Factors Affecting Toxic Response

- Toxicant properties (purity, physical state)
- Exposure Conditions (route, frequency, duration, other agents/chemicals, dose)

Routes of Exposure

- Ingestion
- Inhalation
- Dermal
- Intravenous

Example: Oral Rat LD_{50} (mg/kg)

sugar	29,700
Salt	3000
Aspirin	1000
2,4-D	375
DDT	100
Arsenic	48
Nicotine	1
Dioxin (TCDD)	.001
Botulinus Toxin	.00001

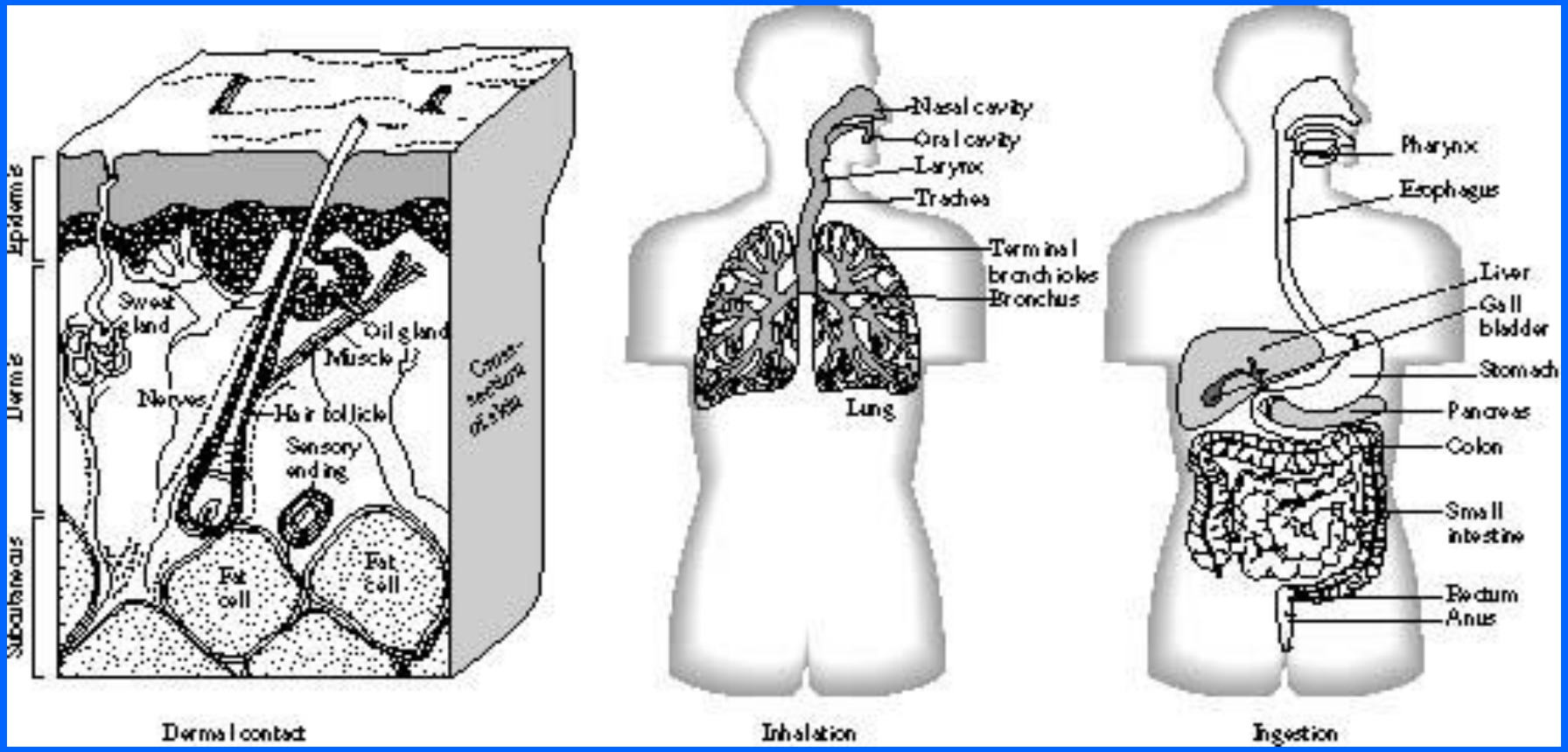


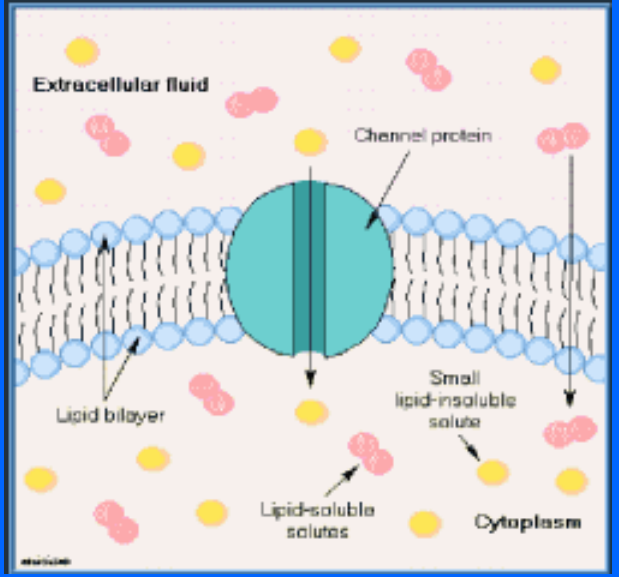
FIGURE 5- 1

Exposure routes for chemical agents in hazardous waste.

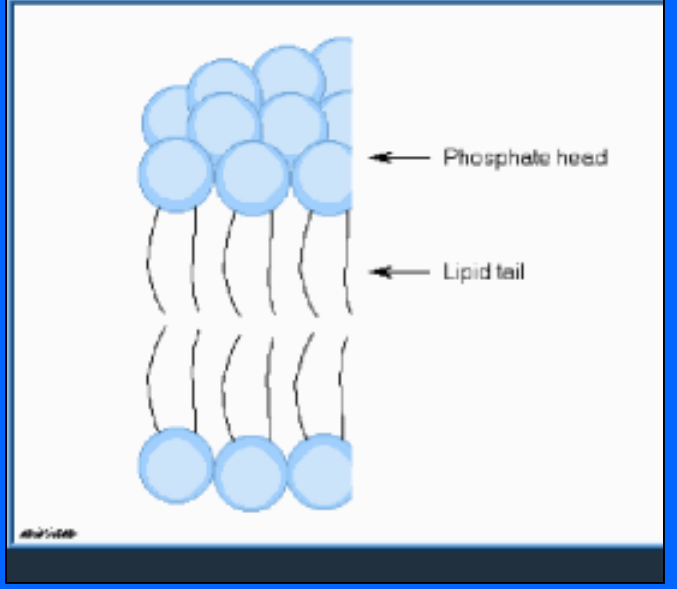
Overton's Rule

- Small, nonpolar molecules which are *lipid soluble*, cross cell membrane easily.
- Polar molecules which are *small*, cross cell membrane easily.

Cell Membrane



Phospholipid bilayer

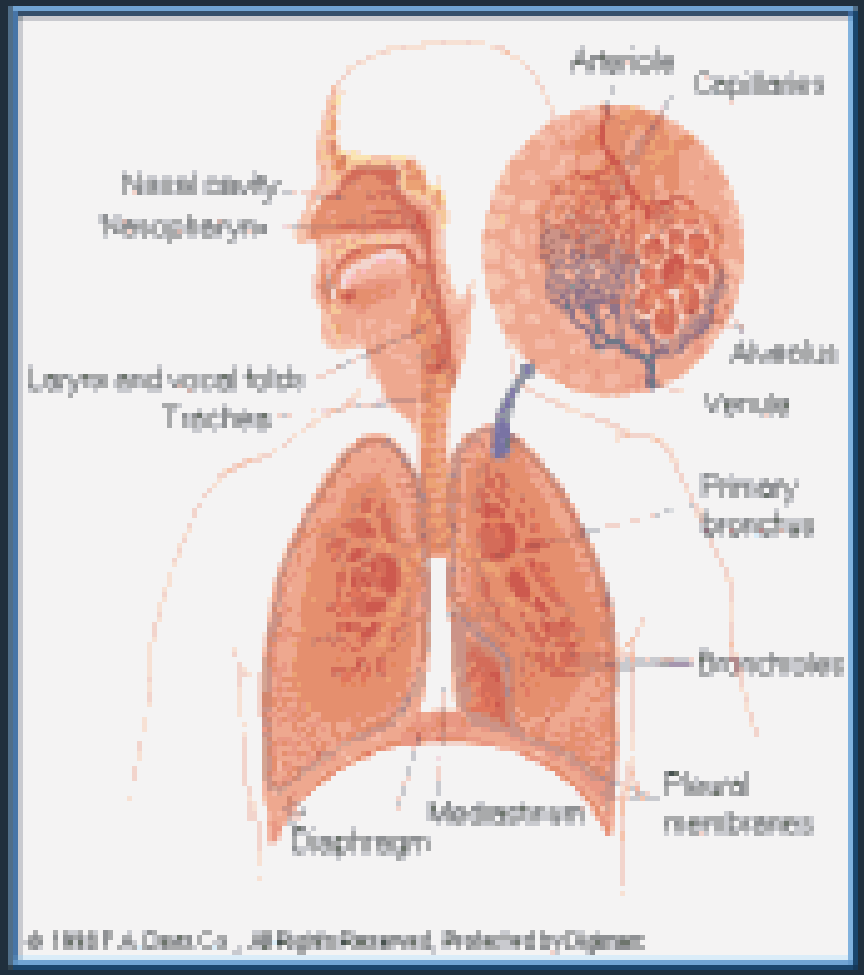


Inhalation Route

- Gases/Vapors - simple molec. diffusion; limited by toxicant's solubility in blood
  - ethylene v. chloroform
- Particulates - size is critical; air speed determines penetration;
  - 5-30 um: expelled or swalled in nasopharyngeal
  - 1-5 um: sedimentation in tracheobronchial
  - ≤ 1 um: deposited to alveoli

