Dioxin and Related Compounds in the Human Food Chain

Food Toxicology
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Learning Objectives

• Explore dioxins and dioxin-like compounds in the food supply
• Summarize the structural similarities of cogeners of dioxins and furans.
• Understand Toxicity Equivalency Factors (TEF) and Toxicity Equivalents (TEQ) for dioxins and related compounds.
• Summarize the known processes and toxicological endpoints of dioxin exposure.

Learning Objectives

• Describe the controversy and data needs concerning low-level dioxin exposure.
• Describe the observed effects and major findings of animal studies with dioxin.
• Summarize the environmental and food sources of dioxins.
• Summarize the known human risk estimations for dioxins.
• Summarize the regulatory control approaches for dioxin release.

The Organochlorine Legacy

• Halogenated organics have been used as synthetic pesticides and industrial compounds for since before WWII - stable
• Chlorinated compounds can be formed by combustion and natural processes in the presence of chlorine (dioxins)
• Often non-polar and lipophillic, they have the ability to be sequestered in fat tissue
• Can bioaccumulate up the food chain
• Can circulate in the “liposphere”

Organochlorine Compounds
• Often related to immune dysfunction, neurological effects, cancer, endocrine disruption and other toxicological endpoints
• Chlorinated compounds all around us
• Often the effects of low-level exposure are sub-clinical and “biomolecular” and this complicates the risk assessment for low-level exposure

2003 NAS Institute of Medicine Analysis
• Dioxins and Dioxin-like Compounds in the Food Supply (2003)
  – http://newton.nap.edu/catalog/10763.html

Dioxins
• Widespread, low-level contaminants in animal feeds and the human food supply.
• Animal fats are the primary vector of exposure.
• Dioxins metabolize slowly and accumulate in body fat over a lifetime.
• Data show decline in levels.
• Endocrine disruption is a concern.
• Exposure and children’s health and development.
• High public priority to reduce dioxin levels in girls and young women.

Dioxin: Food Supply Exposure
• Animal production systems
  – Airborne deposition on grazing areas or water bodies
– Geographic variability due to sources (incineration)

• Human foods
  – Relatively uniform exposure due to food distribution patterns

• Food-consumption patterns
  – High fat diets
    = higher exposure
  – Animal fats,
    full-fat dairy, fatty fish

Chlorinated Dibenzo Dioxins
PCDDs
Chlorinated Dibenzo Furans
Polychlorinated Biphenyls

Background

• 75 dioxin cogeners and 135 dibenzofuran congeners.
• In general, CDD’s and CDF’s are present in human adipose tissue
  and fish and bird samples at a sub - µg/kg level.
  – Many of these being the less or non-toxic isomers.
• In general, relative toxicity:
• CCD > CDF >> PCB >> CN

Combining Risks from Dioxins

• Dioxins share a “common mechanism of toxicity”.
• Toxicity Equivalency Factors (TEF) compare the toxicity of different
dioxins.
• TEF are expressed in terms of Toxicity Equivalents (TEQ).
• TEQ is the amount of TCDD
  it would take to equal the combined toxic effect of all
  the dioxins found in that mixture.

The TEF Scheme for TEQ_DF

Dioxin Body Burden Levels

Dioxin Exposure Case Studies

• Love Canal (1940s-1950s).
  – Hazardous waste landfill release.
• Times Beach (pre-1982).
  – Chemical mix used to oil streets.
• Agent Orange.
  – Vietnam “Operation Ranch Hand”.
• Seveso, Italy (1976).
  – 2,4,5 Trichlorophenol industrial accident.
• BASF/IB (1953, other).
  – Chlorinated herbicide manufacturing workers.

**Background Serum, US 95-97**

**Dioxin Toxicity**

• TCDD characterized as a “human carcinogen”
  – Other dioxins characterized as “likely human carcinogens”.
• Dioxins can alter the fundamental growth and development of cells.
• Impact of dioxins on cells results in:
  – Adverse effects upon reproduction and development.
  – Suppression of the immune system.
  – Chloracne (a severe acne-like condition).

**Acute Dioxin Poisoning: Chloracne**

**Dioxin Exposure**

• Dioxins are highly persistent and can bioaccumulate.
• 95% of dioxin intake for a typical person comes through dietary intake of animal fats.
• Low exposure:
  – Breathing air containing trace amount of dioxins.
  – Ingestion of soil containing dioxins.
  – Absorption through skin contacting air, soil, or water containing minute levels.

**Dioxin Exposure, 2**

• Environmental processes result in widespread, low-level exposure of the general population.
• Dioxin levels in the environment have declined since the 1970s.
• Dioxin emissions in the US decreased by ~80% between 1987 and 1995.

