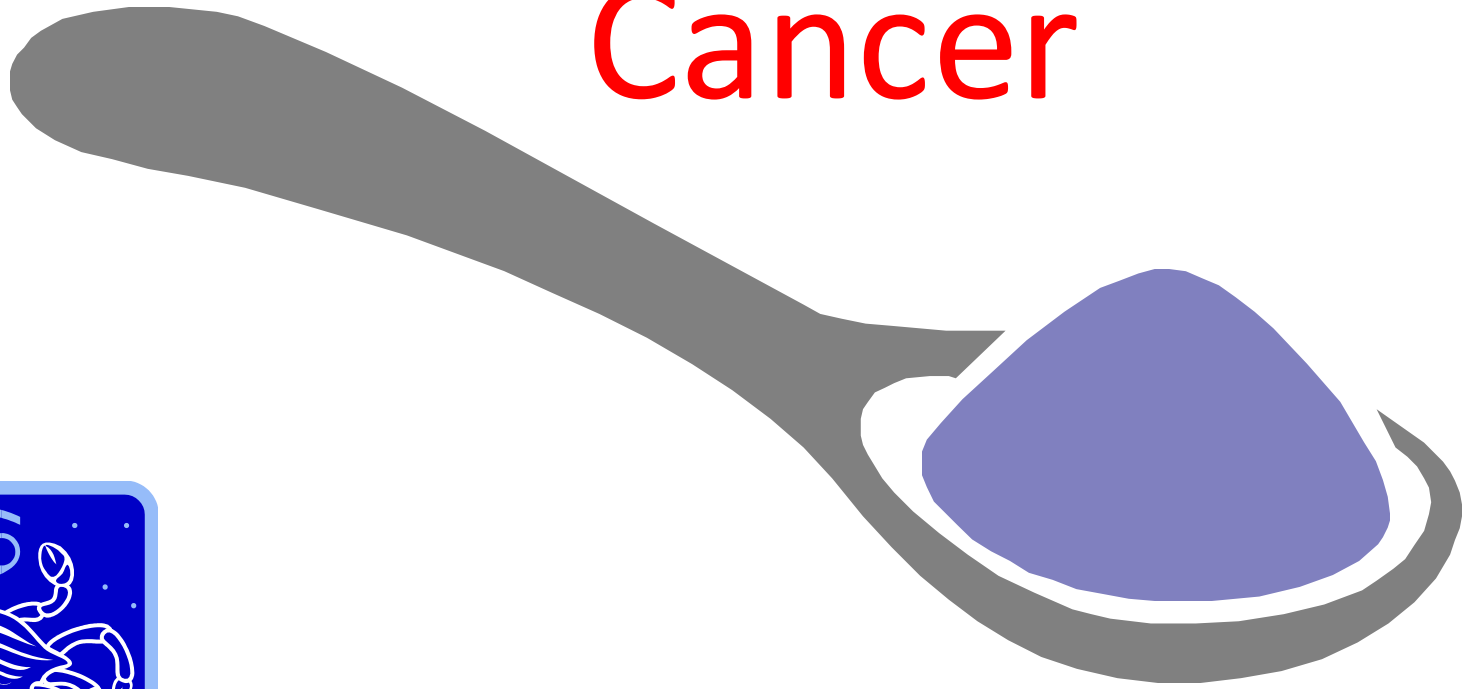
An Introduction To

Toxicology and Cancer



Toxicology Definitions

The study of poisons or
the adverse effects of chemical and
physical agents on living organisms.

Quote / History

"There is no treatment.“

1600 B.C. Egypt

(comment on breast cancer)

Incidence of Breast Cancer

A Women's Risk of Breast Cancer (US)

1940's – 1 in 22

2004 – 1 in 7

Breast Cancer is leading cause of death in women ages 34 to 44.

Hazard and Risk-1

- **Hazard is the potential of a substance to cause damage**

✓ Toxicity is the hazard of a substance which can cause poisoning

- **Risk is a measure of the probability that harm will occur under defined conditions of exposure to a chemical**

✓ If there can be **no exposure** to a chemical, no matter how dangerous (hazardous) it may be, there is no risk of harm

Hazard and Risk - 2

- The relation of risk to hazard may be expressed as;

R = f (H x E) = f (H x D x t)

Where R is risk, f is function of, H is hazard, E is exposure, D is dose and t is time

- Thus, chemicals which pose only a small hazard but to which there is **frequent or excessive exposure** may pose as much risk as chemicals which have a high degree of hazard but to which **only limited exposure** occurs

Safe Exposure

- Control of exposure should ensure that exposure is kept below a "safe" level

- "Safe" exposure levels such as the **Tolerable Daily Intake (TDI)** are determined by:

  establishing the *dose-response* curve, **determining a threshold dose below which no harm occurs in an exposed population** and extrapolating from this to a "safe" exposure by dividing by an uncertainty factor (UF), normally 100 or more.

- The threshold dose may be approximated by

a NOAEL (No Observed Adverse Effect Level)

or

a LOAEL (Lowest Observed Adverse Effect Level)

