

# Developmental and reproductive toxicology

1st SEMESTER, 2020/2021 SESSION

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W E L C O M E !





# Course requirements

- **ELECTIVE COURSES: 5 CFU**
- Number of units: 2 units
- Lecture period: **29- 11/ 2-12 2021**
- 20 hours /week
- One Practical period 20 hours/total
- **Practical sessions in PIANO D'ACCIO**
- Grading

Final Examination

100%



# Course Learning Objectives

Upon successful completion of the course students should:

- Have broad base knowledge about sources, nature and effects of toxic substances present in the environment or food
- Acquire critical thinking and analytical skills in toxicological evaluations
- Have a high level of understanding and interpretative capacity in toxicology interface.



# General program

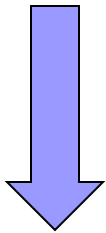
1. Definitions of terms; concepts of toxicology and ecotoxicology
2. Main toxicological compounds having effects on reproductive system
3. Zebrafish as model of toxicological studies
4. Zebrafish anatomy and biology
5. Fish Embryo Acute Toxicity test (practical application of toxicology)

# SOME DEFINITIONS

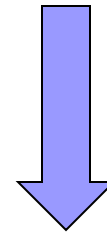
- Safety: is the absence of evidence of toxicity
- Toxicity: is ability to cause harm/adverse effects
- Drugs/pollutants/contaminants: any substance that, when inhaled, injected, smoked, consumed, absorbed via skin, causes a physiological change in the body

# SOME DEFINITIONS

- Contaminant or pollutant?



Natural sources



Antropogenic sources



# SOME DEFINITIONS

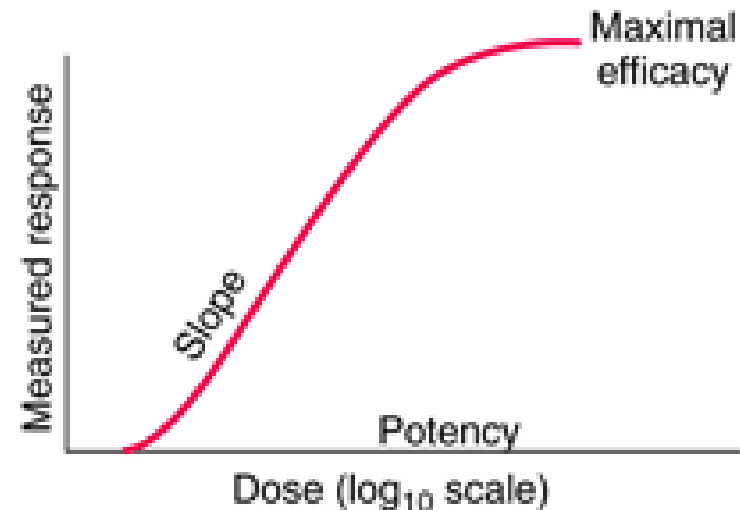
## ■ TOXICOLOGY:

multi-disciplinary application of scientific knowledge to the study of toxins and their effects on people, animals, wildlife and the environment.