**General Population Body Burden**
• US CDD/CDF range = 8.5 pg TEQ/g lipid to 50.0 pg TEQ_{DF-\text{WHO}98}/g lipid
• Mean 21.1 pg TEQ_{DF-\text{WHO}98}/g lipid

General Population Intake
• US CDD/CDF estimate 41 pg TEQ_{DF-\text{WHO}98}/d or 0.59 pg TEQ_{DF-\text{WHO}98}/kg/d
• US CDD/CDF/PCB estimate 65 pg TEQ_{DF-\text{WHO}98}/d or 1 pg TEQ_{DF-\text{WHO}98}/kg/d
• Children: US CDD/CDF estimate 54 pg TEQ_{DF-\text{WHO}98}/d or 3.6 pg TEQ_{DF-\text{WHO}98}/kg/d
  – Decrease with age
• 5 compounds = 70% load
  – TCDD, PeCCD, PeCDF
  – HxCDF, PCB 126

Dioxin Effects in Humans
• The amount of dioxin found in the tissues of the general human population (Body Burden) approaches (within a factor of 10) the levels at which adverse effects occur.
• Despite which, there is no clear indication of increased disease in the general population.
  – Limitation of current data and scientific tools.

Dioxin Effects in Humans
• 1 in 100 to 1 in 1,000 increased chance of experiencing cancer related to dioxin exposure in the general population.
• Cancer risk in 2000 analysis indicates about 10-fold higher chance than estimated in 1994 reassessment.

Children and Concern Groups
• Fetuses, infants, and children may be more sensitive to dioxin exposure because of rapid growth.
  – Data on risks to children is limited.
• U.S. Air Force personnel exposed to Agent Orange during the Vietnam War.
• Other populations have experienced elevated exposure from:
  – Industrial accidents.
  – Unusually high consumption of fish, meat and dairy products.

Dioxin Effect Controversy
• Enzyme induction and indicators of altered cellular function may not clearly indicate toxic response.
• Changes in biology and biochemistry from low-exposure:
  – Adaptive (w/ little or no adverse impact).
  – Adverse(?)

Case Study: Belgium 1999
• Transformer oil added to animal feed at feed mills.
• Poultry: reduction in egg hatchability, reduced weight gain, an increased mortality, edema, ataxia.
• PCBs and dioxins in animals products.
• 60,000,000 kg of animals destroyed.
• Meat product embargo.

Belgium: Dioxins and PCBs in Feedstuffs
Belgium: Dioxins and PCBs in Chicken

Clinicopathologic Concepts
• Syndrome induced by CDDs in a given species of animal is comparable to that induced by CDFs, PCBs, PBBs, CNs.
• Pathogenesis of the disease is the same – suggests that these chemicals involve the same receptors.
  – Typical exposure may be a mixture of isomers and compounds.
  – Best to view the disease syndrome in terms of etiology rather than specific insult.

Clinicopathologic Syndrome
• Varies from animal species to animal species.
• Skin of primates, rabbits (ears), cattle & some mice show characteristic follicular dermatitis.
  – Chloracne: visible and reversible lesion.
• Livers of chickens, rabbits (mice) show necrotic response of lethal severity.
– Guinea pigs, cattle, NH primates: enlarged liver, epithelial hyperplasia of bile duct/gall bladder.

• Some animals show epithelial lesions: GIT, renal.

Clinicopathologic Syndrome

• The one organ that uniformly shows lesions in all species is the thymus.
  – Often weighs 25% less in lethal intoxications.
    • Site of early life formation of lymphocytes and a site of antibody production.
• Severe intoxication in birds accompanied by fluid accumulation (chick edema).
• Interesting feature:
  – Total dose of TCDD required to produce disease is less if the dose is spread over time compared to a single dose.

LD_{50}

Observations

• In general, young animals and females may be more susceptible to intoxication (field).
  – Not observed in lab studies.
• Neonatal death, poor survival of young, female infertility and reproductive failure are indicators of field problems.
• At lethal dose levels, the time between exposure and death is unusually long.
  – Guinea pig, rat, mice: 2-3 wks.
  – Monkeys: 6 wks.

Observations

• Except for animals with severe liver necrosis (chickens, rabbits), cause of death not usually attributed to a specific organ or system pathology.
• In general, animals exhibit wasting disease.
  – Resembles starvation, anorexia.
• In environmental exposures, the disease is complicated by opportunistic infection.

Metabolism of TCDD
• Dog and rat studies.
• Major metabolites are hydroxylated compounds.
• Most is eliminated as parent compound in feces.
• Chronic rodent bioassays, life-term and short duration have addressed the issues of tumor initiation, promotion, co-carcinogenesis, DNA interaction, mutagenesis and clastogenesis.

Carcinogenicity - Mutagenicity
Suggested Mechanisms

• Toxicity and carcinogenicity.
  – Alteration of cell membrane function and cell-cell communication.
  – Effect on Vitamin A function.
  – Membrane lipid peroxidation.
  – Thyroid hormones.
  – Hormonal alterations.
  – DNA modifications.

Hepatotoxicity Mechanisms

• Experiments suggest O$_2^-$ (superoxide) formation and initiation of peroxidation by Fe$^{2+}$.
  – Progressive liver damage.
• TCDD inhibits hepatic Se-GSHpx and reduced glutathione.
  – Good correlation of GSHpx activity and survival.
  – Lipid peroxidation endpoint.