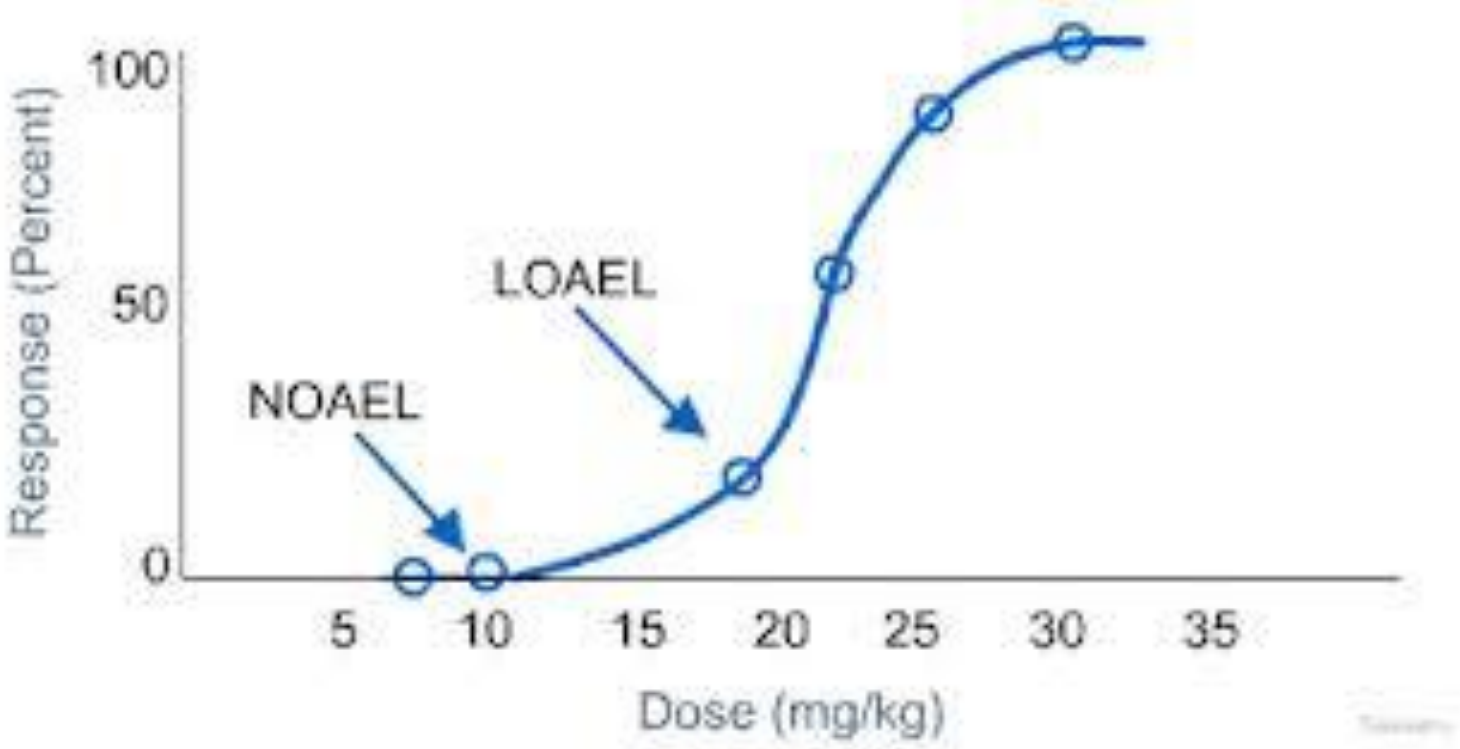
Dose-Response Curve

- A dose response curve records the percentage of a population showing a given quantal (all or nothing) response such as death when each individual member of the population is subjected to the same dose of toxicant (reflecting a given exposure)

- The **LD50** is the median dose associated with the death of **50%** of the population

ED10%??? Effective dose

TD30%??? Toxic dose

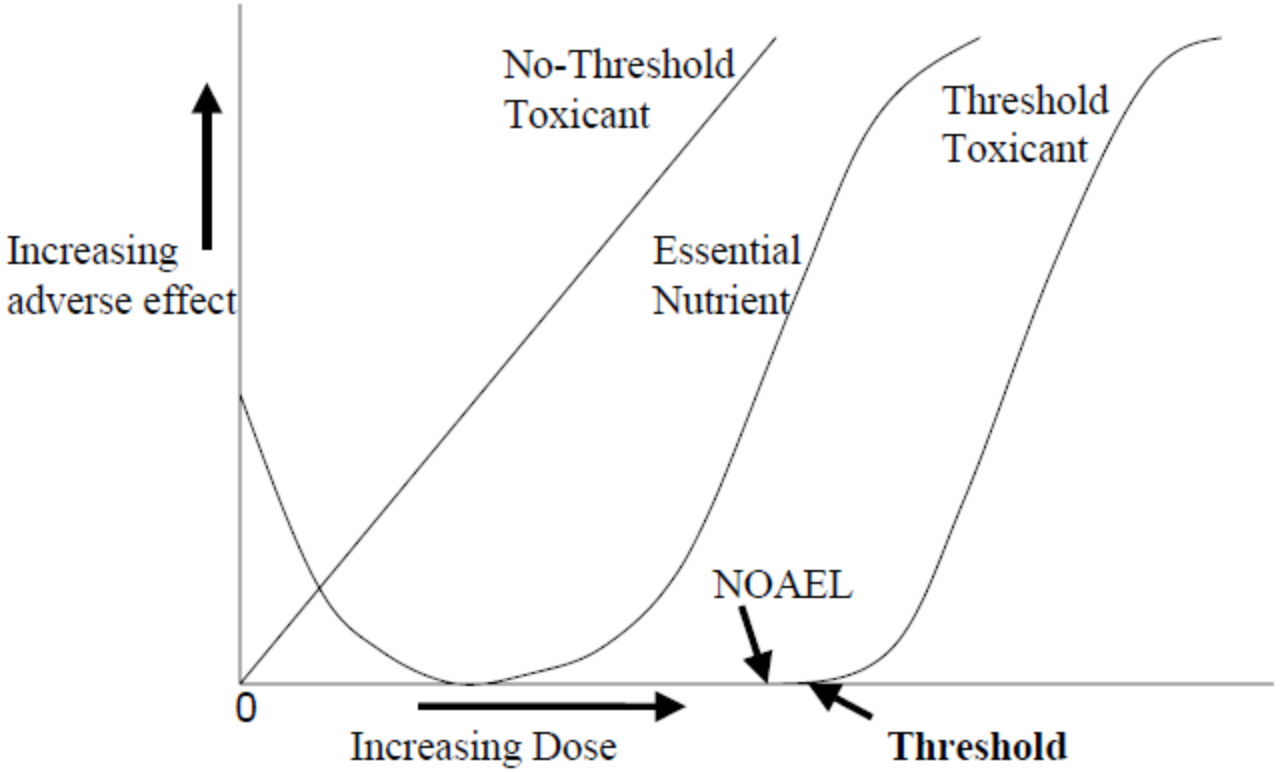

100
50
0
Response (Percent)
LOAEL
NOAEL
5
10
15
20
25
30
35
Dose (mg/kg)

Dose-Effect Curves

- The relationship between dose and effect illustrates what happens in an individual as dose increases
- The curves are similar to dose-response curves
- Note the curve for an essential nutrient
  - For such substances there is an optimum range of dose required for good health
- Note the curve for no threshold toxicants
  - Carcinogens are believed to have no safe threshold of exposure

Duffus & Worth, ©IUPAC

Dose-Effect Curves



Duffus & Worth, ©IUPAC

9

"Safe" Exposure Levels - 1

- Important regulatory "safe" exposure levels are those for food of which the Tolerable Daily Intake (TDI) is Typical

- The Tolerable Daily Intake is an estimate of the daily intake of a chemical contaminant which can occur over a lifetime without appreciable health risk.

The concept of a "TDI" generally applies to unavoidable and undesirable contaminants of food or water which have no useful purpose.

The term "tolerable" is intended to signify permissibility rather than acceptability

“Safe” Exposure Levels - 2

- In the United States, the “Reference Dose (RfD)” has a very similar definition to that of the Tolerable Daily Intake

- Exposures above the TDI or RfD are not necessarily dangerous because a large margin of safety is allowed in their calculation but every effort should be made to keep below these values

Chemicals That Can Cause Cancer

• In the absence of data in humans to the contrary, chemicals which can induce cancer in experimental animals are regulated as if they could induce cancer in humans

• There is a generally held assumption that **there is no threshold for safe exposure to substances which may cause cancer** by mutation of the genetic information in DNA.

•This may not be the case but it ensures that regulatory levels are set very far below those which might carry a significant risk.