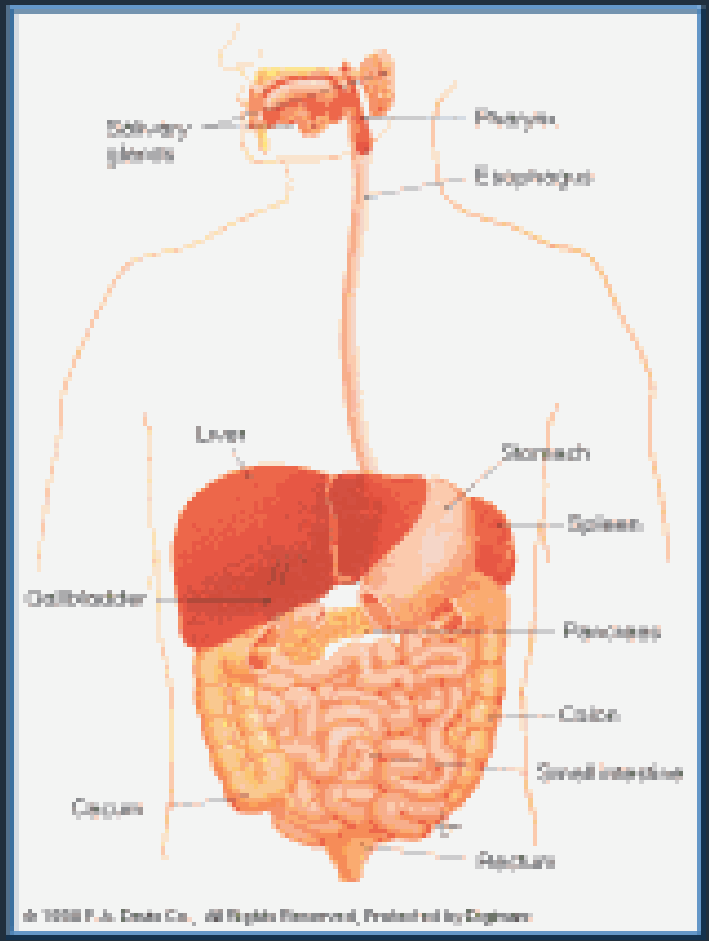
INHALATION ROUTE

- Parts of Respiratory System
  - Nasopharyngeal (nostrils to larynx)
  - Tracheobronchial (windpipe to bronchioles)
  - Alveolar
- Large surface area close to blood vessels



Ingestion Route

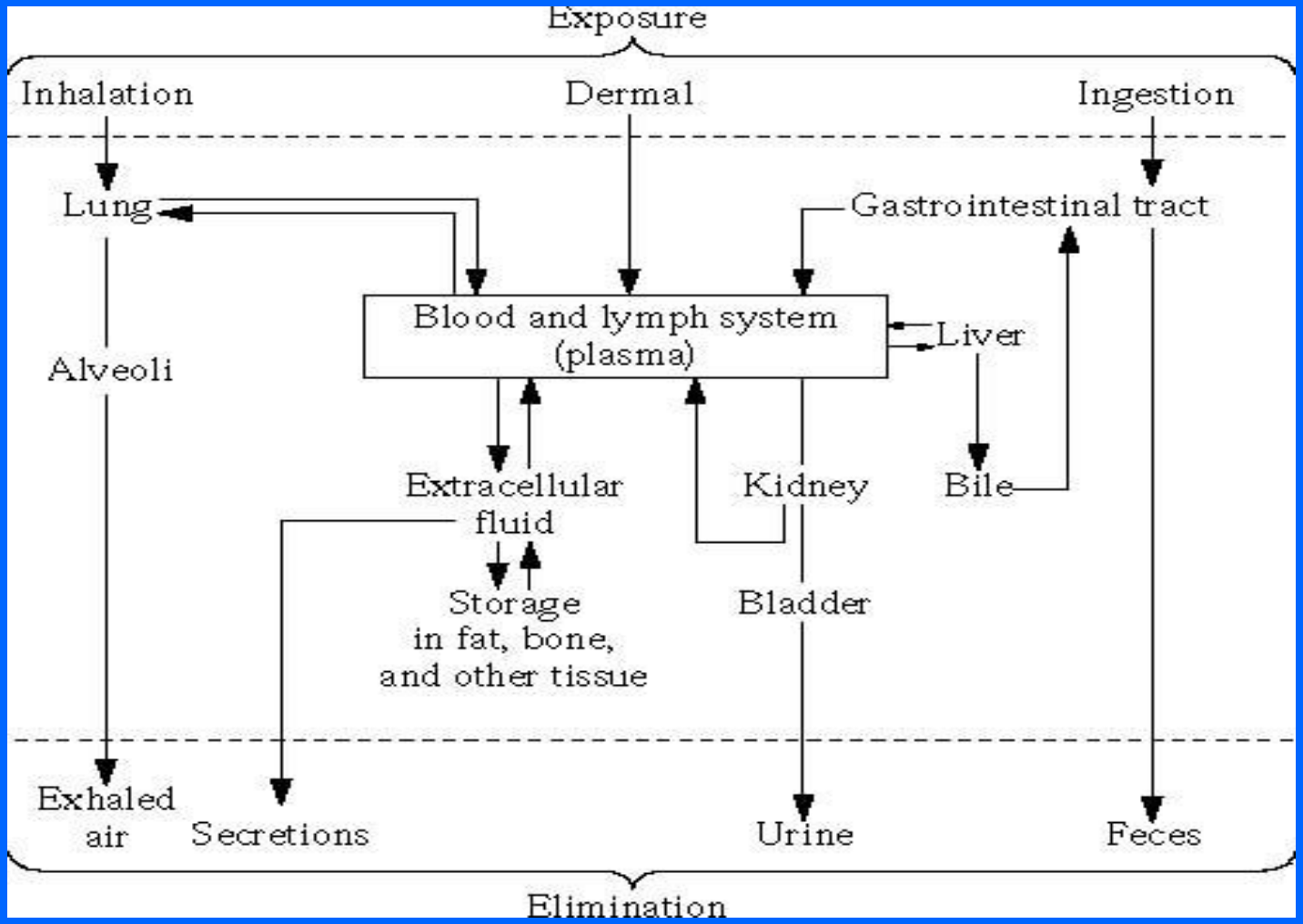
- Gastrointestinal Tract: mouth to stomach to intestines to anus
- 3 absorption factors:
  - lipophilicity
    - ability to cross cell membranes
  - acidity
    - least polar form = most lipid soluble form = most easily absorbed form



