EPA
United States
Environmental Protection
Agency

# Health Effects of Dioxins

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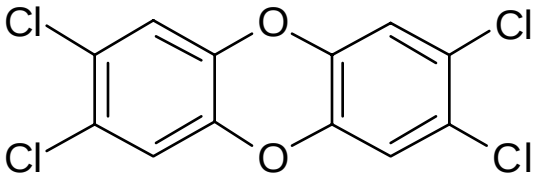
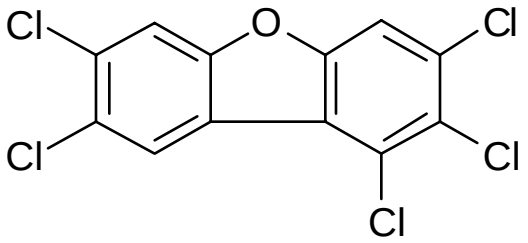
# Outline

- What are Dioxins
- Exposures to Dioxins
- Health Effects
  - Animals
  - Humans
- Dose Response
- Summary

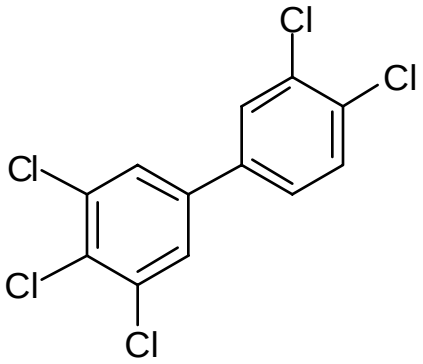
# Dioxins



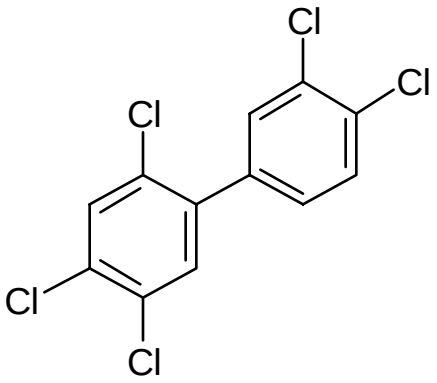

2,3,7,8-Tetrachlorodibenzo-p-dioxin
"DIOXIN"