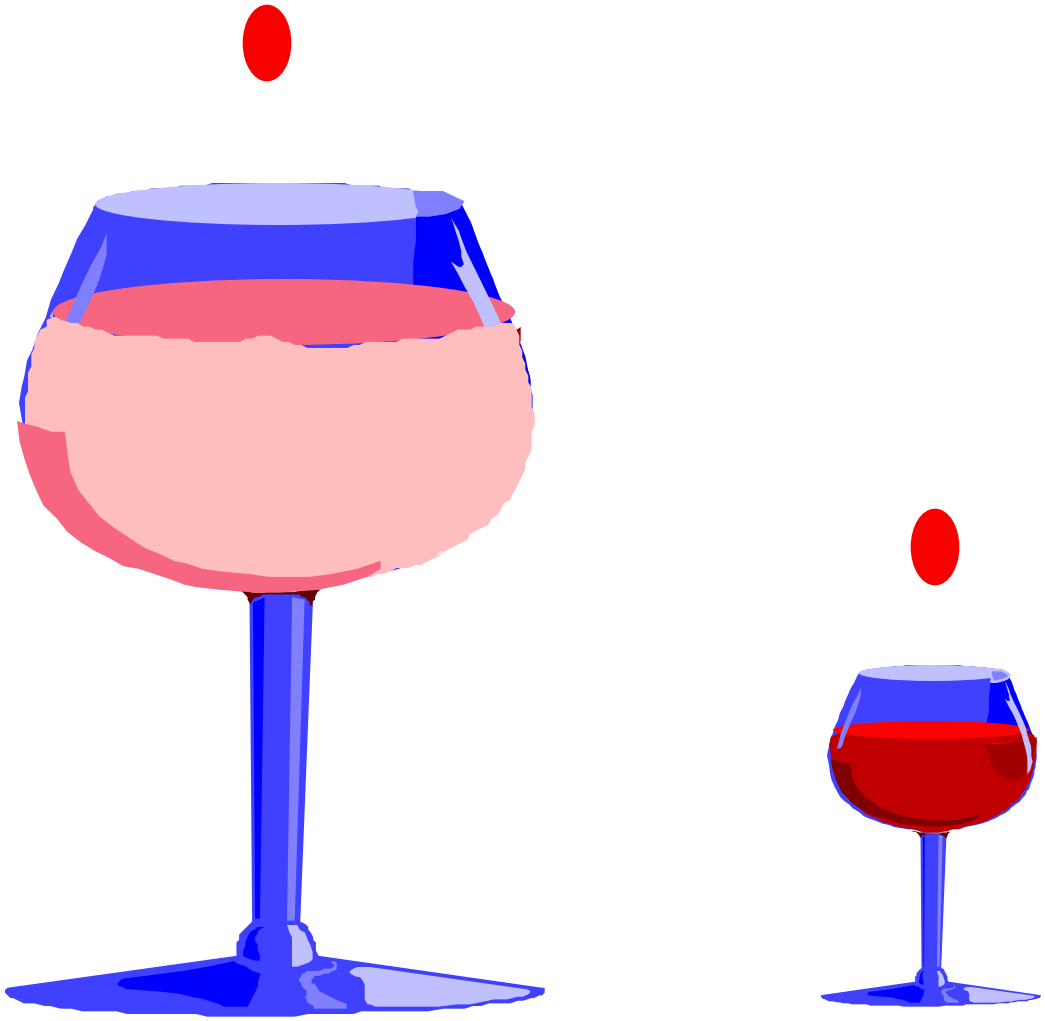
Regulation of Agents that Can Cause Cancer

• Regulatory permitted levels of agents that can cause cancer (for which no safety threshold of exposure can be established) are based on calculations of lifetime risk

•It is generally considered that exposure levels corresponding to a calculated **increased lifetime risk of 1 in a million are acceptable** since an increased incidence of cancer at this level would be undetectable with current epidemiological methods; calculations are based on the worst possible case and the true increase is likely to be much less

Effects of Amount on Response

Effects of Size on Response



Case Studies

1. Thalidomide
2. Ethanol (Alcohol)
3. Methyl mercury
4. Lead
5. PBDEs

Thalidomide

Introduced in 1956 as sedative (sleeping pill) and to reduce nausea and vomiting during pregnancy

Withdrawn in 1961

Discovered to be **a human teratogen** causing absence of limbs or limb malformations in newborns