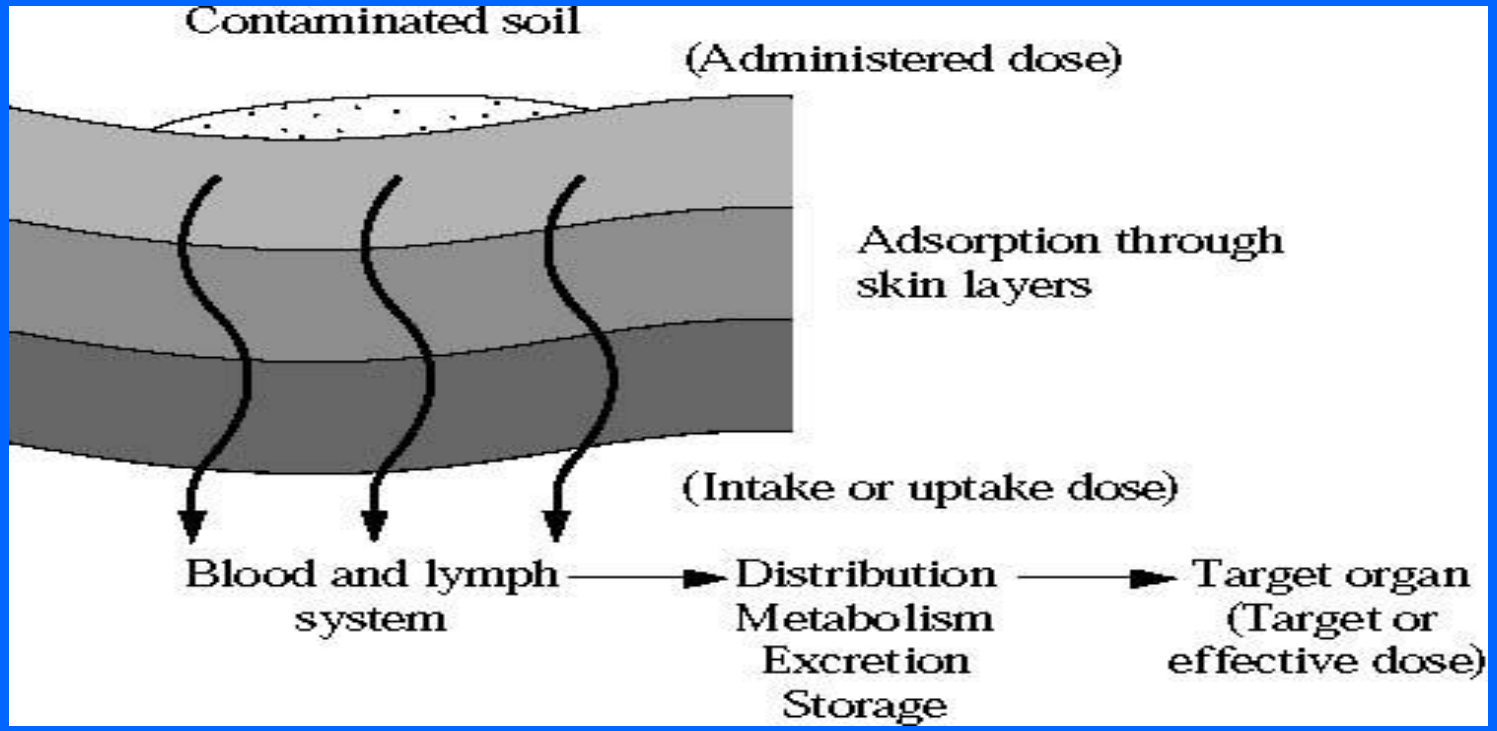
Gastrointestinal Tract

- 3 absorption factors (cont.):
  - acidity (cont.)

    - stomach acid pH = 2 (weak organic acid is least polar in stomach and is absorbed there)
    - intestines pH = 6 (weak organic base is least polar in intestine and is absorbed there)
  - binding (interaction with food)
    - may reduce or enhance absorption and toxicity



Overview of absorption, distribution, storage, transformation, and elimination of a toxic substance in the human body.



Types of doses for dermal contact with contaminated soil.

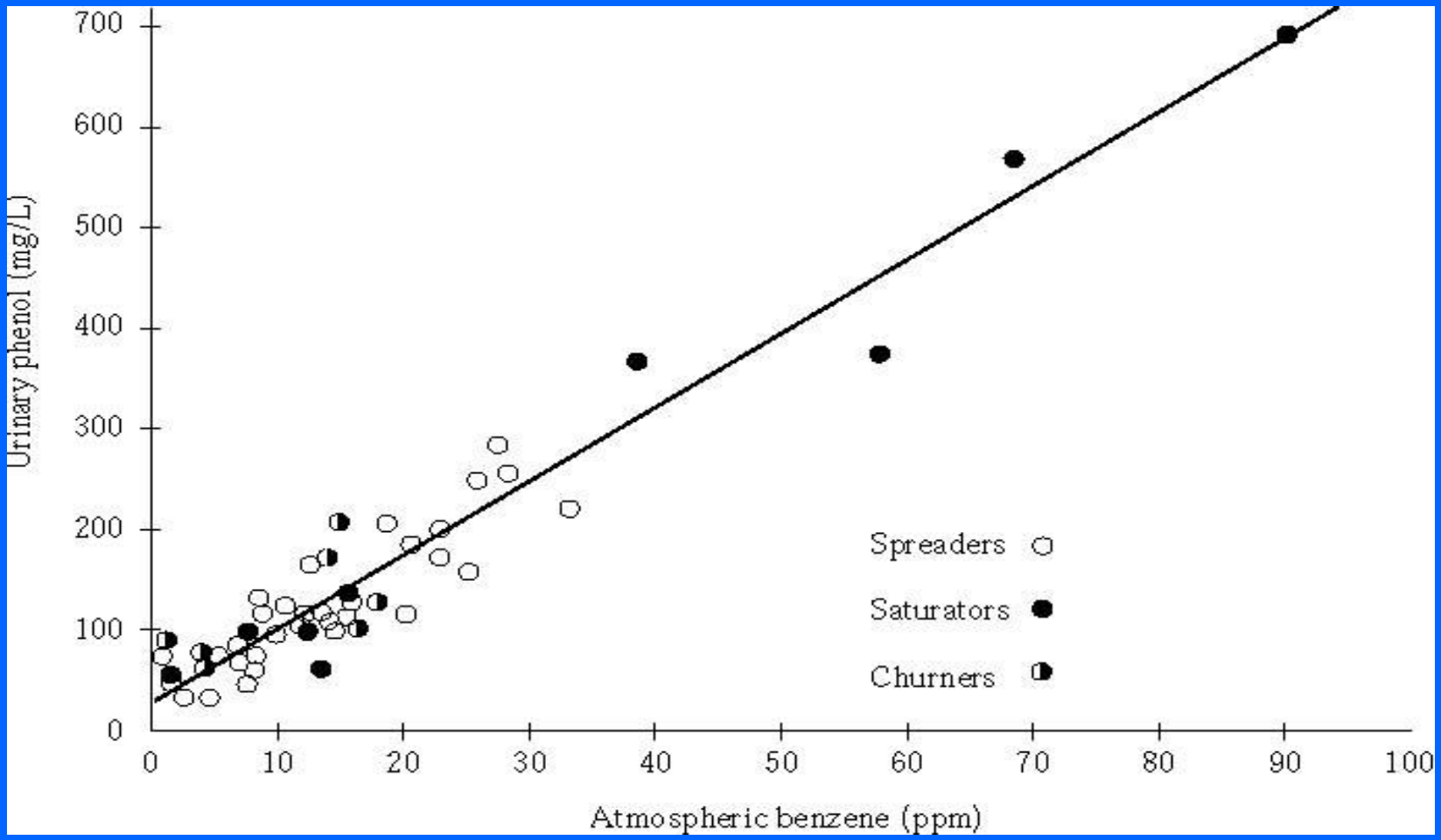
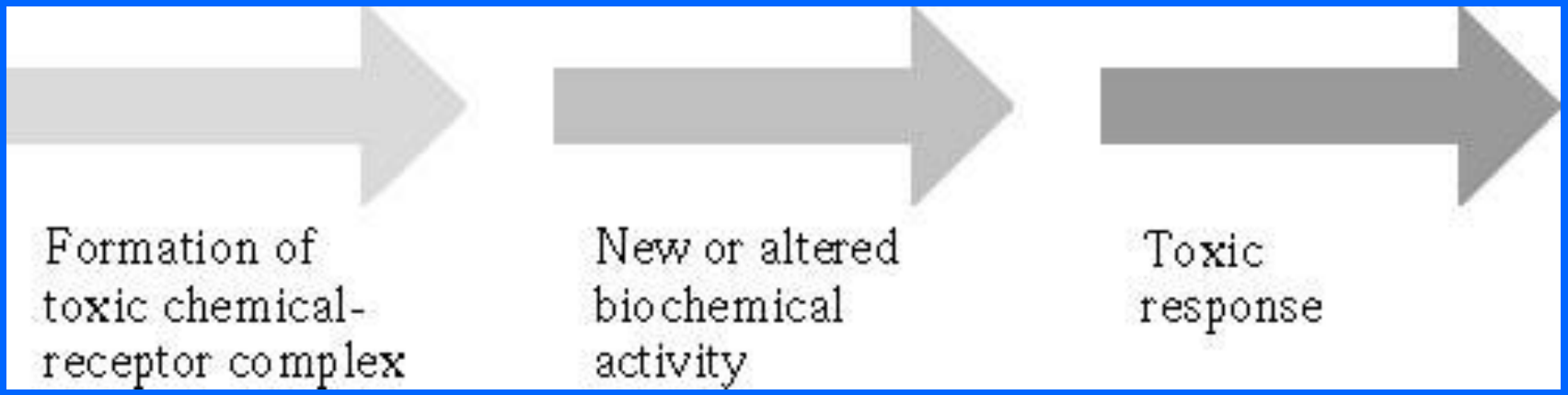
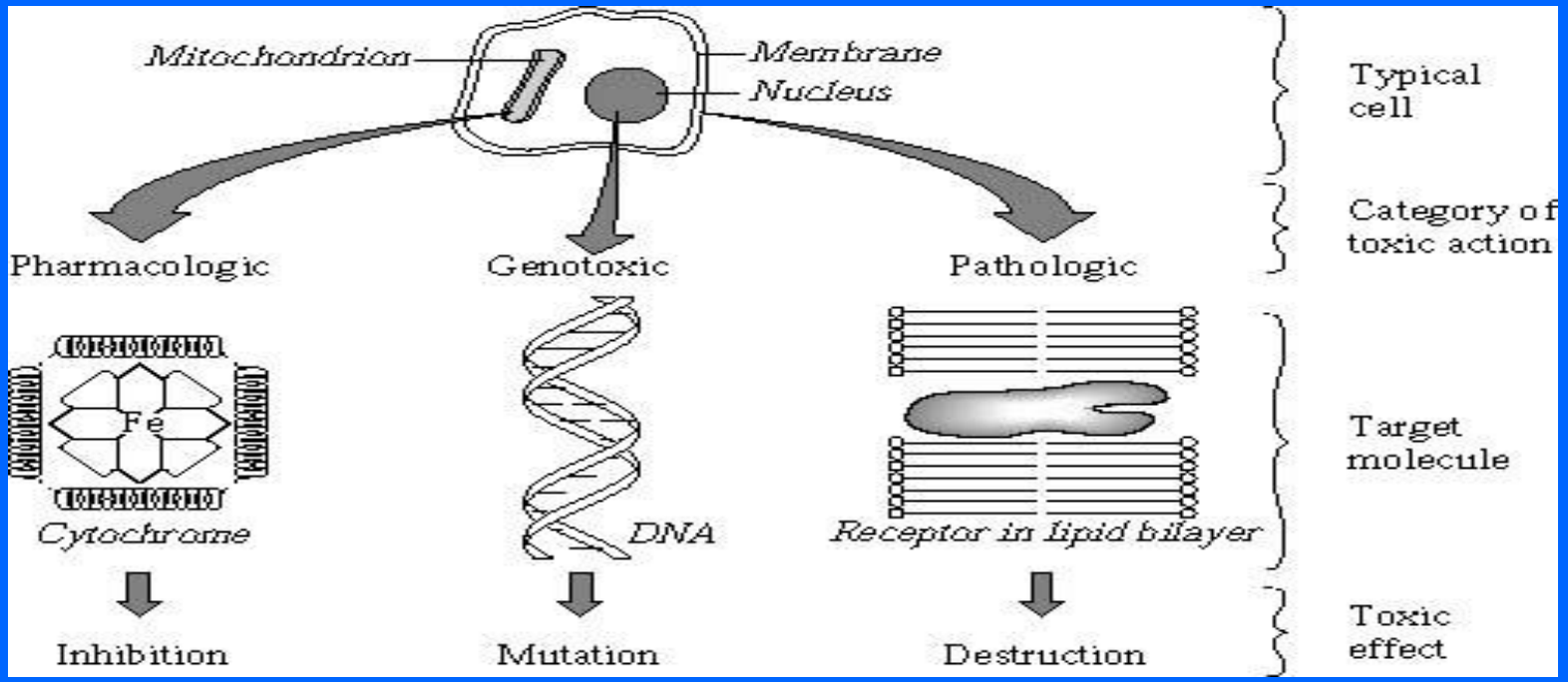


