Introduction to Toxicology

Richard R. Rediske, Ph.D.

Annis Water Resources Institute

Grand Valley State University

Toxicology

Formerly

The Science *of Poisons*

Now

The science that deals with the adverse effects of chemicals on living organisms and assesses the probability of their occurrence

Outline

- History of Toxicology
- Dose Response
- Types of Toxicants
- Case Studies of alcohol and lead
- The Future

Historical Perspective

“...the appearance of disease in human populations is influenced by the quality of air, water, and food; the topography of the land; and general living habits.”

The ancient-Greek physician Hippocrates in his treatise Air, Water and Places

400 BC

http://classics.mit.edu/Hippocrates/airwatpl.mb.txt

All substances are poisons;

there is none that is not a poison.

The right dose

differentiates a poison and a remedy.

Paracelsus (1493-1541)

The Father of Modern Toxicology

History

Spanish physician Orfila (1815) established toxicology as

a distinct scientific discipline.

Toxicology Today

Mechanistic toxicology: The study of how a chemical causes toxic effects by investigating its absorption, distribution, and excretion.

Descriptive toxicology: The toxic properties of chemical agents are systematically studied for various endpoints using a variety of different organisms.

Clinical toxicology: They study of toxic effects of various drugs in the body, and are also concerned with the treatment and prevention of drug toxicity in the population.

Toxicology Today

Forensic toxicology: A branch of medicine that focuses on medical evidence of poisoning, and tries to establish the extent to which poisons were involved in human deaths.

Environmental toxicology: The study of the effects of pollutants on organisms, populations, ecosystems, and the biosphere.

Regulatory toxicology: The use scientific data to decide how to protect humans and animals from excessive risk. Public or Private Sector.

Dose

The amount of chemical entering the body

This is usually given as

mg of chemical/kg of body weight = mg/kg

The dose is dependent upon

* **The concentration**
* **The properties of the toxicant**
* **The timing and frequency of exposure**
* **The length of exposure**
* **The exposure pathway**

What is a Response?

The degree of responses depend upon the dose and the organism

- Change from normal state
  - could be on the molecular, cellular, organ, or organism level--the symptoms
- Local vs. Systemic
- Reversible vs. Irreversible
- Immediate vs. Delayed
- Monotonic – response increases with dose (cyanide and many traditional toxicants)
- Nonmonotic – response does not increase with dose (hormones, endocrine disruptors, micronutrients and vitamins)

CHEMICALS: Major Types of Toxicity

- **Toxins – biological compounds (Ricin, botulism)**
- **Carcinogens - may induce cancer or increase its incidence and can affect any cells or tissues (benzene, vinyl chloride, benzo(a)pyrene)**
- **Mutagen - may induce hereditary genetic defects or increase their incidence and effect on the germ cells (gonads). (radiation, nitrosoamines)**
- **Teratogens - may induce non-hereditary congenital malformations or increase their incidence and effect on the growing fetus (*rubella*, thalidomide, PCBs, Dioxins)**
- **Endocrine disruptor – hormone mimic (PBDE, BPA)**

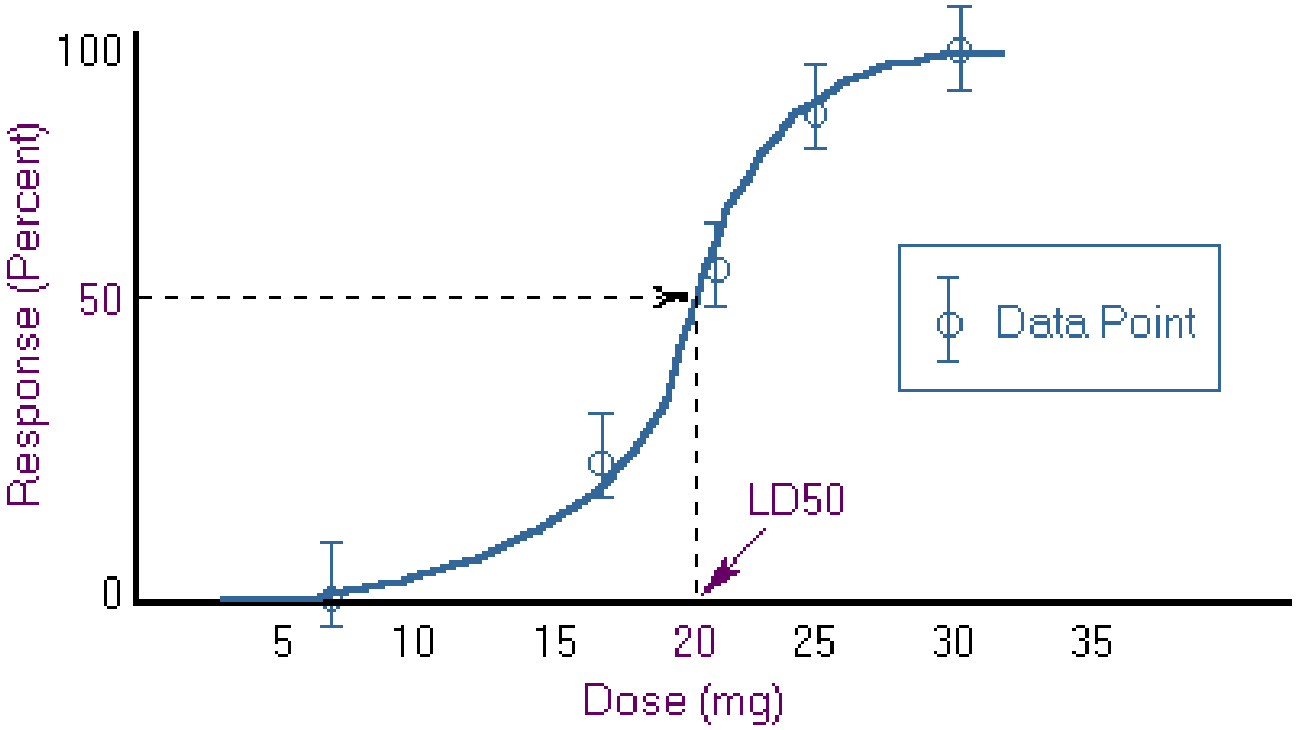
CHEMICALS: Major Types of Toxicity

- **Chronic toxicity: It involves Sub-lethal concentration and long-term exposure**
- **Chronic toxicity test is used to derive Effective Dose (ED_{50}): Is the dose by which half of the population has been affected**
- **Effect could be anything but death**
- **ED_{50} is obtained by plotting, for a given dose the proportion of the population that responded to that dose and all lower doses**

CHEMICALS: Major Types of Toxicity

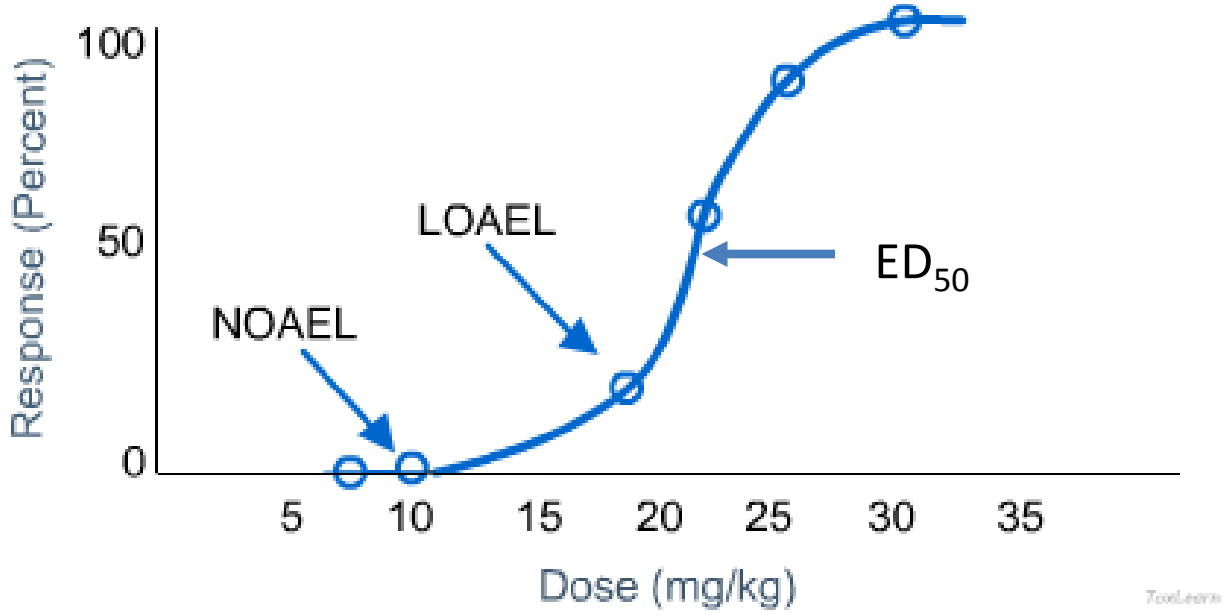
- **Acute toxicity: It involves lethal concentrations and short-term exposures**
- **The end point is usually death**
- **An LD_{50} is a dose of a toxic chemical that kills half of the population.**
- **LD_{50} is obtained by plotting, for a given dose the proportion of the population that responded to that dose and all lower doses**