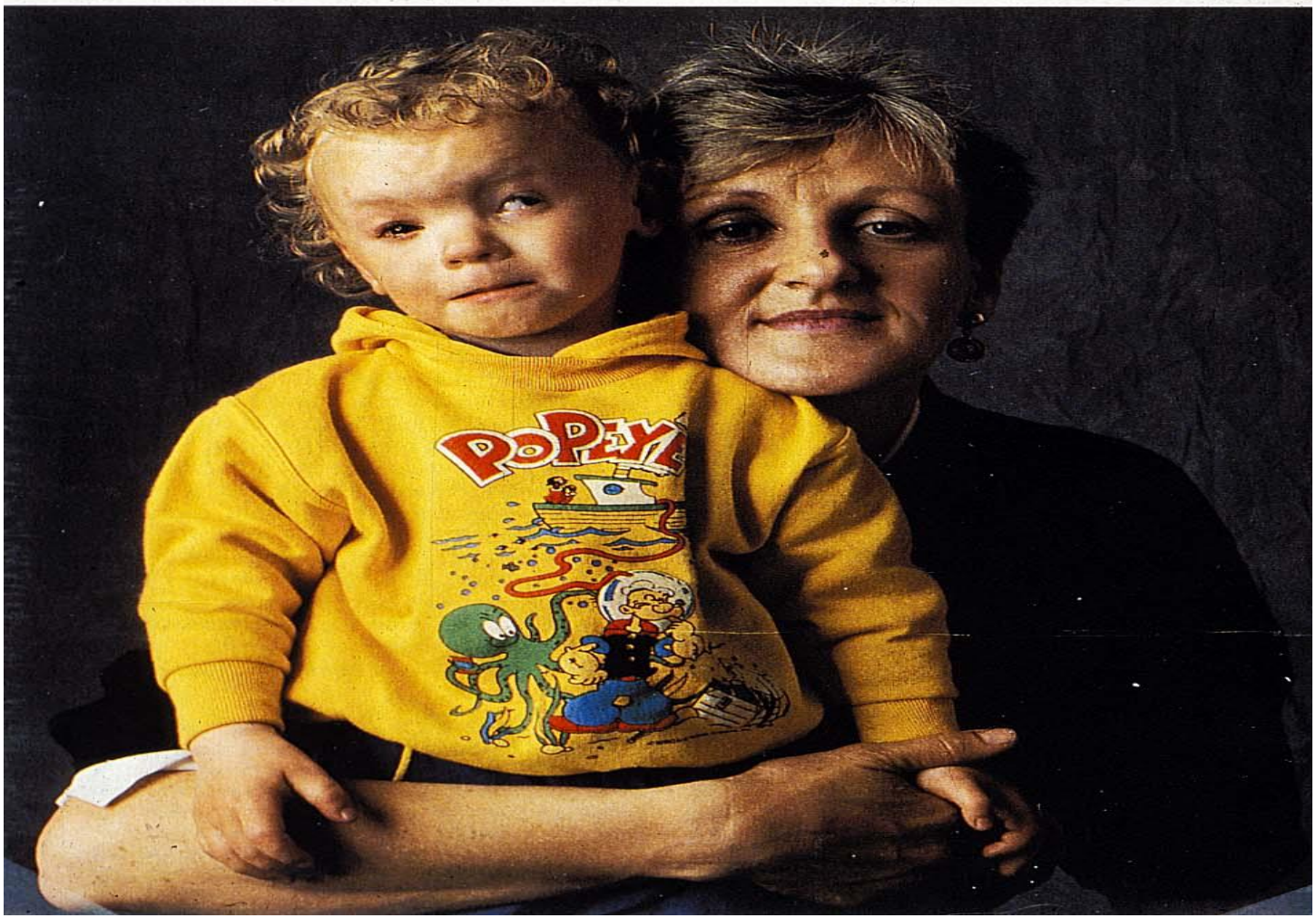
5000 to 7000 infants effected

Resulted in new drug testing rules

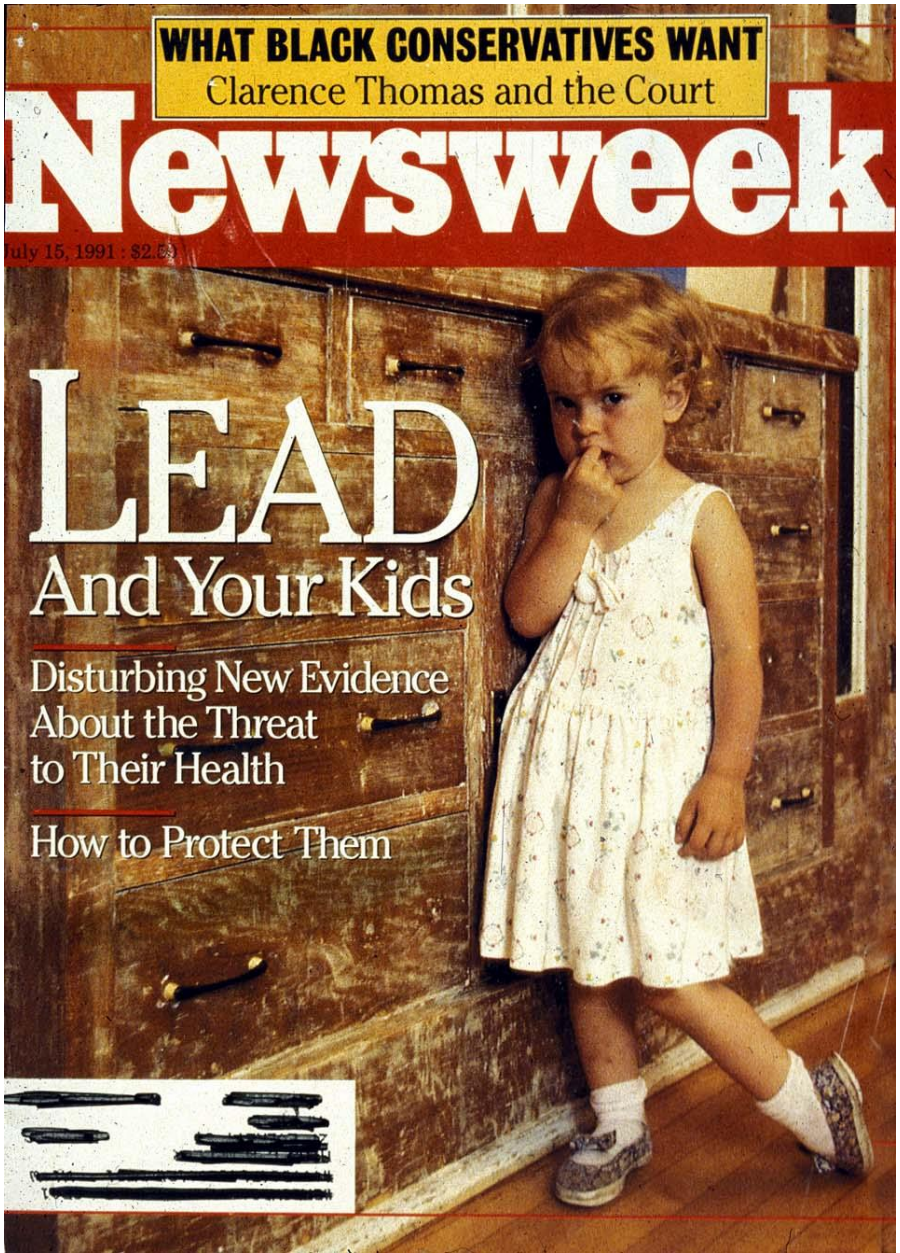
THE PREVENTABLE TRAGEDY

FETAL ALCOHOL SYNDROME

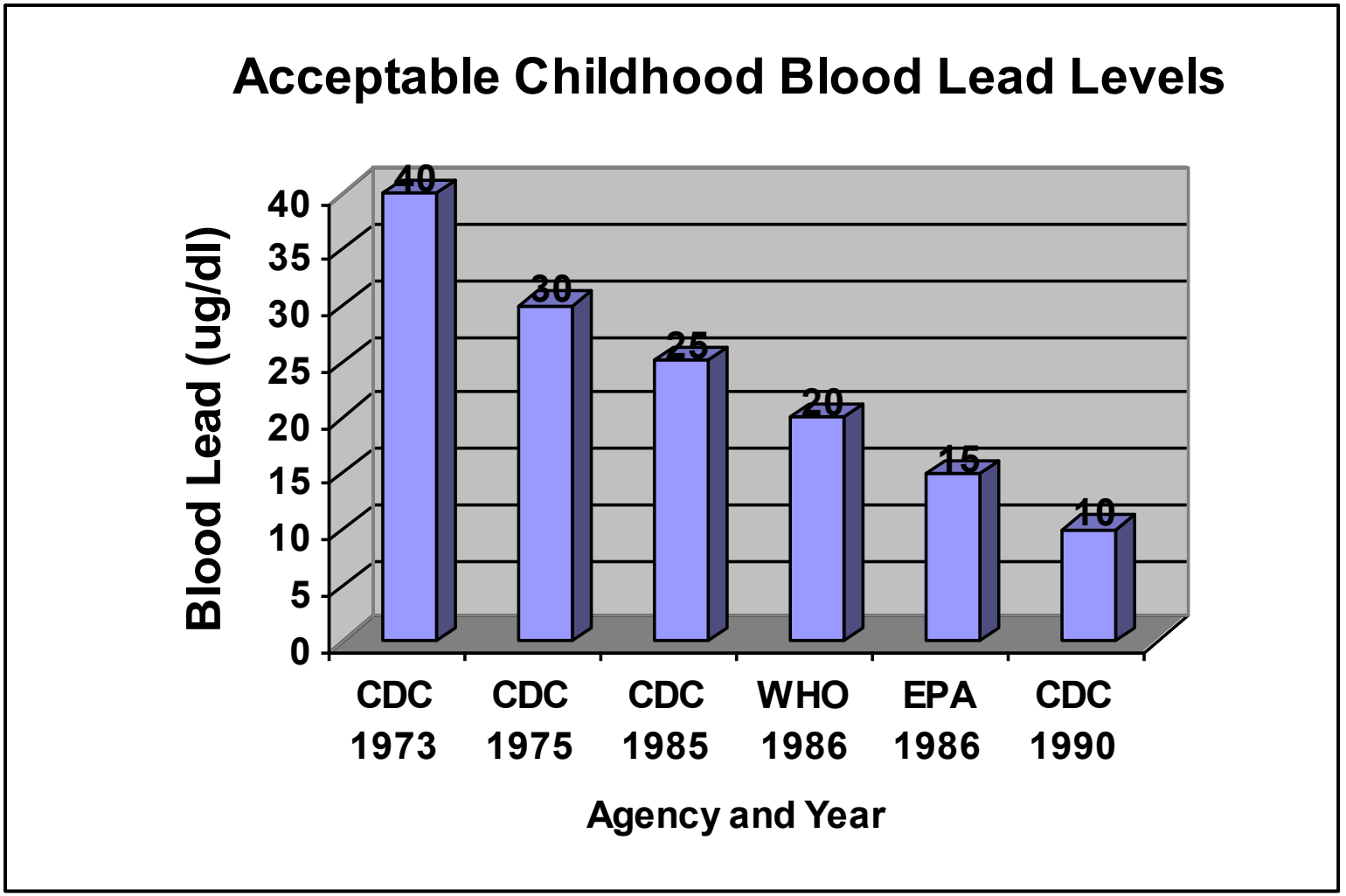
Text and photographs by GEORGE STEINMETZ