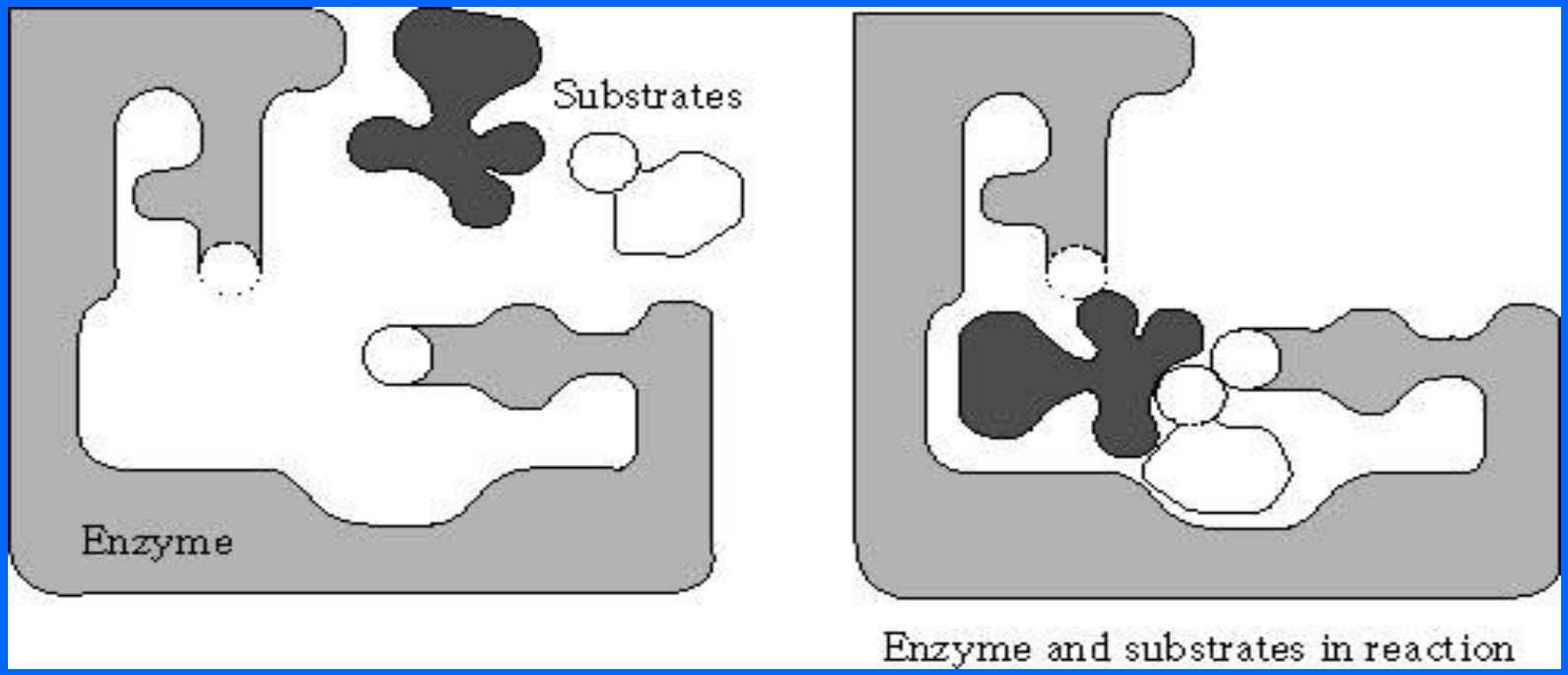
FIGURE 5-4
Correlation of atmospheric benzene concentrations with urinary phenol levels in workers in a rubber coating plant.



Sequence of events leading up to a toxic response.

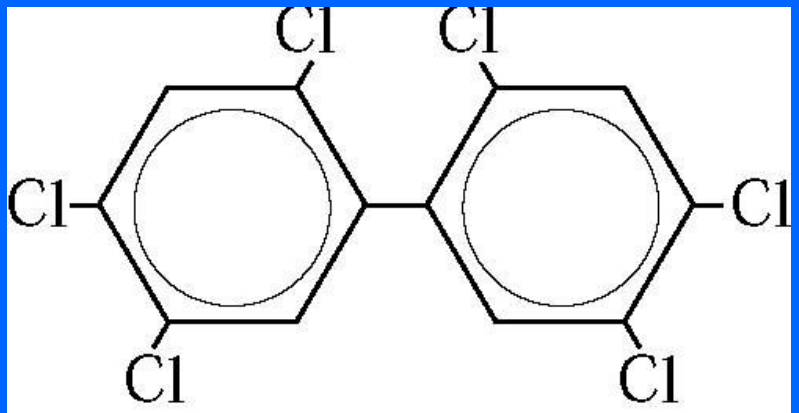


Representative cellular targets for toxic action.

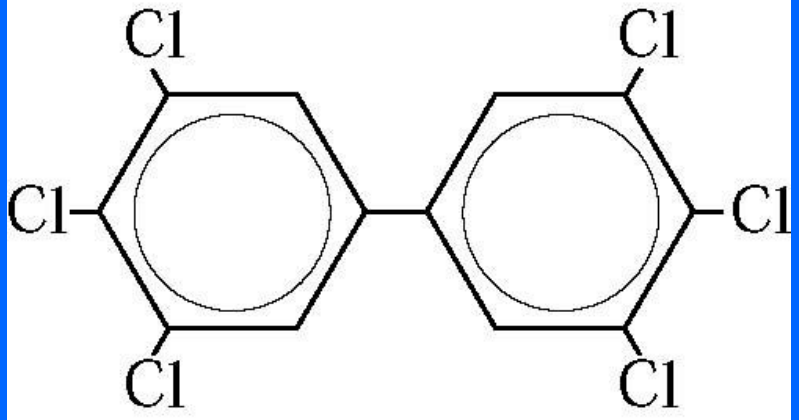


Lock-and-key model for toxic action.

Example of compounds with identical molecular formula but different toxicity.