2,3,4,7,8-Pentachlorodibenzofuran

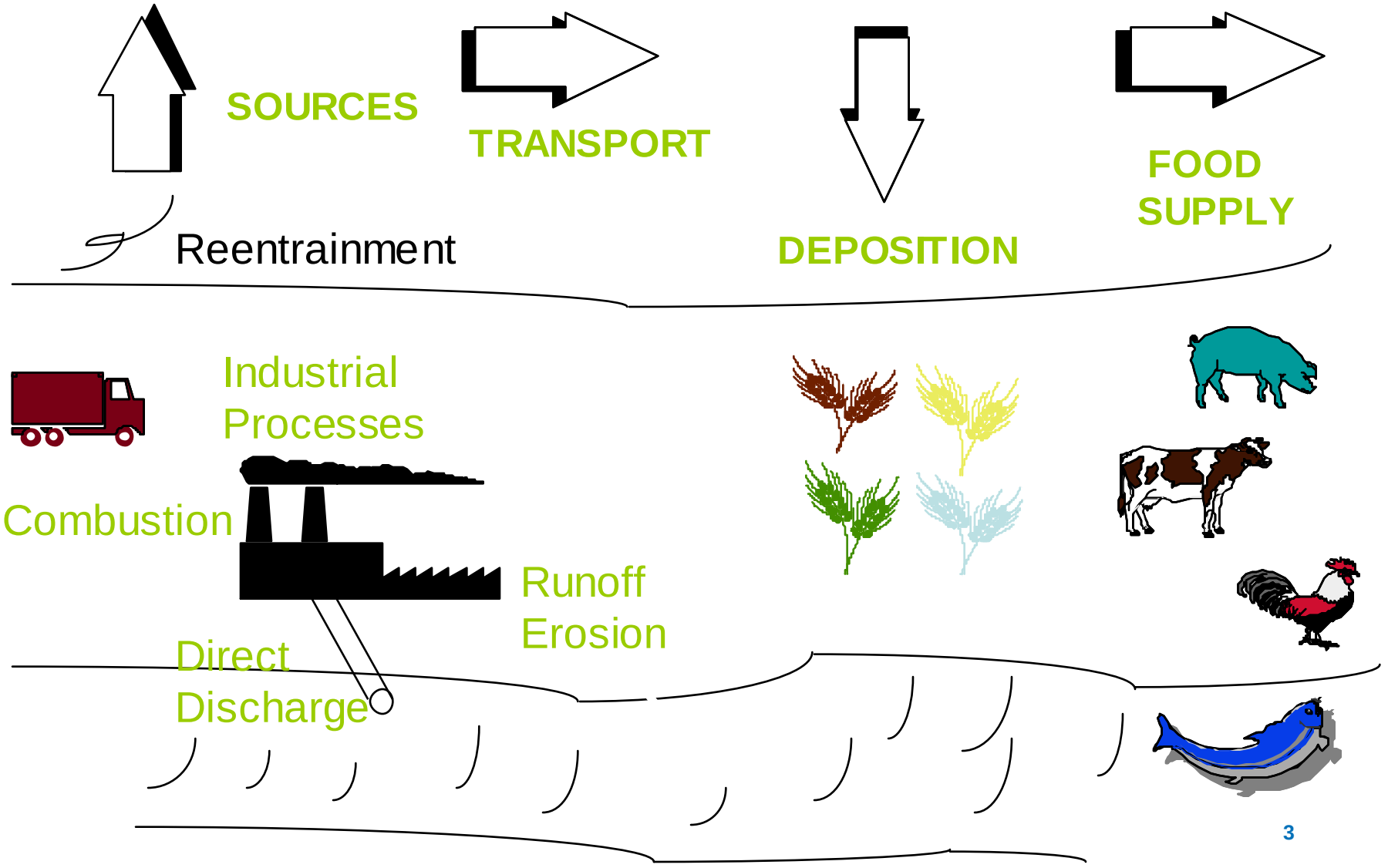



3,3',4,4',5-Pentachlorobiphenyl
PCB 126



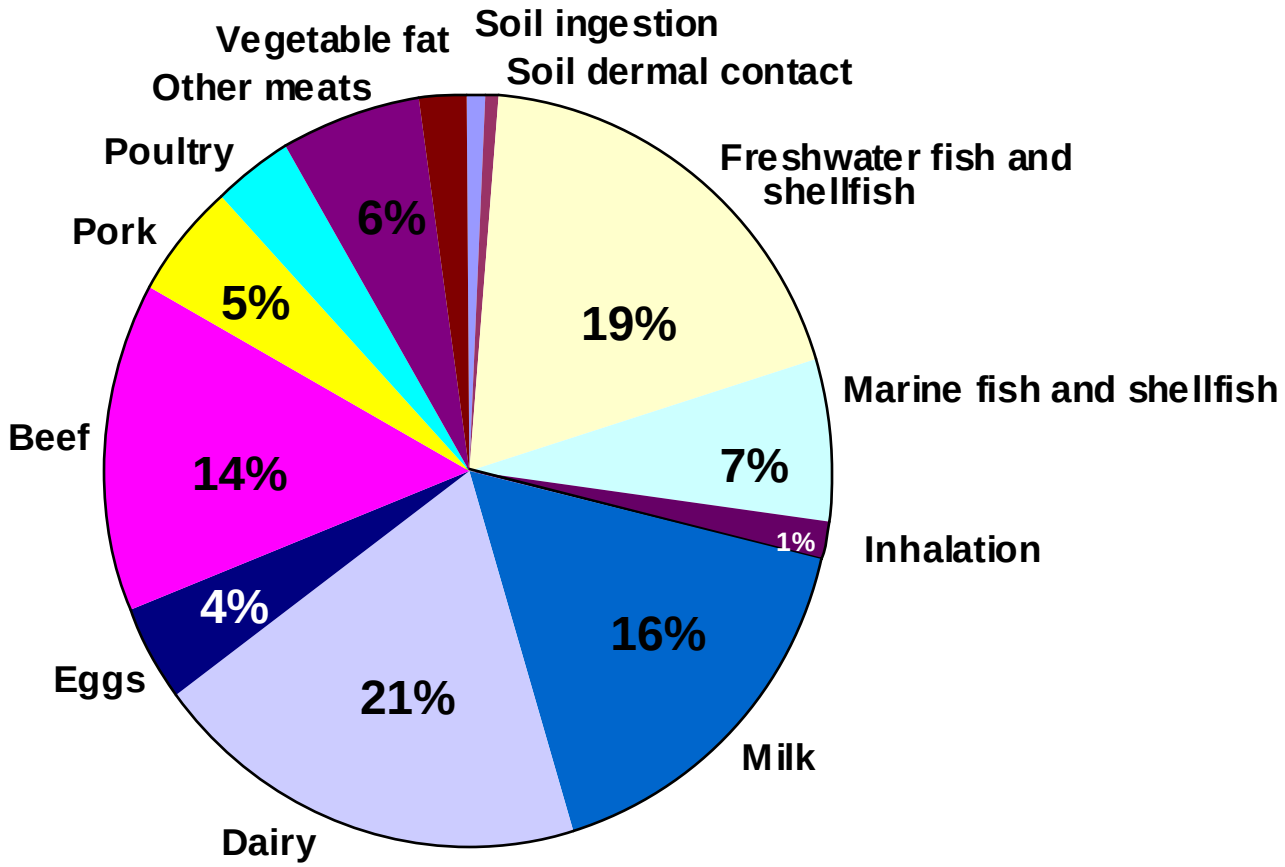

2,3,3',4,4'-Pentachlorobiphenyl
PCB 118

# Sources and Pathways to Human Exposures



# U.S. Adult Average Daily Intake of CDDs/CDFs/Dioxin-Like PCBs

***65 pg $TEQ_{DFP}$-$WHO_{98}$/day***

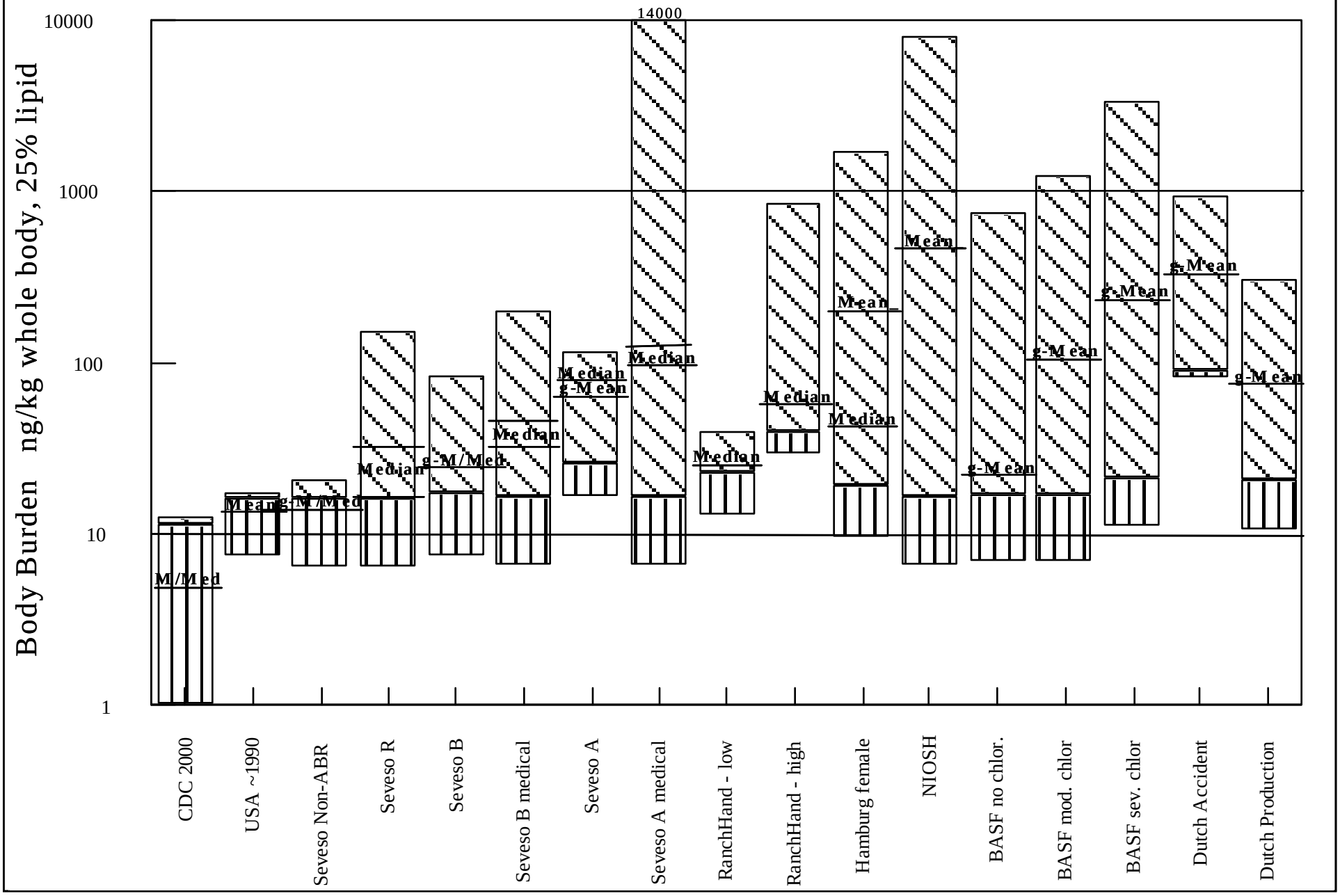


# Dioxin Exposure Trends

- **Environmental levels:**