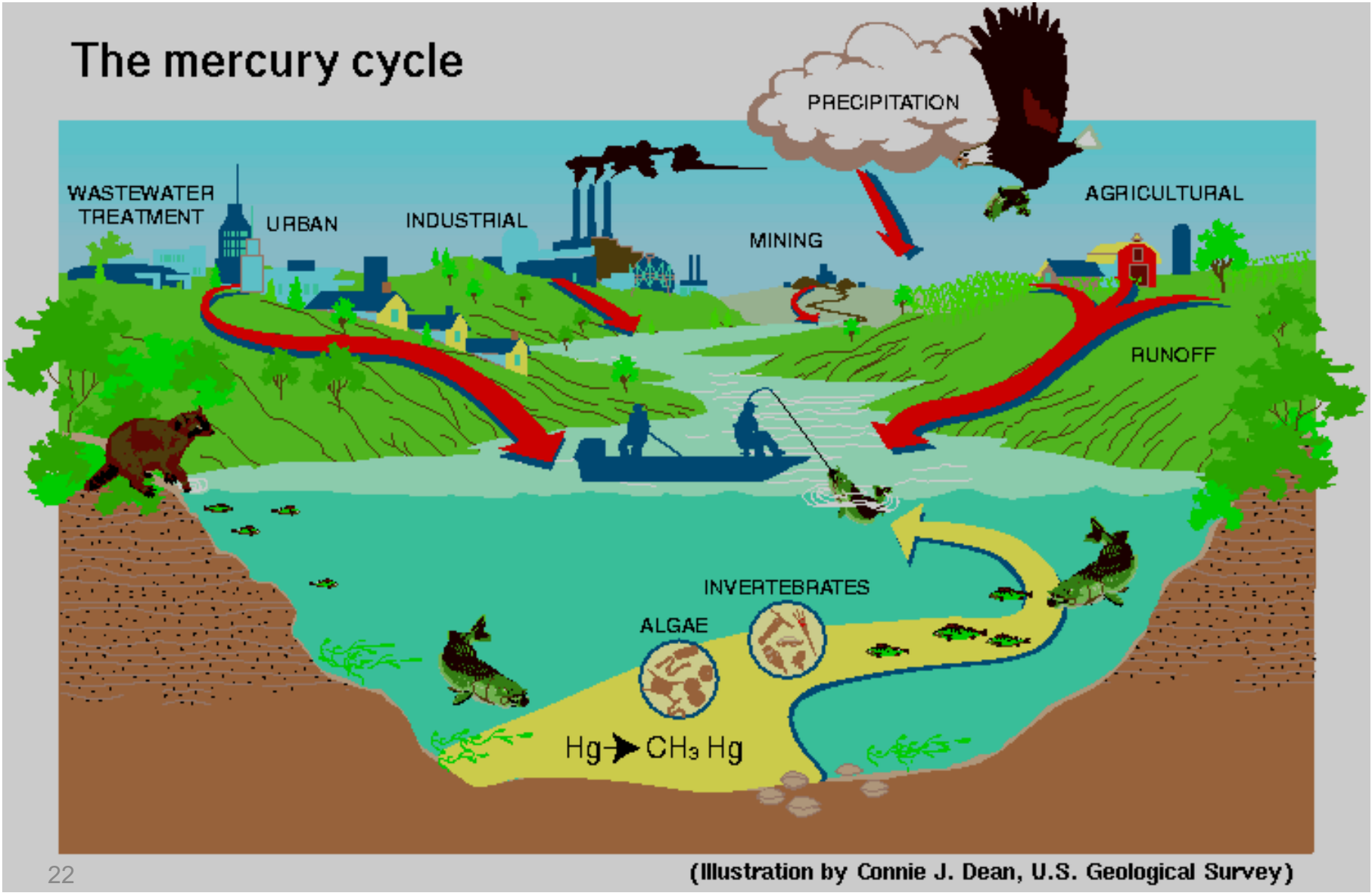
Lead In Homes



CDC Blood Lead Levels

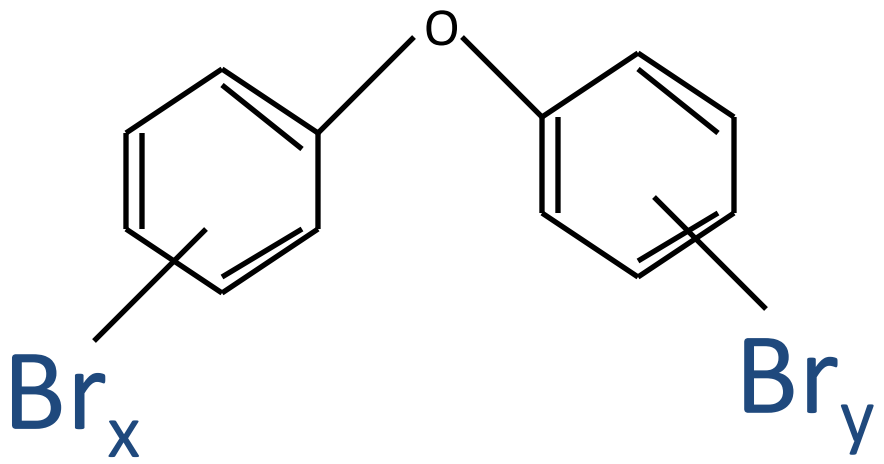


The Mercury Cycle



Structure of PBDEs

PolyBrominated Diphenyl Ether



X & Y are number of Bromine atoms
Common Penta, Octa, and Deca

Ancient Awareness

- 80 Million years ago – Dinosaur bones show evidence of cancer
- 3000 BC - Egyptian mummies – bone cancer
- 1600 BC – Egypt – 8 cases of breast tumors (or ulcers)
  Treated by cauterization – with the “fire drill” - Edwin Smith Papyrus

Ancient Awareness

- 300 BC – Hippocrates named tumors as carcinos or carcinoma – tumors spread out like legs of a crab
- 1500 – autopsy start to provide a greater understanding of cancer
- 1650 – more knowledge with advance in medical science tools like the microscope

Human Cancer Awareness

1700 – Occupational cancer – High incidence of breast cancer among nuns

1775 – Percivall Pott – Occupational – cancer of scrotum in chimney sweeps

1895 – Bladder cancer in workers in aniline dye industry

Animal Cancer Models

1915 – skin tumors in rabbits treated with coal tar on the skin

1930s – isolation of polycyclic aromatic hydrocarbon from coal tar

1932 – benzo(a)pyrene synthesized

1935 – feeding azo dyes to rats can cause liver cancer

Recent Awareness

- 300 million tons of organic chemical manufactured each year
- 100,000+ compounds

What is Cancer?