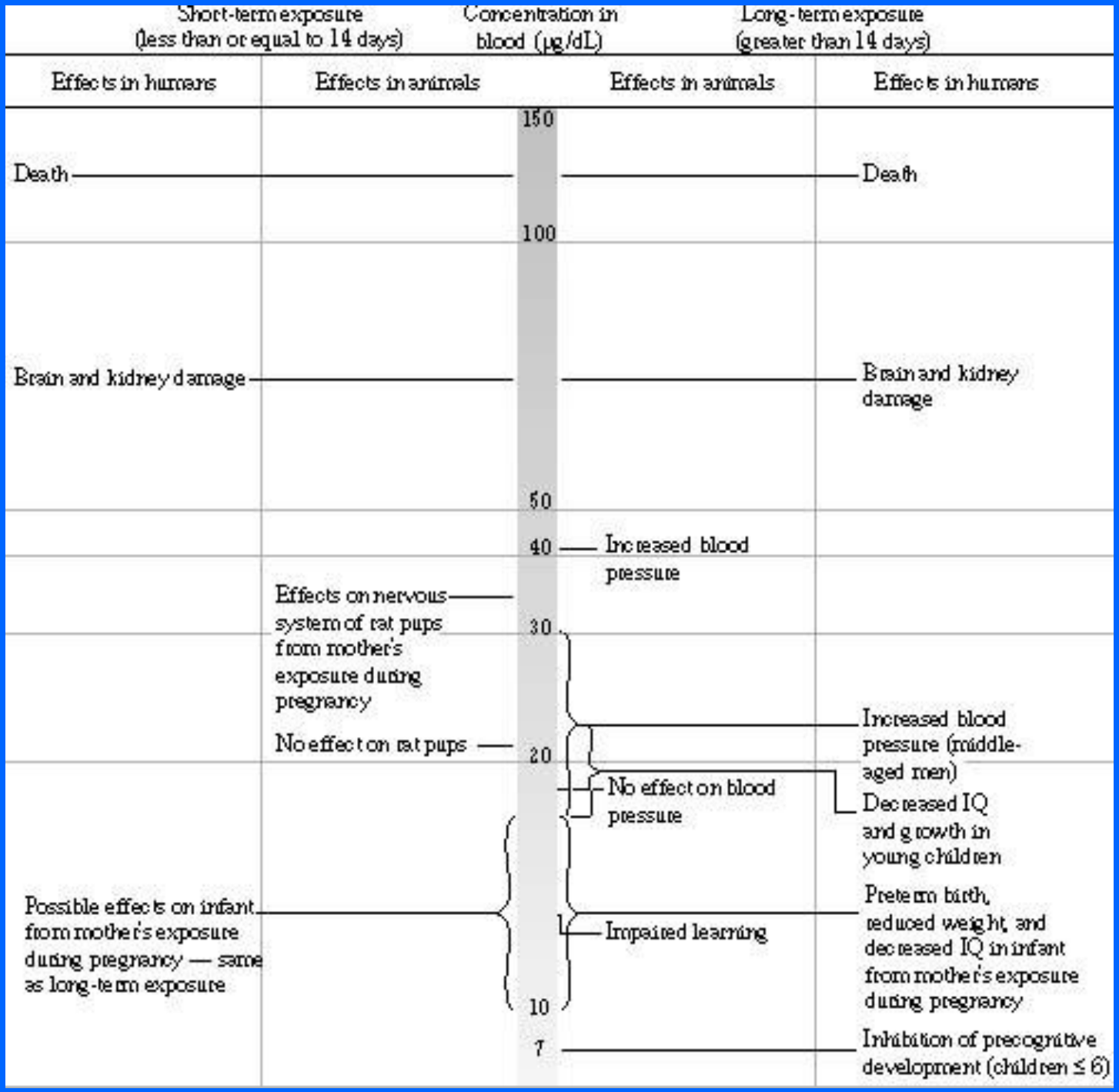


Low toxicity PCB

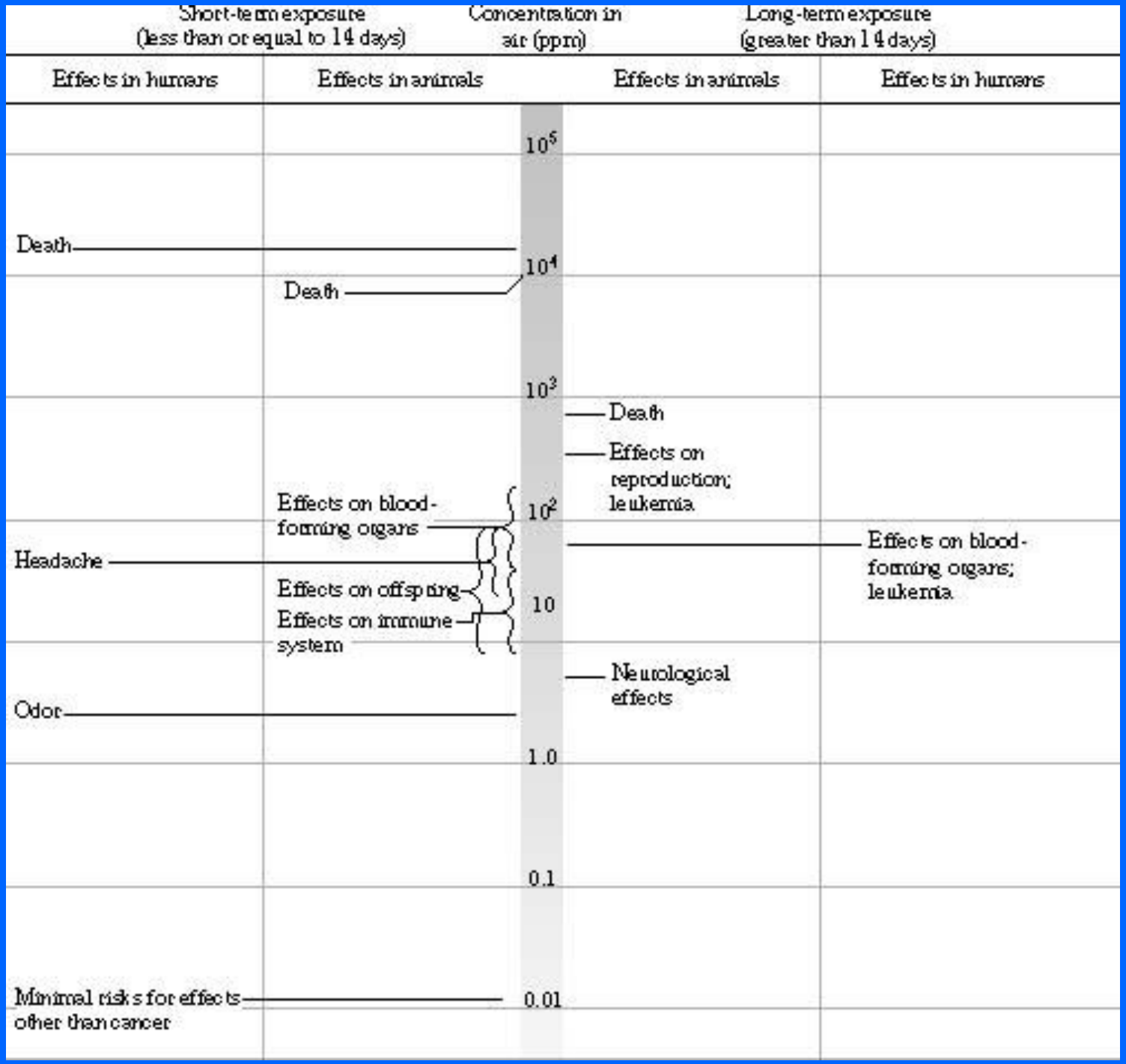


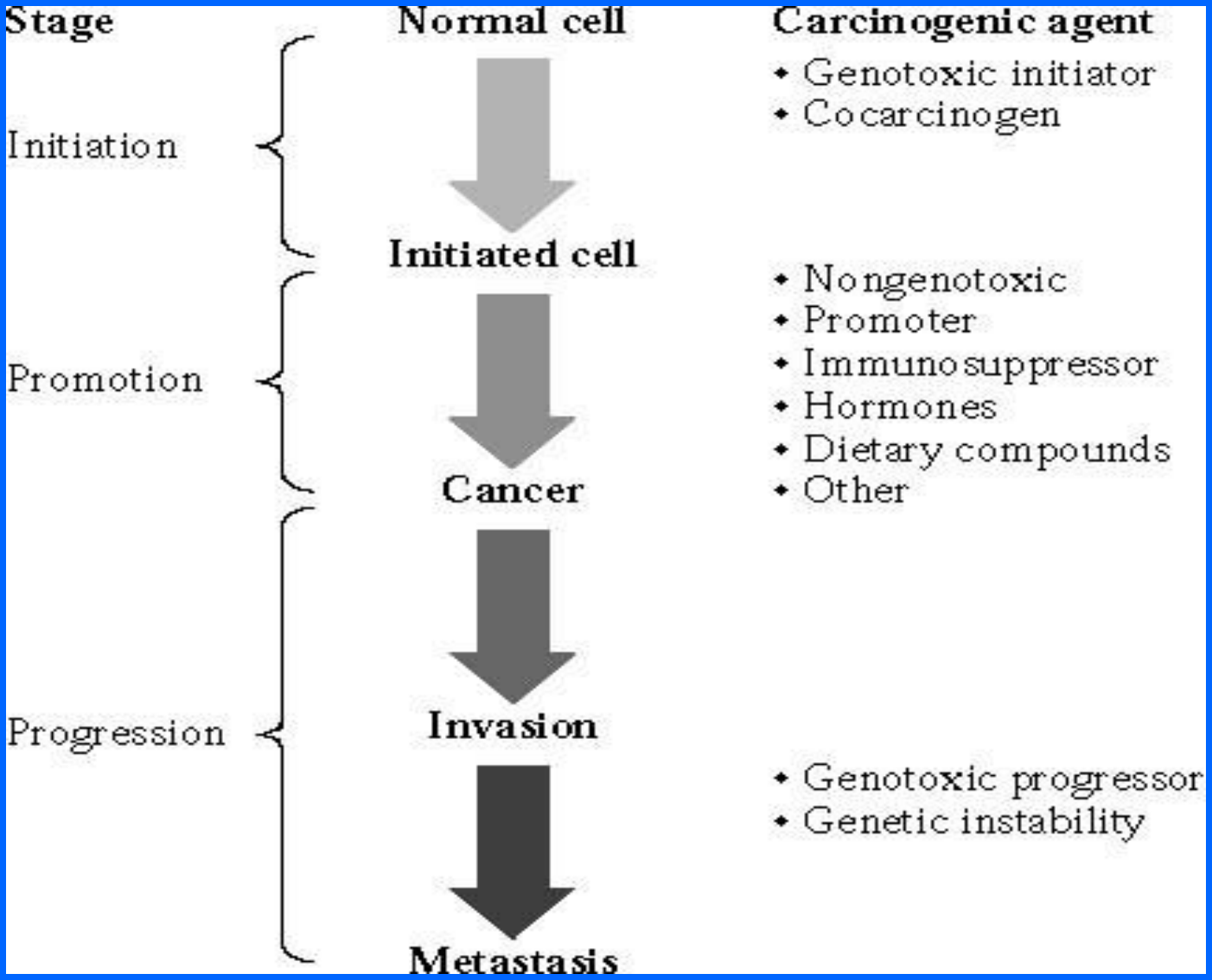
High toxicity PCB

Health effects from breathing and/or ingesting lead.