Early Molecular Events

• Diffusion into the cell.
• Binding of the AhR protein.
• Dissociation from hsp90.
• Active translocation from cytoplasm.
• Association with Arnt protein.
• Conversion of liganded receptor heteromer to enhancer DNA.
• Enhancer activation.
• Altered DNA configuration.
• Histone modification.
• Recruitment of additional protein.
• Nucleosome disruption.
• Increased accessibility of transcriptional promoter.
• Binding of transcription factors to promoter.
• Enhanced mRNA and protein synthesis.

Effects of TCDD and Related Compounds
Environmental Source Types

- Combustion and incineration sources.
- Metals smelting, refining and processing.
- Chemical manufacturing/processing.
- Reservoir sources (e.g. soils).
- Biological and photochemical processes.

- Significant regulatory pressure to limit release.

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\begin{align*}
\text{TEQ}_{\text{DF}} \text{ Releases - Air}_{\text{US}} \\
\text{TEQ}_{\text{DF}} \text{ Releases – Air}_{\text{US}}, 2 \\
\text{TEQ}_{\text{DF}} \text{ Releases – Air}_{\text{US}}, 3 \\
\text{TEQ}_{\text{DF}} \text{ Releases – Water}_{\text{US}} \\
\text{TEQ}_{\text{DF}} \text{ Releases – Land}_{\text{US}} \\
\text{TEQ}_{\text{DF}} \text{ Releases – Overall}_{\text{US}} \\
\text{Unquantified Sources}
\end{align*}
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Source Release Reduction

- 80% decrease between 1987 and 1995 of dioxin and CDDs/CDFs to air, water and land.
  – Due to reduction in air emissions from municipal and medical waste incinerators.
  – Regulations promulgated in 1995 for municipal waste combustors and in 1997 for medical waste incinerators should result in greater than 95% reduction in dioxin emissions from these two categories.

Control Efforts for Air

- The Clean Air Act (CAA) and its amendments requires emission limits based on “maximum achievable control technology” (MACT).
  – Changes in 1995 for municipal waste and 1997 for medical waste incinerators should result in greater than 95% reduction in dioxin emissions.

- CAA and the Resources Conservation and Recovery Act (RCRA) authorize the
regulation emissions from facilities that burn HW.

Control Efforts for Water

• The Clean Water Act (CWA) manages releases through risk-based and technology-based tools.
  – 1984 ambient water quality for 2,3,7,8-TCDD – a guidance for state water quality criteria.
• National Pollutant Discharge Elimination System (NPDES) regulates discharge based on state ambient water quality.

Control Efforts for Water, 2

• Pulp and paper facilities were the largest known industrial dischargers of dioxin into water.
  – 1998 CWA guidelines will reduce dioxin discharge from pulp and paper facilities by at least 96%.
• NPDES will places stringent performance requirements through combination of technology-based, health-based and state water quality standards.

Control Efforts for Water, 3

• 1992 maximum contaminant level goal (MCLG, a non-enforceable, voluntary health goal) of zero.
• Safe Drinking Water Act (SDWA) enforces a maximum contaminant level (MCL) of $3\times10^{-8}$ mg/l for TCDD.

Control Efforts for Land

• Superfund and RCRA Corrective Action programs for dioxin (Times Beach and Love Canal).
• Hazardous Waste Identification and Disposal Rules under RCRA designed to prevent future contamination.
• The Toxic Substance Control Act (TSCA) authorizes restricted use of dioxin – contaminated pulp and paper sludge.
• 1999 regulations limit dioxin content of cement kilns and sludge from POST facilities when by-product material is used as soil additives.

Control Efforts for Products
• The Federal Insecticide Fungicide and Rodenticide Act (FIFRA) and TSCA authorizes control or elimination of certain chemicals.
  – 2,4,5-T and pentachlorophenol (PCP).

  Environmental Media
  Estimate Levels in Food
  % Contribution of Food Dioxin Intake Children 1-5 Yrs
  Background/Body Burden Changes

  • Body burdens late 1980s
    30 – 80 pg TEQ/g lipid (30 – 80 ppt)
    – Midpoint of ~55 pg TEQ/g lipid including all dioxins, furans, and dioxin-like PCBs.
  • High-end estimates (~ 1% of general pop.) may be 3 times higher.
    – Based on blood-level data and consumption of fat as surrogate for dioxin intake.
  • CDD/CDF/PCB body burden in late 1990s
    25 ppt (TEQ, lipid basis).

  Risk

  • Receptor binding and most early biochemical events are likely to demonstrate low-dose linearity.
    – If findings imply low-dose linearity in biologically-based cancer models, then the probability of cancer risk will be linearly related to exposure to TCDD at low doses.
  • Until the mechanistic relationships are better understood, the shape of the dose-response curve for risk can only be inferred with uncertainty.