Monotonic Dose Response

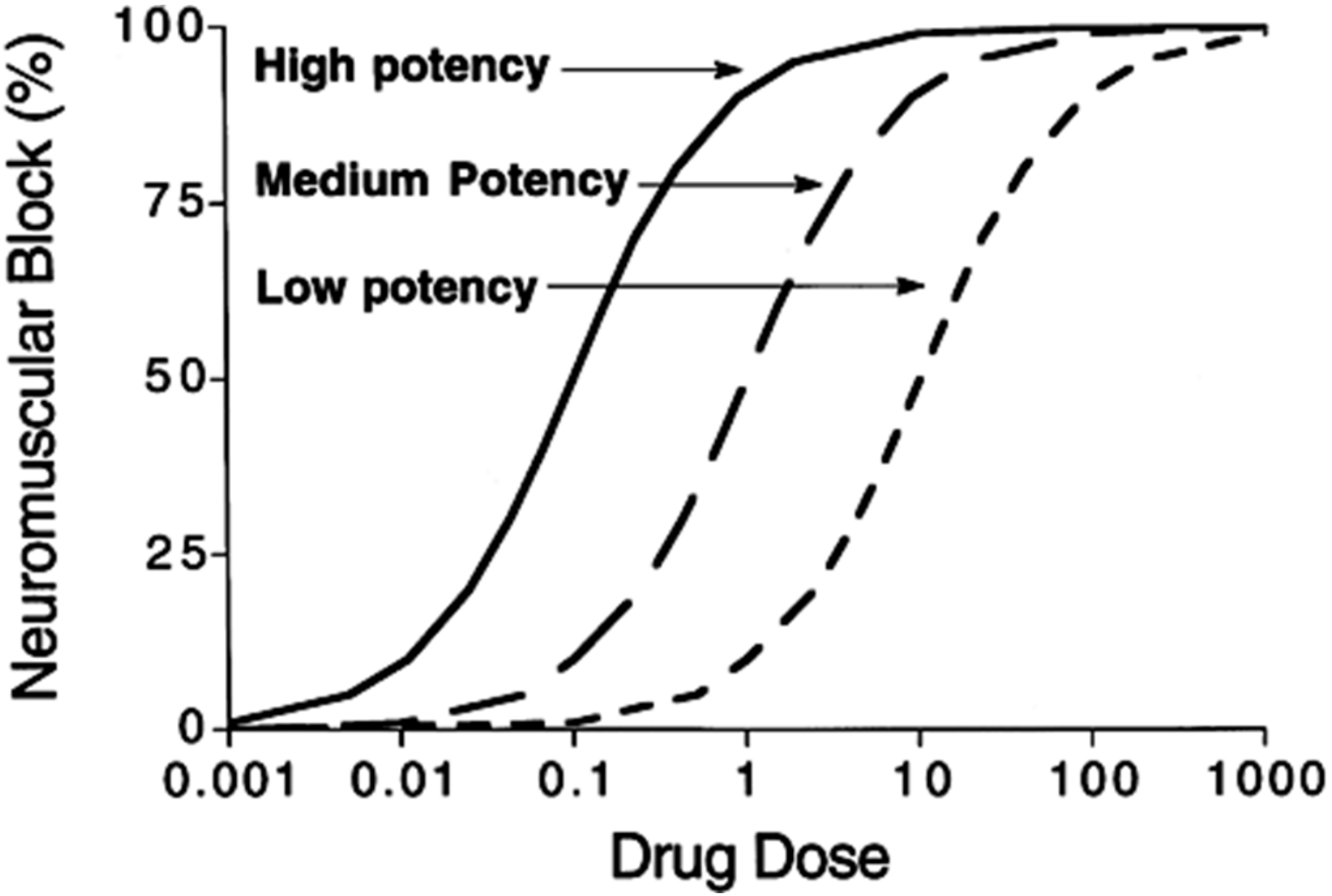


CHEMICALS: Major Types of Toxicity

- **No Observable Adverse Effect Level (NOAEL) – the threshold where no effects are observed.**
- **Lowest Observable Adverse Effect Level (LOAEL) – the concentration level where effects are observed.**



Potency – concentration to produce an effect.



CHEMICALS: Major Types of Toxicity

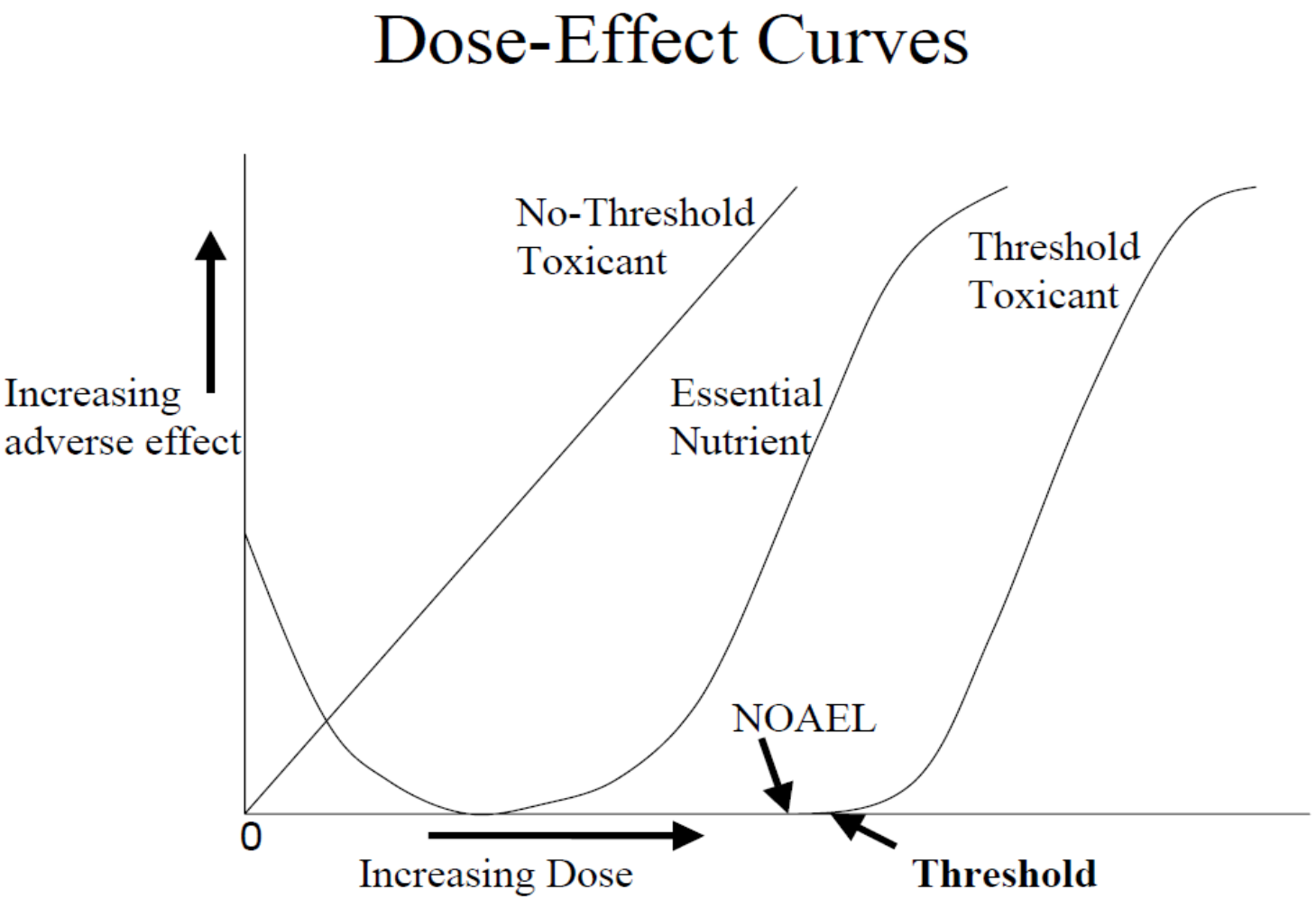
Cancer causing chemicals are assessed by risk

- **One mutation has an inherent risk so one molecule of a toxicant may pose a theoretical risk.**
- **Organisms have repair functions for protection**
- **1:1,000,000 risk is considered acceptable. (note: we can only measure 1:100 in the laboratory and must extrapolate the low risk level).**
- **Toxicity cannot be estimated by high dose experiments**

Hormesis – U shaped dose response curve (nonmonotonic)

- **Characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect.**
- **Essential nutrients, vitamins, ionizing radiation, aspirin, alcohol**

Dose Response Curves



Duffus & Worth, ©IUPAC

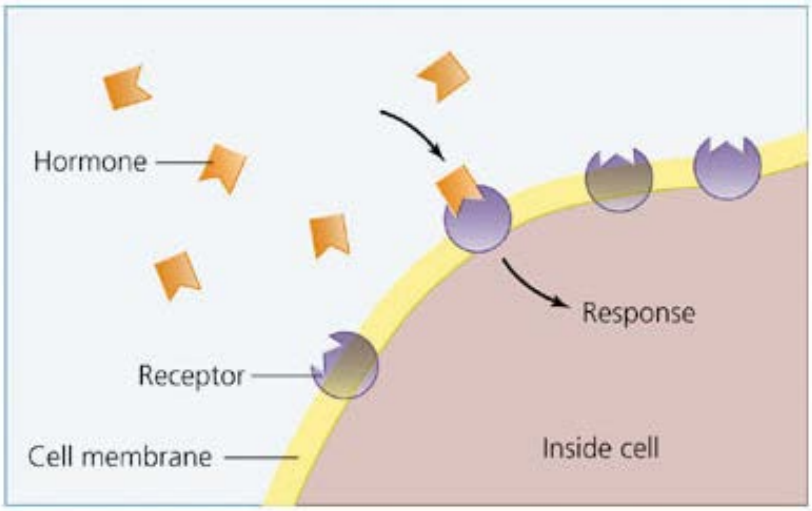
Endocrine disruptors:

