Development of Dose - Response Models

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DOSE Response Models Chapter Outline

Introduction
- Link to Other Chapters
- Receptor Models for Pharmaceuticals

Description of Mathematical Modeling

Animal Models
- Dosimetric Modeling
  - Dose Delivery and Tissue Dosimetry
  - Modeling of Biochemical Responses

EGF Receptor
CYP 1A1 and CYP 1A2
UDP Glucuronyltransferase

Modeling Toxic Effects - Animals

- Tissue Responses
  - Cell Proliferation
  - Enzyme Altered Foci
- Cancer
- Non-cancer Endpoints
  - Immunotoxicity
  - Teratology
  - Reproductive
  - Neuroendocrine

Human Models

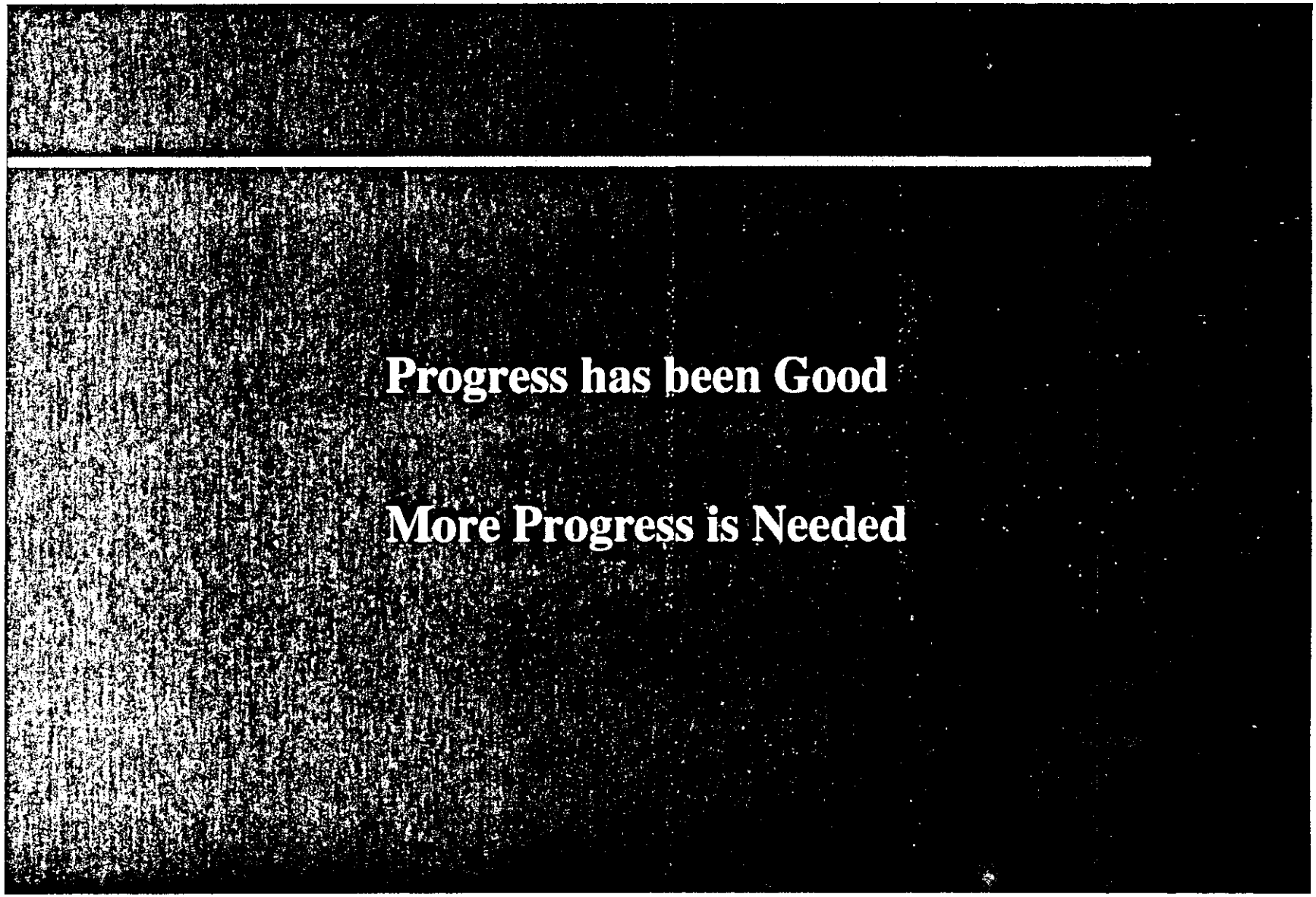
- Qualitative Comparison
- Quantitative Comparison
  - Dosimetric Modeling
  - Biochemical Effects
  - Toxic Effects