  - Peaked in late 60s/early 70s; declined since based on sediment data
  - Decline also supported by Emissions Inventory which shows significant decrease from 1987 to 1995 (~80%)

- **Human tissue data suggest current levels are about 5 times lower than 1980 levels (55 to 10 pg $TEQ_{DFP}$/g lipid)**

# Peak Dioxin Body Burden Levels in Background Populations and Epidemiological Cohorts (Back-calculated)



- Hazard X Exposure = Risk

- Hazard – inherent toxicity of chemical
- Exposure – contact with the chemical
- Risk – estimate of potential health effects

## Evidence of Dioxin Toxicity

- Experimental Studies in Animals
  - Clear relationship between known exposure and response
  - Extrapolation to humans

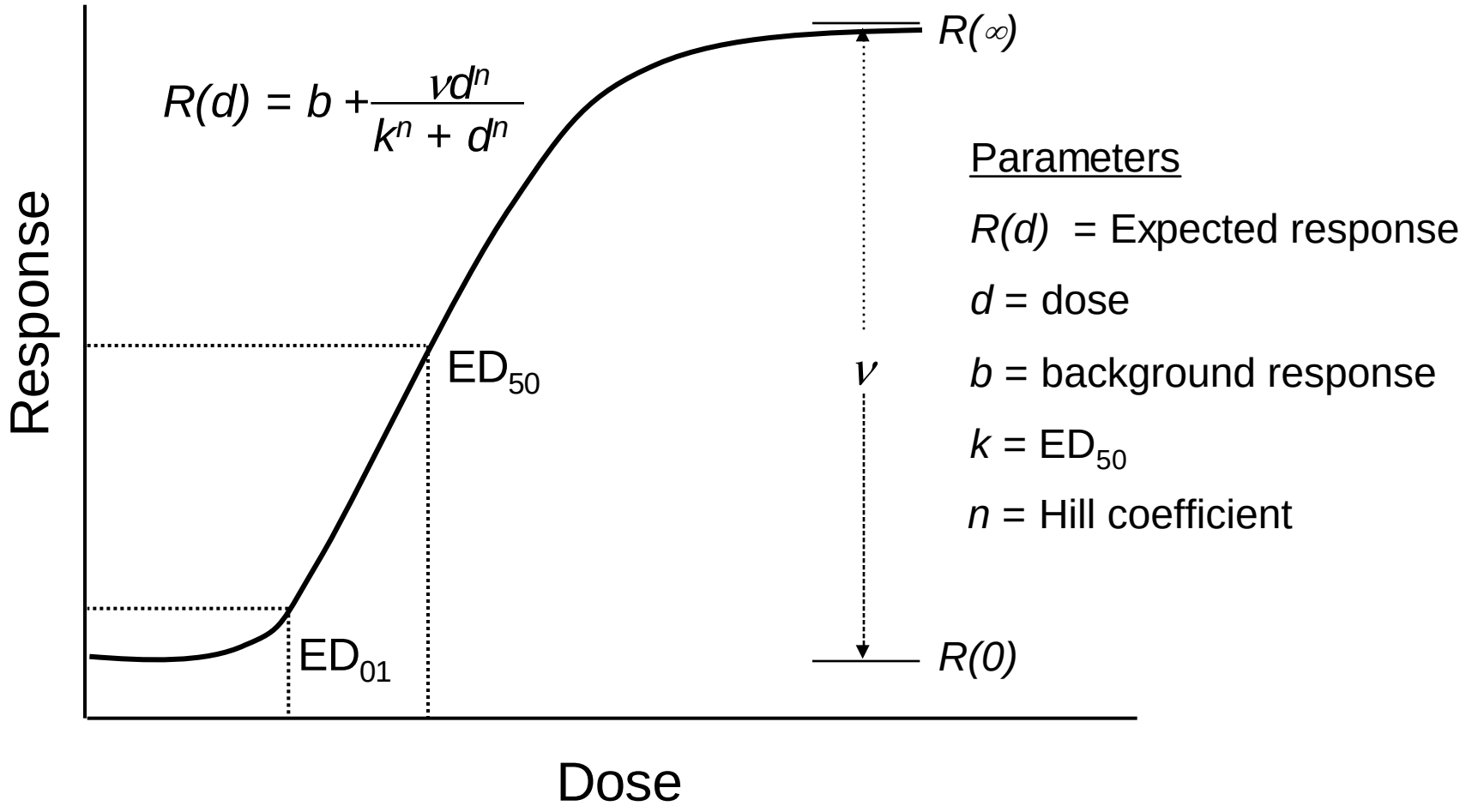
- Epidemiological Studies in humans
  - Demonstrate Associations and sometimes causation
  - Extrapolation to low background exposures
  - Confounders sometimes difficult to control.