# SOME DEFINITIONS

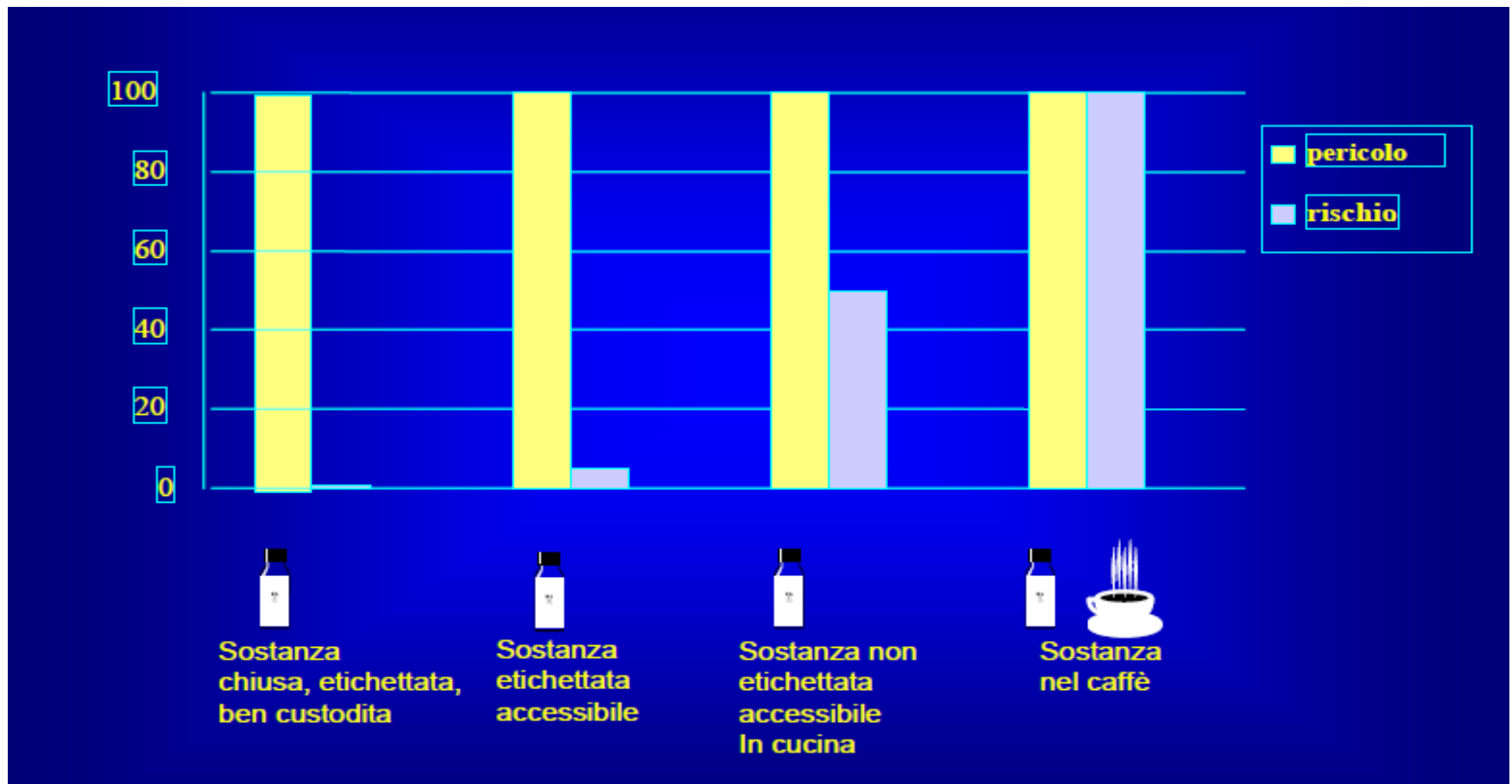
- Safety is relative and there is no absolute safety
- Thus there are toxic and non toxic doses for any substance
- Frequency-response curve: a plot of the % of individual with specific response as a function of dose





A **hazard** is something that can cause harm, e.g. electricity, chemicals, stress, etc.

A **risk** is the chance, high or low, that any hazard will actually cause somebody harm.



# Non dobbiamo dimenticare che

.....

“Tutte le sostanze sono dei veleni; non ne esiste una che non sia un veleno. La giusta dose differenzia un veleno da un rimedio”



**“E’ la dose che fa il veleno”**

- Paracelsus 1493-1541

# *Principles of Toxicology*

*Any synthetic or natural chemical can be harmful if ingested in large enough quantity.*

***THE DOSE MAKES THE POISON***

*Critical questions: what is the lowest level that will cause harm?*



# Principles of Toxicology

*Trace amounts of chemicals in the environment may or may not be harmful.*

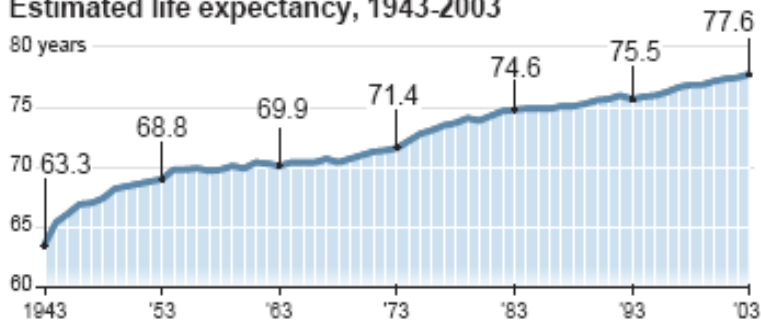
*Some say they are not, look at life expectancy over last several centuries.*

