ES/RP 532
Applied Environmental Toxicology

Lecture 16

Dioxins: Biological Hazards & Risks

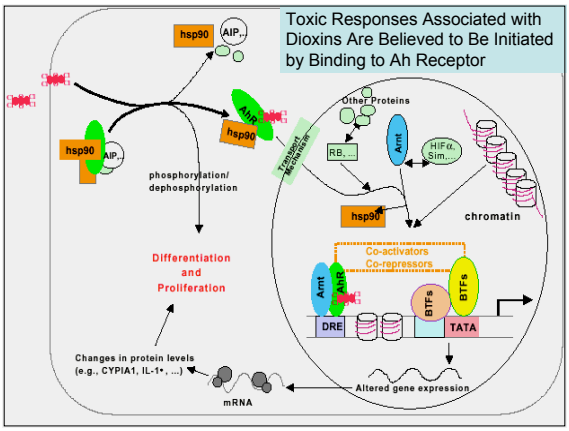
Species & Tissue-Specific Biological Effects Produced by TCDD

- Immunotoxicity
  - Thymic Involution
  - Immune Suppression
- Dermal Toxicity
  - Hyperkeratosis
  - Chloracne
- Lethality
- Tumor Promotion
- Porphyria
- Wasting Syndrome
- Hepatotoxicity
- Teratogenicity
  - Cleft Palate

Responses
- Hydronephrosis
- Pericardial Edema
- Embryotoxicity

- Induction of Gene Expression
  - Cytochrome P4501A1/2
  - Cytochrome P4501B1
  - Glutathione S-Transferase Ya
  - Quinone Reductase
  - Aldehyde Dehydrogenase 3
  - UDP-Glucuronosyl Transferase 1*06
  - γ-Aminolevulinic Acid Synthase
  - Prostaglandin Endoperoxide H Synthase 2
  - Interleukin 1β
- Endocrine Disruption
  - Alterations in Endocrine Homeostasis
  - Reduction in Steroid -Dependent
- Modulation of Cell Growth, Proliferation and Differentiation
- Modulation of Gap Junction

Dension & Heath-Pagliuso (1998)
Bull. Environ. Contam. Toxicol. 61:557



Do Dioxin TEQs "Cause" Cancer in Humans?

- The World Health Organization & the EPA now consider dioxin (TCDD) to be a human carcinogen
  - EPA has estimated that exposure to levels about 3X current background may be carcinogenic to humans
- What is the evidence?
  - "High dose" rodent feeding studies
  - Epidemiological

Carcinogenic Potency of Dioxins: Rodents

Congener	Species	Dose Level (μg/kg/day)	Response (Data based on Kociba 1991)
TCDD	Rat (S-D)	0.1	Heptocellular carcinoma; squamous carcinoma of oropharynx & lung
		0.01	Hepatocellular nodules
		0.001	None
TCDD	Rat (O-M)	0.07	Hepatocellular carcinoma; thyroid tumors
		0.007	Non significant thyroid tumor increase
		0.0014	None
TCDD	Mouse	0.1, 0.01, 0.001	Increase in heptacellular tumors at 0.01 only!
Hexachloro	Rat	5, 2.5, 1.25	Males: no response; females @ 5
Hexachloro	Mouse	10, 5, 2.5, 1.25	High Dose response only

Carcinogenic Potency: Rodents

- Data compiled by Kociba 1991 from the Banbury Report (*Biological Basis for Risk Assessment of Dioxins & Related Compounds*) showed
  - No significant tumorigenic response from exposure to unsubstituted dioxin nor dichloro substituted dioxin
  - Response to TCDD significant only at highest dose (or at mid dose)
  - At least one dose of TCDD (i.e., the lowest dose) without an effect

Tissue levels of TCDD after Exposure in a Carcinogenicity Assay

Kociba 1991

Dose of TCDD | Response | TCDD ppt (wet wt.)

TCDD (µg/kg/day)	ppt in Diet	Tumors	Other Toxicity	Fat	Liver
0.1	2200	Yes	Yes	8100	24000
0.01	210	No	Yes	1700	5100
0.001	22	No	No	540	540

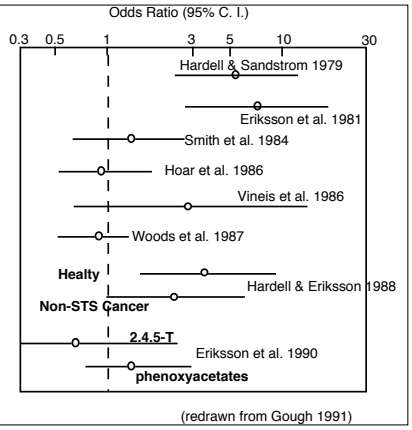
To transform wet weight ppt of TCDD to fat normalized basis, divide the wet weight ppt by the fraction of tissue as lipid