- **Synthetic or naturally occurring chemicals that affect the Endocrine or hormonal system of animals**
- May either:
  - **Mimic hormones**
  - **Block hormone activities**
  - **Directly stimulate or inhibit the endocrine system**

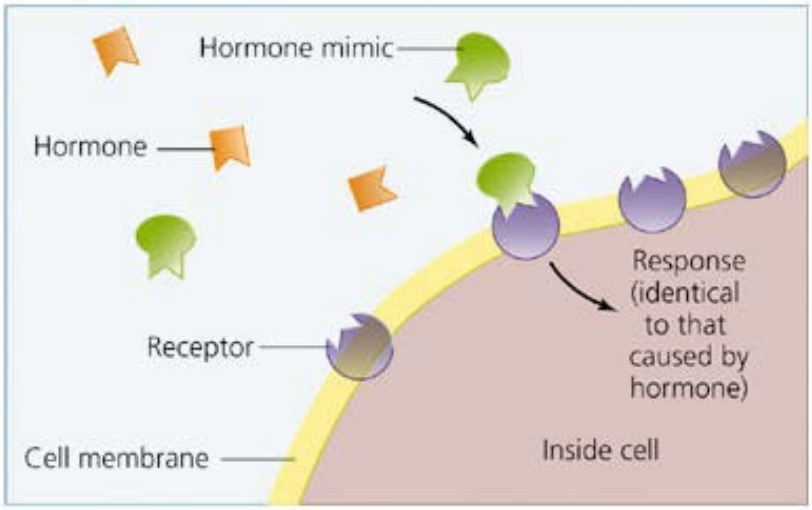
Hormones and Endocrine Disruptors

- **Bind to receptor molecules**
- **Nonmonotonic dose response curves**
- **Stimulate at low doses**
- **No increasing effect at high doses due to receptor saturation**
- **Very complex reactions and cross reactivity**
- **Very low doses are significant**
- **Effect cannot be estimated by high dose toxicity testing**

Endocrine Disruptors



(a) Normal hormone binding



(b) Hormone mimicry

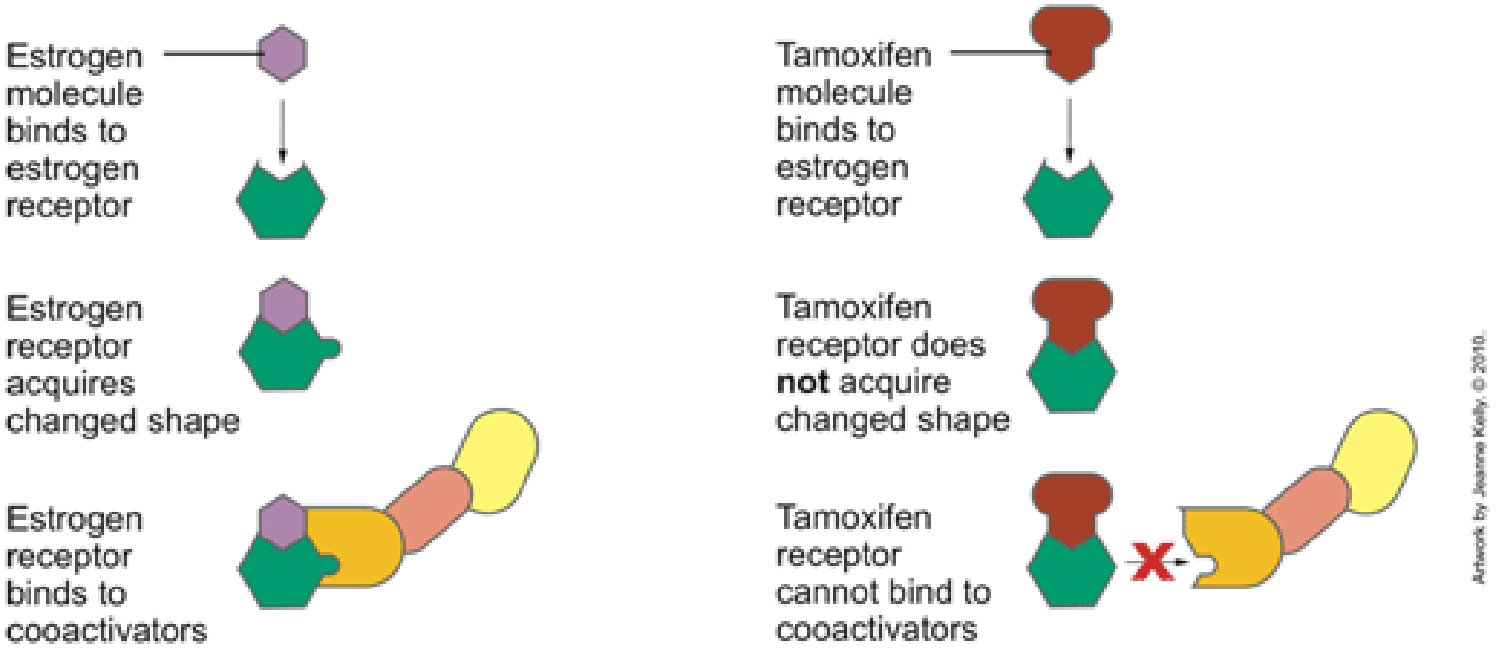
Some chemicals, once inside the bloodstream, can "mimic" hormones.

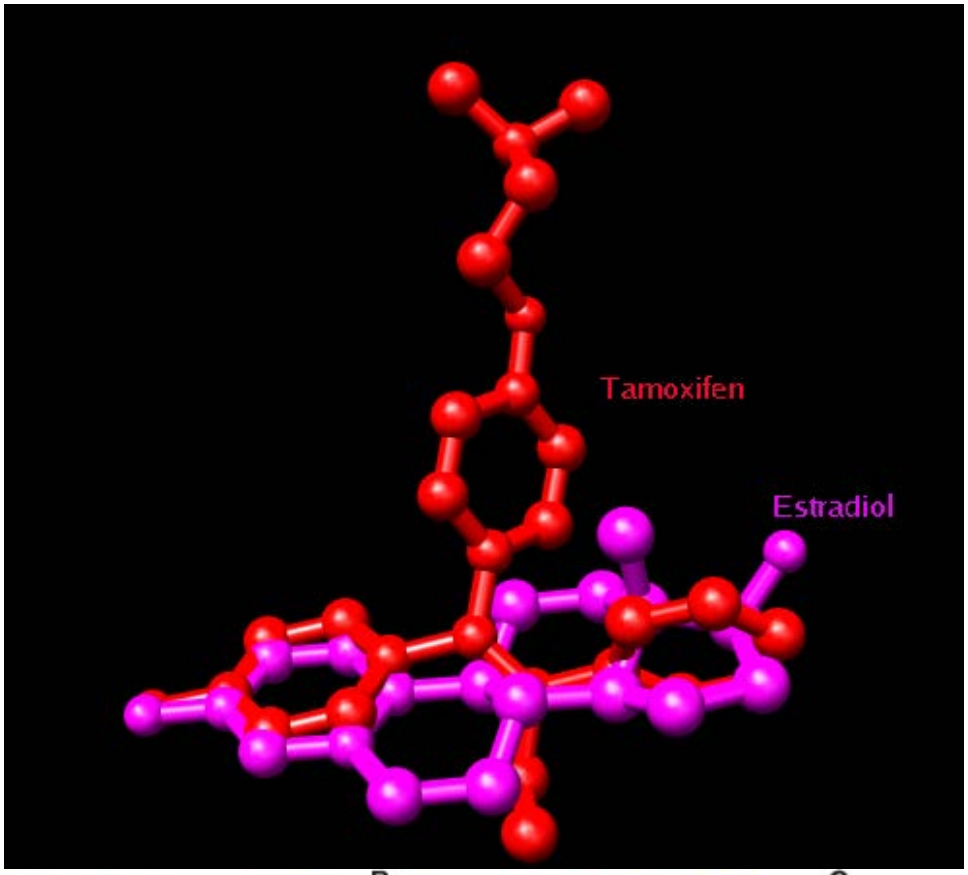
If molecules of the chemical bind to the sites intended for hormone binding, they cause an inappropriate response.

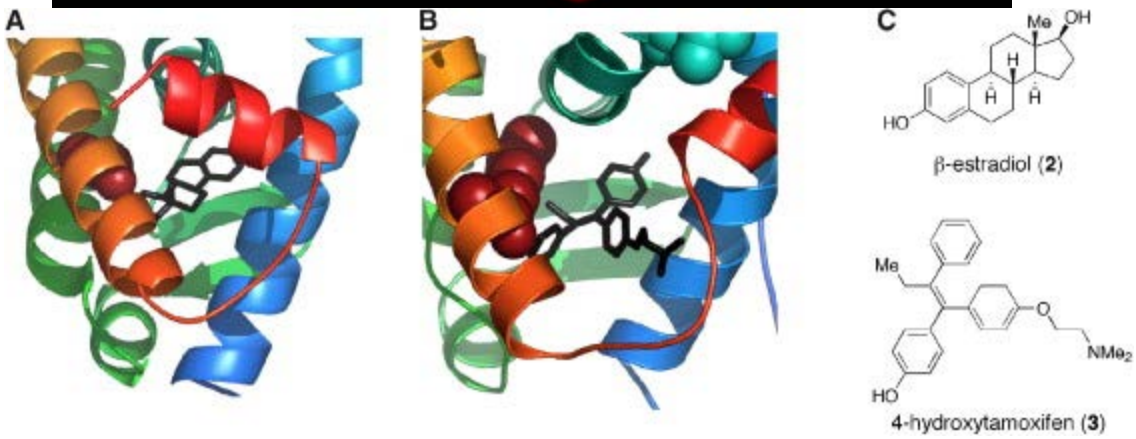
Thus these chemicals *disrupt* the *endocrine* (hormone) system.

