Exposure – Dose –Health Effects

Understanding the links

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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

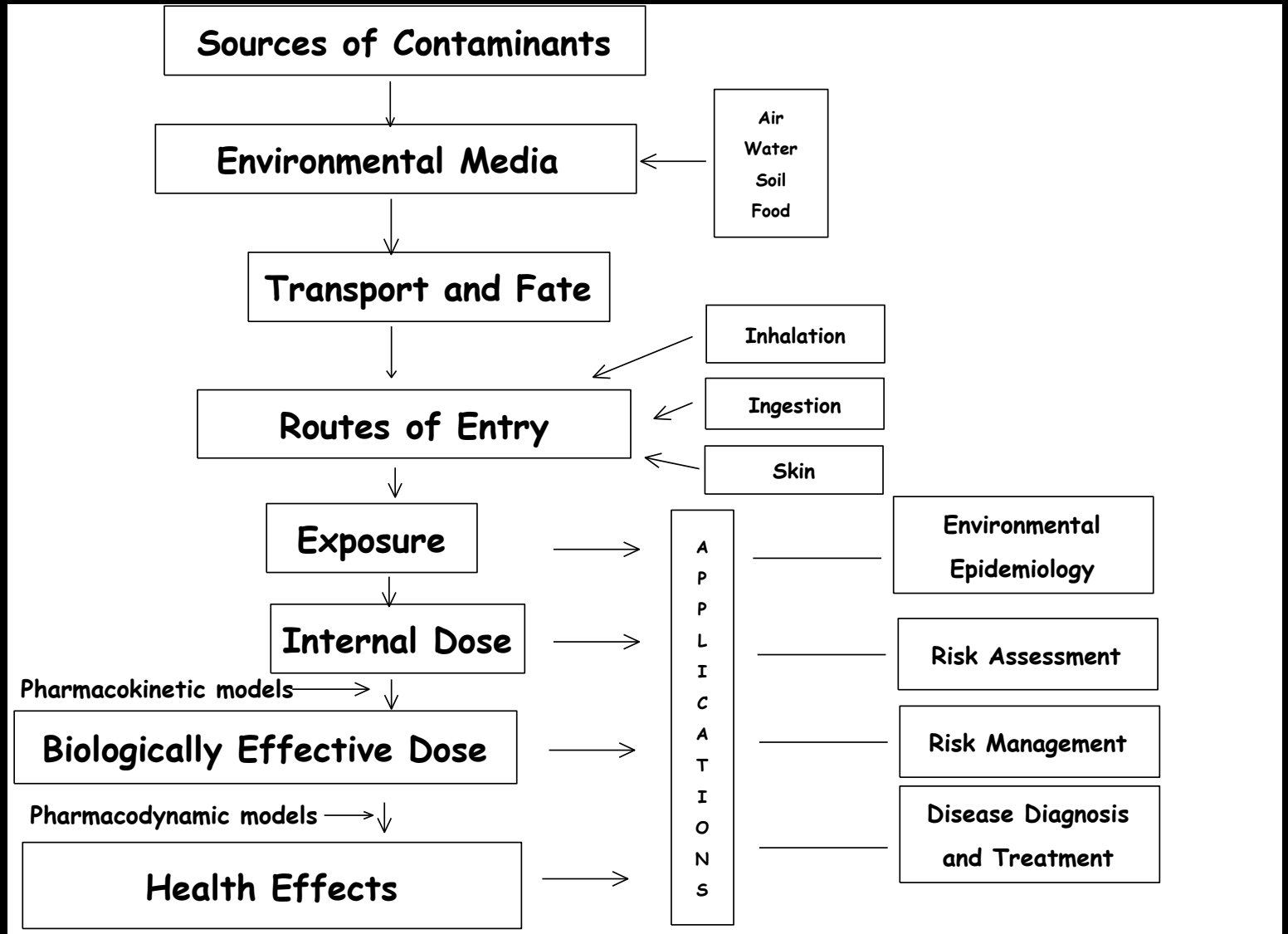
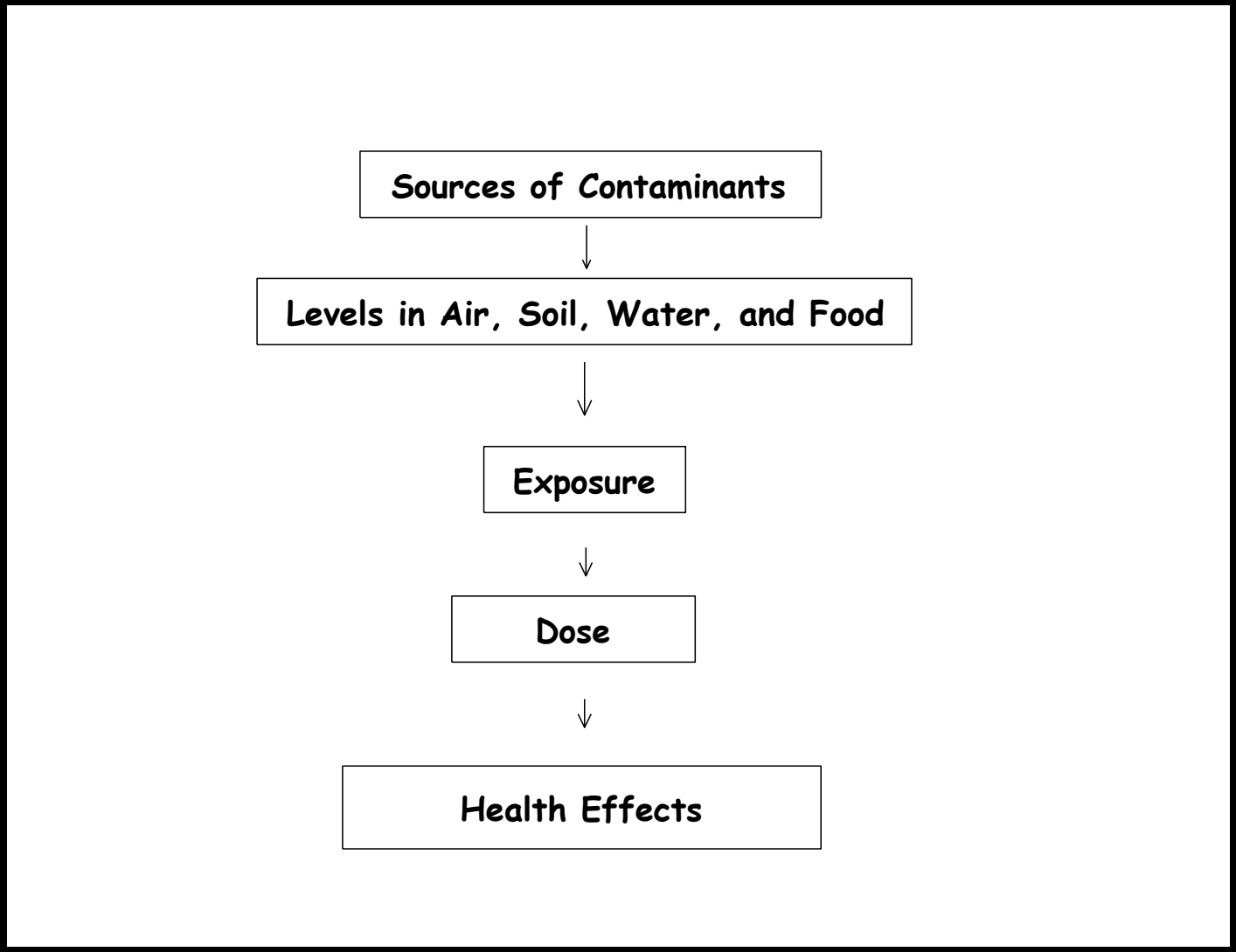
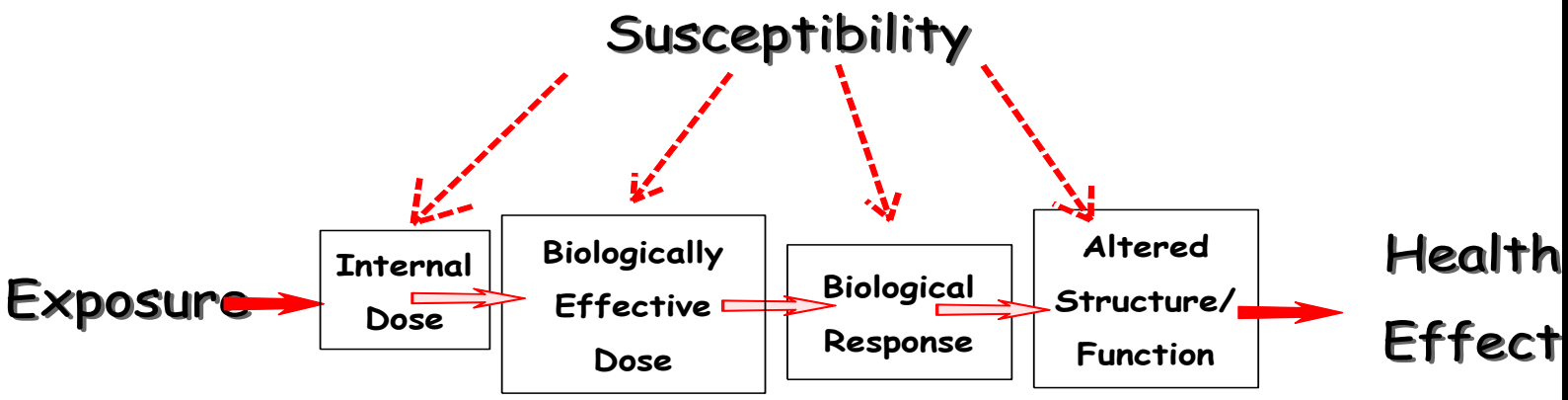