Dioxins (ppt, wet wt) & Dioxin-TEQ (pg/g) Residues in Human Tissues (Humans at Autopsy)

Analyte	Abdomen	Sub-cutaneous	Adrenal	Liver	Muscle	Spleen	Kidney
TCDD	6.6	4.9	3.8	2.5	ND	1.3	ND
Total PCDDD	743	825	495	352	141	51	47
Total PCDD TEQ	29	17	10	8	2	5	0.5
% Lipid	73	71	27	14	8	2	3

Kociba 1991

Early epidemiology evidence based on contamination of PCPs & 2,4,5-T with TCDD & incidence of soft tissue sarcoma



(redrawn from Gough 1991)

Results from a "Negative" Soft Tissue Sarcoma Study

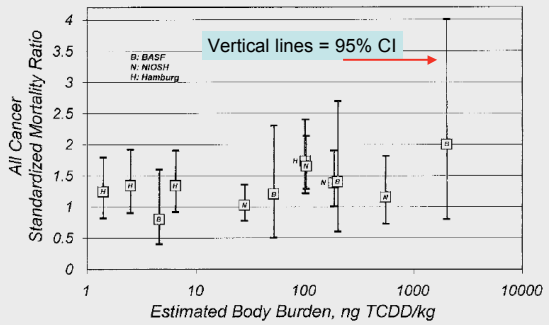
	First Study	Second Study	Combined Studies
No. of cases	82	51	133
No. of controls	92	315	407
No. of exposed cases	17	6	23
No. of exposed controls	13	46	59
Odds ratios	1.6	0.7	1.1
Confidence limits (90%)	0.8-3.2	0.3-1.5	0.7-1.8

Smith & Pearce 1986

Concentration of Dioxin in Highly Exposed Populations

Exposed Population	Number Of People	Range (ppt)	Mean (ppt)	Calculated One-Time Median Dose
U. S.				
New Jersey	103	2-3390	293	
Missouri	32	3-1290	177	
German workers				
Total	45	6-2252		
w/ chloracne	12	6-2252	362	
Seveso children				
highest level	1	56,000		
w/ chloracne	5	828-27,821	21,873	3,125
no chloracne	4	1772-10,439	4,750	677

Starr (2001) concluded that a metanalysis of the relationship between body burden TCDD levels and cancer SMRs (I.e., odds ratio) showed essentially no slope (I.e., increased OR not related to body residues)



Relative Potency for Teratogenic Effects

Congener	Relative Potency
TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin)	1.000
TBDD (2,3,7,8-tetrabromodibenzo-p-dioxin)	0.235
TCDF (2,3,7,8-tetrachlorodibenzofuran)	0.049
TBDF (2, ,3,7,8-tetrabromodibenzofuran	0.100
1 PeCDF (1,2,3,7,8-pentachlorodibenzofuran)	0.026
1 PeBDF (1,2,3,7,8-entabromodibenzofuran)	0.004
4 PeCDF (2,3,4,7,8-pentachlorodibenzofuran)	0.095
4P PeBDF (2,3,4,7,8-pentabromodibenzofuran	0.005
HCDF 1,2,3,4,7,8-hexachlorodibenzofuran)	0.010
HBN (1,2,3,4,6,7-hexabromonaphthalene)	0.002
2,3,4,5,3',4'-HCB (hexachlorobiphenyl)	0.00003

Endocrine System Effects

- TCDD and congeners found to be antiestrogenic
  - Interaction with the Ah receptor seems to cause a cascade of events (at the gene level) that prevents normal functioning of the E2 (estrogen) receptor
    - ✓Seems to work at the level of inhibiting promotion of the E2 regulated genes
    - ✓Thus, in rodent uterus and mammary gland and in human breast cancer cells, TCDD dampens development and growth of cancer cells

Endocrine System Effects

- Effect on sex ratio
  - Seveso, Italy: major industrial plant explosion
  - Extensive dioxin contamination
  - Cohort of most exposed people showed offspring sex ratio significantly skewed toward female
  - Hypothesis of both anti-androgenic effects as well as an ovo-pathology that selects against male (xy containing) eggs.

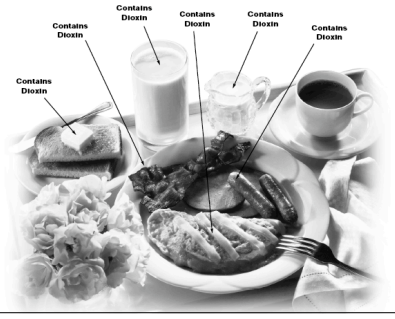
Developmental Effects in Wildlife

- TCDD seems to have little effect on amphibians (in contrast to PCBs) compared to fish (Jung and Walker 1997)
  - Faster elimination (half-life in days) for exposed tadpoles (24-h exposure)
  - Metamorphosis may have been speeded up
- Ecoepidemiological study of bird deformities in the Great Lakes (Larson et al. 1996)

Crossed bill deformity in Lake Michigan region cormorants

(Larson et al. 1996)

Guess what you had for breakfast this morning?

