

Exposure - Dose - Health Effects

Understanding the links

Elaine Symanski, PhD
Mary Ann Smith, PhD



THE UNIVERSITY
of TEXAS

SCHOOL OF PUBLIC HEALTH

The starting basis*

- How are pollutant levels detected and measured in the human body?
- If there is some level of contamination, whether or not disease results, can the contaminant be cleansed from the body? If so, how?
- How much exposure do we get from breathing and how much do we get on the skin? Which is worse?

*From the Deer Park CAC

Overview

- The Environmental Health (EH) Paradigm
 - Moving from sources of a contaminant to health effects
- Focus on a part of the EH Paradigm
 - Exposure
 - Dose
 - Health effects
- Concluding remarks
- Questions

Environmental Health Paradigm

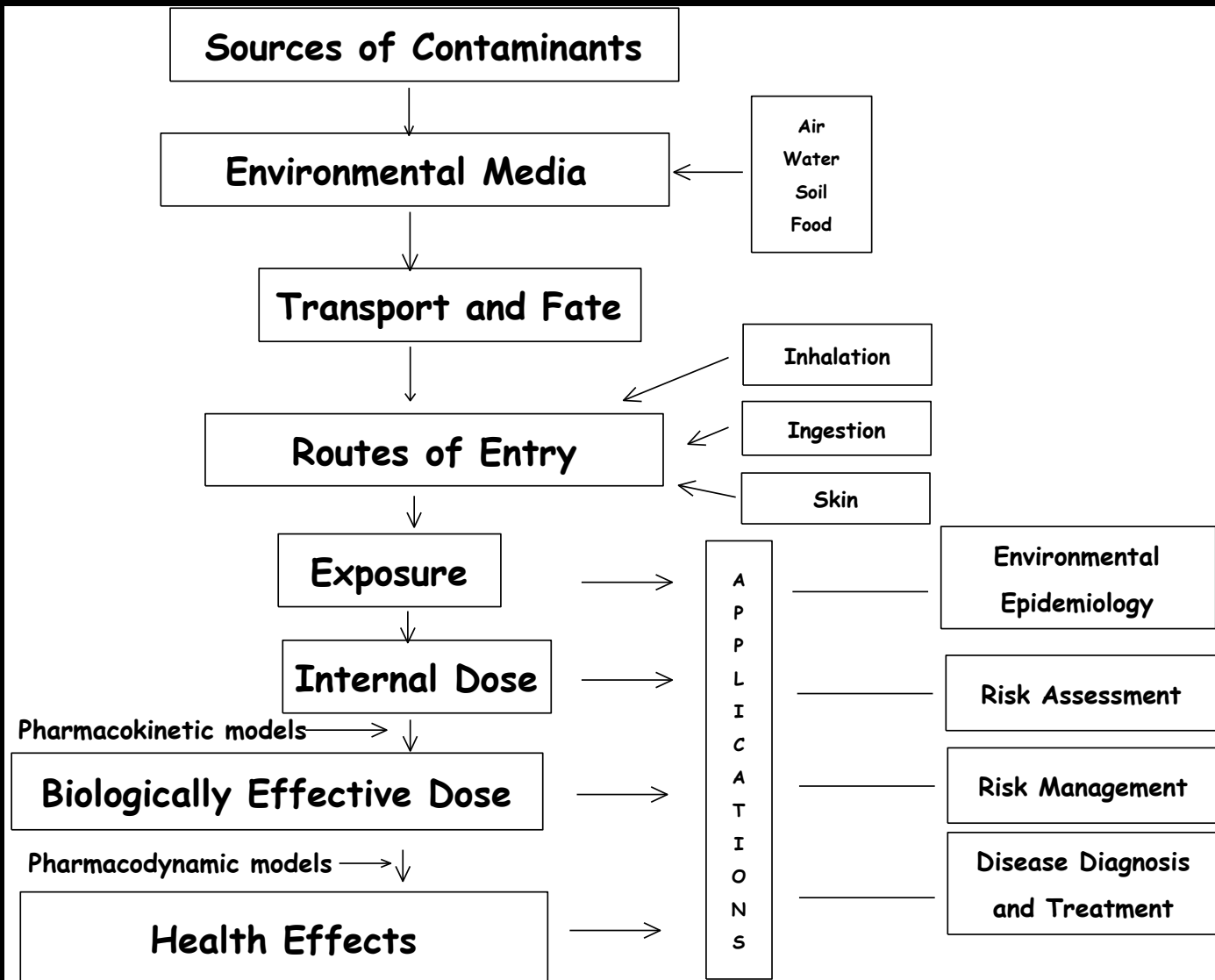
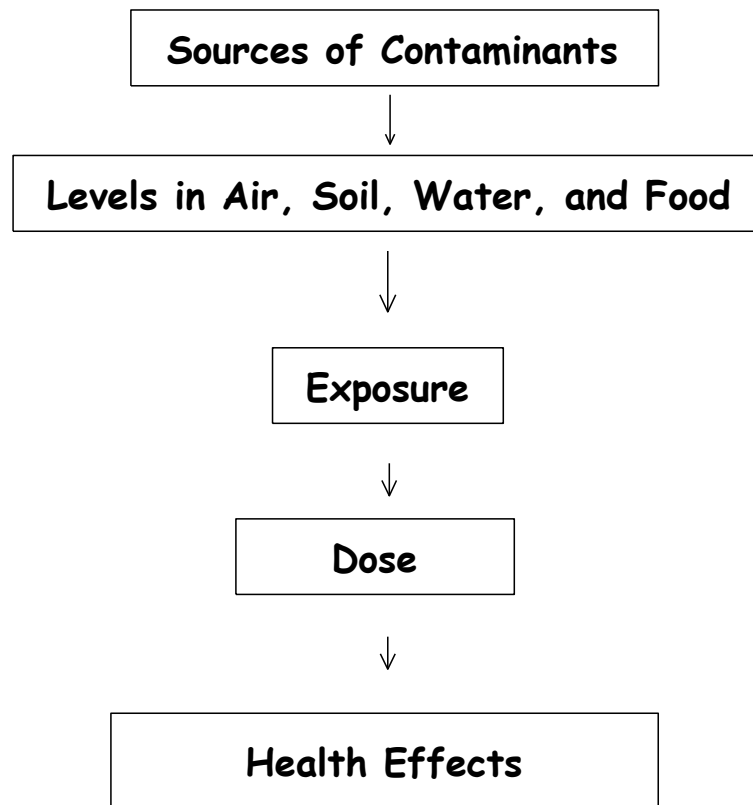
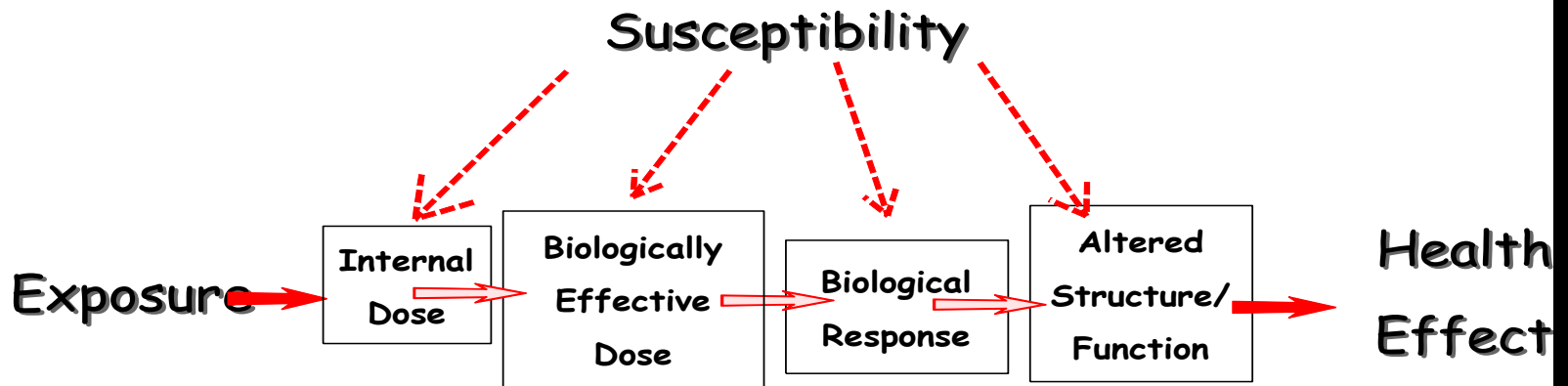