Knowledge Gaps

- Dose Surrogates
- Mechanisms of Diversity of Receptor-Mediated Responses
- Species Conversion Factors
- Interindividual Variation
- Early Life Exposure
- Experimental Prioritization List

Utility For Risk Assessment

- Example Applications - Cancer
- Comparison to Old Default Methodology
- Description of Uncertainies


Progress has been Good
More Progress is Needed

Characterization of Toxicity and Risks of 2,3,7,8-TCDD and Related Chemicals in Aquatic Environments

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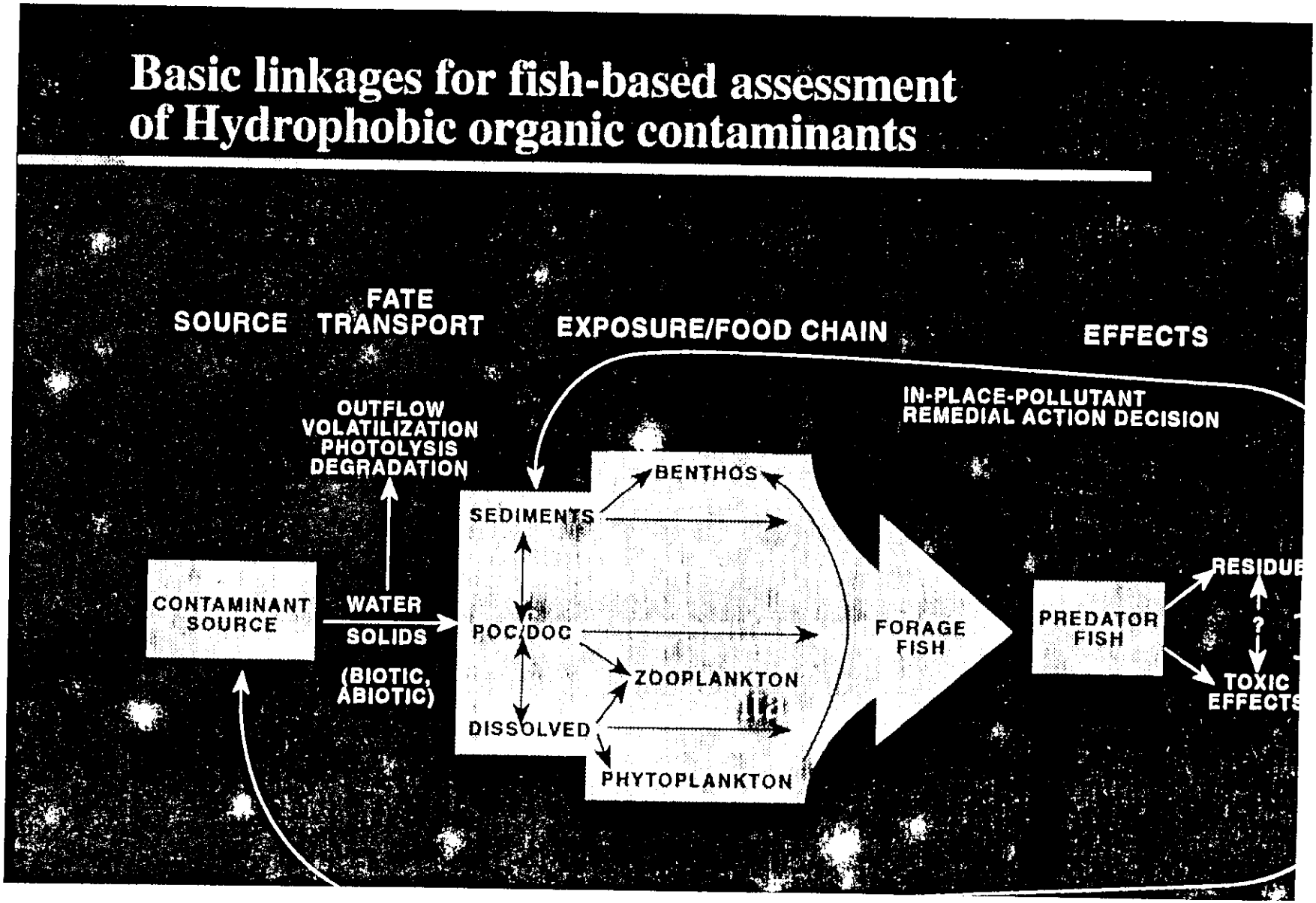
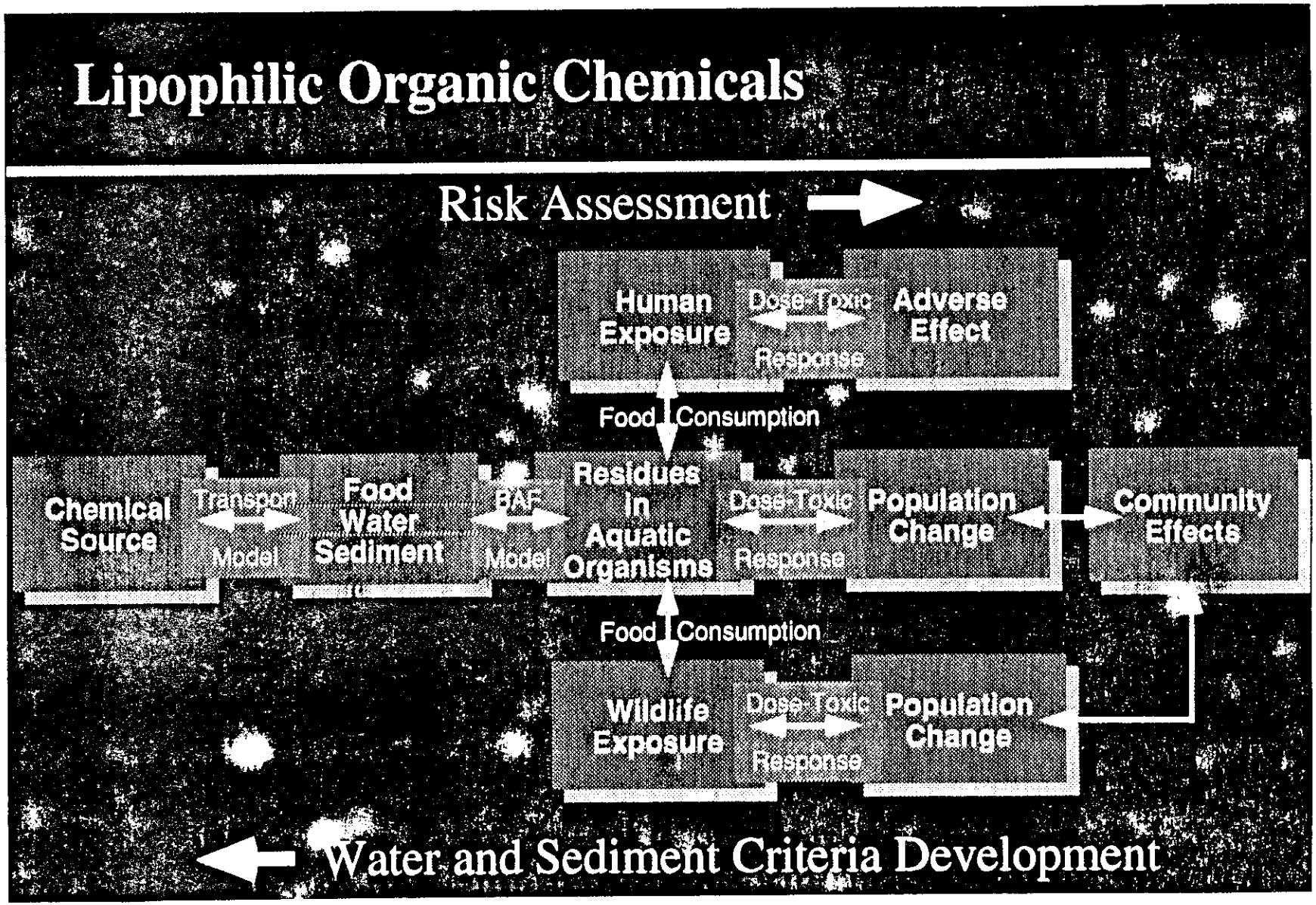
Minimum Levels of Detection: 2,3,7,8-TCDD