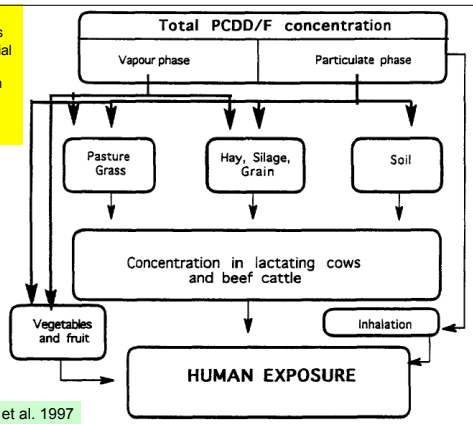


Food Is Main Source of TEQ Exposure

Food type	CDD/CDFs (pg TEQ_{DF}-WHO_{98}/g fresh weight)	PCBs (pg TEQ_{P}-WHO_{98}/g fresh weight)	Total (pg TEQ_{DFP}-WHO_{98}/g fresh weight)
Beef	0.2	0.094	0.29
Pork	0.22	0.09	0.31
Eggs	0.032	0.1	0.13
Chicken	0.11	0.044	0.15
Milk	0.031	0.016	0.047
Dairy products	0.12	0.058	0.18
Marine fish	0.36	0.25	0.61
Freshwater fish	1.2	1.2	2.4
Marine shellfish	0.79	0.042	0.83
Vegetable fats	0.056	0.037	0.093
Water	0.00056 (pg/L)	NA	NA

EPA 2000

Current Hypothesis of Terrestrial Sources Pathway in Addition to Aquatic Sources



Doueben et al. 1997

EPA Estimates of Putative Effects & Body Burden

Effect	Species	Estimated Body Burden of Dioxin (ng/kg or ppt) Associated with Effects
"Background" Level	Human	9
"Causally Associated"		
Chloracne	Human	45 - 3000
	Monkey	1000
"Associated"		
Cancer	Human	109 - 7000
	Hamster	500
	Mouse	1000
Decreased testosterone	Human	83
Decreased testis size	Human	14
	Rat	10,200

EPA Estimate of Daily Intake by Humans

Age Range	Intake (mass basis), pg TEQs/day	Intake, body wt. Basis (pg TEQs/kg/day)
1 - 5 yr	54	3.6
6 - 11	58	1.9
12 -19	63	1.1
Adult	70	1

EPA Estimates of Daily Intake by Source

Exposure route	Contact rate	Dioxins and furans		Dioxin-like PCBS		Total
		Concentration TEQ_{DF}-WHO_{98}	Intake (pg TEQ_{DF}-WHO_{98}/kg-d)	Concentration TEQ_{P}-WHO_{98}	Intake (pg TEQ_{P}-WHO_{98}/kg-d)	intake (pg TEQ_{DFP}-WHO_{98} /kg-d)
Soil ingestion	50 mg/d	12 pg/g	0.0085	NA	NA	0.0085
Freshwater fish	6 g/d	1.2 pg/g	0.13	1.2 pg/g	0.11	0.24
Marine fish	12.5 g/d	0.36 pg/g	0.064	0.25 pg/g	0.045	0.11
Marine shellfish	1.6 g/d	0.79 pg/g	0.018	0.042 pg/g	0.0096	0.028
Inhalation	13.3 m^3/d	0.12 pg/m^3	0.023	NA	NA	0.023
Milk	175 g/d	0.031 pg/g	0.078	0.016 pg/g	0.040	0.12
Dairy	55 g/d	0.12 pg/g	0.094	0.058 pg/g	0.046	0.14
Eggs	0.24 g/kg-d	0.032 pg/g	0.0077	0.10 pg/g	0.024	0.032
Beef	0.67 g/kg-d	0.20 pg/g	0.13	0.094 pg/g	0.063	0.19
Pork	0.22 g/kg-d	0.22 pg/g	0.048	0.009 pg/g	0.0020	0.05
Poultry	0.49 g/kg-d	0.11 pg/g	0.054	0.044 pg/g	0.022	0.076
Vegetable fat	17 g/d	0.056 pg/g	0.014	0.037 pg/g	0.0090	0.023
Water	1.4 L/d	0.0005 pg/L	0.000011	NA	NA	0.000011
Total			**0.65 (45 pg/d)**		**0.35 (25 pg/d)**	**1.0 (70 pg/d)**

Serum Levels of Dioxin-TEQs in Humans Population Distributional Analysis

Proportion of Population	TEQs (pg/g lipid)	TCDD (pg/g lipid)
Median (50th percentile	18.7	1.9
Mean	22.1	2.1
95th Percentile	38.8	4.2