Figure 10.5

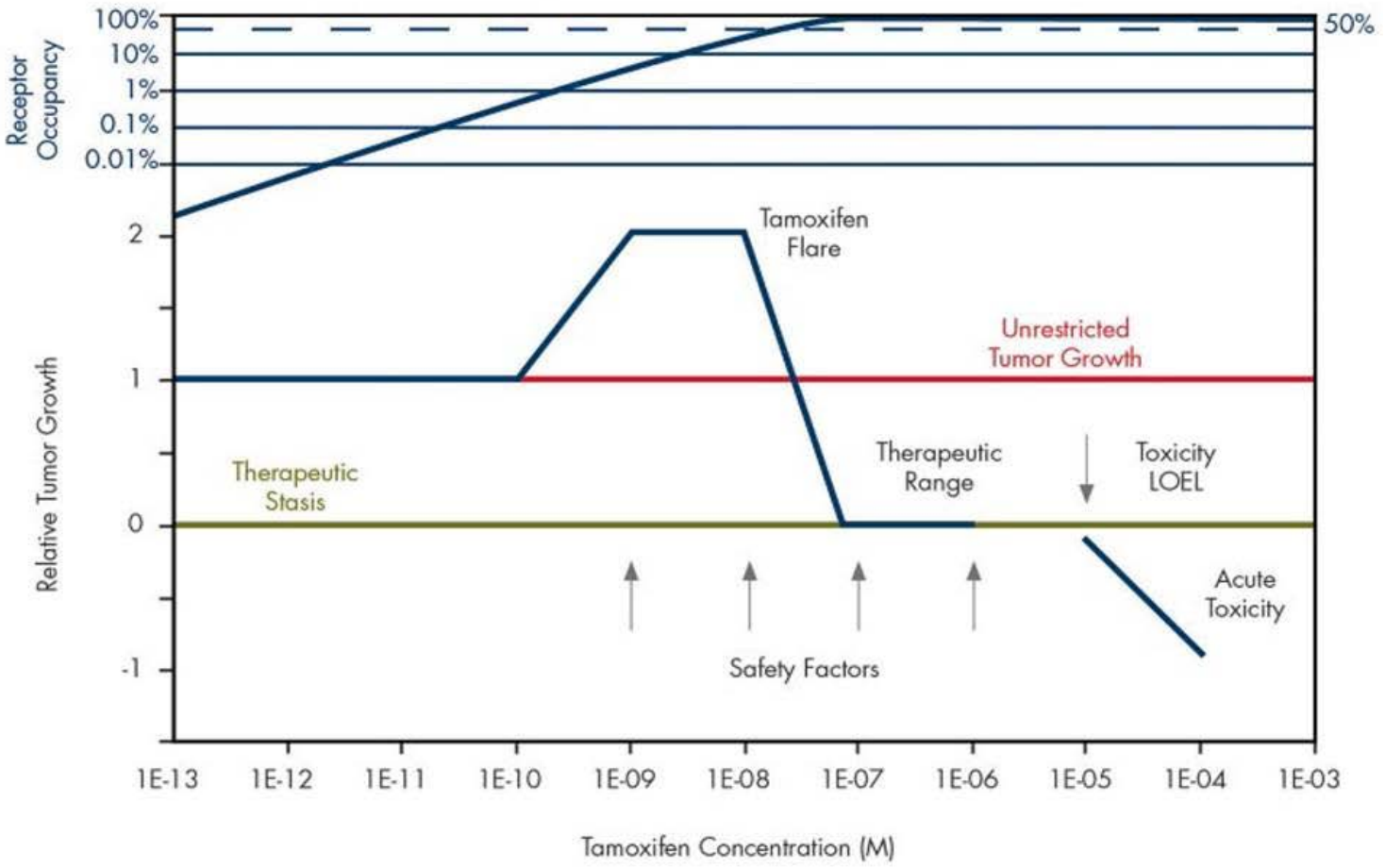
Tamoxifen and Cancer





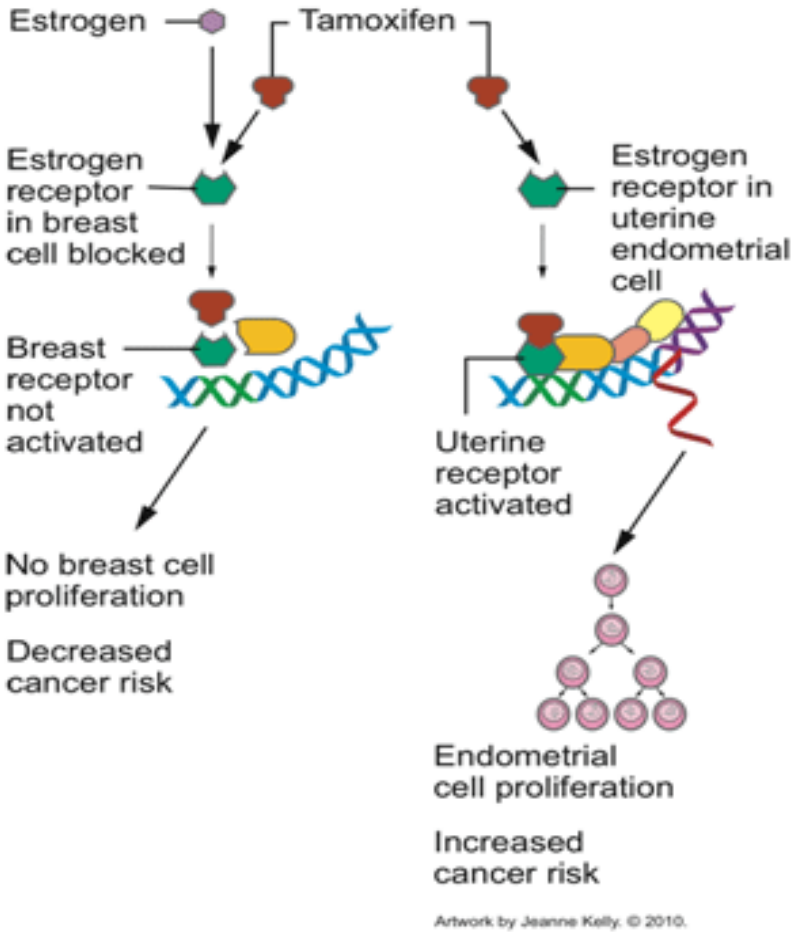


http://maptest.rutgers.edu/drupal/?q=node/273



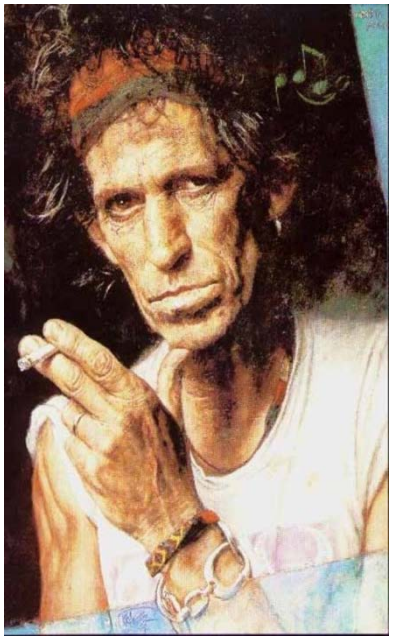
Vandenberg et al. 2012

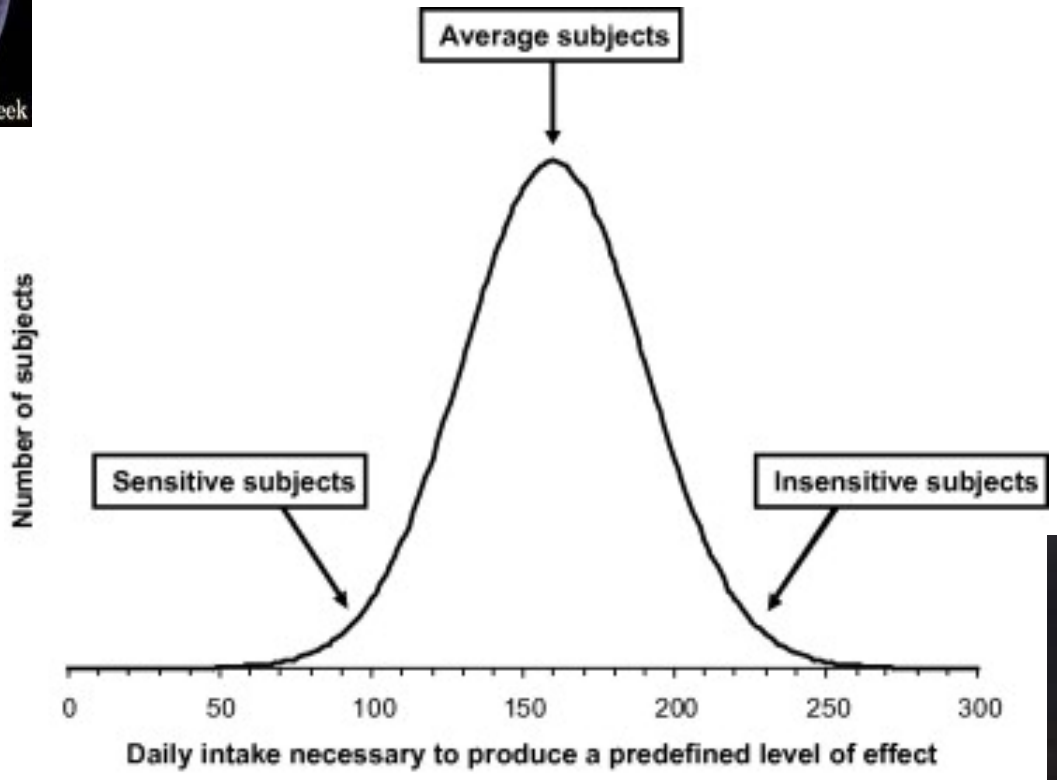
Tamoxifen as a Cause of Uterine Cancer



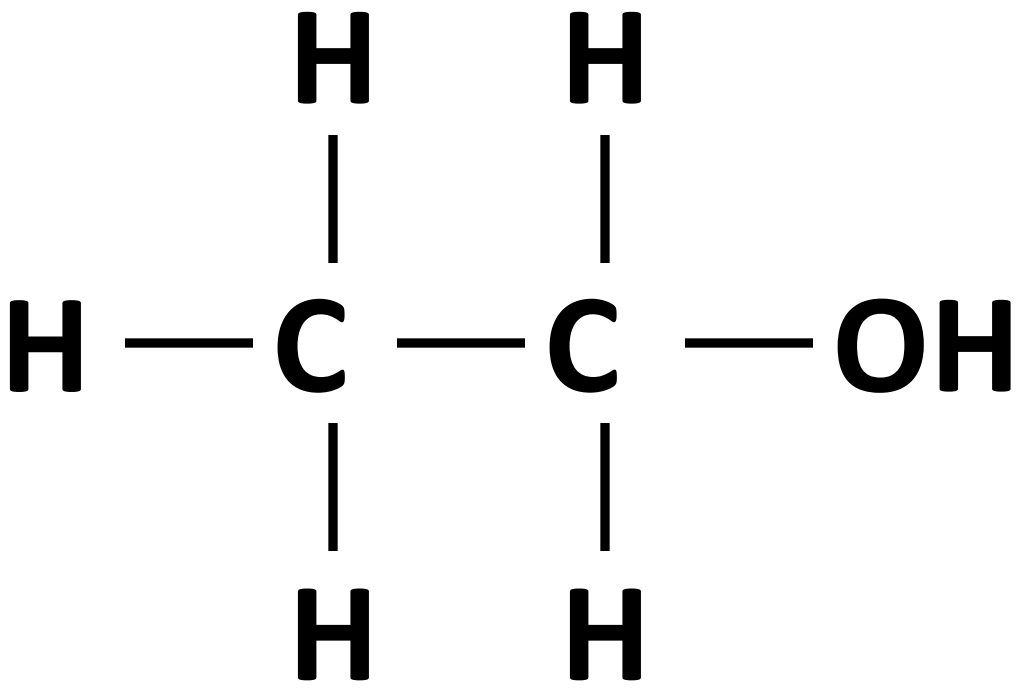
http://www.cancer.gov/cancertopics/understandingcancer/estrogenreceptors/AllPages

Populations
(Drugs of abuse)





Ethanol



Perceptions About Chemicals

- What drives our perceptions? Are chemicals bad?

HUMAN RISK PERCEPTION... is affected by the degree of pleasure / displeasure associated with the particular risk

Agent	LD-50 (mg/kg)
Ethyl alcohol	10,000
Salt (sodium chloride)	4,000
Iron (Ferrous sulfate)	1,500
Morphine	900
Mothballs (paradichlorobenzene)	500
Aspirin	250
DDT	250
Cyanide	10
Nicotine	1
Tetrodotoxin (from fish)	0.01
Botulinum Toxin	0.00001

What type of toxic chemical is alcohol ?

- **Group 1 known Human Carcinogen**
- **Exhibits hormesis – small amounts are beneficial (cardiovascular system)**
- **Teratogen - fetal alcohol syndrome**

"Of all the substances of abuse (including cocaine, heroin, and marijuana), alcohol produces by far the most serious neurobehavioral effects in the fetus."

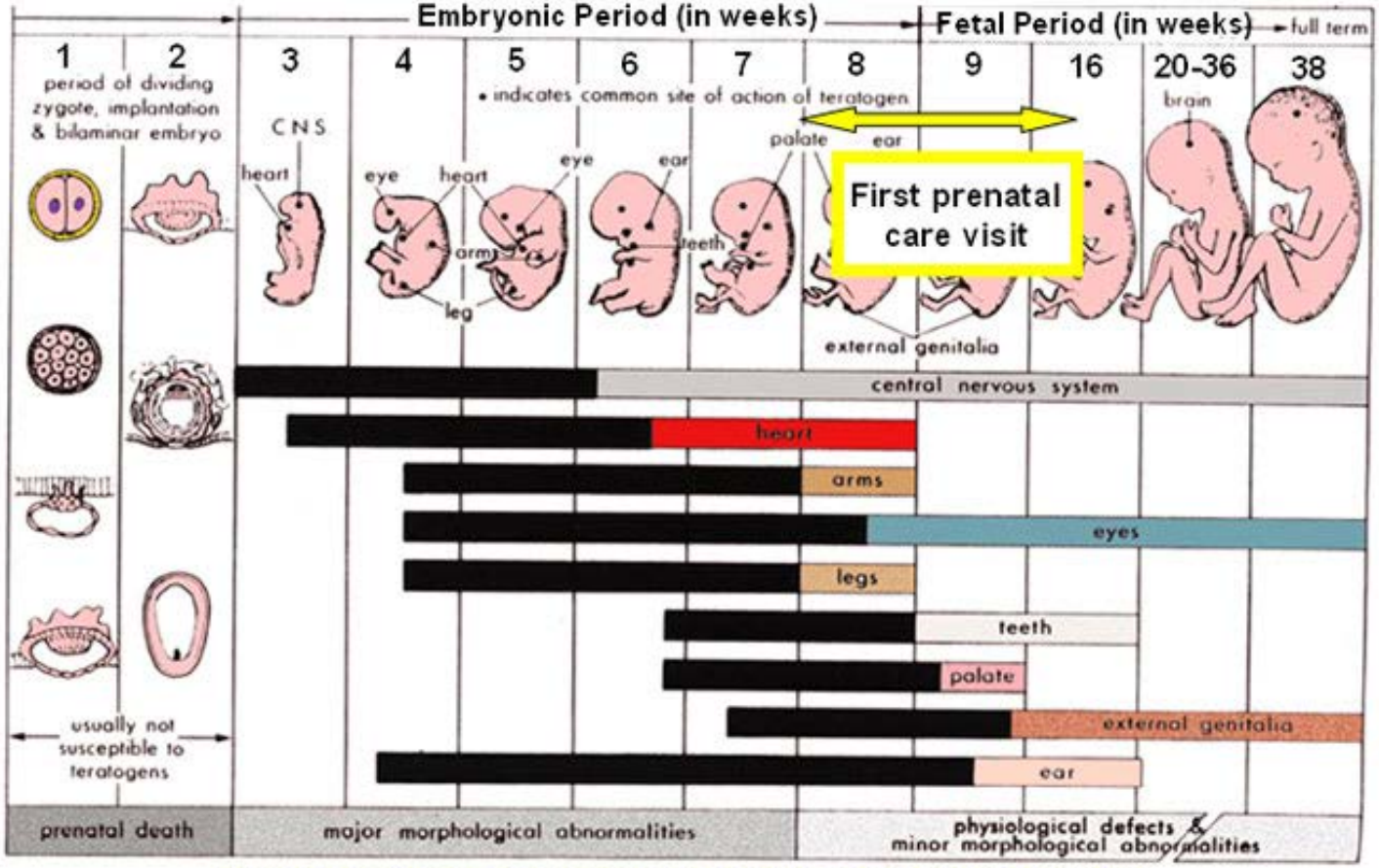
—*Institute of Medicine Report to Congress*, 1996.

Fetal Alcohol Syndrome Facts

- **Alcohol diffuses through placenta**
- **Concentration in fetal blood is the same as in the mother's blood within a few minutes**
- **The fetus is able to metabolize alcohol 10% as fast as the mother**