Figure 1. Contaminant sources and effects continuum (from NAS, 1991)

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

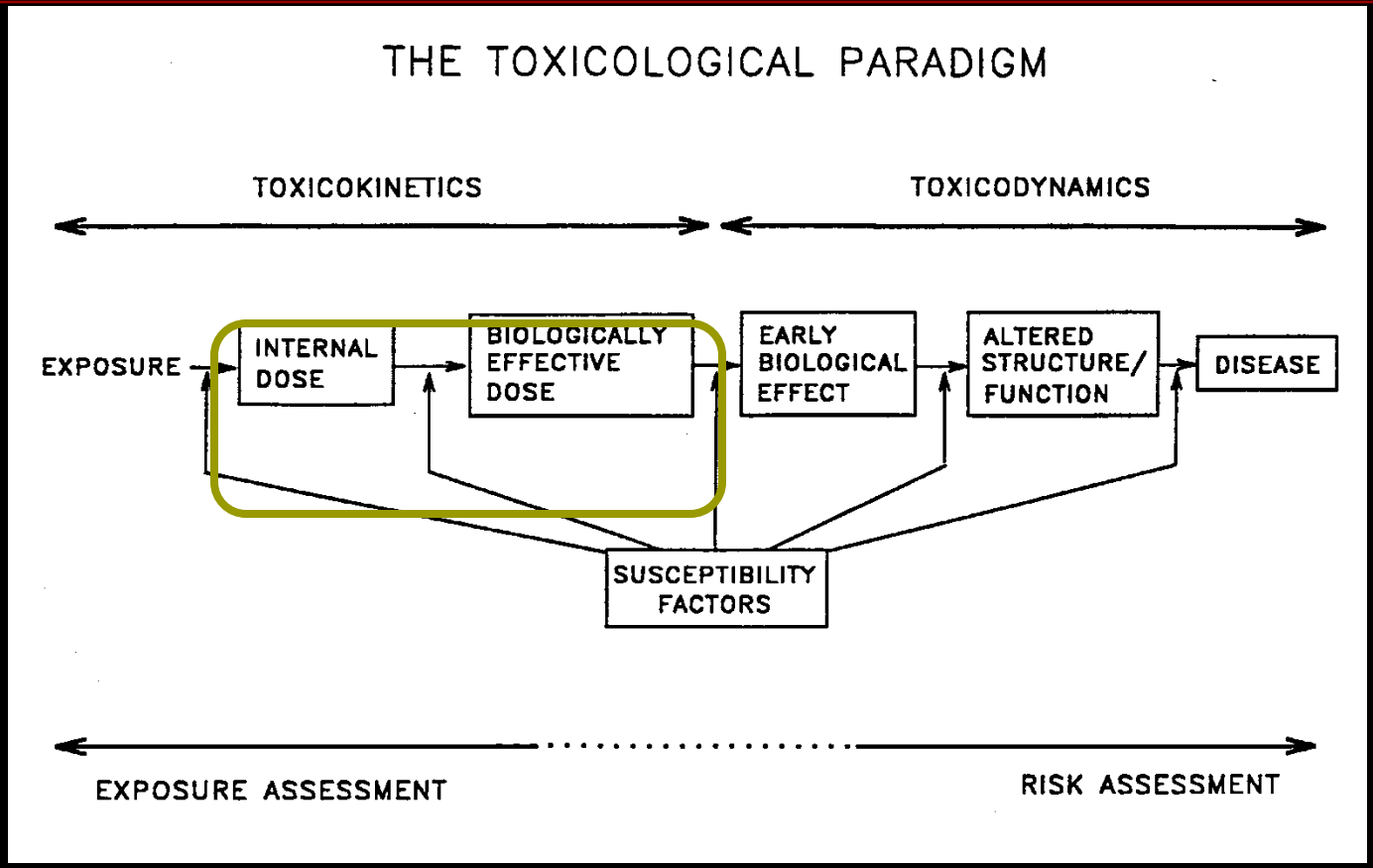
Example: Same media, contact in multiple ways

- 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

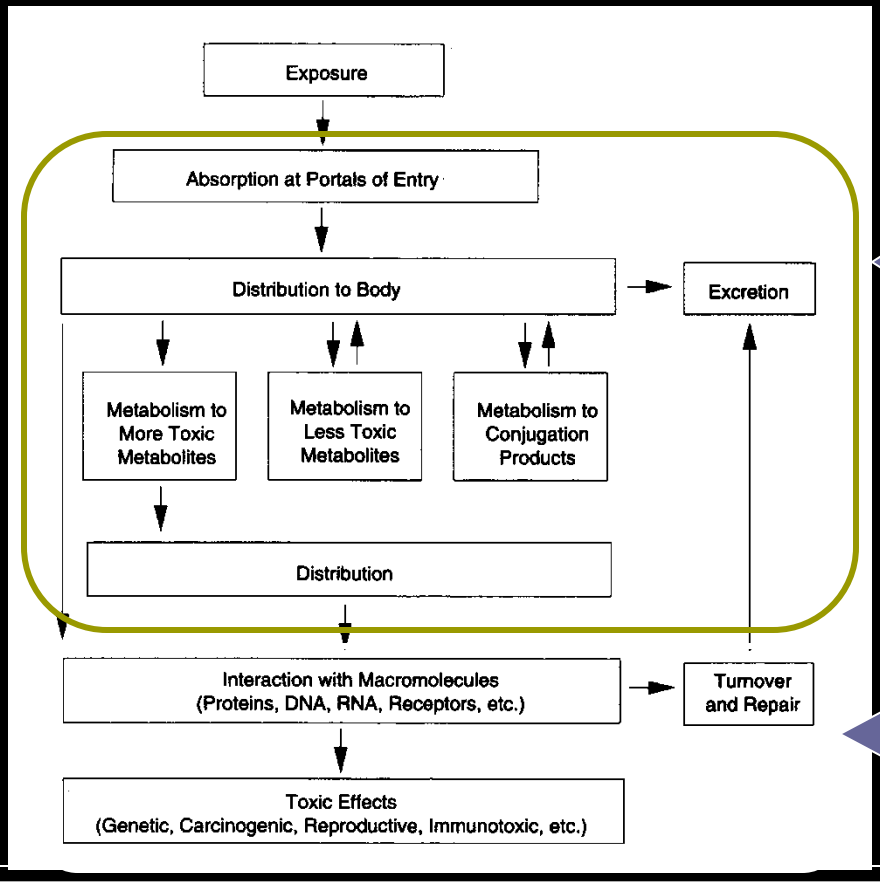


Adapted from Kensler, T.W. Society of Toxicology Continueing Education Course1994.