*Some say they are, look at cancer rates and say it is hard to know long-term impacts.*

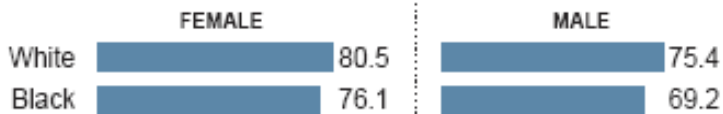
## Life expectancy reaches all-time high

Declines in death rates from most major causes have pushed Americans' life expectancy to a record 77.6 years.

### Estimated life expectancy, 1943-2003



### By race and gender, 2003



SOURCE: Centers for Disease Control and Prevention

AP

# 1. Concentrations units

**ppm** = 1 part per million = 1 mg/Kg or 1  $\mu$ g/g or 1 mg/L

**ppb** = 1 part per billion = 1 ug/Kg or 1 ng/g or 1 ug/L

**ppt** = 1 part per trillion = 1 ng/Kg or 1 pg/g or 1 ng/L

## 2. Half-life

- **Biological half-life**: this is the period of time required for the concentrations or amount of drug in the body to be reduced by one half.

Compound	Half-life
DDT	15 years
Lindane	2 years
Parathion	130days
Malathion	11 days

## Measurement Units and Concentration Analogies

### Parts Per Million (ppm)

1 milligram/kilogram (mg/kg) = 1 ppm

1 milligram/liter (mg/l) = 1 ppm

1 microgram/gram ( $\mu\text{g/g}$ ) = 1 ppm

0.0001 % = 1 ppm

**1 ppm = 1,000 ppb = 1,000,000 ppt**

### Parts Per Billion (ppb)

1 microgram/kilogram ( $\mu\text{g/kg}$ ) = 1 ppb

1 microgram/liter ( $\mu\text{g/l}$ ) = 1 ppb

1 nanogram/gram (ng/g) = 1 ppb

**0.001 ppm = 1ppb = 1,000 ppt**

### Parts Per Trillion (ppt)

1 nanogram/kilogram (ng/kg) = 1 ppt

1 nanogram/liter (ng/l) = 1 ppt

1 picogram/gram (pg/g) = 1 ppt

# Dose-response Relationship

- Dose
  - amount of drug per body weight
  - mg/kg
- Drug effects are variable
- Group dose-response curves
  - % of population responding
  - Response magnitude
- Different for each individual effect
  - i.e., temperature, respiration, euphoria, etc.



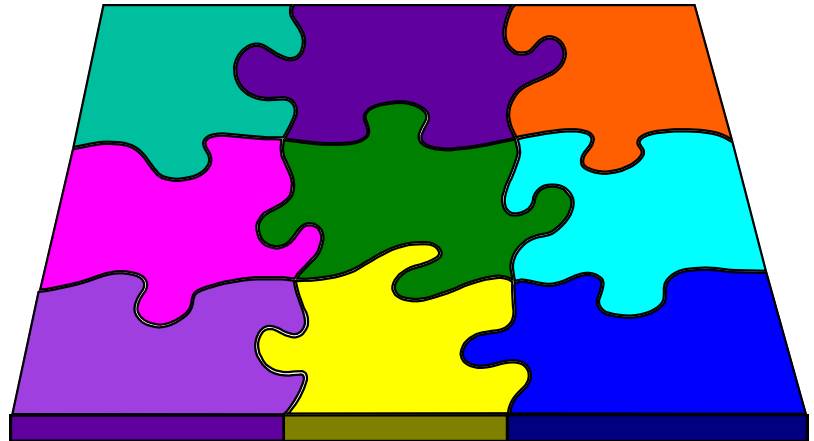
# Dose response curves


- Dose response relationships describe the effect on an organism caused by differing levels of exposure (or dose)
- Dose levels are usually expressed in mg/kg body weight of the test animal for solids and mg/m<sup>3</sup> or parts per million for aerosols/vapours
- The dose response curve is a valuable tool to understand the levels at which substances begin to exert adverse effects and the degree of harm expected at various levels