- **1 in 200 individuals are affected by prenatal alcohol exposure.**

Sequence of Human Development

Embryonic Development



Developmental Progression & Susceptibility to Teratogens & Fetal Loss

(Modified from Keith Moore, *The Developing Human: Clinically Oriented Embryology, 3rd Ed.*, W.B. Saunders Co.: Philadelphia, PA, 1983.)

Black- most sensitive

What is lead

- **Lead is a soft gray metal element that occurs naturally in the earth.**

- **For many years, lead was added to**
  - **paint,**
  - **gasoline,**
  - **Pipes and solder**
  - **batteries**

- **Banned in 1973 in paint**
- **Banned in 1976 in gasoline**
- **Banned in solder in 1993**

What are the Sources of Lead

- Homes that have cracked and peeling old lead paint on their walls.
- Home renovations that disturb old lead paint can spread invisible lead dust.
- Lead from old lead paint may contaminate household dust and nearby soil.

How are people exposed to lead?

- Ingestion of foods, water, alcohol may be significant for certain populations.
- Ingestion of dusts is primary way general population, especially children, are exposed to lead.
- Inhalation of lead dust contributes to a build up in the body.

Childhood Risk Factors for Elevated BLLs (>10µg/dl)

Pre-1946 Housing

Non-Hispanic Black	21.9%
Mexican American	13.0%
White	5.6%
Low Income	16.4%
High Income	0.9%

NHANES III, and CDC Recommendations for BL Screening of Young Children (Dec. 2000)

SOURCES OF LEAD-
House Dust

Uncontaminated- New inner-city home

Floor Surface**-** 2-24 µg/sq ft

Contaminated- Old inner-city home

Floor Surface- 33-486 µg/sq ft

How Does Lead Enter the Body?

