors, recreational/non-recreational.
- Exposed population- general population, population subgroups, individuals.
- Geographic scope- site/source specific, local, regional, national, international, global.
- Time frame- past, present, future, trends.

Mathematical Expressions- Exposure and Dose

Table 2. Mathematical expressions for some important exposure-related and dose-related events

Exposure

$$E = \int_{t_1}^{t_2} C(t) dt$$

Potential dose for intake processes

$$D_{\text{applied}} = \alpha \int_{t_1}^{t_2} C(t) IR(t) dt$$

Applied dose

$$D_{\text{potential}} = \int_{t_1}^{t_2} C(t) IR(t) dt$$

Internal dose

$$D_{\text{internal}} = D_{\text{applied}} \int_{t_1}^{t_2} f(t) dt$$

E , magnitude of exposure; $t_2 - t_1$, exposure duration; α , availability factor; $C(t)$, exposure concentration as a function of time; IR , ingestion or inhalation rate; $f(t)$, nonlinear absorption function (Sexton et al., 1995a)

Exposure and Dose Assessment Relationship to the Environmental Health Paradigm

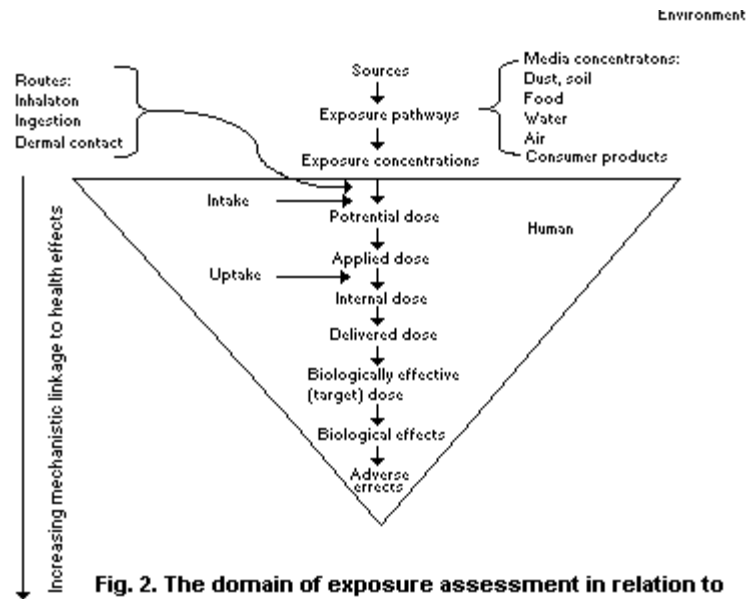


Fig. 2. The domain of exposure assessment in relation to an environmental health paradigm (adapted from IPCS, 1993; Sexton et al., 1995a)