High Resolution Gas Chromatography/Mass Spectrometry

Sample Matrix	Environmental Range	MDL
Tissue (pg/g)	0-100	0.5000
Sediment (pg/g)	0-1000	1.0
Water-solids (pg/ml)	0-.001	0.0050
Water-dissolved (pg/ml)	0-.0001	0.0005

Basic linkages for fish-based assessment of Hydrophobic organic contaminants




Lipophilic Organic Chemicals
Risk Assessment
Human Exposure
Dose-Toxic
Response
Adverse Effect
Food Consumption
Chemical Source
Transport
Model
Food
Water
Sediment
BAF
Model
Residues In Aquatic Organisms
Dose-Toxic
Response
Population Change
Community Effects
Food Consumption
Wildlife Exposure
Dose-Toxic
Response
Population Change
Water and Sediment Criteria Development

Dioxin Toxicity in Fish and Wildlife
Epidemiology

- Herring Gulls - Lake Ontario
  - Reproductive failure ~ 1960-1977
  - Chick edema syndrome
- Terns - Green Bay
  - Reproductive impairment
  - Congenital deformaties
- Lake Trout - Lake Ontario, Lake Michigan
  - Blue-sac disease
  - Reproductive failure
- Mink - Lake Ontario
  - Population decline
- Bald Eagle - Great Lakes
  - Reproductive impairment

Relative Lethal Dose for 2,3,7,8-TCDD

Mammal [a]	LD50 (µg/kg)	Fish	50% Lethality Accumulated Residue (µg/kg)
Hamster	5000		
Dog	>300		
Mouse	114		
Rabbit	115		
Monkey	<70		
Rat (female)	46		
Rat (male)	22		
		Fathead Minnow [b]	10.0
		Medaka [b]	2.4
		Carp [b]	2.2
		Rainbow Trout [c]	1.0
Guinea Pig	1		
		Rainbow Trout-ELS [d]	0.4
		Lake Trout-ELS [d]	0.065

a. Poland and Knutson, 1982
b. ERL-Duluth (U,S, EPA)
c. Mehrle et al, 1988
d. Walker et al, 1991

Goals for Research Defining Ecological Risks Associated with 2,3,7,8-TCDD and Related Chemicals in Aquatic Systems

- Identify the most sensitive toxic effects of TCDD that are likely to result in population declines for organisms in aquatic food webs.
- Provide dose-toxic effects data suitable for development of water quality and/or sediment quality criteria for TCDD.
- Develop and validate dioxin toxicity equivalence factors (TEF) for 2,3,7,8-TCDD mode-of-action chemicals that are bioaccumulated by aquatic species.

Features of Dioxin Toxicology Important for Risk Characterization

1. Delays of mortality from acute exposures.
2. Slow uptake and elimination kinetics.
3. Importance of food route of exposure.
4. Effects of DOC and POC on bioavailability.
5. Insensitivity of invertebrates versus fish.
6. Sensitivity of developmental endpoints.

Presence or Absence of Ah Receptor in Aquatic Species (Hahn et al)

Species	Ah Receptor
Mammal	
beluga (*D. leucas*)	+
Teleosts	
rainbow trout (*O. mykiss*)	+
killifish (*F. heteroclitus*)	+
scup (*S. chrysops*)	+
winter flounder (*P. americanu*)	+
PLHC-1 cells (*P. lucida*)	+
Elasmobranchs	
smooth dogfish (*M. canis*)	+
spiny dogfish (*S. acanthisa*)	+
little skate (*R. erinacea*)	(-)
Cyclostomes	
Atlantic hagfish (*M. glutinos*)	-
sea lamprey (*P. marinus*)	-

Species	Ah Receptor
Echinoderm	
sea star (*A. forbesi*)	-
Arthopods	
northern lobster (*H. americanus*)	-
spiny lobster (*P. argus*)	-
spiny crab (*M. crispata*)	-
giant acorn barnacle (*B. nubilus*)	-
horseshoe crab (*L. polyphemus*)	-
Annelid	
clam worm (*N. virens*)	-
Molluscs	
gumboot chiton (*C. stelleri*)	-
blue mussel (*M. edulis*)	-
long-finned squid (*L. pealei*)	-

TCDD Exposure Characterization for Aquatic Toxicity Tests

TCDD Concentrations - Scintillation (Tritiated TCDD)

High Resolution GC/MS Analyses

- Water or food
- Tissue residue - whole fish
- Tissue residue - target organ

Other Exposure Markers

- P450 enzyme induction
- Gonadotropin hormone levels

Test Water

- Temperature
- DO, NH3
- Hardness, pH

TCDD Effect Endpoints - Fish

General

- Growth
- Mortality
- Behavior
- P450 enzyme induction
- Histopathology

Reproductive

- Gonadosomatic index
- Spawning behavior/timing
- Fecundity
- Fertilization
- Mortality-eggs, sac fry
- Development of embryo
- Histopathology-ovary, eggs, sac fry