Figure 1. Contaminant sources and effects continuum (from NAS, 1991)

Environmental Health Paradigm - A Simplified Version



Exposure-Disease Continuum



Adapted from: Hulka et al. *Biological Markers in Epidemiology*, Oxford University Press, 1990.

What is Exposure?

- Contact with a toxic substance (could be a chemical, physical or biological agent) at the boundary between an individual and the environment over some specified period of time
 - What? How? Who?
 - How much? How long? How often?

What? How? Who?

- Nature of the agent
 - Gases/vapors versus aerosols
 - Lipophilic (chemical prefers to be in fat) versus Hydrophilic (chemical prefers to be in water)
- Route of Exposure
 - Inhalation, Dermal absorption, Ingestion
- Who?

- How much?

- Level

- How long?

- Duration: 1 day, 1 month, 1 year, lifetime?

- How often?

- Continuous versus intermittent?
- Every day, 5 days a week, 8 times a month, twice a year?

The Exposure Pathway

- The way in which a person may come into contact with a contaminant
 - Source
 - Media
 - Exposure point
 - Route of exposure
 - Receptor

Exposure Pathway - the pieces defined

- *The source*
 - How does the contaminant get into the environment?
- *The media*
 - How does the contaminant move through the environment?
- *The exposure point*
 - How do people come in contact with the contaminant?
- *The exposure route*
 - How does the contaminant enter the body?
- *The receptor*
 - Which population is exposed?

Exposure Pathway - examples of the pieces

■ *Source*

- Landfill, Pond, Incinerator, Factory

■ *Media*

- Soil, Animals/plants, Groundwater, Surface water, Air

■ *Exposure point*

- Residence, Workplace, Playground, Waterway

■ *Exposure route*

- Ingestion, Inhalation, Dermal absorption

■ *Receptor*

- Residents, Workers, Children, Pregnant women

Example: Same contaminant, multiple exposure pathways

- Exposure pathway 1
 - Ingestion of mercury present in fish from water contaminated with mercury-containing effluent from a pulp and paper processing plant
- Contact occurs in the stomach lining of someone who has eaten the fish

Mercury Exposure

- Exposure pathway 2
 - Inhalation of mercury in the ambient air due to living in close proximity to a coal-fired power plant
- Contact occurs in the lungs of someone who has breathed in the contaminant