# TOXICOLOGY IS MULTIDISCIPLINARY

- CHEMISTRY
- BIOCHEMISTRY
- PHYSIOLOGY
- PATHOLOGY
- IMMUNOLOGY
- PHYSICS
- ENGINEERING
- STATISTICS

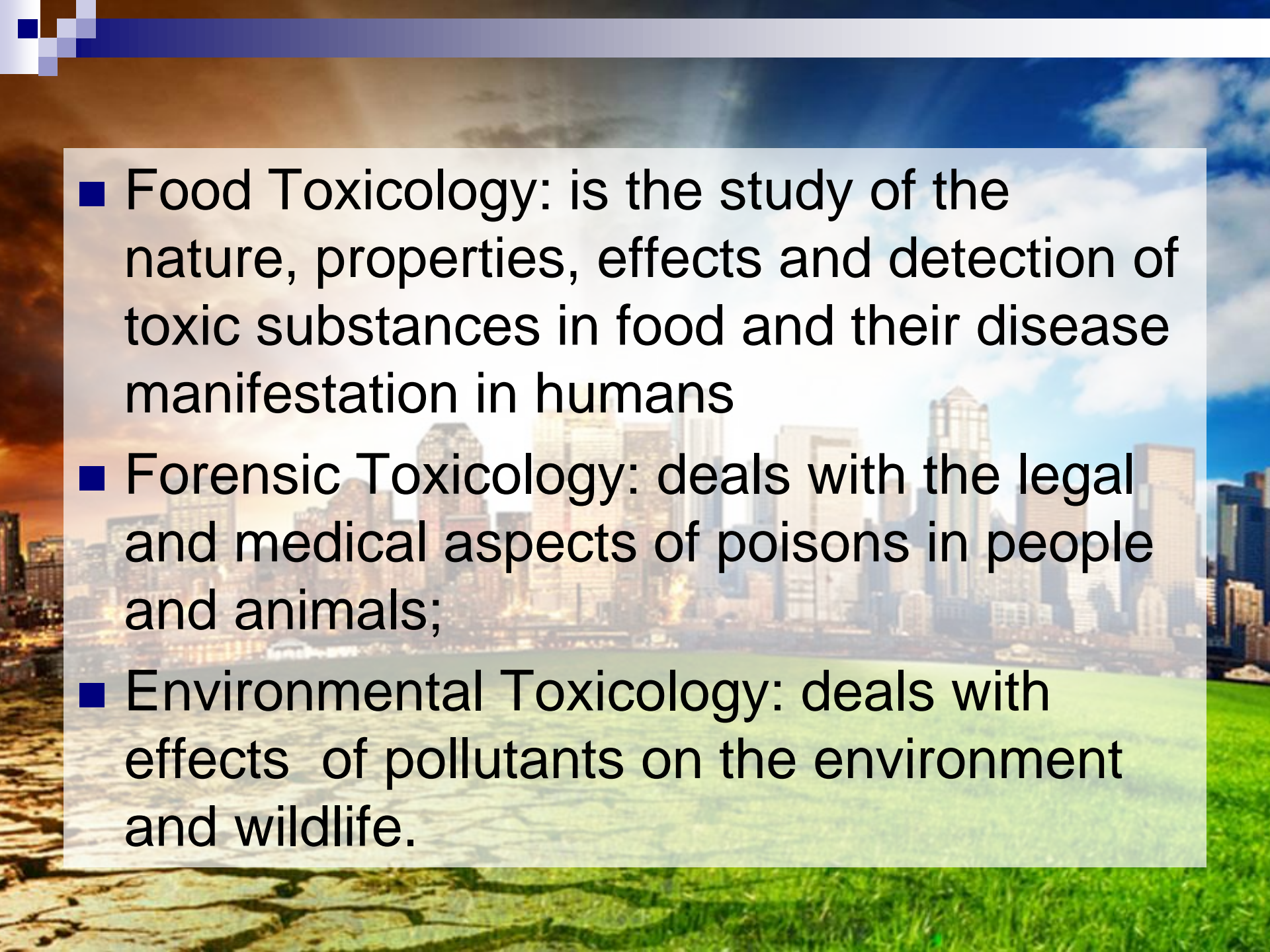




- **Toxicology is the most diversified of all scientific disciplines, so toxicologists usually specialize in some aspect of toxicology**