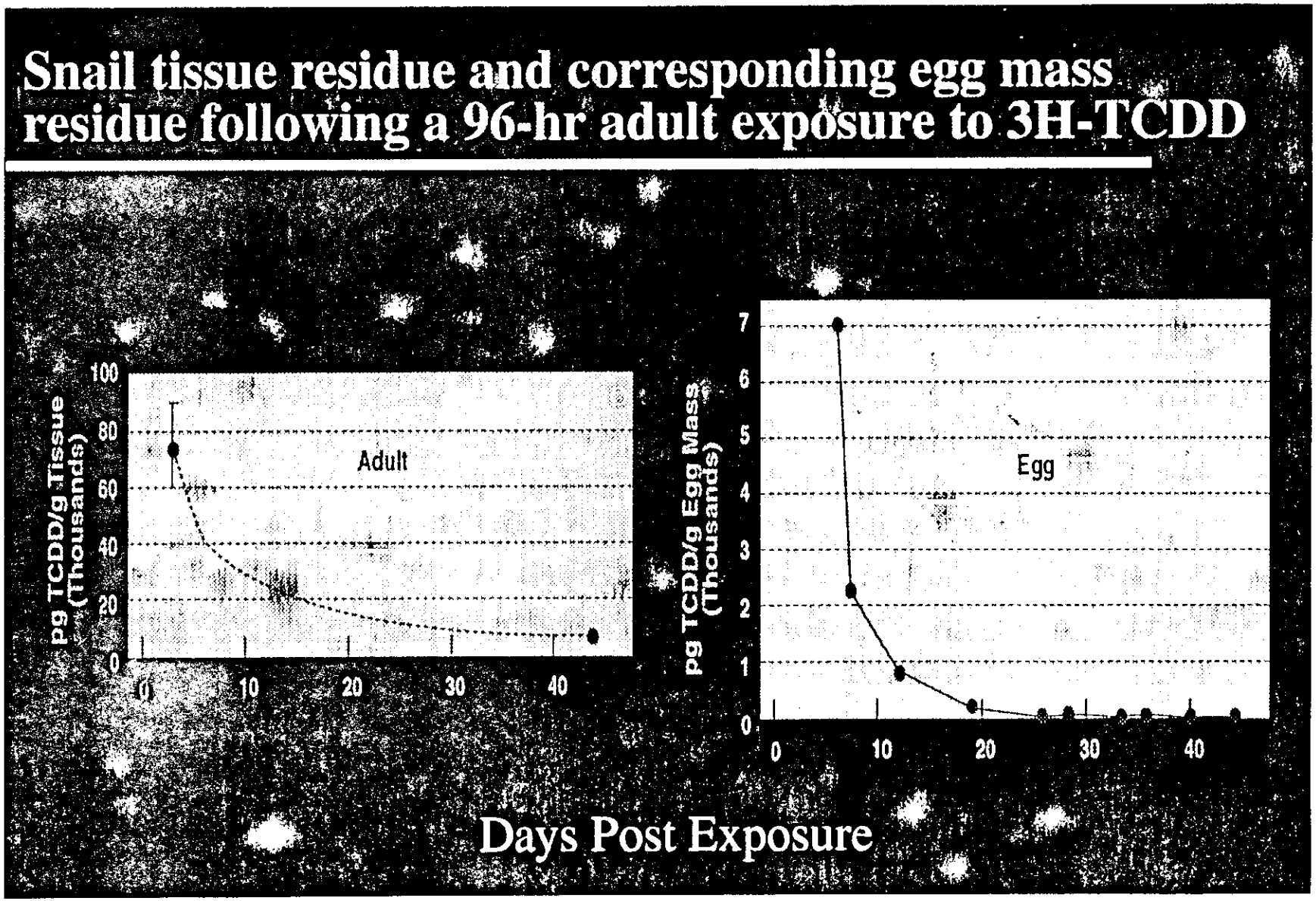
2,3,7,8-TCDD Bioassay Timetable

Organism	Bioassay Completion	Comments
Medaka	March 92	Complete
Fathead Minnow	March 92	Complete, may be rerun
Snail	February 92	Complete
Mayfly	April 92	In progress
Midge	April 92	In progress
Water Flea	April 92	In progress
Scud	April 92	In progress
Oligochaete	April 92	In progress
Leopard Frog	June 92	Tentative
Brook Trout	January 93	Systems in progress

Snail

Age at exposure:	Adult
Length of exposure:	4 days
Route of exposure:	Aqueous
Target dose:	As high as possible
Biological endpoints:	Survival
	Reproduction
Dose correlates:	Whole body residue
	Whole egg residue

Snail tissue residue and corresponding egg mass residue following a 96-hr adult exposure to 3H-TCDD