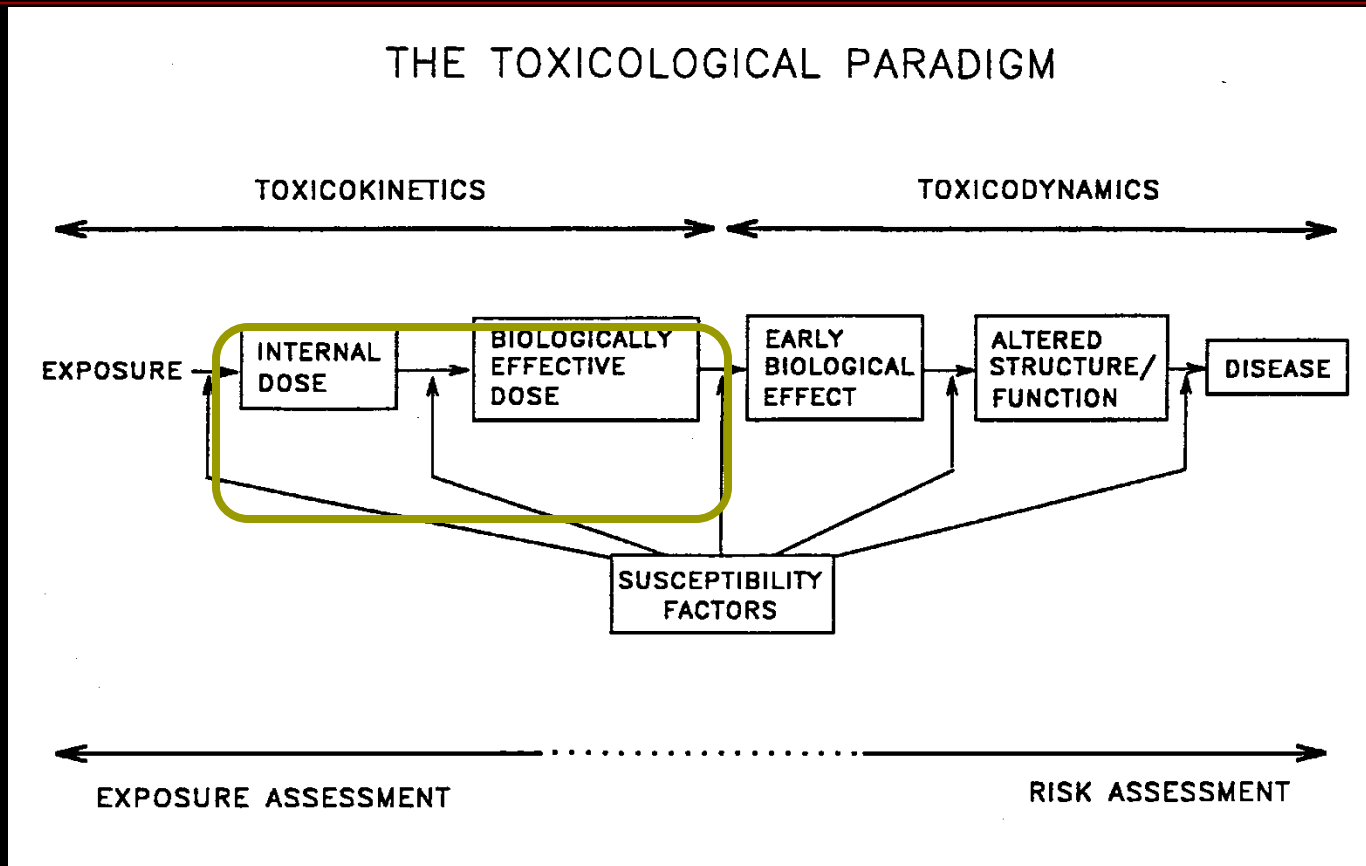
Example: Same media, contact in multiple ways

- Groundwater and Surface Water
 - Exposure could occur if someone drinks the water, ingests it while swimming, or if it comes into contact with their skin while showering or swimming
- Air
 - Exposure could occur if someone breathes the contaminant or if a person's skin absorbs the contaminant - generally, inhalation is considered the primary route of exposure for airborne contaminants

Exposure - the critical issue

- Exposure is not a 'constant'
 - For any given individual, exposure changes over time
 - For a group of individuals, exposure varies between persons
- Why does exposure vary?
 - Changes in the source (emissions)
 - Changes in meteorology
 - Differences in time-activity patterns

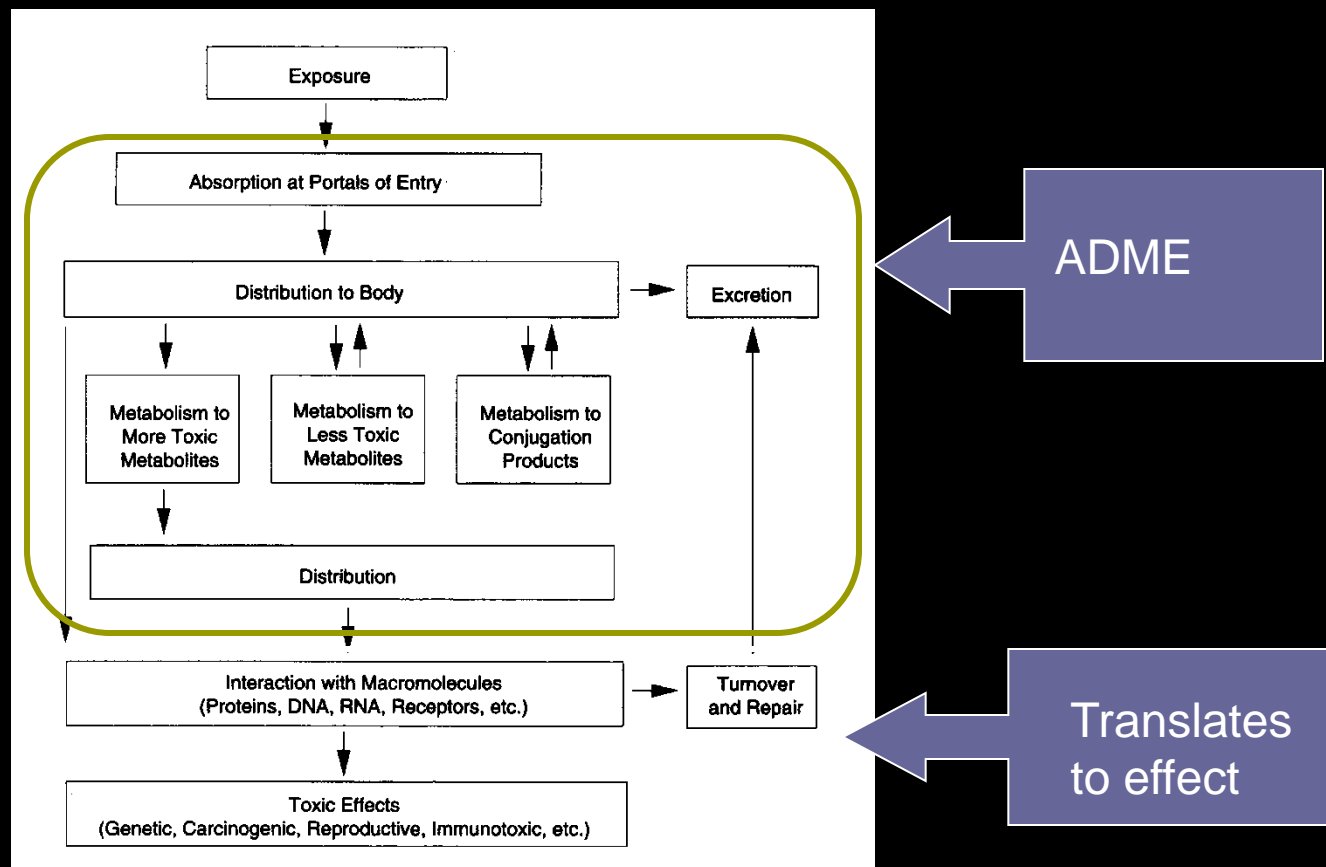
The Toxicological Paradigm



What determines the concentration of chemical at the site of action?