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

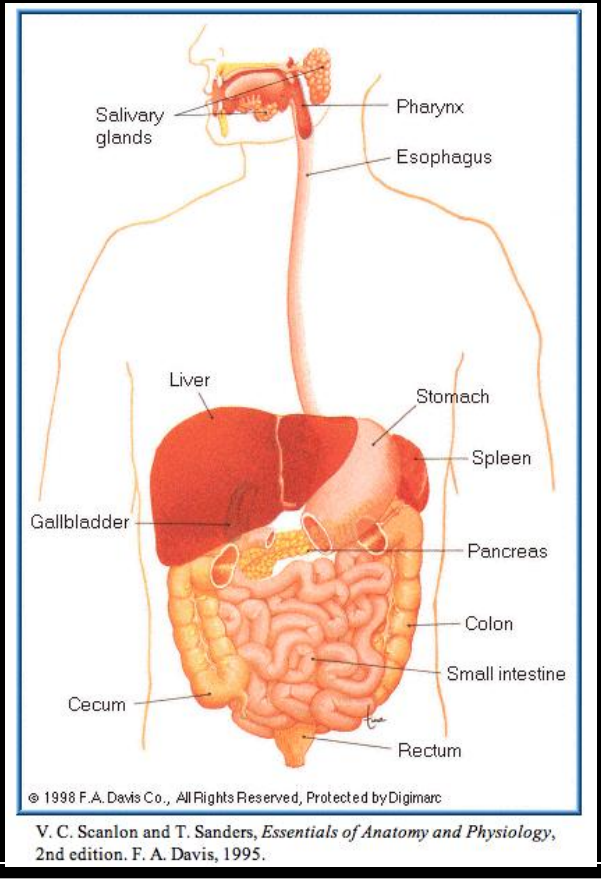
- Movement of a chemical through the body is a dynamic process
- It must first be absorbed and distributed to its site of action *prior* to causing an effect
- The body then works to change the chemical in order to excrete it….metabolism (biotransformation) & excretion

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

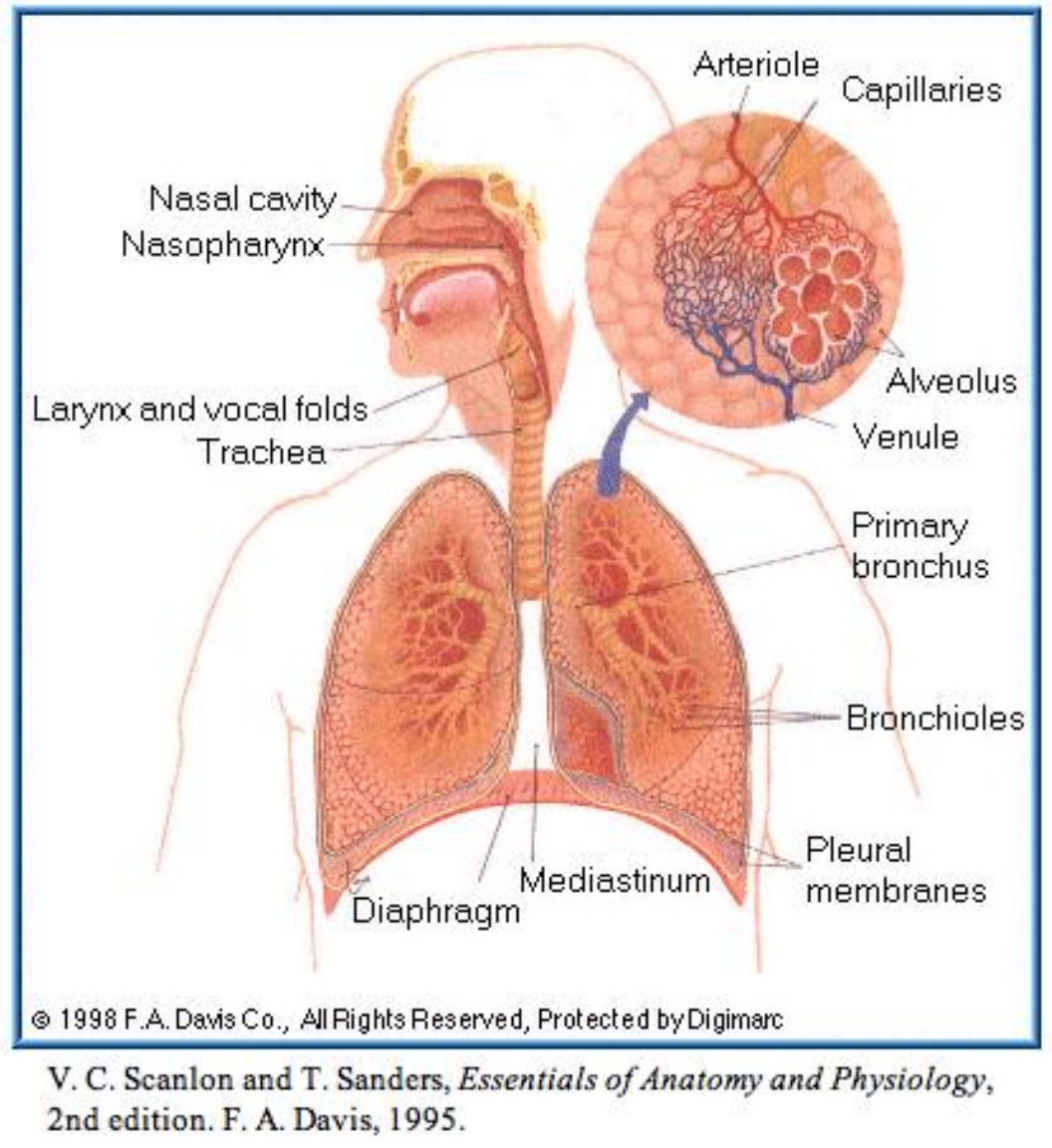
- Occurs along entire length
- Almost everything absorbed at least to small extent
- Lipid soluble more readily absorbed than water soluble