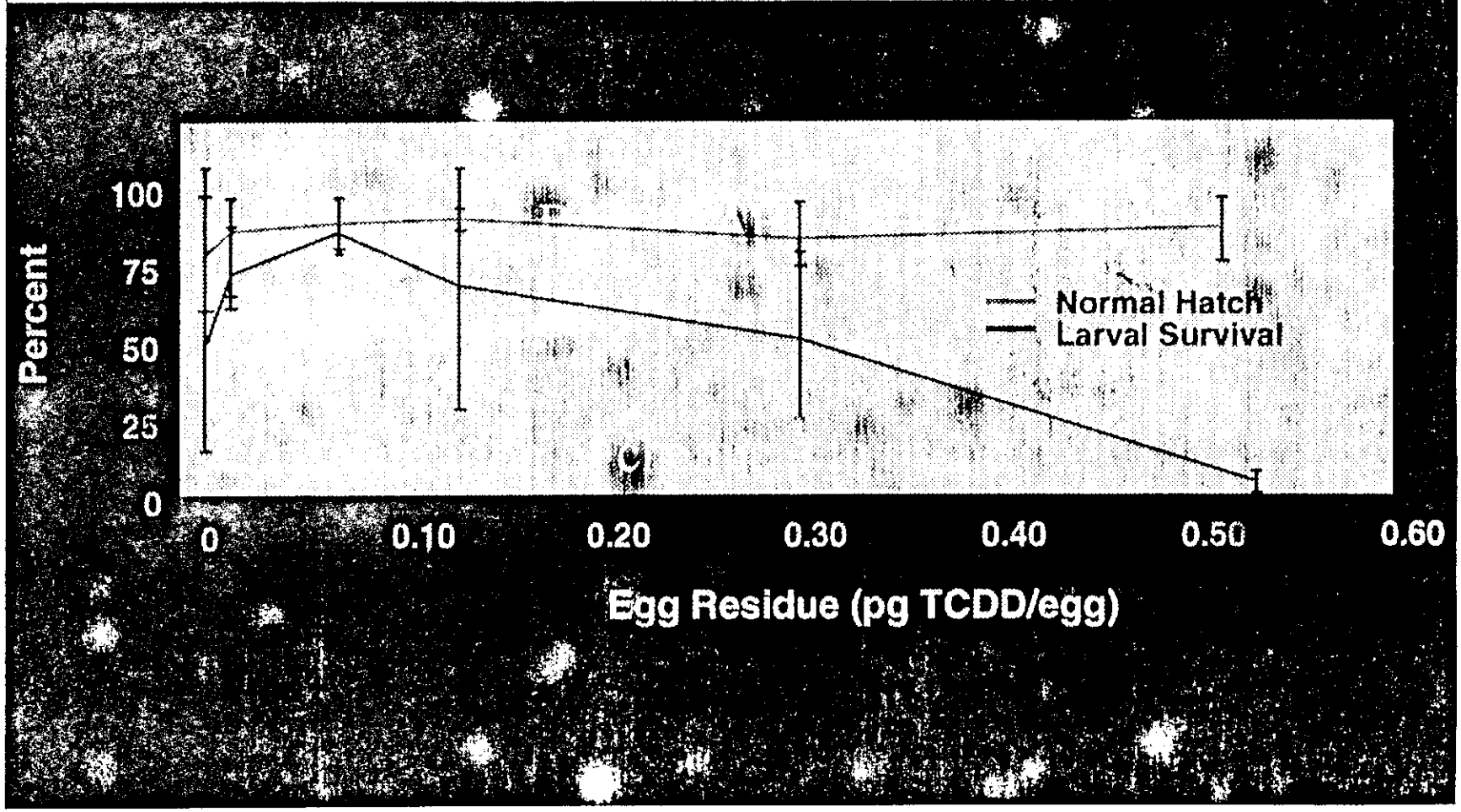
Fathead Minnow

Age at exposure:	Juvenile
Length of exposure:	4 days
Route of exposure:	Aqueous
Target dose:	10 µg/kg whole body residue
Biological endpoints:	Survival
	Growth
Dose correlates:	Whole body residue

Medaka

Age at exposure:	Adult
Length of exposure:	4 day/28 day
Route of exposure:	Aqueous
Target dose:	5 µg/kg whole body residue
Biological endpoints:	Survival
	Growth
	Reproductive success
	Embryolarval survival
	Histopathology
Dose correlates:	Whole body residue
	Whole egg residue
	% Total lipids