- **Medical Toxicology/ Clinical Toxicology: diagnosis and treatment of human diseases caused by poisons**

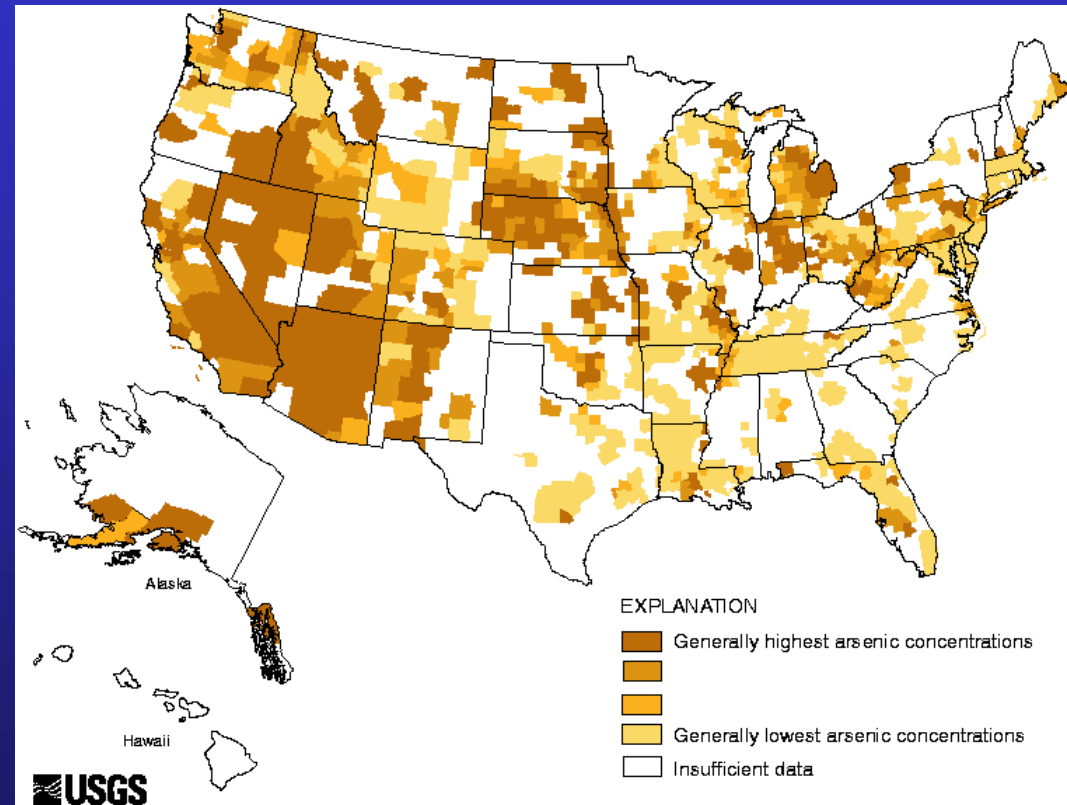
- **Veterinary Toxicology: diagnosis and treatment of diseases of domesticated and wildlife caused by poisons**

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- **Food Toxicology:** is the study of the nature, properties, effects and detection of toxic substances in food and their disease manifestation in humans
  - **Forensic Toxicology:** deals with the legal and medical aspects of poisons in people and animals;
  - **Environmental Toxicology:** deals with effects of pollutants on the environment and wildlife.