Ingestion

Adults absorb about 6% of ingested lead. Fasting adults absorb **more**.

Children absorb **much more** lead

(30-50% if well fed, and more, if fasting or malnourished).

It takes **>10 years** to turn over one half the body's stored lead. Bone source slowly leaches into the blood.

Lead Exposure *in utero*

- Lead crosses the placenta in plasma.
- Pregnancy (and lactation) causes lead release from bone stores into plasma
- Plasma lead is about 10% of circulating blood lead.
- Epidemiologic effects on CNS have been documented.
- Peak transfer is at 12-14 weeks gestation

Cognitive Performance Deficits in Lead- Exposed Children

Deficits:

Psychomotor performance

Auditory and language processing

Sustained attention & concentration

Measured outcomes:

Less likely to graduate High School

More likely to be convicted of felonies

What happens when lead enters the body

- Lead is stored for long periods in mineralizing tissue such as teeth and bones.

- Lead is can be released again into the bloodstream from these sources during times of bodily stress, such as
  - ~ pregnancy
  - ~ breastfeeding
  - ~ calcium deficiency
  - ~ osteoporosis (thinning of the bones)

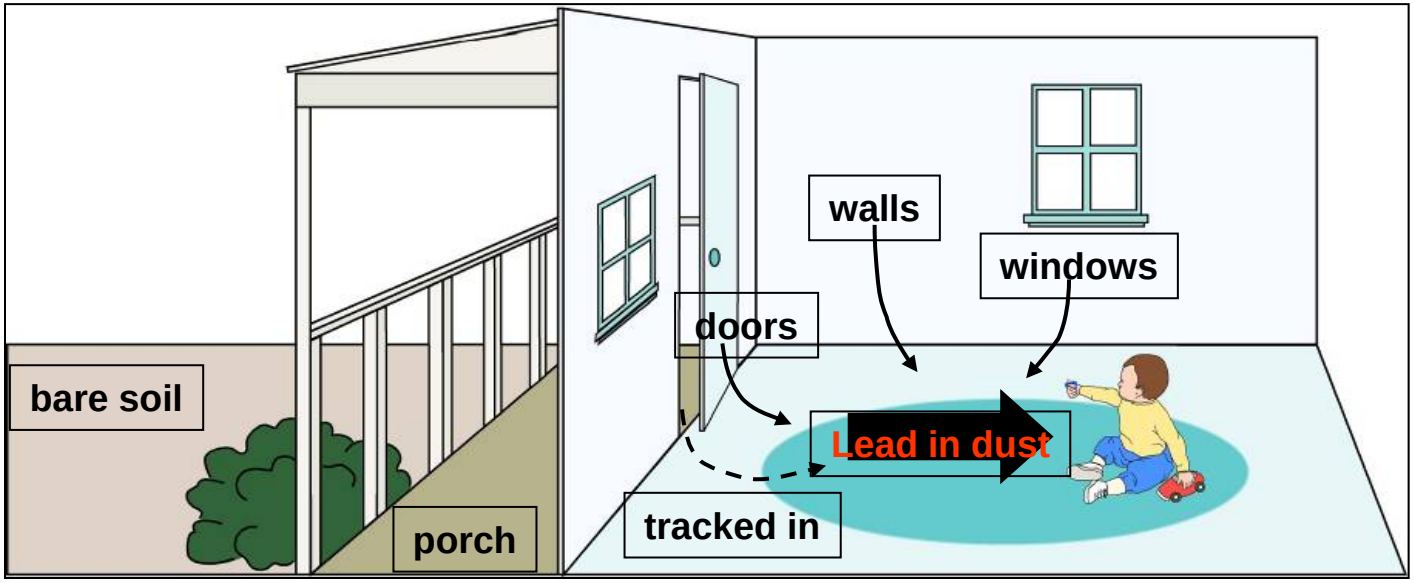
Lead Exposure

- Most lead exposure in the U.S. today occurs in older homes with deteriorated leaded paint.
- Children are at greatest risk of lead poisoning from their homes.
- Most children are exposed to lead in dust
(not by eating paint chips).

Lead in home environments (continued)

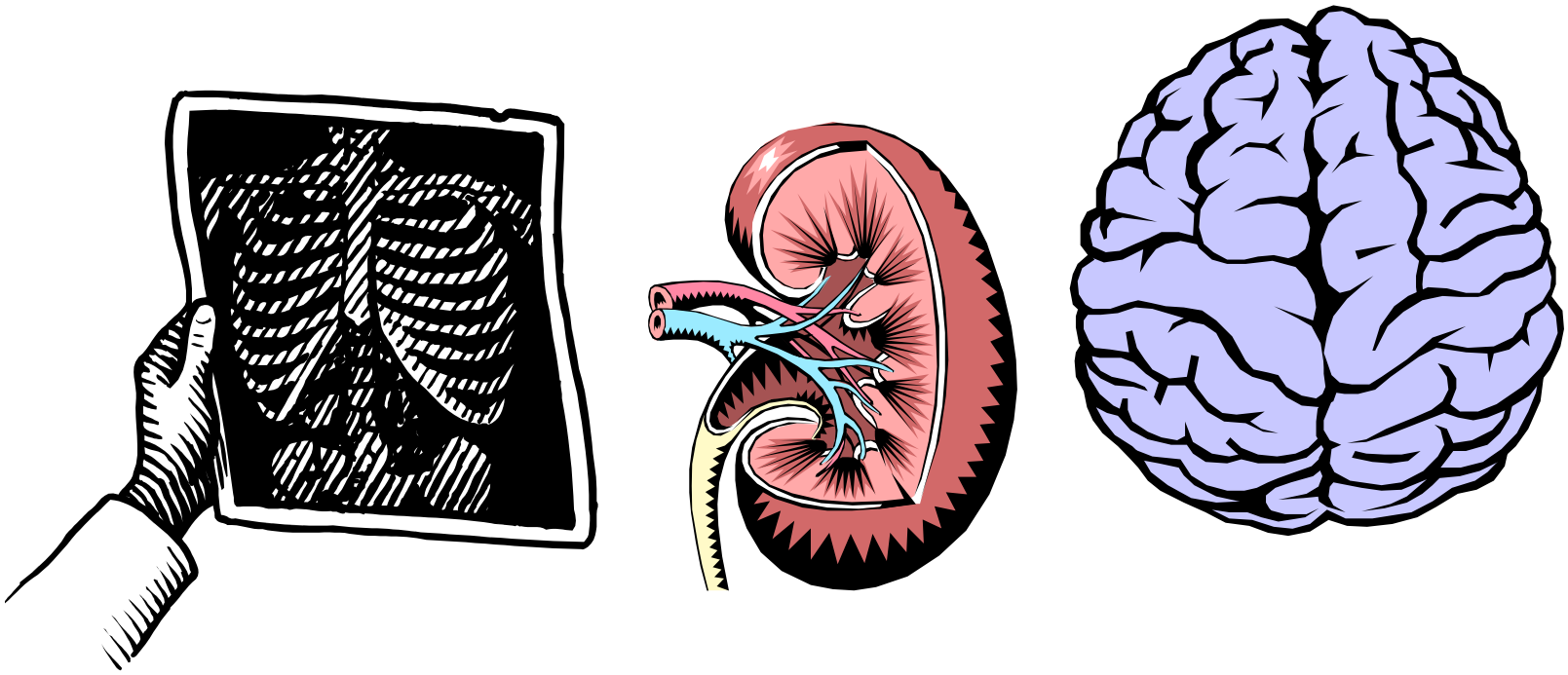
Lead in home dust

- The more lead in the dust in a home, the higher the levels of lead in children.
- There is no safe threshold for lead.



What parts of the body does lead affect?

- The brain is very sensitive to lead.
- Exposure to high levels of lead can permanently affect the brain, bones, kidneys, and the heart.



What levels cause health effects

- Lead can cause harm even at very low levels, especially in young children.
- There is no safe threshold for lead.
- At very high levels, lead can brain damage, coma
- Adults experience similar effects, but generally at higher levels of exposure.

What are the effects of lead exposure on young children?

- Lowered IQ
- Learning disabilities
- Attention deficit and hyperactivity
- Other behavioral issues
- Impaired hearing
- Anemia
- Decreased growth