Medaka Embryo Hatch and 14-d Post Hatch Larval Survival - Second Incubation



Effect Residues of 2,3,7,8-TCDD in Medaka

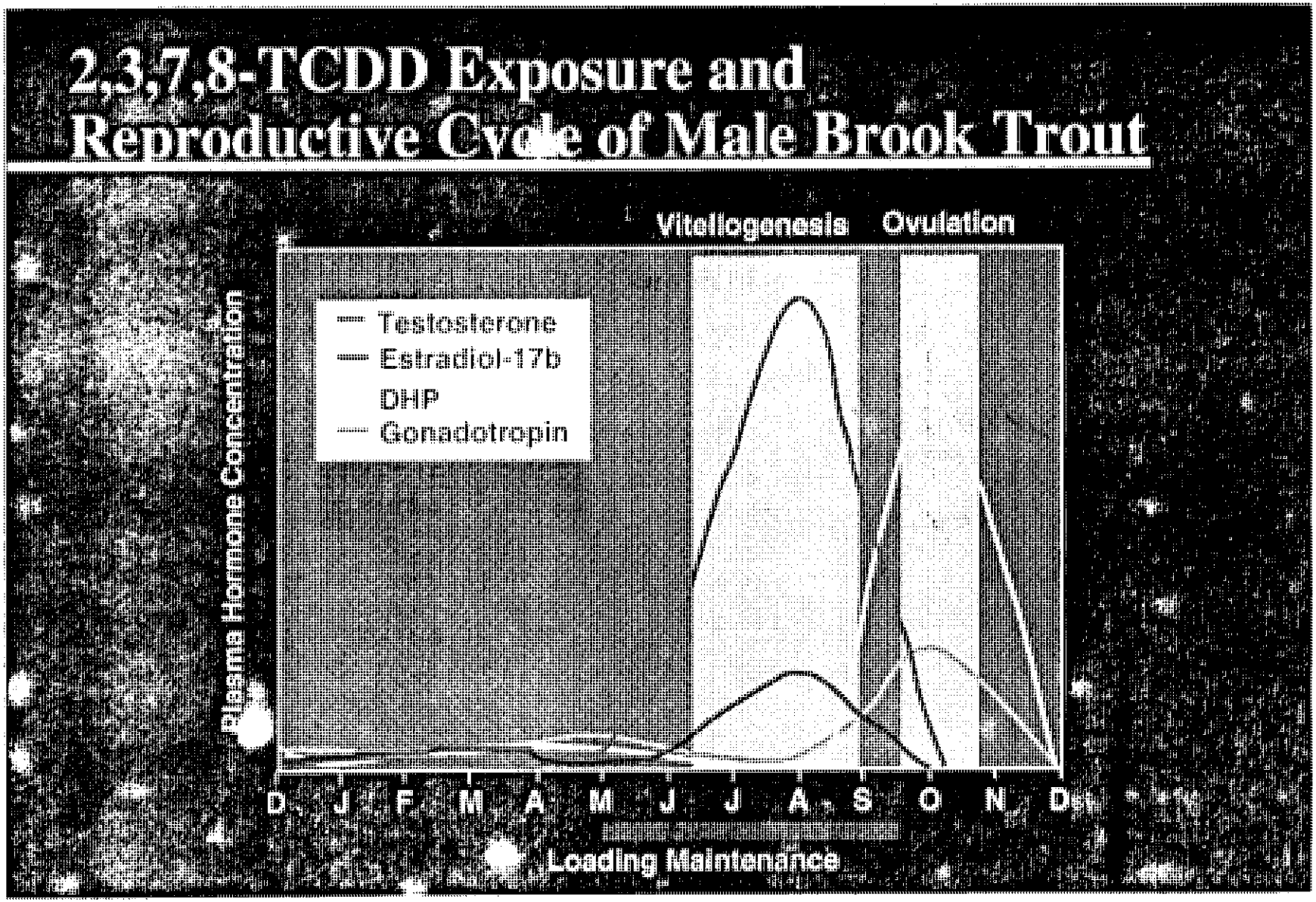
Effect	LOER [1] (NG/G)	NOER [1] (NG/G)
Growth	<5.64	2.11
Survival	2.11	0.93
Histopathology		
Neoplastic	2.11	0.93
Non-neoplastic	0.93	0.50
Reproductive Output	<4.61	2.74
Larval Survival	0.53 [2] (2.74 [3])	0.27 [2] (1.28 [3])

1 - Based on initial residues
2 - Based on egg residues
3 - Based on initial maternal residues