- Dependent on many variables
 - Absorption, distribution, binding or localization in tissues, biotransformation and excretion
 - These variables affected by many factors.
 - Age, diet, disease, etc.

Toxicodynamics



Adapted from: Hodgson, E. & Levi, P.E. *A Textbook of Modern Toxicology* 2nd Edition, 1997. Appleton & Lange.

Absorption, Distribution, Metabolism, Excretion

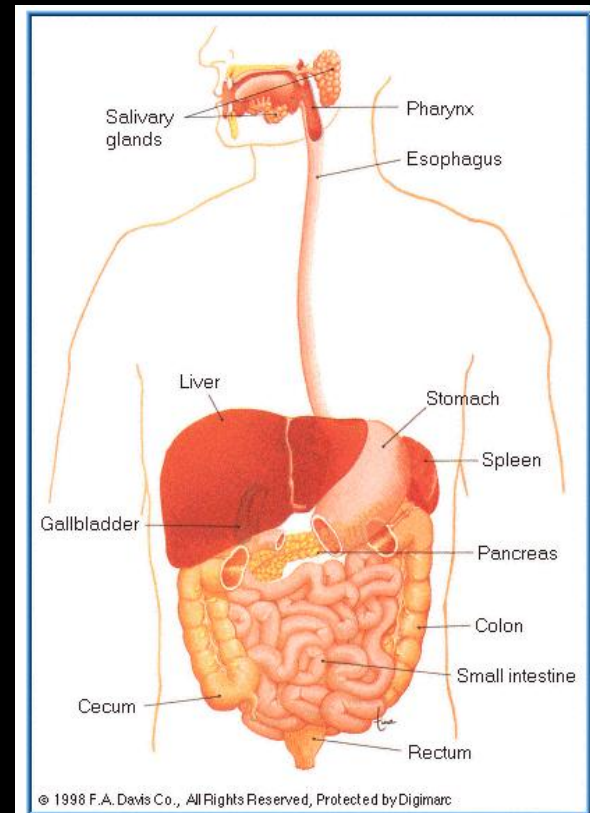
- Movement of a chemical through the body is a dynamic process
- It must first be absorbed and distributed to its site of action *prior* to causing an effect
- The body then works to change the chemical in order to excrete it...metabolism (biotransformation) & excretion

Factors that Modify Absorption

- Chemical solubility & dissolution
- Available surface area
- Concentration gradient
- Blood flow
- Route of exposure
 - Absorption through the lungs is usually faster than absorption through the skin

Absorption of Chemicals Through the G.I. Tract

- Occurs along entire length
- Almost everything absorbed at least to small extent
- Lipid soluble more readily absorbed than water soluble

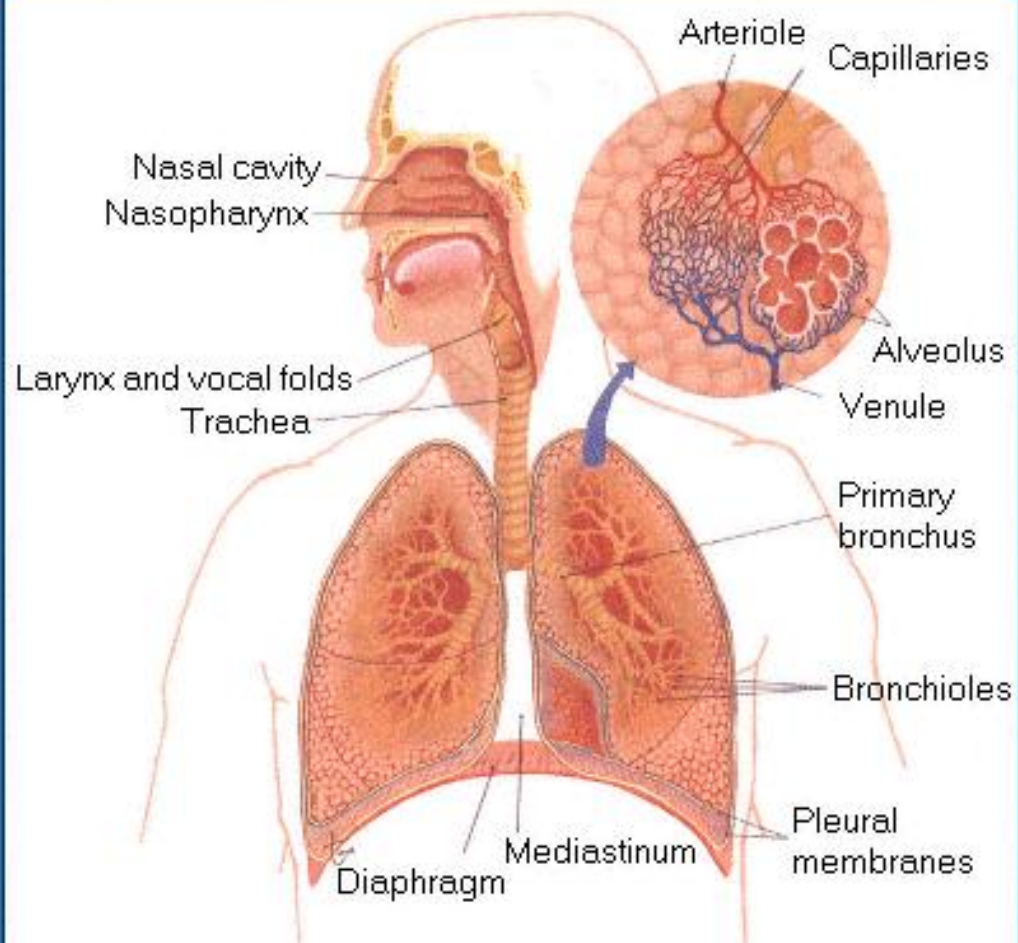


© 1998 F.A. Davis Co., All Rights Reserved, Protected by Digimarc

V. C. Scanlon and T. Sanders, *Essentials of Anatomy and Physiology*, 2nd edition. F. A. Davis, 1995.

Absorption of chemicals by lungs

- Important route for many chemicals
 - Gases, vapors, aerosols
- Anatomical structure is good for absorption
 - Large surface area
 - High blood flow
 - Capillaries close to cells