## Extrapolation

- Animals
  - Dose/Pharmacokinetics
  - Pharmacodynamics - What dioxin does

- Epidemiological Studies (Humans)
  - Exposure Scenario
  - Dose Response

# Dose Response Relationship



## Dioxin-like Compounds are Receptor Mediated Toxicants in Animals

- ➔ Developmental Toxicity
  - ***Targets:***
    - ➢ Developing Immune System
    - ➢ Developing Nervous System
    - ➢ Developing Reproductive System
    - ➢ Developing Bones
- ➔ Immunotoxicity
- ➔ Endocrine Effect
- ➔ Chloracne
- ➔ Cardiovascular
- ➔ Cancer

## Dioxins are Growth Dysregulators

- **Growth**
  - **Cell death**
  - **Cell proliferation**
  - **Cell differentiation**

- **Cancer**
- **Developmental toxicities**
- **Immunotoxicity**
- **Endocrine effects**

# Dioxins act through the Ah Receptor
# What do we know about the Ah Receptor

- Highly conserved across species
  - Found in C. elegans though humans
    - Fish, clams, birds, mammals
- Member of PAS protein family
  - Biosensors
    - Oxidative stress, light, circadian rthyms.
- Polymorhpisms
  - Binding affinity for TCDD ranges approximately 10 fold in humans

## Margin of Exposure

- **Metric for evaluation of safe or tolerable exposures to environmental contaminants.**
- **Does not apply uncertainty or safety factors,**
- **Does not provide any assumptions on the shape of the dose-response curves.**
- **Is not probabilistic.**