- Cancer is the uncontrolled multiplication of cells.
- Benign – cancerous cells are contained in one place
- Malignant – cancerous have spread to other areas

Case Studies - Soot

- 1775 – Percivall Pott – Occupational – cancer of scrotum in chimney sweeps
- 1892 – scrotal cancer rare on European content but still high in England – attributed to hygiene
- 1915 – skin tumors in rabbits treated with coal tar on the skin
- 1930s – isolation of polycyclic aromatic hydrocarbon **PAH** from coal tar
- Now – smoking and organic fuels

Case Studies - Benzene

C_6H_6 – Clear, colorless, high flammable, vaporizes at room temp

Known human carcinogen – effect bone marrow causing leukemia

Acute inhalation – CNS effects, dizziness

In US gasoline 2% benzene but up to 5% in other countries

Metabolized by liver to more toxic metabolites

US EPA water standard 0.005 mg/L (5 ppb)

US OSHA – 1 ppm in workplace air over 8 hrs

Case Studies - Asbestos

Cause serious lung disease

- Asbestosis – scarring of the lung
- Mesothelioma– cancer of lung lining

Known since ancient times – commercial use started in early 1900's with wide spread use during World War II

Used in 1000s of consumer and industrial products

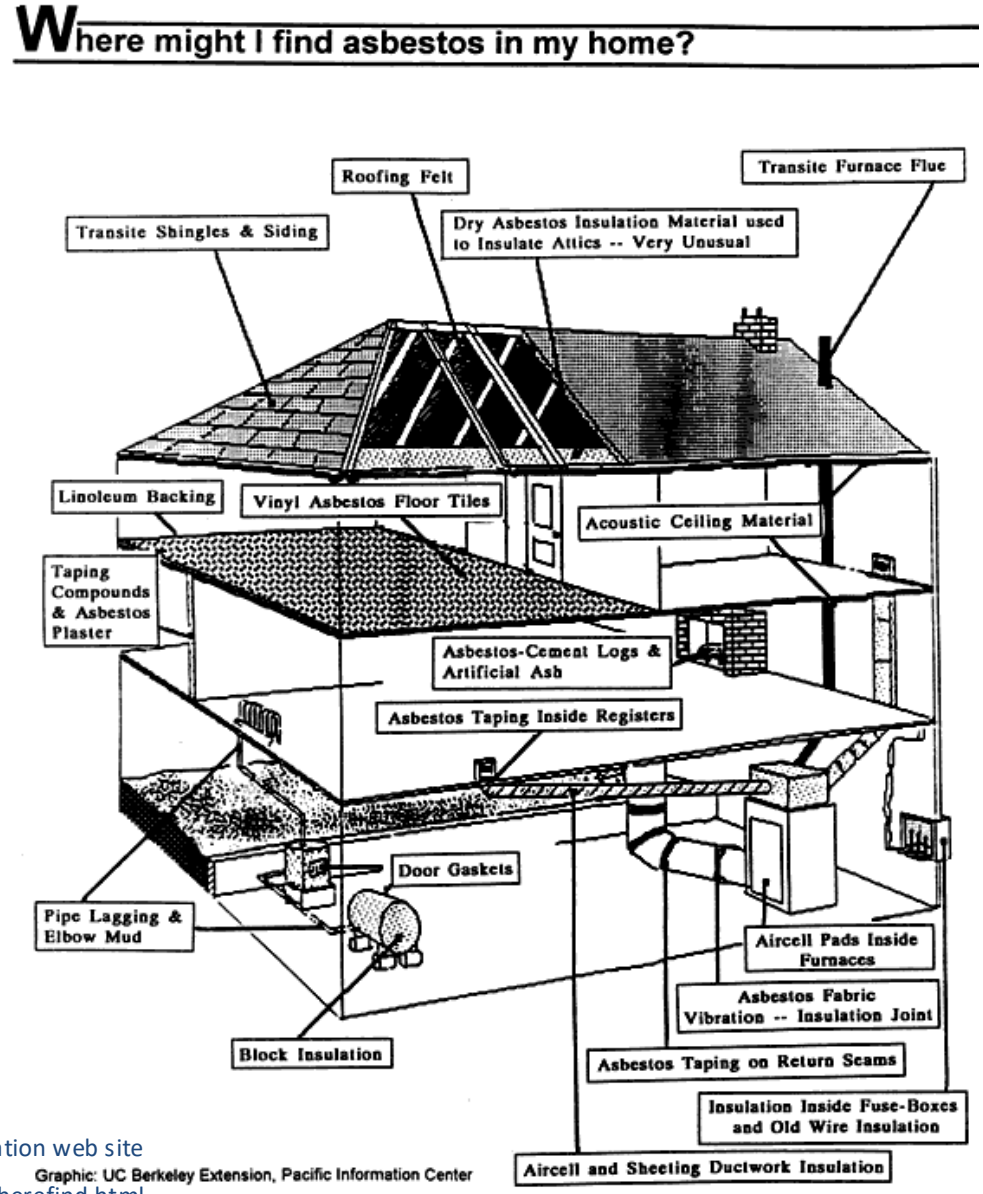
First health effects seen in early 1900s

Dose response and latency effects established in 1930s

Regulation and banning started in 1970s

Millions of people exposed

Asbestos – In the Home



 From The White Lung Association web site
http://whitelung.org/pubs/aith/wherefind.html

Case Studies - Radon

1400's lung disease in miners

1879 – lung cancer in European Miners

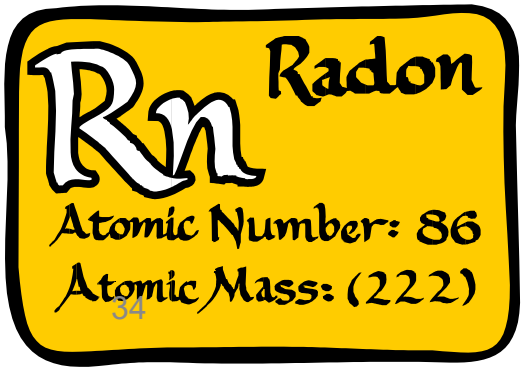
Colorless, odorless radioactive gas

Decay product – uranium to radium to the gas radon to the solid polonium

Polonium sticks to lung tissue – decays releasing an alpha particle which damages cellular DNA causing cancer