From: NIH Tox Tutor

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



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

From: NIH Tox Tutor

Absorption of gases & vapors

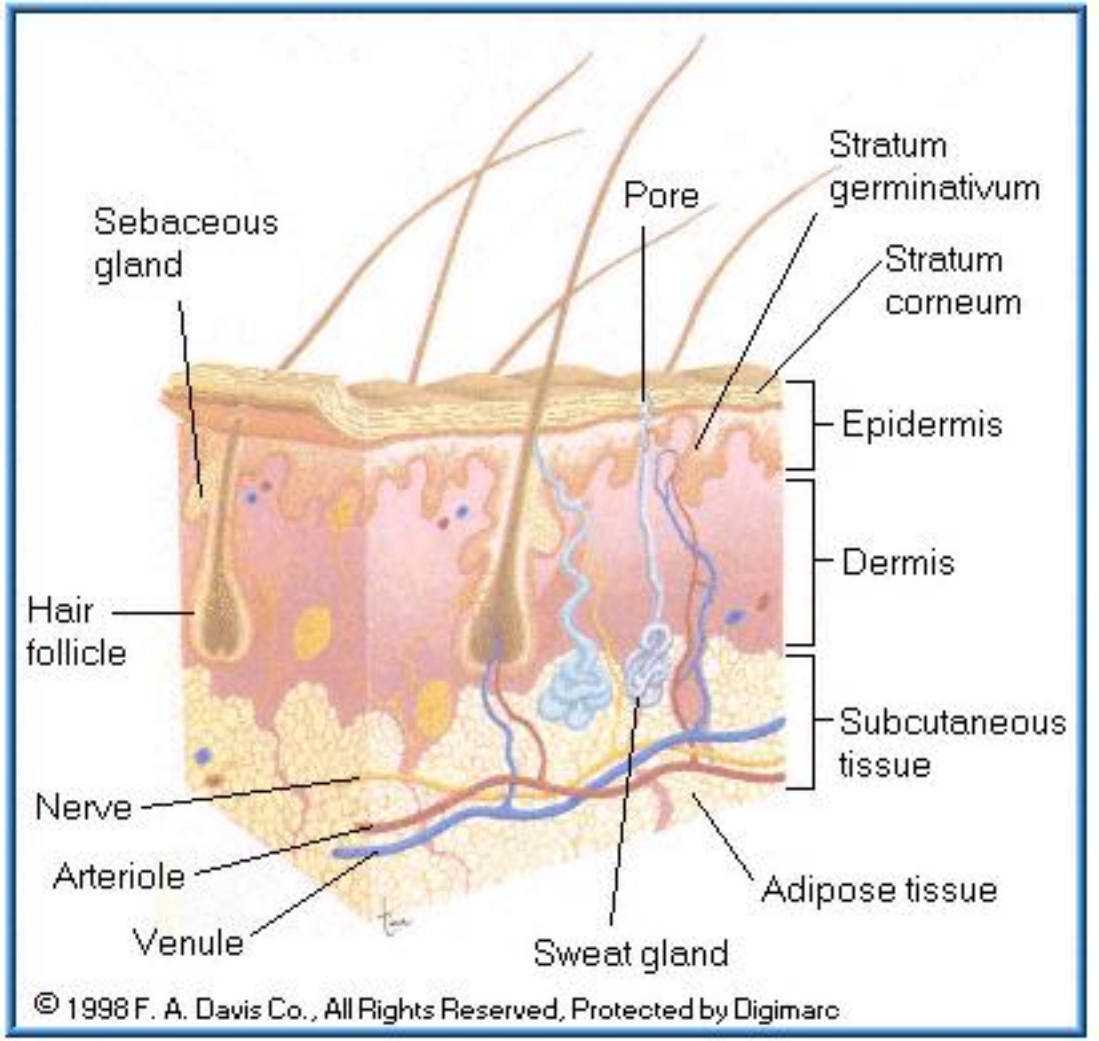
- Must first pass through nasal turbinates before reaching lungs
  - ‘scrubber’ effect
  - Protection vs. target
  - Absorption dependent on solubility in blood
  - Respiration rate and blood flow are important factors