© 1998 F.A. Davis Co., All Rights Reserved, Protected by Digimarc

V. C. Scanlon and T. Sanders, *Essentials of Anatomy and Physiology*,
2nd edition. F. A. Davis, 1995.

Absorption of gases & vapors

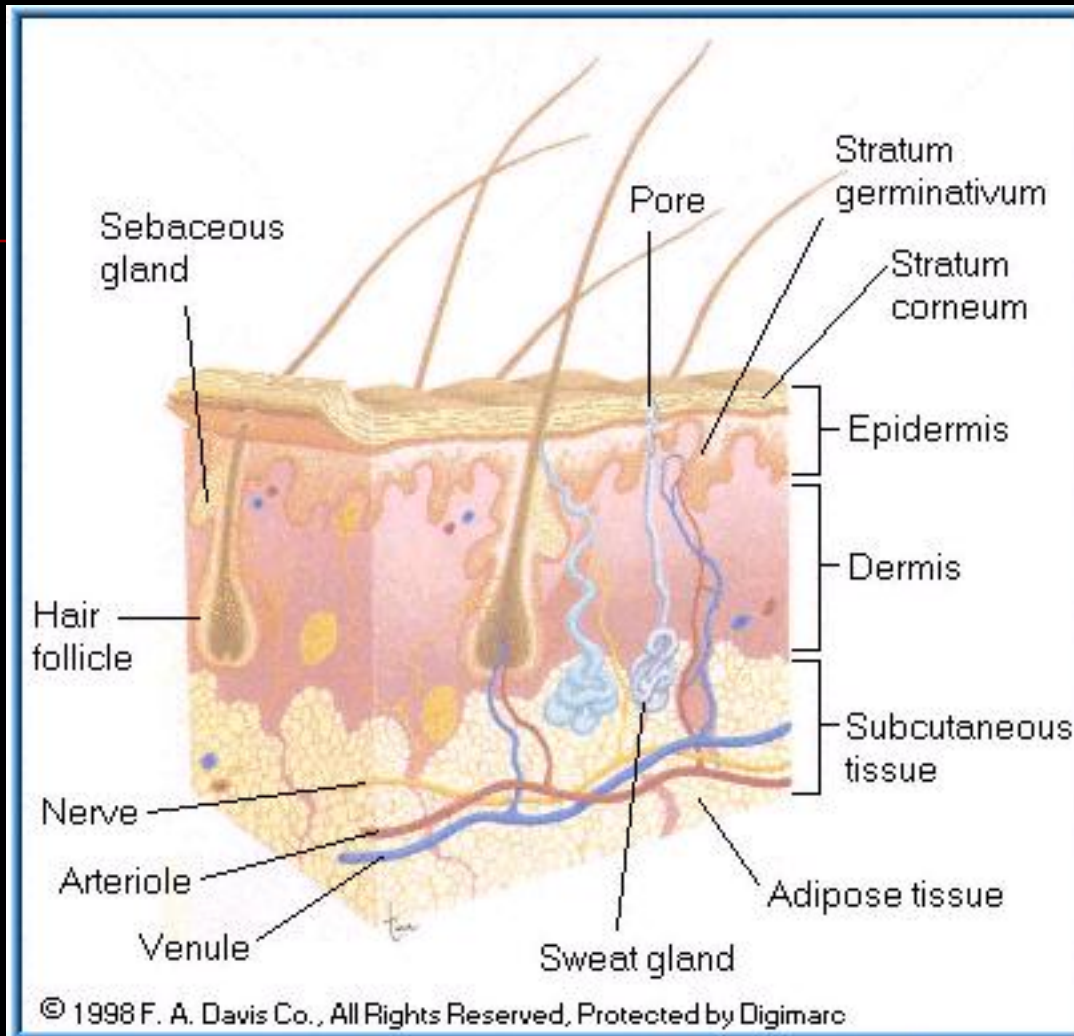
- Must first pass through nasal turbinates before reaching lungs
 - 'scrubber' effect
 - Protection vs. target
 - Absorption dependent on solubility in blood
 - Respiration rate and blood flow are important factors

Absorption of aerosols

- Dependent on aerosol size and water solubility
- $5\mu\text{m}$ or $>$ deposited in nasopharyngeal region
- $2 - 5 \mu\text{m}$ deposited in tracheobronchiolar regions
- $\leq 1\mu\text{m}$ penetrates alveolar sacs

Absorption through skin

- Skin is effective barrier
 - Must pass through several layers before entering small capillaries in the dermis
 - Compounds mainly absorbed through epidermis



V. C. Scanlon and T. Sanders, *Essentials of Anatomy and Physiology*,
2nd edition. F. A. Davis, 1995.

Factors affecting absorption through skin

- Abrasion or chemical burn
- Hydration
- Solvents

Distribution of chemicals throughout the body

- Movement of compounds to various sites within the body.
 - Primary determinant.....blood flow.
 - Concept of volume of distribution.
 - Localization to plasma water, organs, bone, or fat.

Storage of Chemicals in Tissues

- Plasma proteins
- Partitioning into organs
- Fat
- Bone

Absorption vs excretion

- Lipophilicity favors absorption
- Biotransformation to a water-soluble metabolite favors excretion

Purpose of Biotransformation (Metabolism)