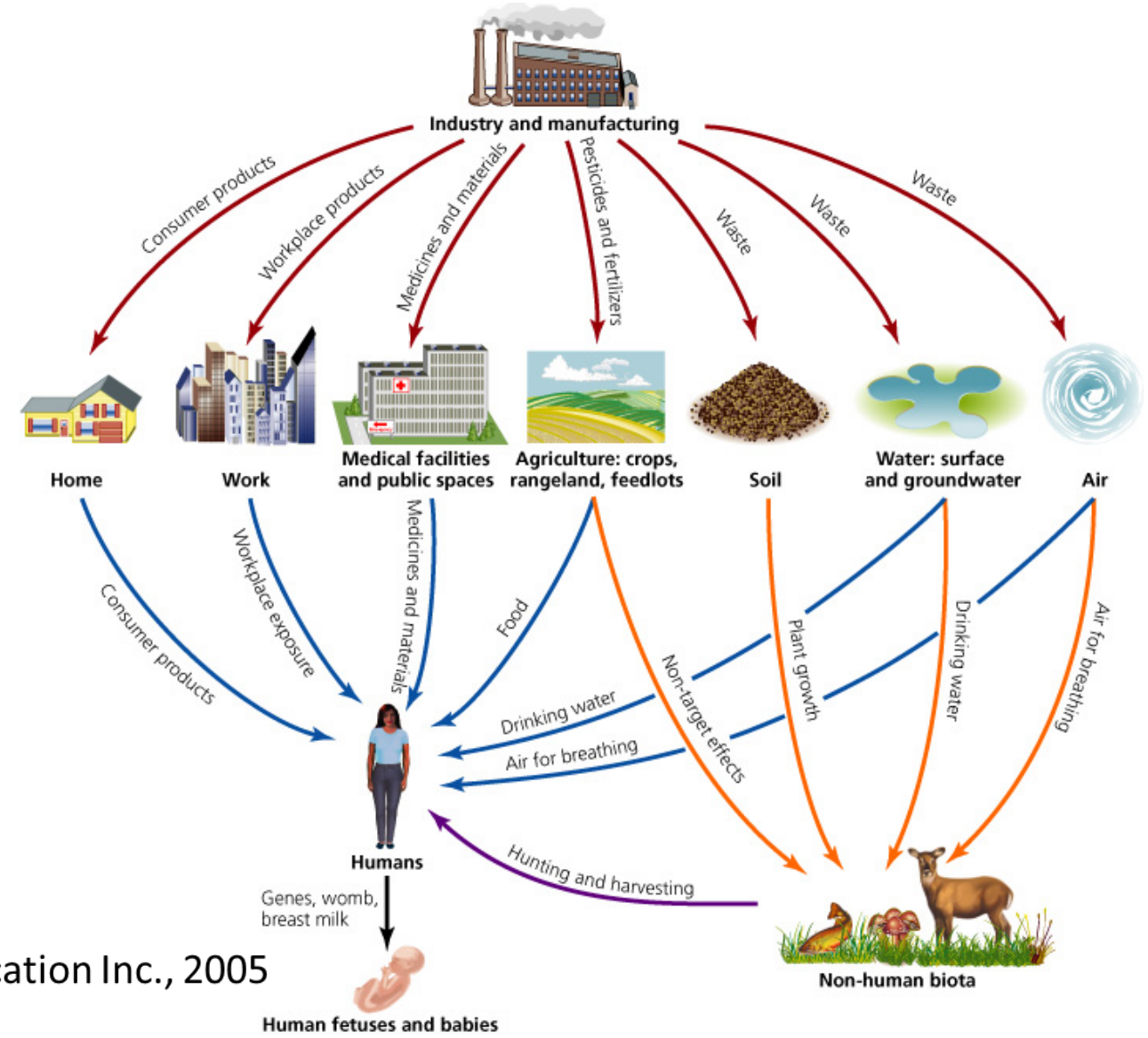
How to test for lead exposure

- Children should have their blood tested at ages one and two.
- Older children at risk of lead poisoning should also be tested.
- Adults who may be exposed to lead at work should also be tested.

How to prevent lead exposure

- If your home was built before 1978, you should have it tested for lead.
- Make sure all paint is in good condition.
- Wet-clean all surfaces, especially window sills, at least every week.
- Wash children's hands frequently.
- Cover bare soil in the yard.
- Learn about lead-safe work practices when doing work on your home that disturbs paint.

Toxicants take many routes through the environment often as mixtures.



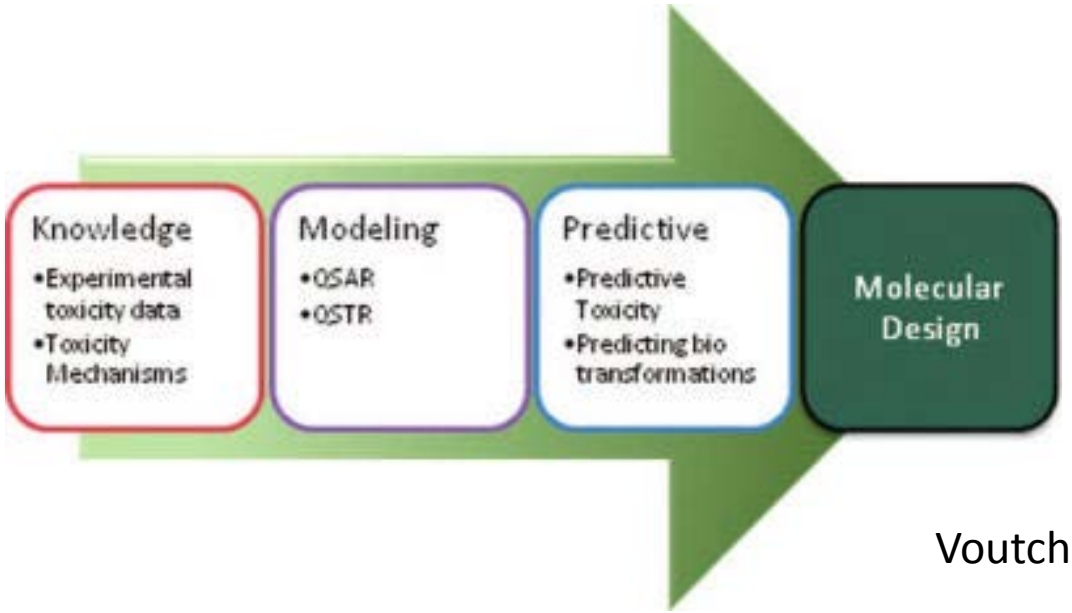
Pearson Education Inc., 2005

What is the role of Toxicology in Green Chemistry

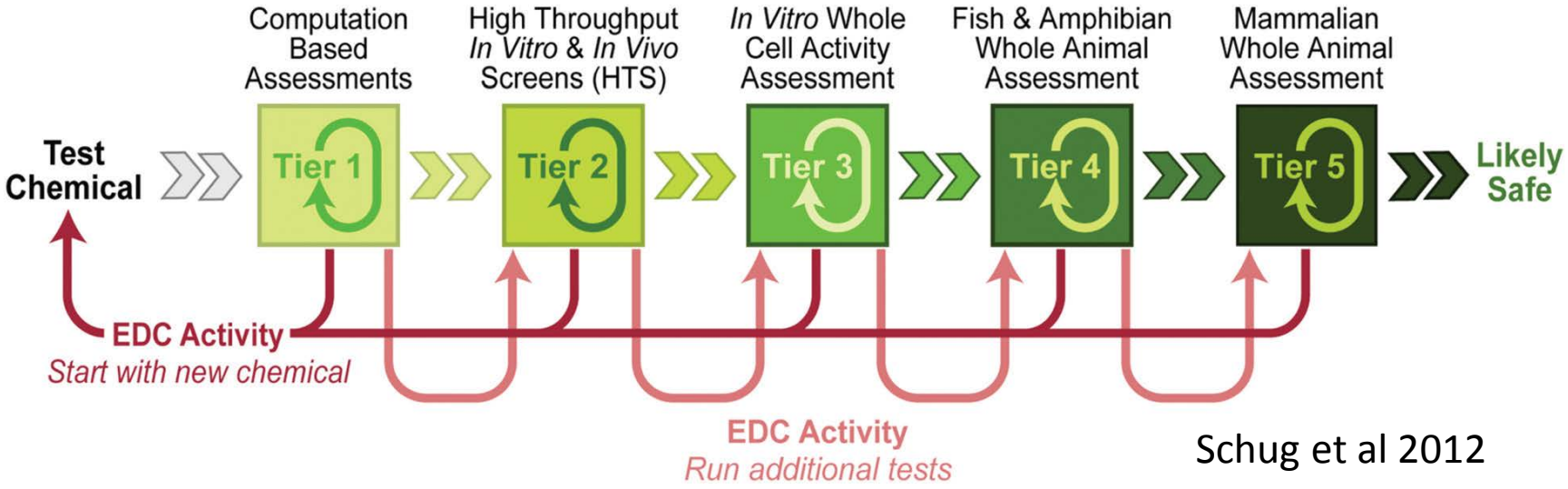
- Linking molecular structure to hazard
- Focus less on minimizing risk through reducing exposure
- Focus more on minimizing hazard by designing safer chemicals
- Risk = Hazard x Dose (Exposure)
- The hazardous nature of a substance can be controlled through structure manipulation

*NRC. 1983. Risk Assessment in the Federal Government: Managing the Process. National Research Council. National Academy Press, Washington, DC. ISBN: 0-309-03349-7.