Absorption of aerosols

- Dependent on aerosol size and water solubility
- 5µm or > deposited in nasopharyngeal region
- 2 - 5 µm deposited in tracheobronchiolar regions
- ≤ 1µm 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



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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)

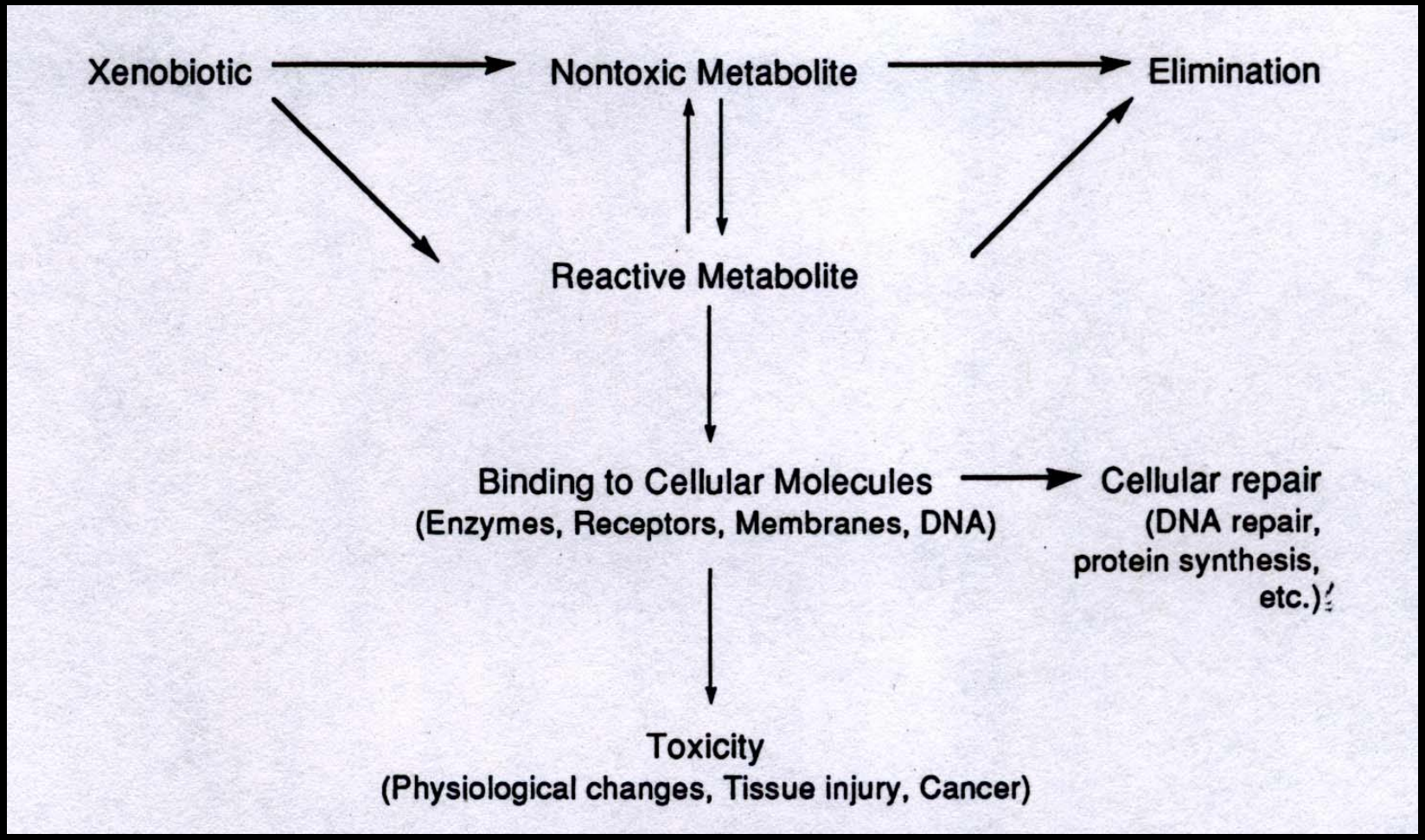
- Lipophilic (fat loving) vs hydrophilic (water loving)
  - mechanism to convert compounds from a chemical structure that favors absorption to one that favors elimination
  - Exception is excretion via inhalation, where the conversion to hydrophilic form will slow elimination