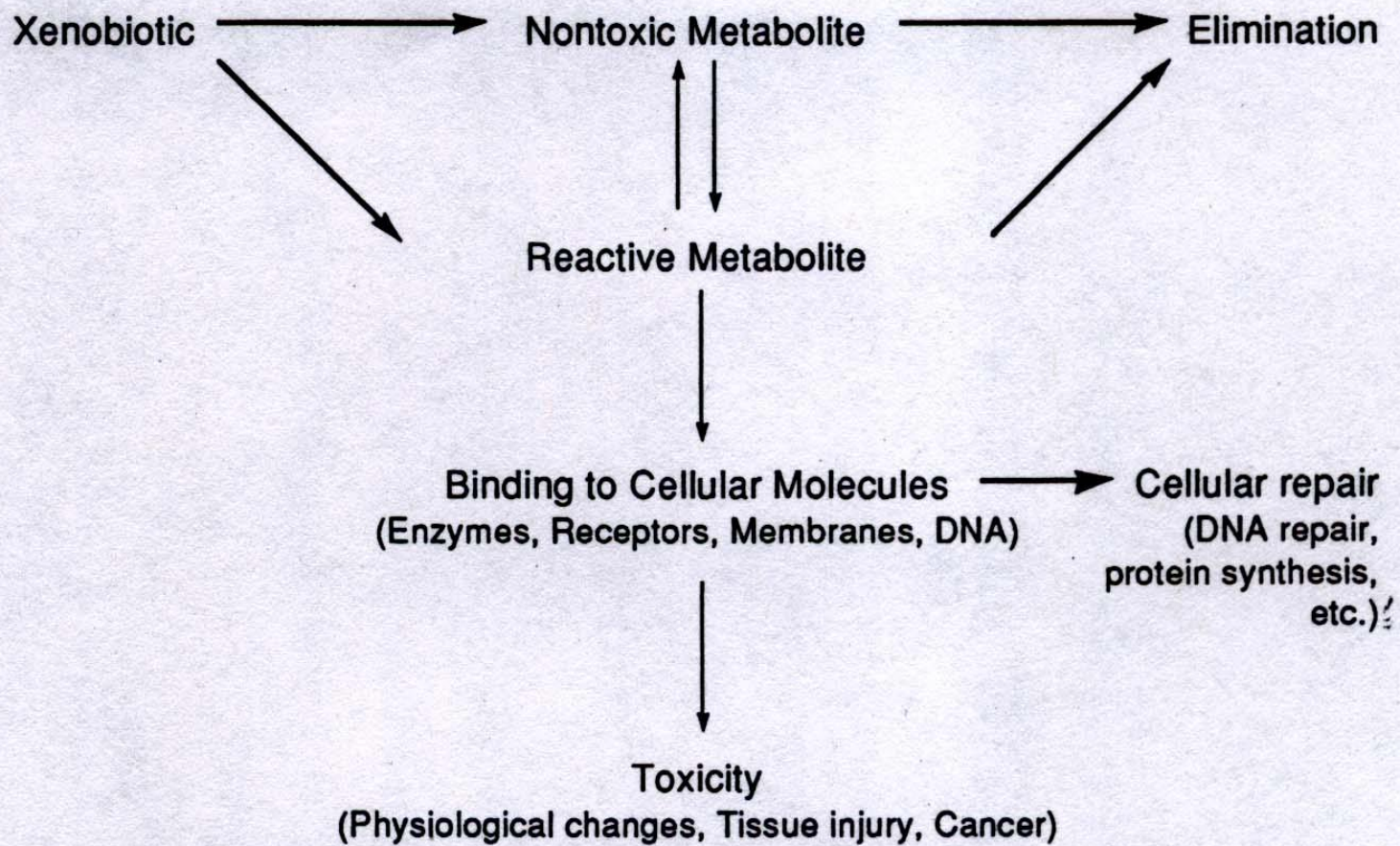
- Lipophilic (fat loving) vs hydrophilic (water loving)
 - mechanism to convert compounds from a chemical structure that favors absorption to one that favors elimination
 - Exception is excretion via inhalation, where the conversion to hydrophilic form will slow elimination

Consequences of Biotransformation

- Changes the length of time the chemical stays in the body.
- Decreases “activity” of the compound
 - Termination of effect
 - inactivation of toxic parent compound.

Activation

- Sometimes biotransformation results in “activating” the chemical to a more reactive, toxic species.



Adapted from: Hodgson, E. & Smart, R.C. *Introduction to Biochemical Toxicology 3rd Edition*, 2001. Wiley Interscience.

Where does biotransformation occur?

- Liver is the primary site
 - “first pass” metabolism
- Extrahepatic metabolism
 - Kidneys, lungs, and other tissues

Factors Affecting Rates of Biotransformation

- Enzyme induction (biotransformation occurs at a faster rate)
 - Induction can either enhance detoxification or enhance bioactivation
- Enzyme inhibition (biotransformation might be slowed or stopped)

Factors Affecting Rates of Biotransformation

- Gender Differences
- Age
- Diet
- Liver Injury
- Circadian rhythms
- Hormonal influences
- Species / strain differences
 - Genetic polymorphisms

Excretion of chemicals

- Urinary excretion (kidneys)
- Fecal excretion (gastrointestinal tract)
- Exhaled breath
- Other routes
 - Sweat
 - Saliva
 - Breast milk

Factors affecting excretion

- Age
- General health
 - Kidney function
 - Diabetes
 - High-blood pressure
 - G.I. tract function

Response / Effect

- Duration & Frequency of Exposure can affect Outcome
 - Acute versus chronic exposure
 - Chronic toxic effects
 - Accumulation
 - Irreversible interactions
 - Recovery interval vs exposure frequency

Acute vs chronic ethanol

- Acute effects
 - Primary central nervous system depressant
- Chronic effects
 - Hepatotoxicity
 - Metabolic effects
 - Link to esophageal cancer

What do we mean by dose?

- Exposure dose
- Absorbed dose
- Biologically effective dose

The Dose-Response Relationship

- Fundamental principle of toxicology

“All substances are poisons;