Approaches



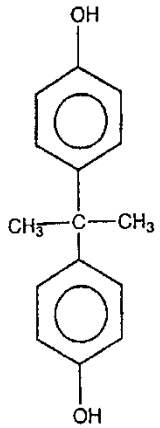
Voutchkova et al 2009



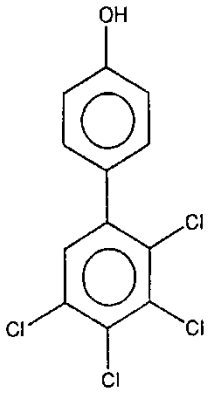
Schug et al 2012

Estrogen vs Hormonally Active Agents

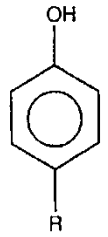
Estrogen



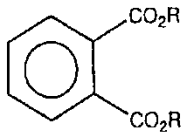
Bisphenol A



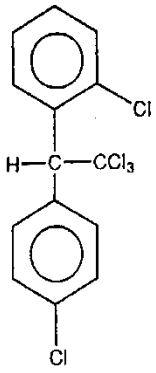
Hydroxy-PCB



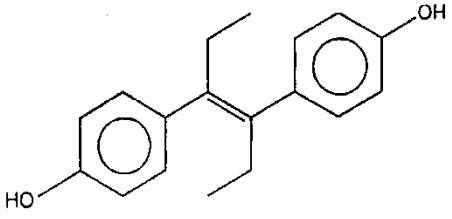
4-Alkyphenols



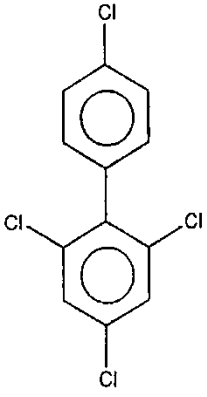
Phthalates



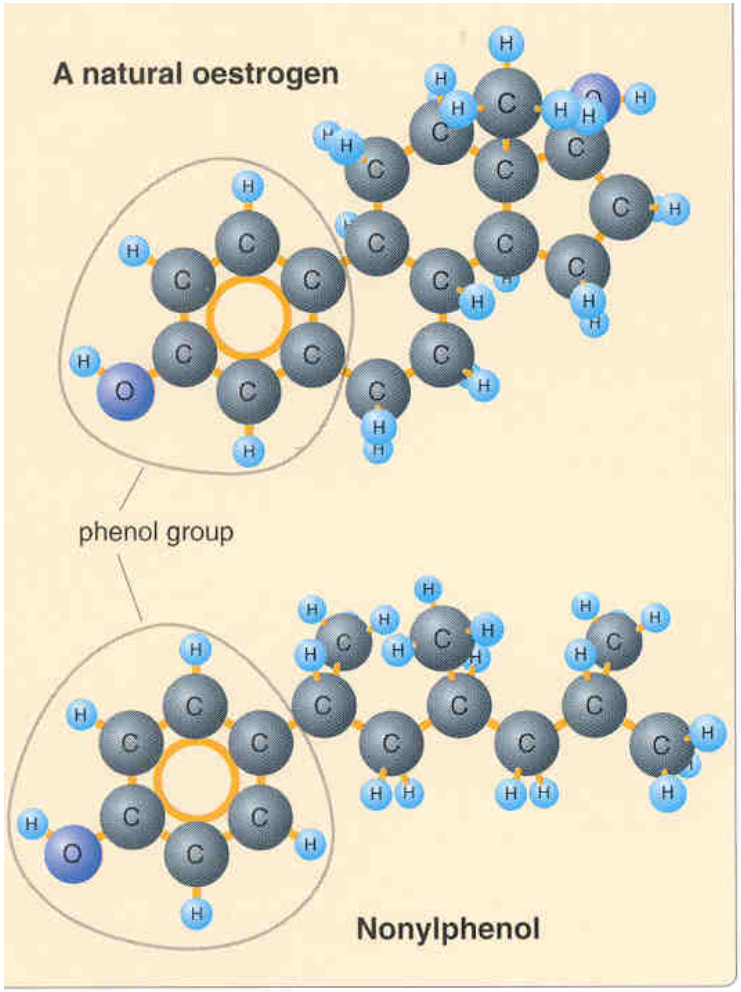
o,p'-DDT



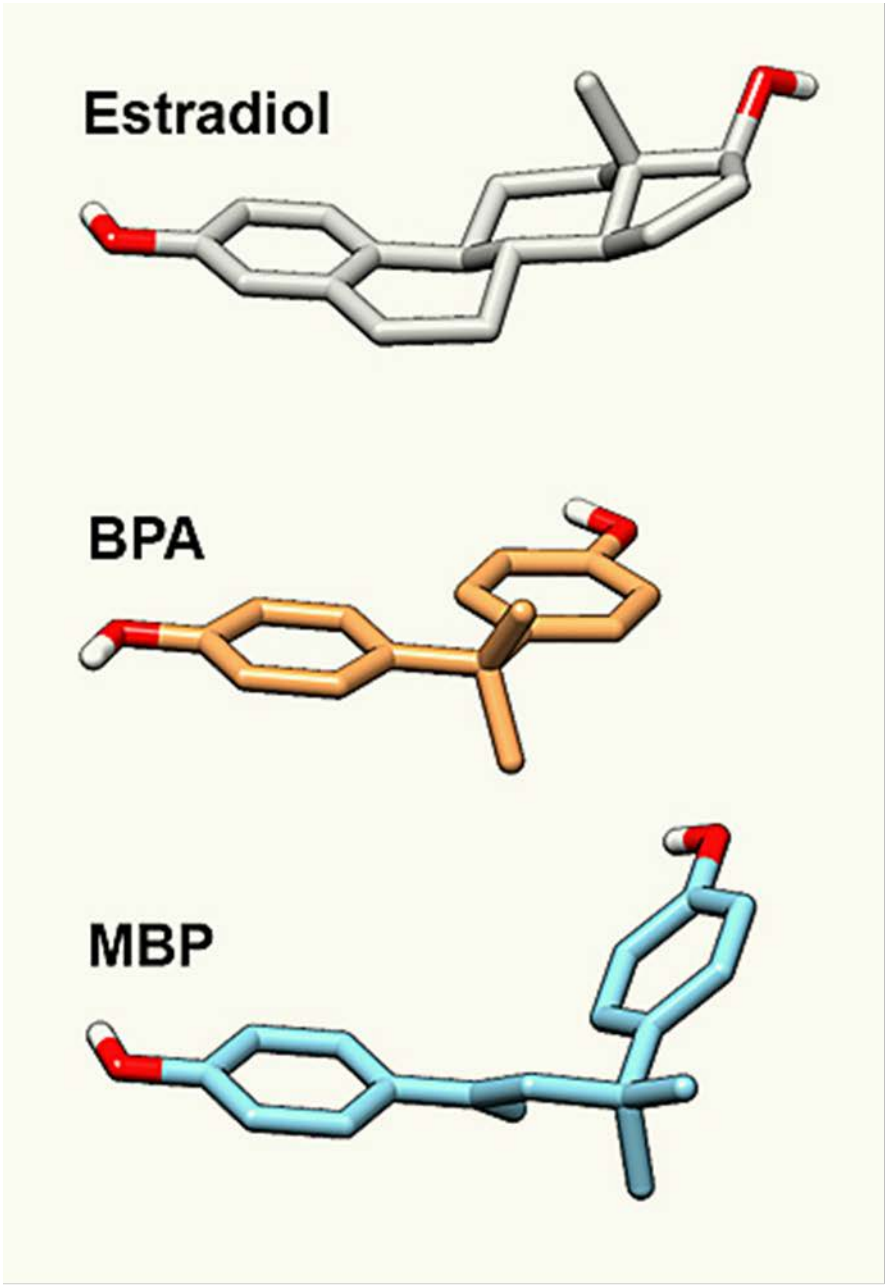
Diethylstilbestrol

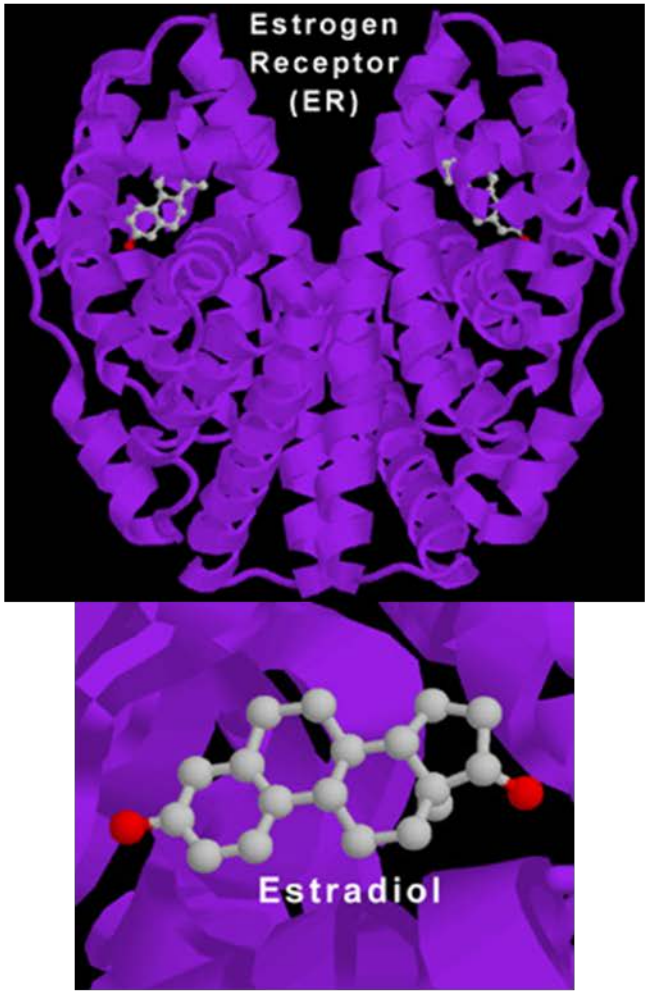


2,4,4',6-tetraCB



mindfully.org





Baker and Chandsawangbhuwana 2012

Summary

- Toxicology is a complex science based on the principle of dose and response.
- Environmental exposures further adds to this complexity.
- Focus more on minimizing hazard by designing safer chemicals
- Green chemistry can provide solutions!

Summary

Toxicology is a fascinating science that makes biology and chemistry interesting and relevant.

Understanding HOW (i.e. mechanism)

something produces a toxic effect can lead to new ways of preventing or treating chemically-related diseases. Animal use in research is essential for medical progress.

Many diseases are the result of an interaction between our genetics (individual variability) and chemicals in our environment.

Toxicology provides an interesting and exciting way to apply science to important problems of social, environmental, and public health significance.

Your Role

Risk is a part of everyday life, and one's decisions as to the 'acceptability' of a particular risk is influenced by knowledge.

We can try to increase the public's knowledge about the risks and benefits of all things chemical.

You play a critical role in this effort, and we can't do it without YOU.