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

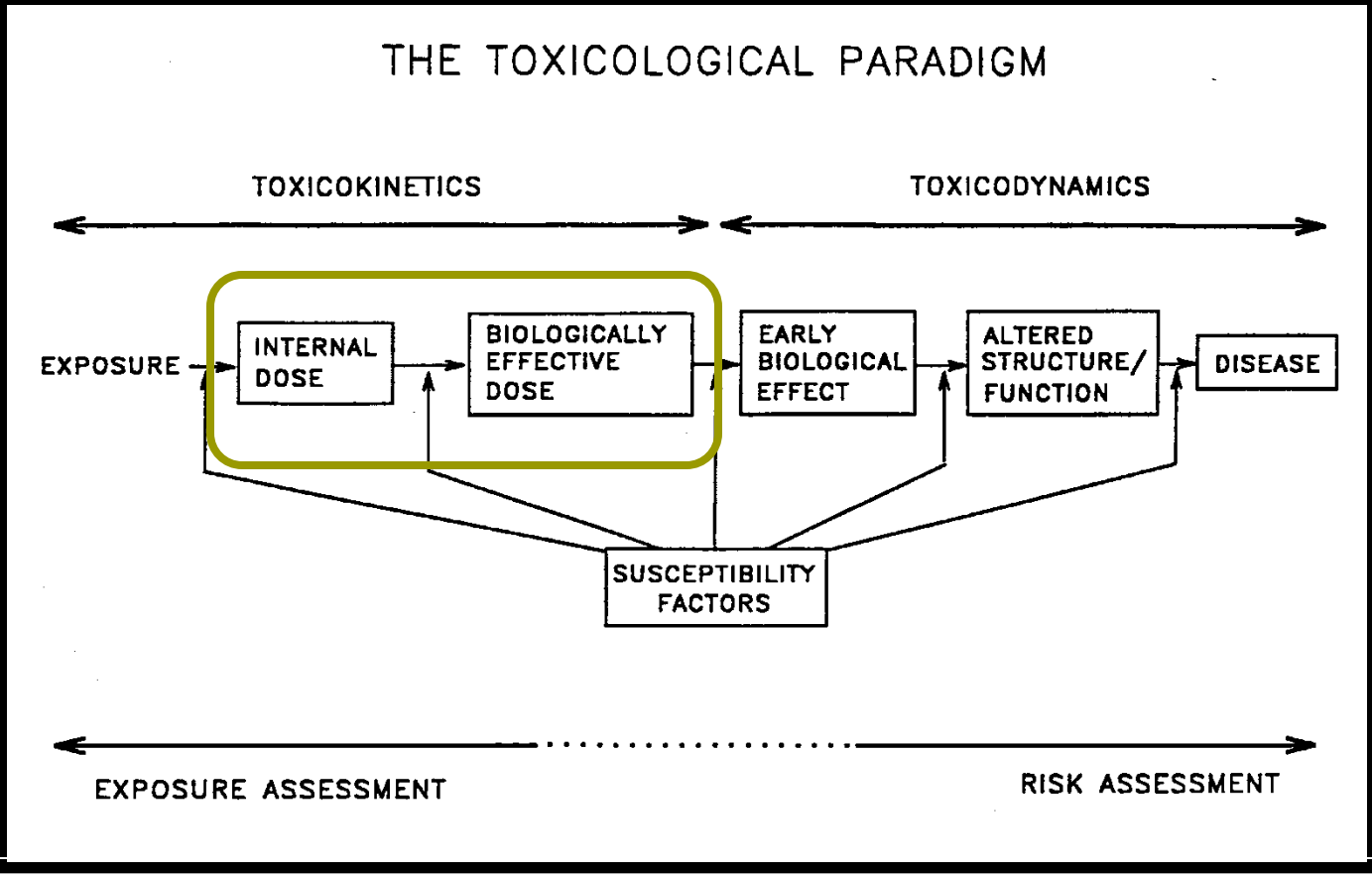
The Dose-Response Relationship

- 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



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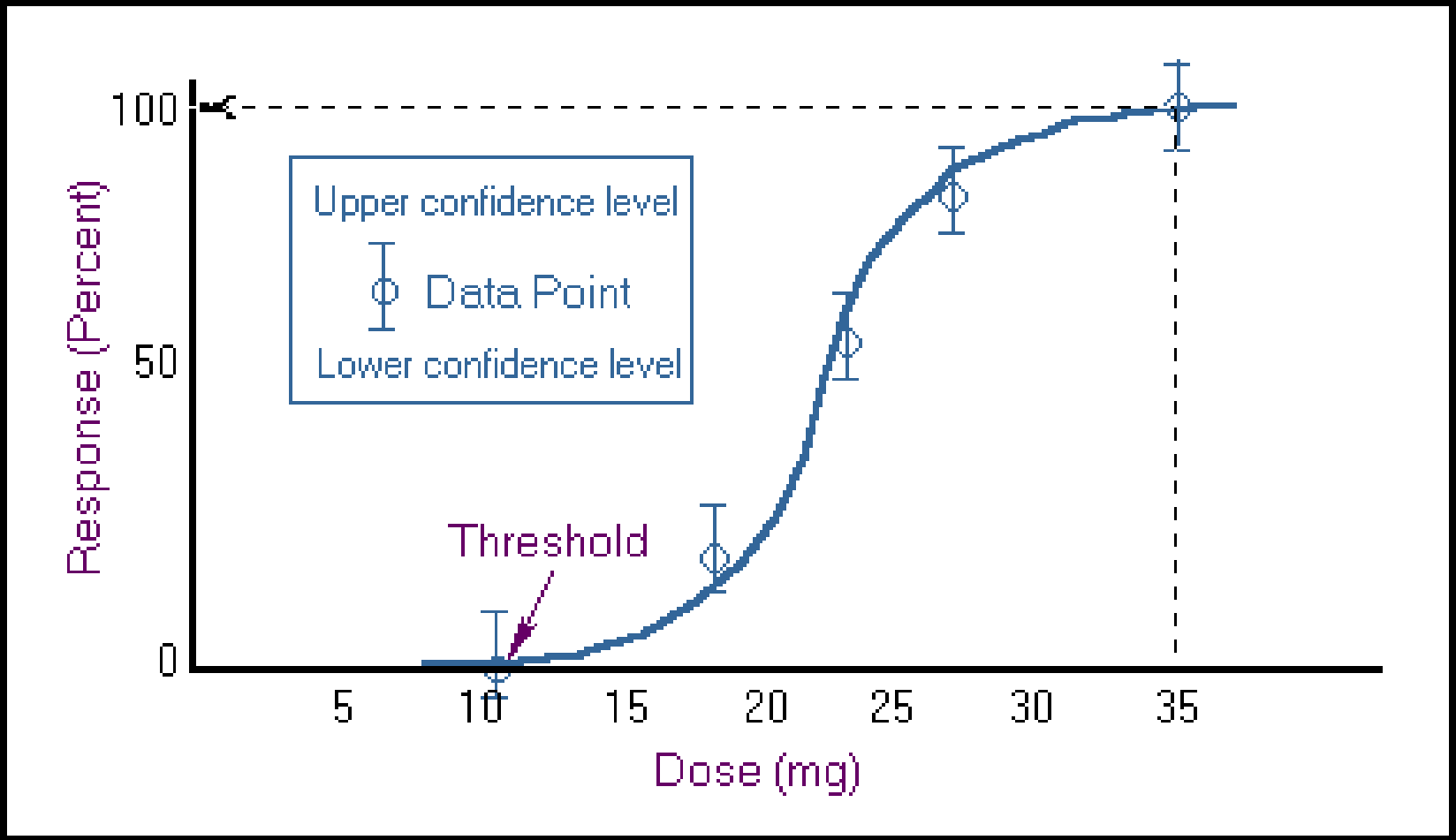
Range of toxic doses