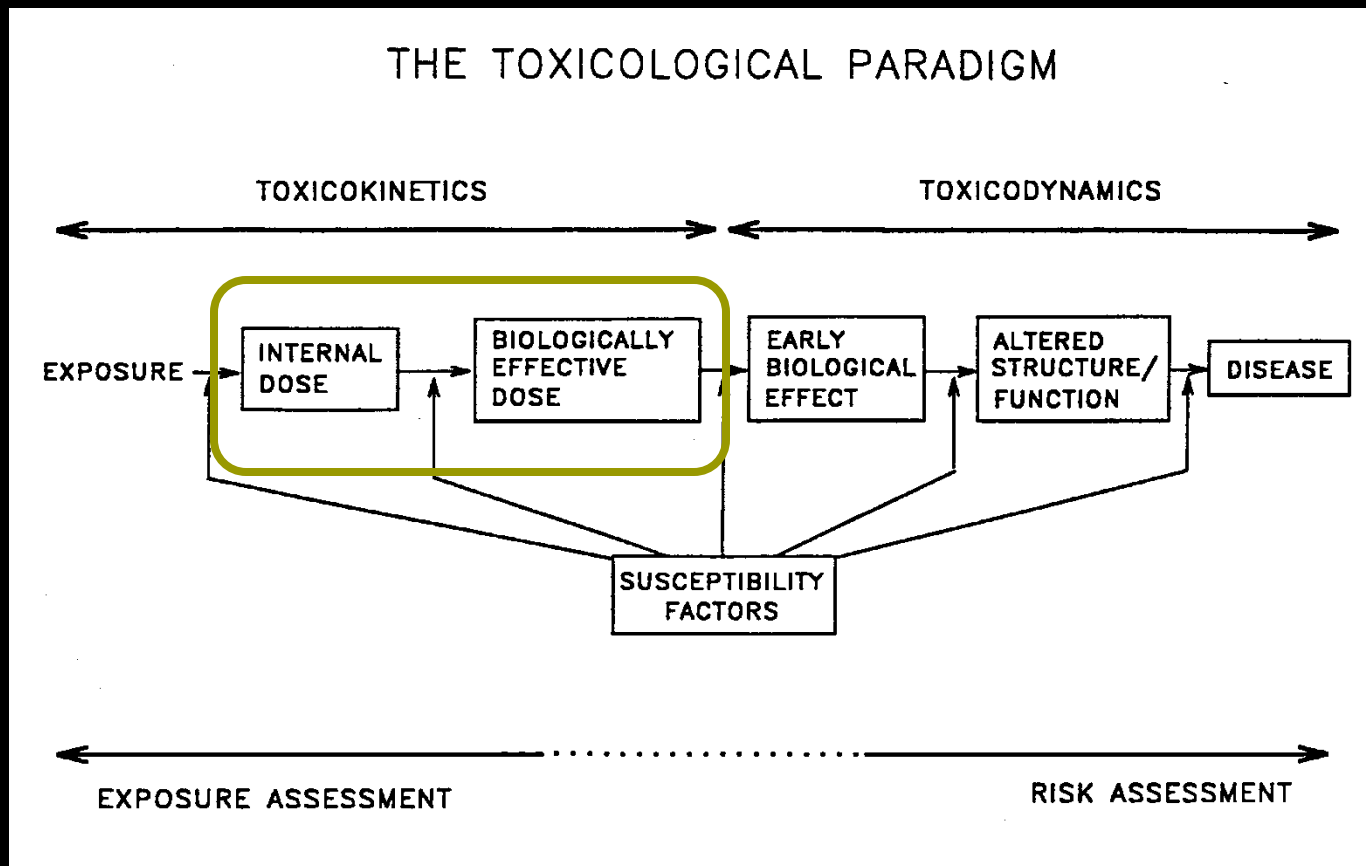
There is none which is not a poison.

The right dose differentiates a poison

From a remedy.”

Paracelsus

The Toxicological Paradigm



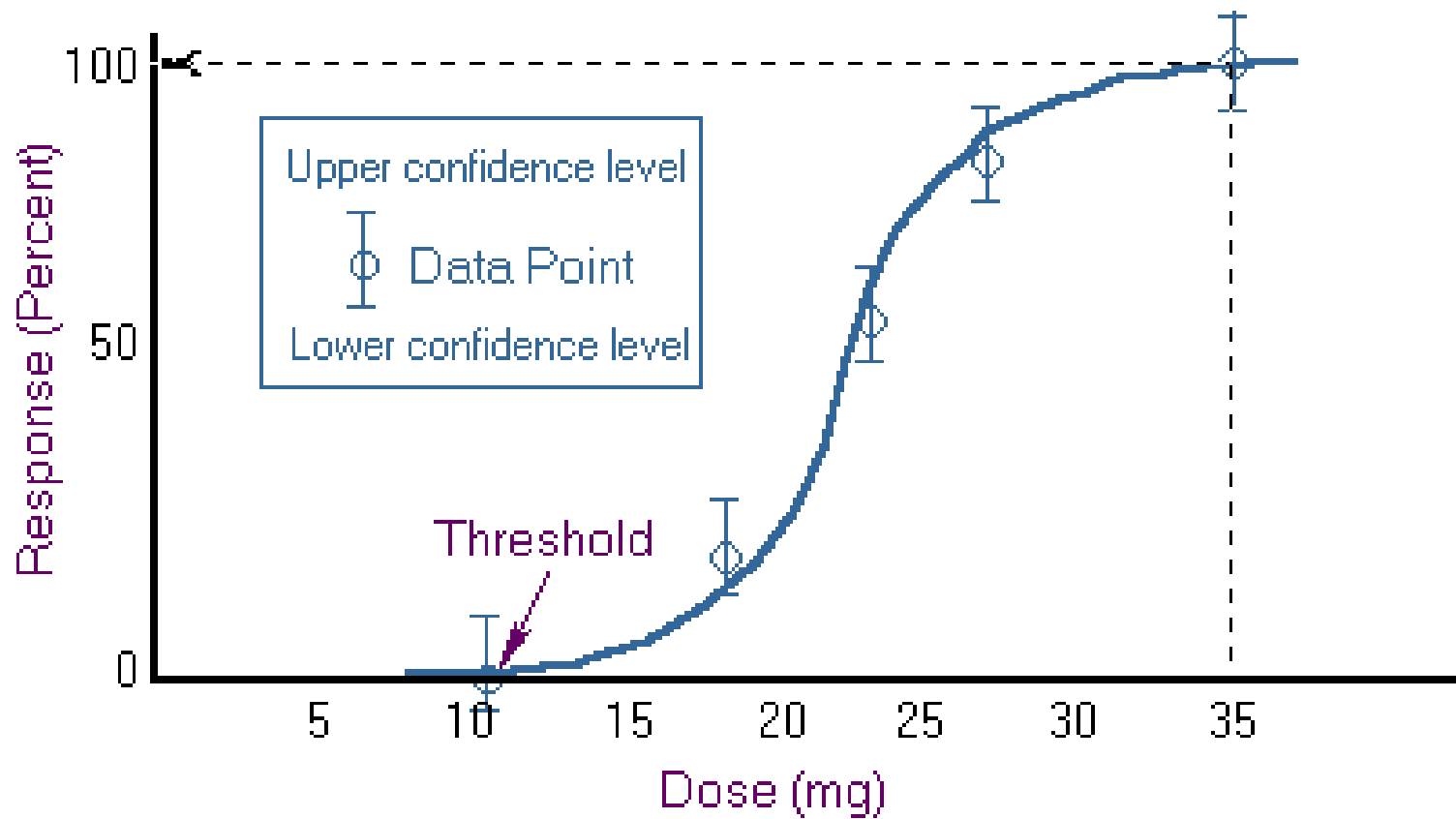
Adapted from Kensler, T.W. Society of Toxicology Continuing Education Course 1994.