# Margin of Exposure

$$\frac{AnimalDose}{HumanDose}$$

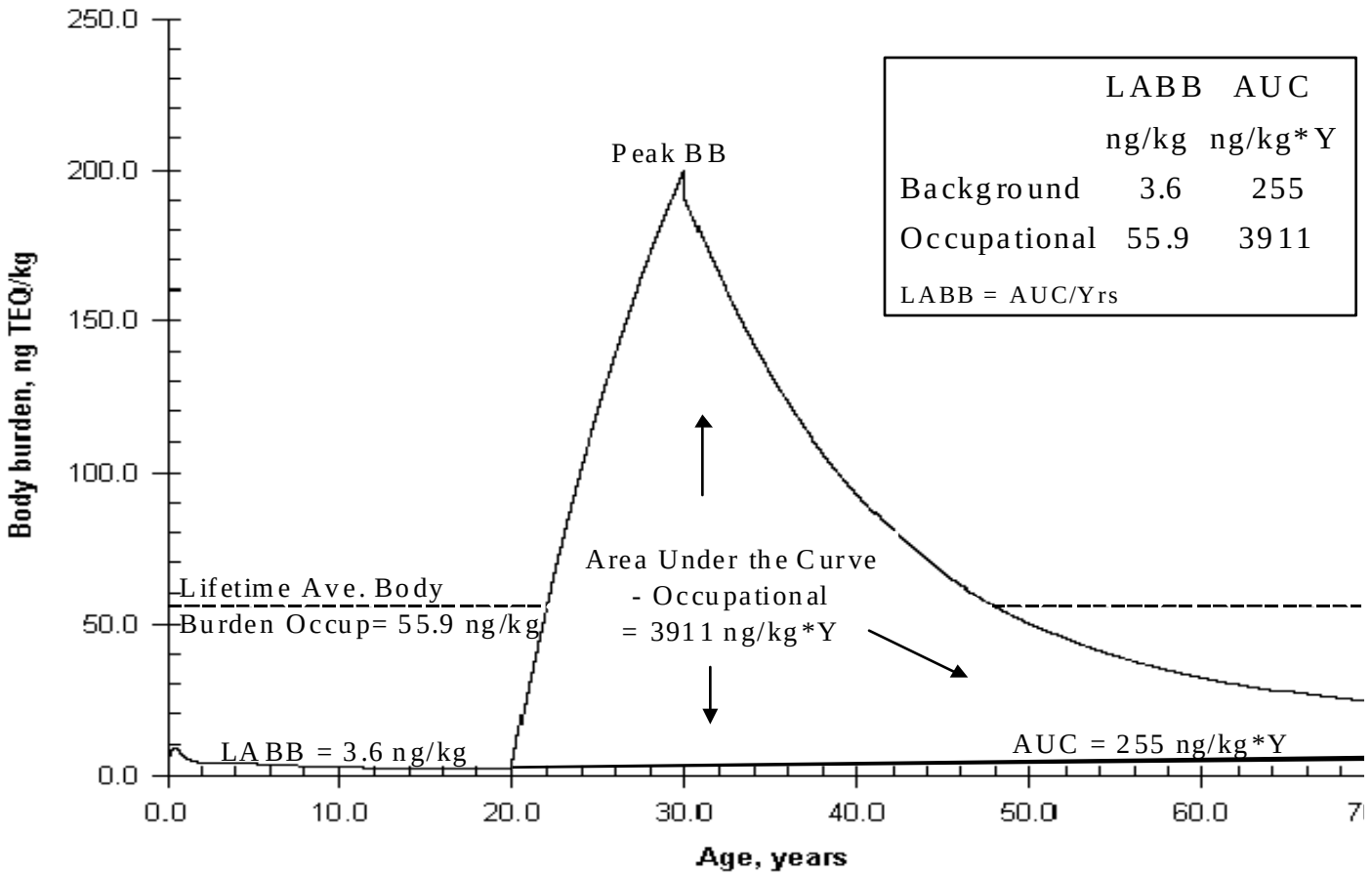
# *Body Burdens Associated with Effects*

| | Body Burden (ng/kg) | Margin of Exposure |
|---|---|---|
| ADVERSE EFFECTS | | (Effect level/current av. US BB, 5ng/kg) |
| Developmental Neurotoxicity | 22 | 4 |
| Developmental reproductive toxicity | 0.7 –42 | 0.1 - 8 |
| Developmental immunotoxicity | 50 | 10 |
| Adult immunotoxicity | 1.6 – 12 | 0.3 - 2 |
| Endometriosis | 22 | 4 |
| Cancer | 3.3 - 80 | 0.6 - 16 |
| BIOCHEM. EFFECTS | | |
| CYP1A1 induction | 0.6 -33 | 0.1 - 7 |
| CYP1A2 induction | 2.1 - 83 | 0.4 - 17 |
| Oxidative stress | 10 | 2 |

## Differences between animal and human exposures

- **Animals**
  - **Single acute exposure**
  - **Constant level of repeated exposure**
  - **Single route of exposure**
- **Humans**
  - **Exposure through multiple routes**
  - **Exposure varies with age and occupational vs environmental exposures**

# Comparison of Lifetime Average Body Burden and Area under the Curve in Hypothetical Background and Occupational Scenarios



## Dioxin-like Compounds are High Potency *Human* or *Likely* Human Carcinogens

**TCDD** ➔ Characterized as a human carcinogen

**Others** ➔ Likely to be carcinogenic

***Based on:***

- Unequivocal animal carcinogen
- Limited human information (epidemiologic/other)
- Mechanistic plausibility

*Cancer potency increasing with focus on human studies*

**Note: In February 1997, the International Agency for Research on Cancer (IARC) classified 2,3,7,8-TCDD as a Category 1, "Known" human carcinogen; HHS/ROC proposed the same in 1999**

## Non-Cancer Effects Observed At or Near General Population Body Burden Levels

- Enzyme induction
- Immune system changes
- Developmental milestones
- Glucose tolerance/diabetes
- Hormone levels
- Others?

***Generally considered to be adaptive changes, but potential to be adverse.***

# Summary and Challenges

- Continue and maintain the trend for lower emissions and lower exposures in the population
- Better characterize the source to exposure pathways in order to more efficiently decrease exposures
- Better understand biological basis of the actions of dioxins in order to predict adverse health effects of exposed populations.