1 in 15 (6%) homes in US elevated Radon

U.S. EPA action level 4 pCi/L

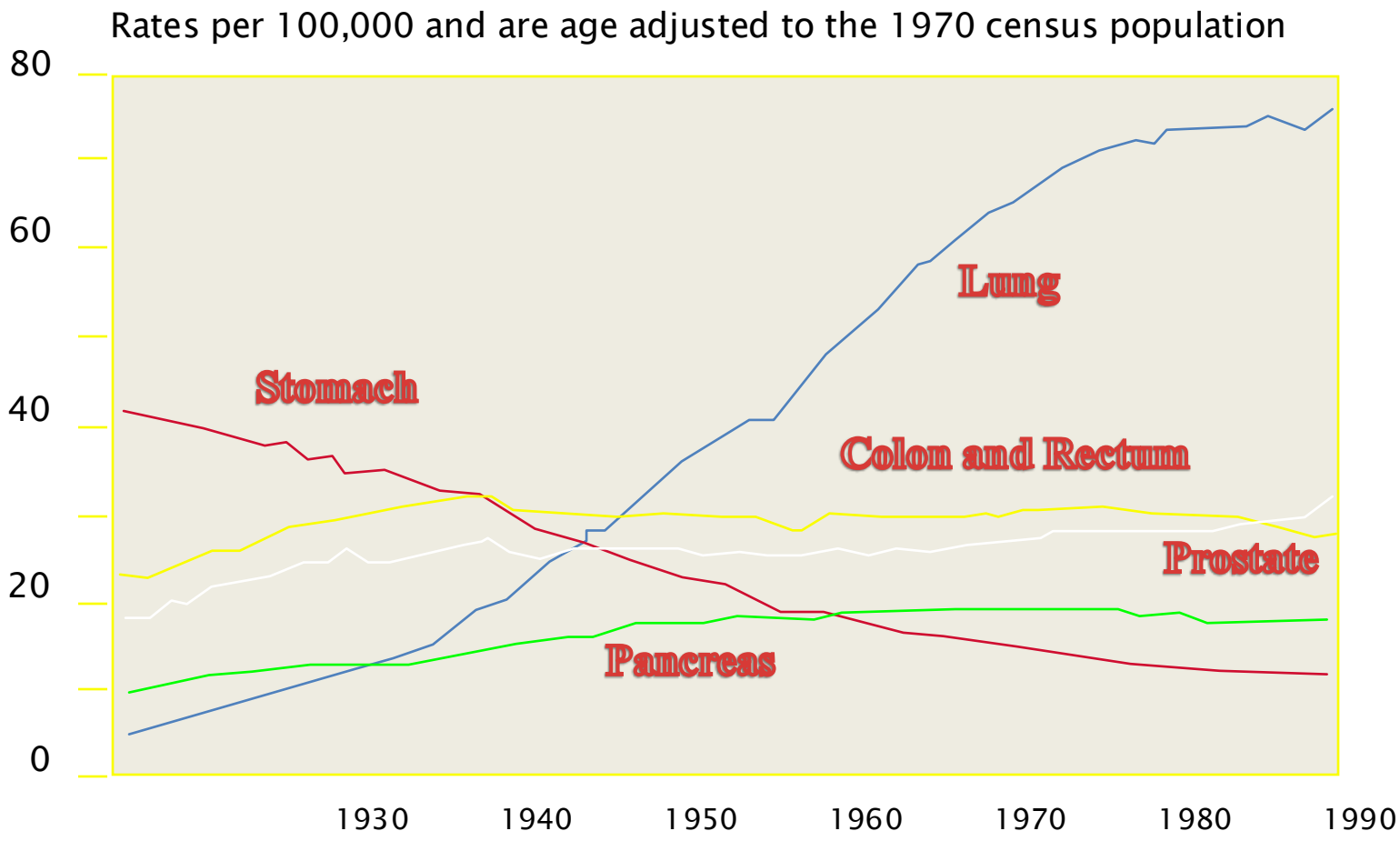


Environmental Factors and Cancer Deaths

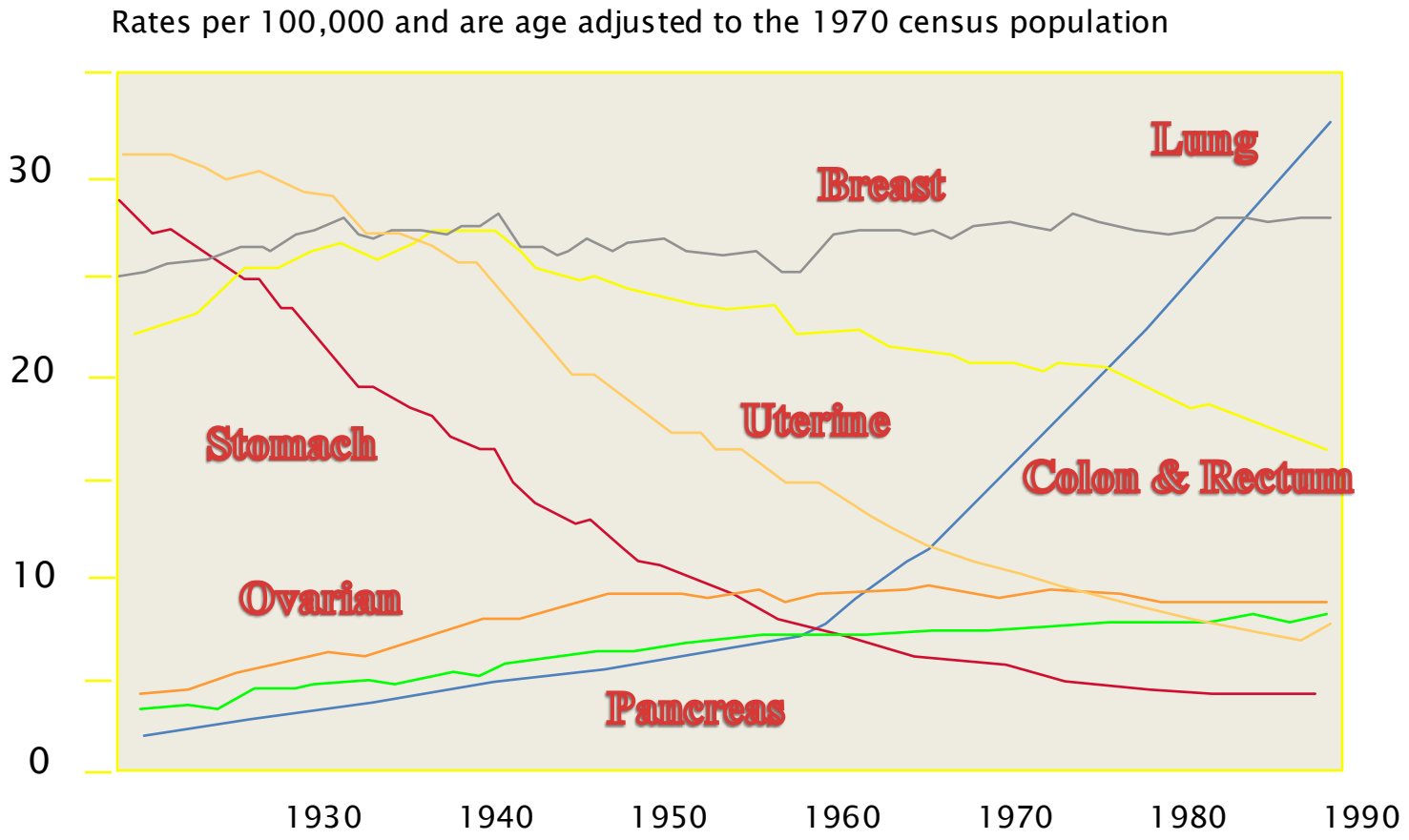
1. Diet	**35% (10-70%)**
2. Tobacco	**30% (25-40%)**
3. Infection	10% (?)
4. Alcohol	3% (2-4%)
5. Reproductive and sexual behavior	7% (1-13%)
6. Occupation	4% (2-8%)
7. Pollution	2% (<1-5%)
8. Geophysical factors	3% (2-4%)
9. Medicines and medical procedures	1% (0.5-3%)
10. Industrial Products	1% (<1-2%)

Adapted from Doll and Peto, 1981; Casarett and Doull's Toxicology, 5th Ed.