Health effects from breathing benzene.





Three stages in carcinogenesis.

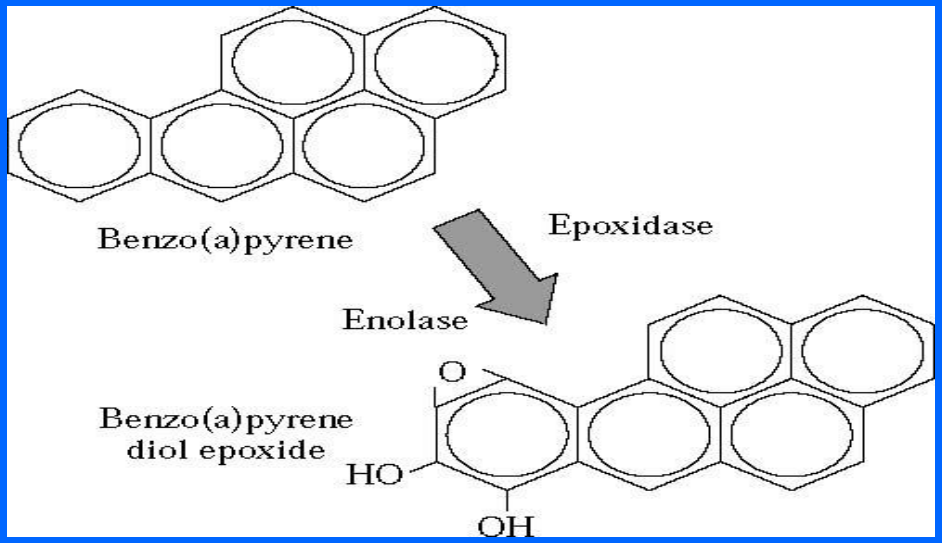
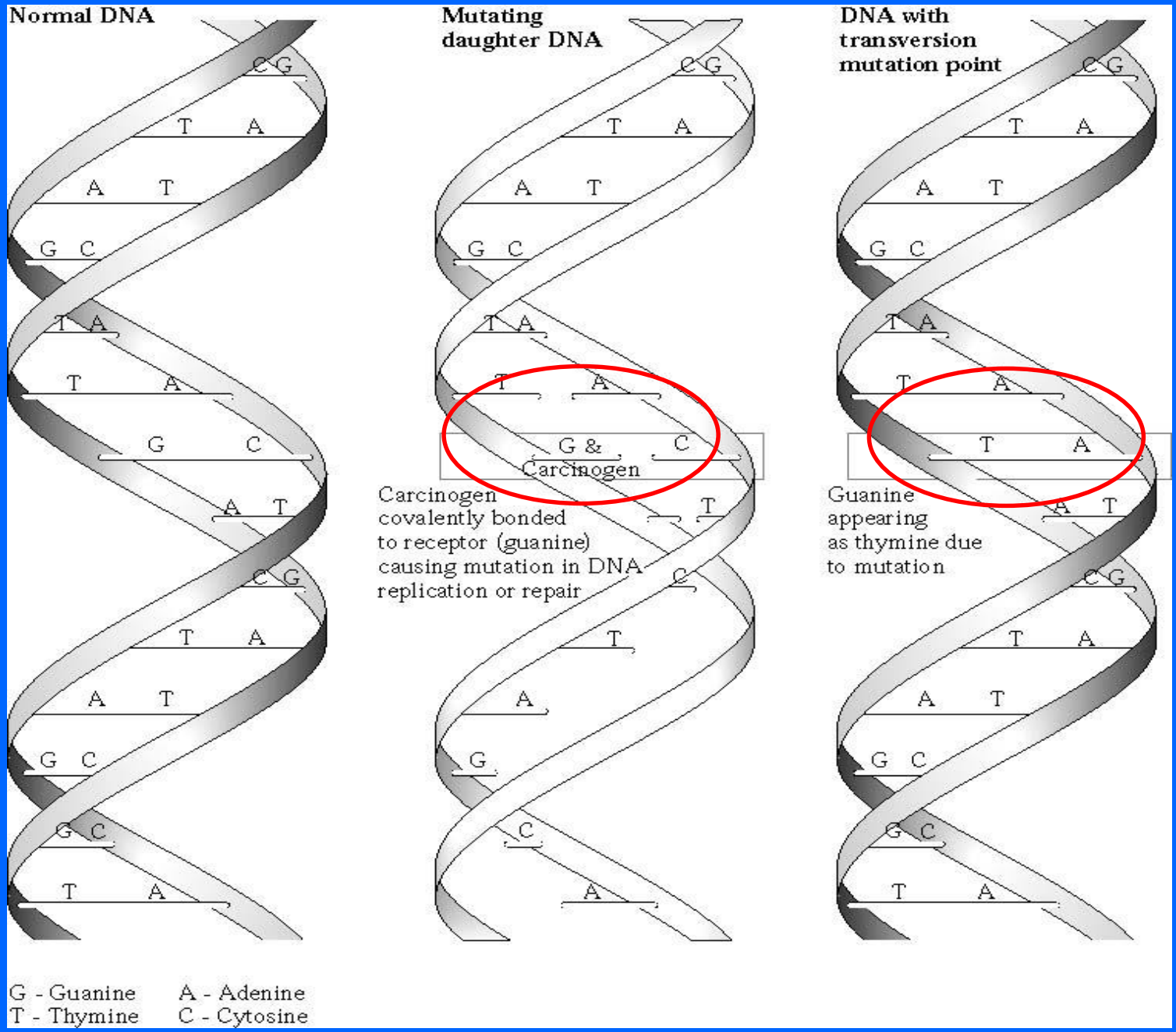
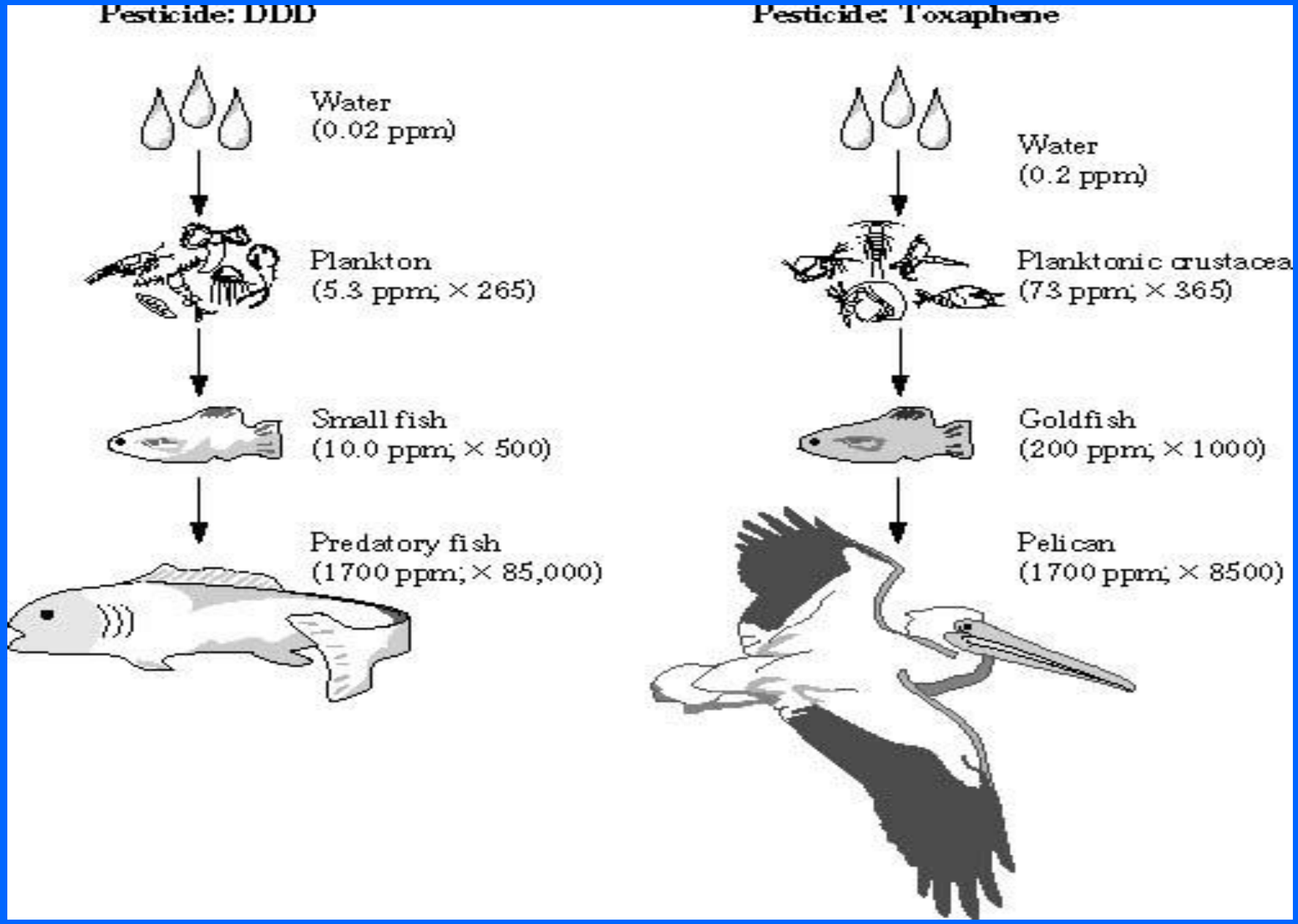