- 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



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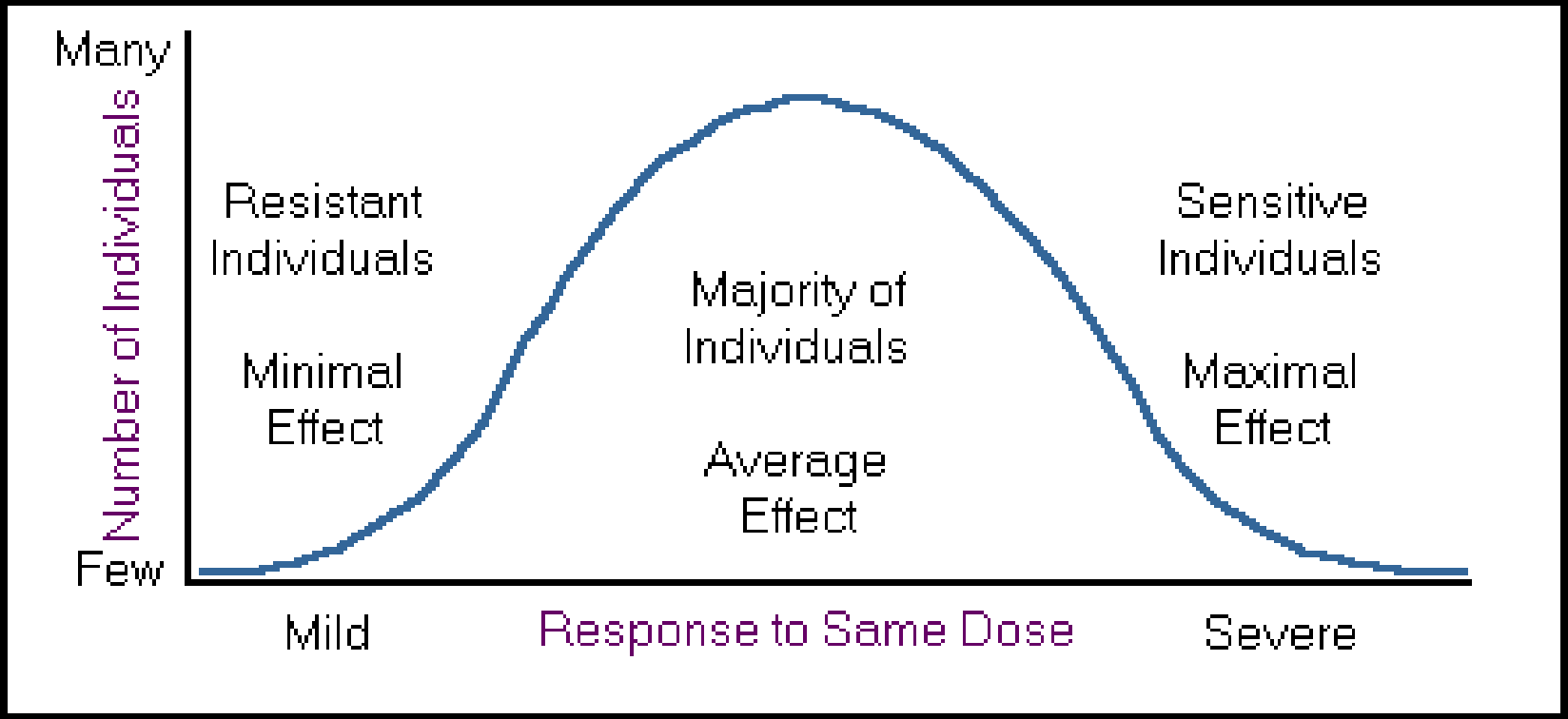

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Biomarkers to Evaluate Exposures, Effect & Susceptibility

- 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/