Cancer Death Rates by Site Male



Cancer Death Rates by Site Female



Time of Exposure

- During Fetal Development
  - Rapidly dividing cells
- Infancy (soy formula?)
- Childhood
- Puberty
- Occupational exposure

What causes cancer?

- Organic chemicals
- Inorganic chemicals
- Fiber
- Radiation (EMF?)
- Hormonal Carcinogenesis
- Mixtures – Multiple Exposures

What causes cancer?

- **Internal Factors**
  1. Hormones
  2. Immune Conditions
  3. Inherited Conditions (Genetics)
- **External Factors**
  1. Lifestyle Habits (Smoking, Diet, Alcohol)
  2. Viruses
  3. Chemicals
  4. Radiation

Genetic Factors

- **Breast Cancer ---**

  Less 1 in 10 cases in women with a genetic predisposition (10%)

- **Environmental factors?**

Chemical Agents

- Gasoline additives – benzene
- Solvents & degreasing agents
- Polycyclic aromatic hydrocarbons (PAHs)
- Cigarettes / tobacco products
- Phthalates
- PBDEs?
- PCBs, DDT, DDE

Precautionary Principle

"When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."

Wingspread Conference, 1998.

What Can We Do??

1. Phase out chemicals known to cause cancer and genetic harm
2. Educate the public about health effects of radiation
3. Monitor the chemical body burden and health outcomes
4. Hold Corporation accountable for hazardous practices.
5. Enforce existing environmental protection laws
6. Practice “healthy purchasing”
7. Adapted the “Precautionary Principle”

Adapted from - State of the Evidence (3rd ed) – Breast Cancer Fund

Ancient Awareness

399 BC Death of Socrates by Hemlock

Socrates was charged with religious heresy and corrupting the morals of local youth.

The active chemical used was the alkaloid coniine which, when ingested causes paralysis, convulsions and potentially death.

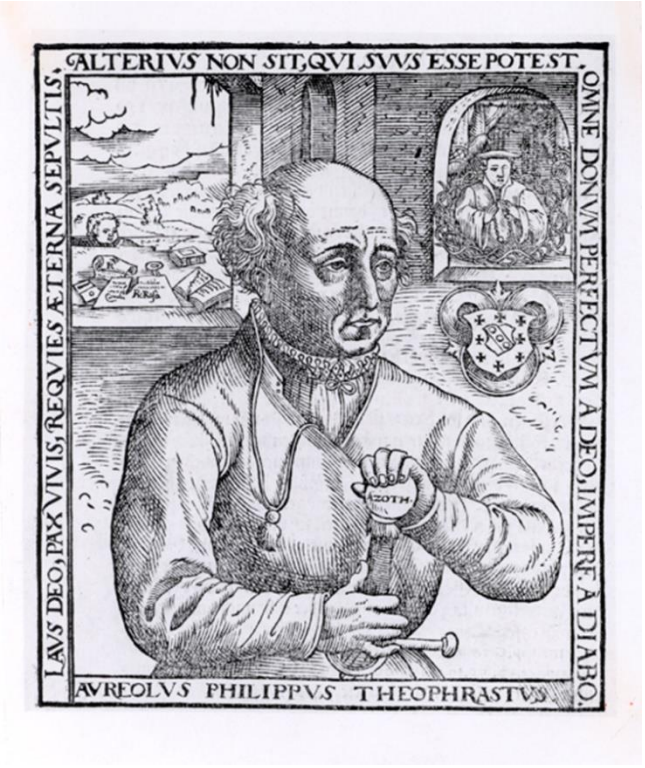
Historical Awareness

From Romeo and Juliet - act 5

Come bitter pilot, now at once run on
The dashing rocks thy seasick weary bark!
Here's to my love! O true apothecary!
Thy drugs are quick. Thus with a kiss I die.

Shakespeare (1564-1616)

Paracelsus



"All substances are poisons; there is none which is not a poison.
The right dose differentiates a poison from a remedy."

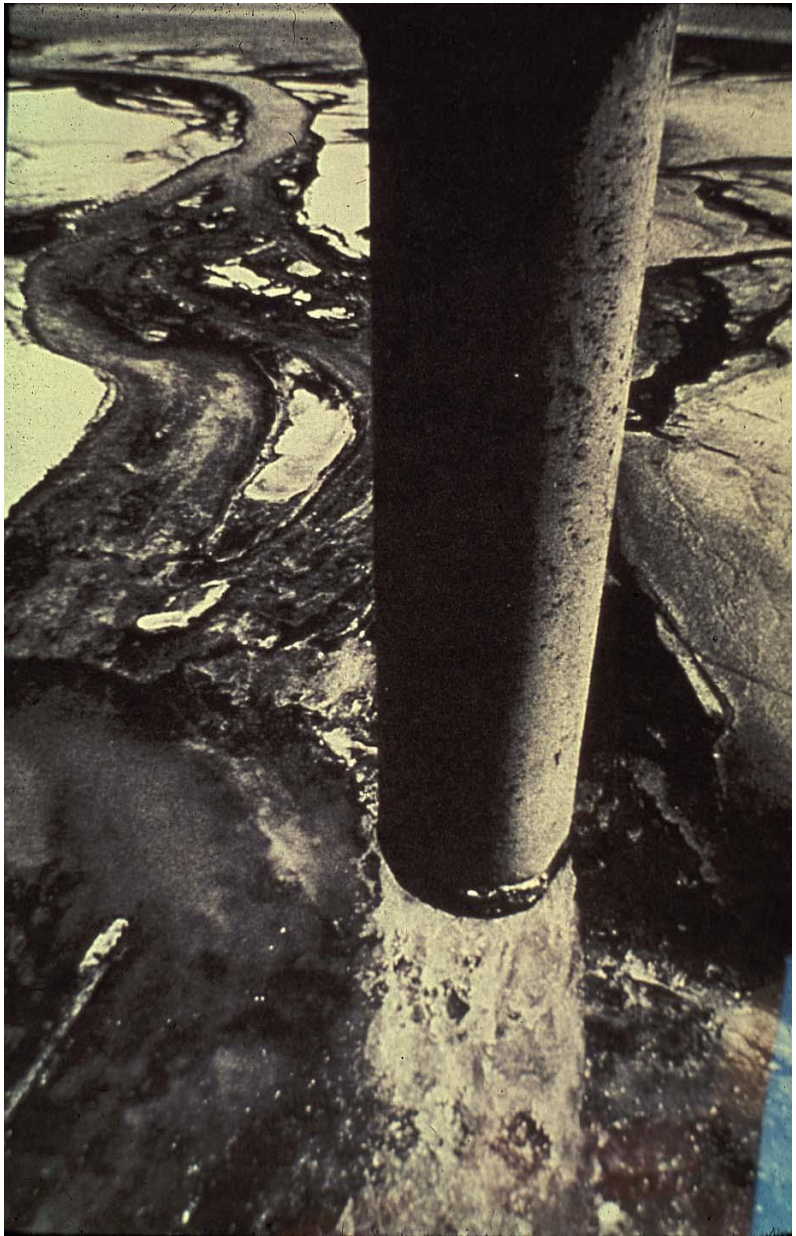
Paracelsus (1493-1541)

An Individual View

"The sensitivity of the individual differentiates a poison from a remedy. The fundamental principle of toxicology is the individual's response to a dose."

S. G. Gilbert (1997)

Discharge in Minamata Bay



Fetal Effects of MeHg