FIGURE 5-20

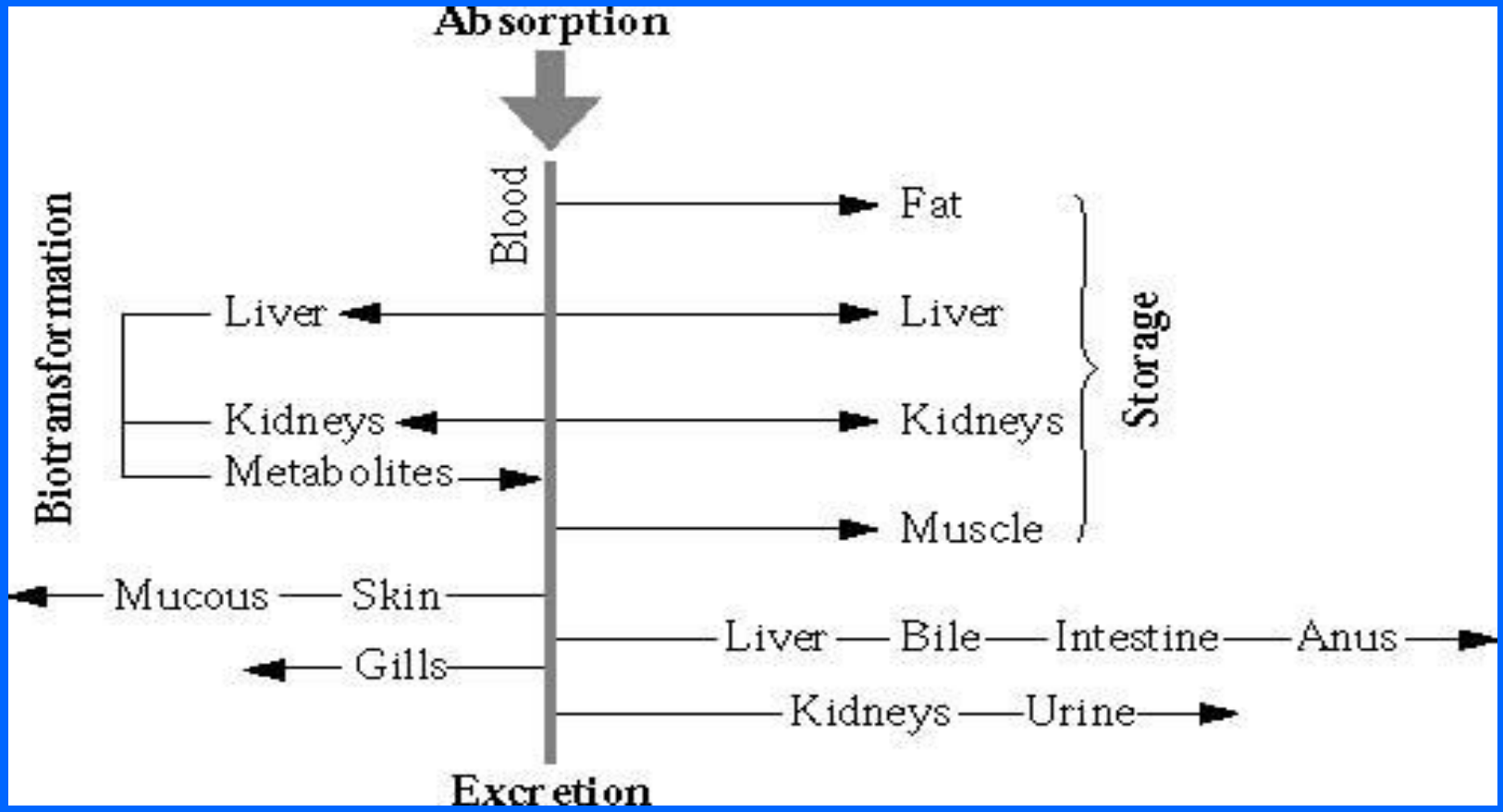
Metabolic activation of benzo(a)pyrene.

Example of a point mutation through base pair substitution.





Biomagnification of pesticides in aquatic food chains.



Possible movement and fate of a contaminant after absorption into the bloodstream of fish.

Paracelsus: "All substances are poisons. The right dose differentiates a poison and a remedy."

- Examples

Substance	RDA (mg/day)	Toxic Level (mg/day)
Zinc	15	60 (LOAEL)
Selenium	0.05-0.2	0.8-1.0 0.35 RfD
Chromium	0.05-2 (+3)	70 (+3) RfD 0.35 (+6) RfD

RDA = Recommended Daily Allowance
LOAEL = lowest observed adverse effect level
RfD = reference dose for oral intake by 70 kg person

- Toxicology = study of adverse effects to organisms due to chemical exposure
  - –Controlled; lab; animals
- Epidemiology = study of distribution of diseases and causes in humans
  - –Avoids extrapolation from animals
  - –Observational - correlation but not causation
  - –Sensitivity problems - population or dose too small to see effect
  - –Months, years, or lifetimes req'd for study

- Few compounds have enough human data to quantitatively determine negative effects
  - –Worker exposure
    - Miners, hat makers, manufacturing,….
  - –Accidental catastrophes
    - Bhopal, Sveso Italy, ….
- Most toxicity data based on animal studies

Toxic Effects of Chemicals

- Exposure to chemical
  - –3 routes: skin absorption, inhalation, ingestion
  - –Uncertainty: conc in soil, air, water, food; contact time, cumulative over time?
- Dose of chemical
  - –Amount in body to target organs
  - –Net = input - elimination
- Response to chemical
  - –Death, illness, cancer, sensory effects,…..

. . UNCERTAINTY . . .

Response vs Dose

- Non-carcinogenic effects
  - –Assume a “threshold” below which no adverse effects
- Definitions
  - –ADI = acceptable daily intake
  - –LOAEL = lowest observed advsere effect level
  - –NOAEL = no observed adverse effect level
  - –RfD = Reference Dose; “safe”, ~ ADI
    - NOAEL/UF where UF = uncertainty factor

Extrapolate from lab study with animals to humans

- NOAEL →ADI 1-10x *(UF 1-10)*
  - –Quality of study
- LOAEL →NOAEL 1-10x
- Subchronic animal study →chronic effect 10x
- Chronic ave animal →Ave human 10x
- Ave human →Sensitive human 10x
- Multiple cmpd exposures 1-100x

Example

Data from toxicity study with rabbits and malathion.
50 rabbits per dose group
2 yrs

What is LD50 (lethal dose to 50% of population)?
What is NOAEL?
What is LOAEL?
What is safe dose for humans?