# Impacts of Chemicals on Humans

Chemicals may also impact:

- **Immune system**  
(arsenic, dioxin)
- **Nervous System**  
(neurotoxins, brain, spinal cord, etc.)
- **Endocrine System**  
(levels of hormones)



# *Hormonally Active Agents*



Exposure to low level certain synthetic chemicals may disrupt a bodies hormone levels

- Endocrine disruptors or hormonally active agents

So called, gender benders



# *Establishing Guilt Is Difficult*

Under current laws, most chemicals are considered innocent until proven guilty.

“Toxicologist know a great deal about a few chemicals, a little about many, and nothing about most.”



# ***Establishing Guilt Is Difficult***

U.S. National Academy of Sciences estimates that only 10% of the 80,000 chemicals in commercial use have been tested for toxicity.

## ***Why?***

- Not required (considered innocent)
- Lack of funds, personnel, facilities
- Expensive
- Difficult to test interactions



# How Are We Exposed?

- **In the Air:** Heavy Metals, volatile organic, fine particles, various gasses, molds and spores
- **In the Water:** Bacteria and protozoa, persistent organics chemicals (*DDT, PCB's, dioxin, PBDE's*), pesticides, MTBE from gasoline, fluoride, chlorine and trihalomethanes
- **In The Food We Eat:** Heavy metals, pesticides, hormones, food preparation (*C8 or PFOA from non-stick cookware, Aluminum from cookware*)



# Global Concern



## *It's In the Air*

- Americans – 116 toxic chemicals – up from 27 in 2001
- Asia – 1 million of people die from pollutants
- Sweden – increased risk of diabetes linked to exposure to PCB's, POP's and insecticides
- 1460 metric tons of airborne toxins travel the jet stream around the world

# We're Surrounded

## *It's In the Air*

- Inhale 5000 gallons of air each day
- US facilities released 4.7 B lbs of toxins into the air – 72 M lbs are known carcinogens
- Chicago – 68 days when air was too unhealthy for children, elderly & the ill
- Fine particle pollutants (car exhaust & power plants), correlate with increase risk of dying from any cause



# We're Surrounded

## *It's In the Air*

- Coal-fired power plants spew sulfates, nitrates and mercury into the air—linked to >20,000 premature deaths each year
- 10% of women carry mercury concentrations high enough for fetal damage
- Manufacturing, transportation, electricity generation and other human activities are taking its toll on our health and environment



# We're Surrounded

## *There Must Be Something In the Water*

- 7 M illnesses & 1000 deaths each year in US from waterborne microbes
- Chlorinated chemicals in drinking water linked to increased risk of breast cancer
- Cyanobacterial toxins linked to illness and disease worldwide
- Sewage treatment plant workers at much higher risk of respiratory illness, skin rashes, headaches & body aches



# We're Surrounded



## *Don't Eat That!*

- Environmental toxins work their way into the food chain
- 47 states have advisories to limit intake of freshwater fish due to mercury contamination
- Chlorinated pesticides
  - *FDA finds DDE in 63% of foods surveyed*
  - *Strongly immunotoxic*
  - *Present in 84% of fruit & vegetables to schools*
- Herbicides in food linked to many cancers

# Home Sweet Womb

## *Even Before We're Born*

- Average newborn has 200 different industrial chemicals, pollutants & pesticides in blood
  - *Carcinogens*
  - *Toxic to brain & nervous system*
  - *Abnormal development*
- Urban air pollution linked to chromosomal abnormalities in infants in NYC





# Mothers Give More than Love...

## *To Fetus across the Placenta*

- Pregnancy mobilizes fat soluble POP's (*dioxin, DDT, PCB's, flame retardants like PBDE's*)
- Lead and methylmercury actively transported
- Fetus: immature metabolism results in sequestration in fetal brain
- Multiple studies (US, Netherlands, Canada) document: >200 chemicals in cord blood



# ...And More than Nourishment



## *Toxins in breast milk increase the toxic load*

- ❑ POP's are bio-concentrated in fat
- ❑ Lactation mobilizes fat stores and associated chemicals
- ❑ POP's transmission in milk much greater than placental
- ❑ Heavy metals Mercury, Cadmium, Lead...all concentrated in breast milk
- ❑ Volatile Organics also found in low levels