Range of toxic doses

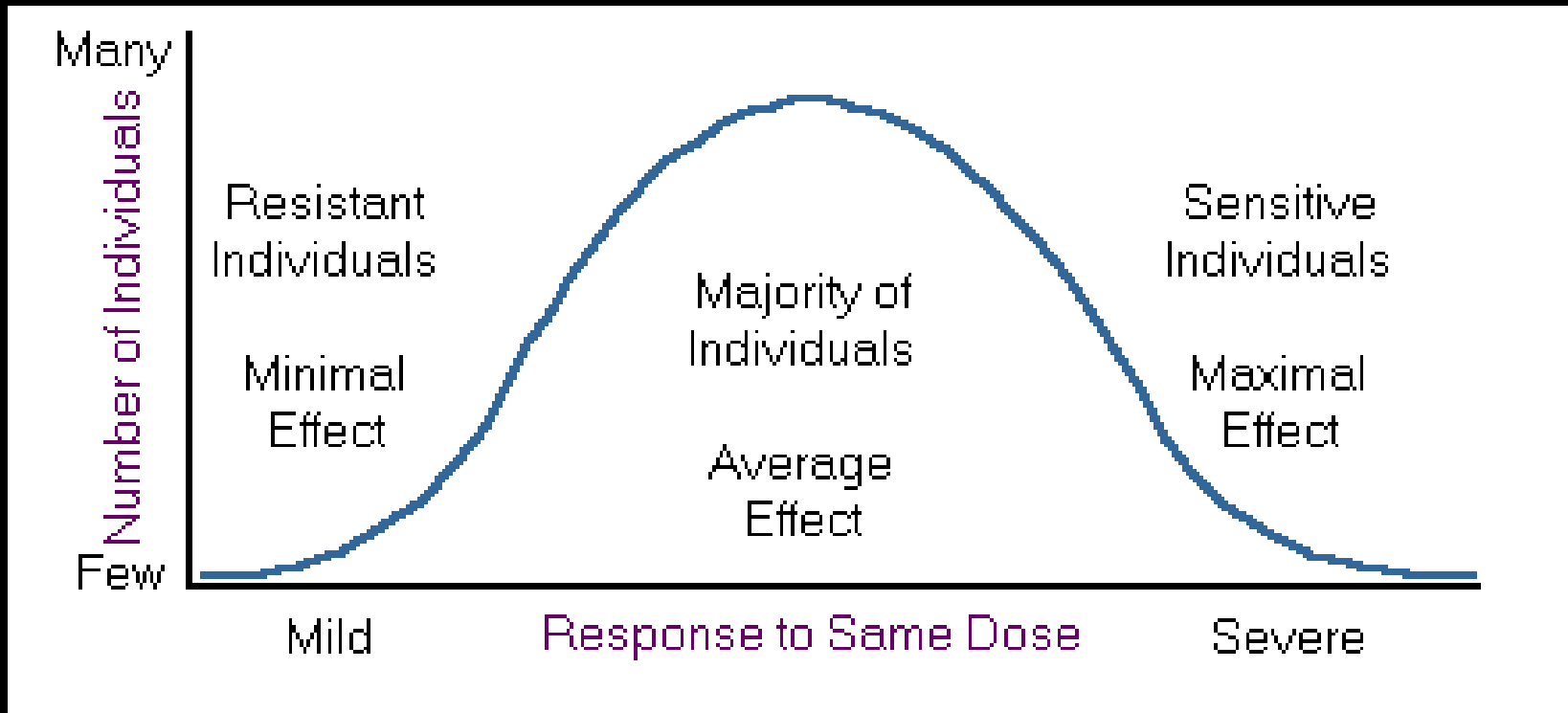
- Death is the ultimate toxic effect
 - Can be the result of an acute exposure at a high dose or multiple exposures at lower doses
- Each compound may in fact have multiple dose-response relationships depending on the endpoint measured.

Dose-Response

- General Issues
 - Individual vs. populations
 - Whole animal vs target organ
 - Multiple sites of action / mechanisms
- Shape of Dose-Response Curve



From: NIH Tox Tutor



From: NIH Tox Tutor

Biomarkers to Evaluate Exposures, Effect & Susceptibility

■ Biomarker

- Indicates events in biologic systems or samples
- Reflect changes in the system as a result of exposure to or effect from toxicant
- Changes can occur at physiologic, cellular, subcellular, or molecular level
- Measurable in biologic media (tissue, cells, fluids)

Classification of Biomarkers

- Biomarker of exposure
 - Parent chemical or its metabolite(s)
 - Product of chemical / target tissue, cell, or molecule interaction that is measurable within the organism or compartment

We live in a world of chemicals

- We are exposed to chemicals in all aspects of our daily lives...where we live, where we work, and where we play
 - Pharmaceuticals
 - Personal hygiene products
 - Consumer use products (insecticides, cleaners)
 - Products used in agriculture
 - Environmental contaminants (industrial, combustion byproducts)
 - Workplace exposures

“How toxic is this chemical?”

- Difficult question to answer
- Need to account for many variables:
 - Spectrum of toxic dose
 - Potency
 - Inter-individual differences
 - Routes & mode of exposure
 - Duration of exposure
- Toxicity is the result of a sequence of events
 - Continuum from exposure to effect

Useful Web Resources

- National Library of Medicine / NIH Toxicology Tutor
 - <http://sis.nlm.nih.gov/enviro/toxtutor.html>
- ATSDR - A Toxicology Curriculum for Communities Trainer's Manual
 - <http://www.atsdr.cdc.gov/training/toxmanual/>
- Society of Toxicology
 - <http://www.toxicology.org/>