Dose, mg/kg-d	# Dead
0	2
4	2
7	7
14	17
23	26

Putting it together: Which of the compounds is more toxic?

CMPD A	CMPD B
LD50 10 mg/kg	LD50 100 mg/kg
CPF 10 kg-d/mg	CPF 100 kg-d/mg
NOAEL 0.1 mg/kg	NOAEL 1 mg/kg

CPF = carcinogenic potency factor

Which interaction is most likely?

- If similar mechanism may be additive
- Synergistic if:
  - –affect the same organ in different ways
  - –Chemical reactions (nitrites+amines=nitrosamines; carcinogen!)
- Antagonistic if:
  - –Chemicals react together (EDTA + metals)
  - –Opposite effects of toxins (stimulant vs depressant)
  - –Competition for the same enyzmes or receptors

ANSWER: Depends on assumptions made!

- Assume ADDITIVE toxicity, then
  - –50% each: LD50 = 18
    - $(0.5/LD50_1 + 0.5/LD50_2 = 1/LD50_{mix})$
  - – 25A/75B: LD50 = 31
- Assume SYNERGISTIC toxicity, then
  - –50% each: LD50 < 18
- ASSUME ANTAGONISTIC toxicity, then
  - –50% each: LD50 > 18

What is the combined toxicity of A and B?

- What is the LD50 if the total dose to which an organism is exposed is 50% A and 50% B by mass ?

- What is the LD50 if the total dose to which an organism is exposed is 25% A and 75% B by mass?

However, unfortunately….

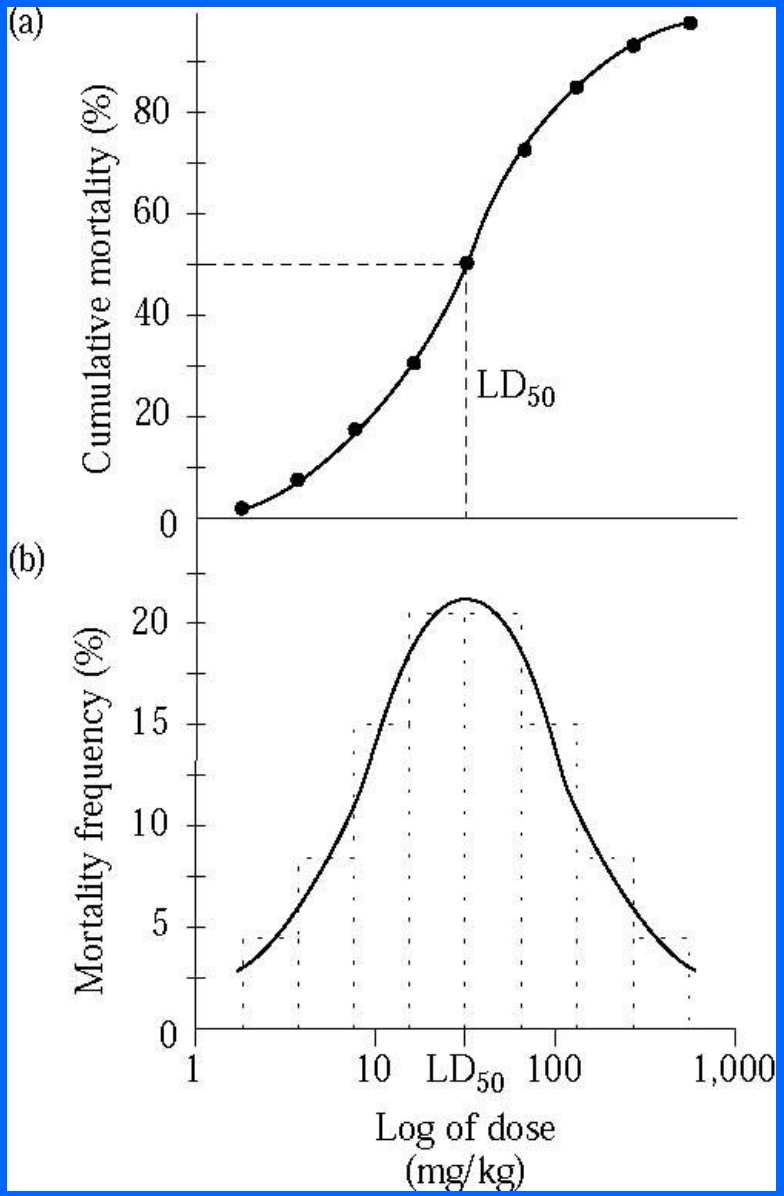
- Interactions of mixtures are difficult to predict
- Optimally have data
  - –Ex: tobacco smoke & asbestos on lungs
  - –Ex: ethanol and CT on liver
- Most often do not have data
  - –Too many chemicals and potential combinations!

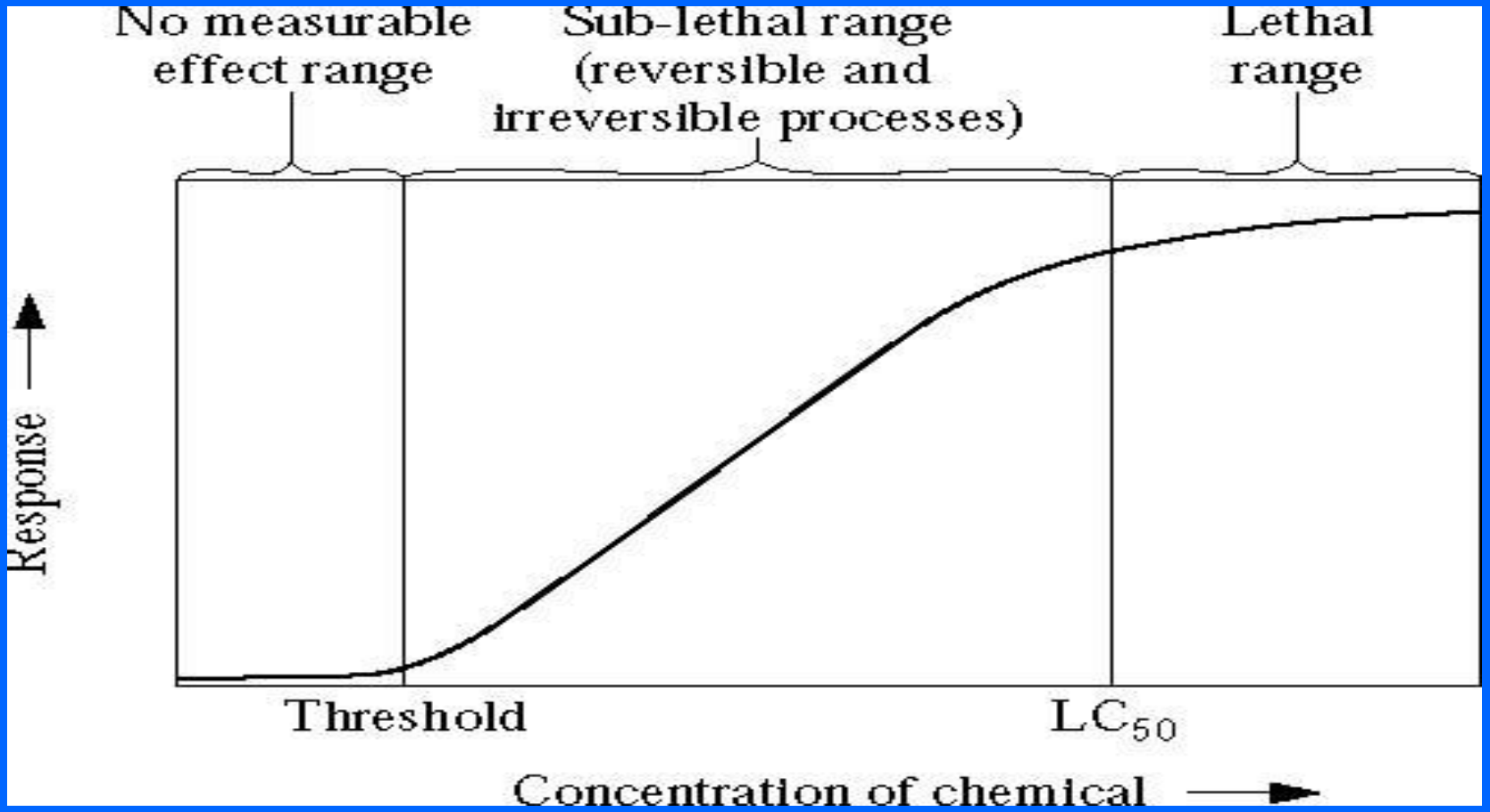
Further complications….

- Not a single value
  - –Ex: LC50 for endosulfan toxicity to fish ranged from 0.68 to 3.30 mg/L in 4 different labs (5x)
- Different organisms respond differently
- Low level effects difficult to detect
  - –Ex: 24,000 mice tested, couldn't detect 1% excess risk (1/100 incidence)
  - –$1.5M for rodent sty of 1 chemical @ >5%

FIGURE 5-11

Dose-response relationship (dose versus mortality).





Idealized plot of dose-response relationship

Location of NOAEL and LOAEL doses with respect to the threshold on a typical dose-response curve.