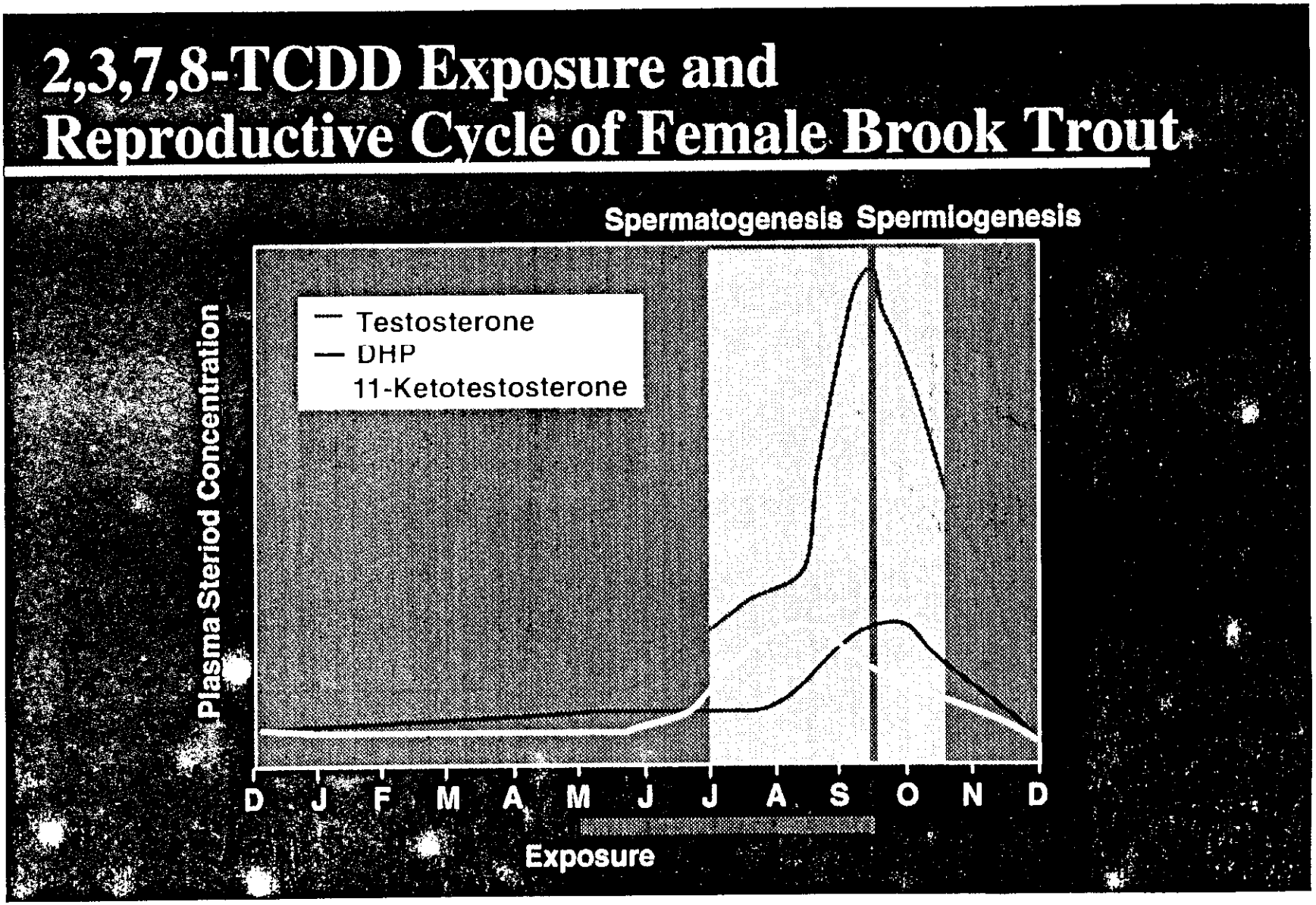
Brook Trout

Age at exposure:	1.5 to 2 years
Length of exposure:	May through October
Route of exposure:	Dietary
Target dose:	1 µg/kg whole body residue
	0.3 µg/kg whole egg residue
Biological endpoints:	Survival / Growth
	Growth
	Reproductive success / Embryolarval survival
	EROD induction / Ah receptor
	Serum steroid hormones/Gonadotropin responsiveness
	Histopathology
Dose correlates:	Whole body residue / Tissue specific residue
	Whole egg residue / % Total lipid

2,3,7,8-TCDD Exposure and Reproductive Cycle of Male Brook Trout



2,3,7,8-TCDD Exposure and Reproductive Cycle of Female Brook Trout



Bioaccumulation Measures

1. Bioconcentration Factor (BCF): $BCF = C_t / C_w$
2. Bioaccummulation Factor (BAF): $BAF = C_t / C_w$
3. Lipid-normalized BAF (BAF_l): $BAF_l = C_l / C_w$
4. Bioavailability Index (BI): $BI = C_l / C_{oc}$

C_t = concentration of chemical in tissue

C_w = concentration of chemical in water

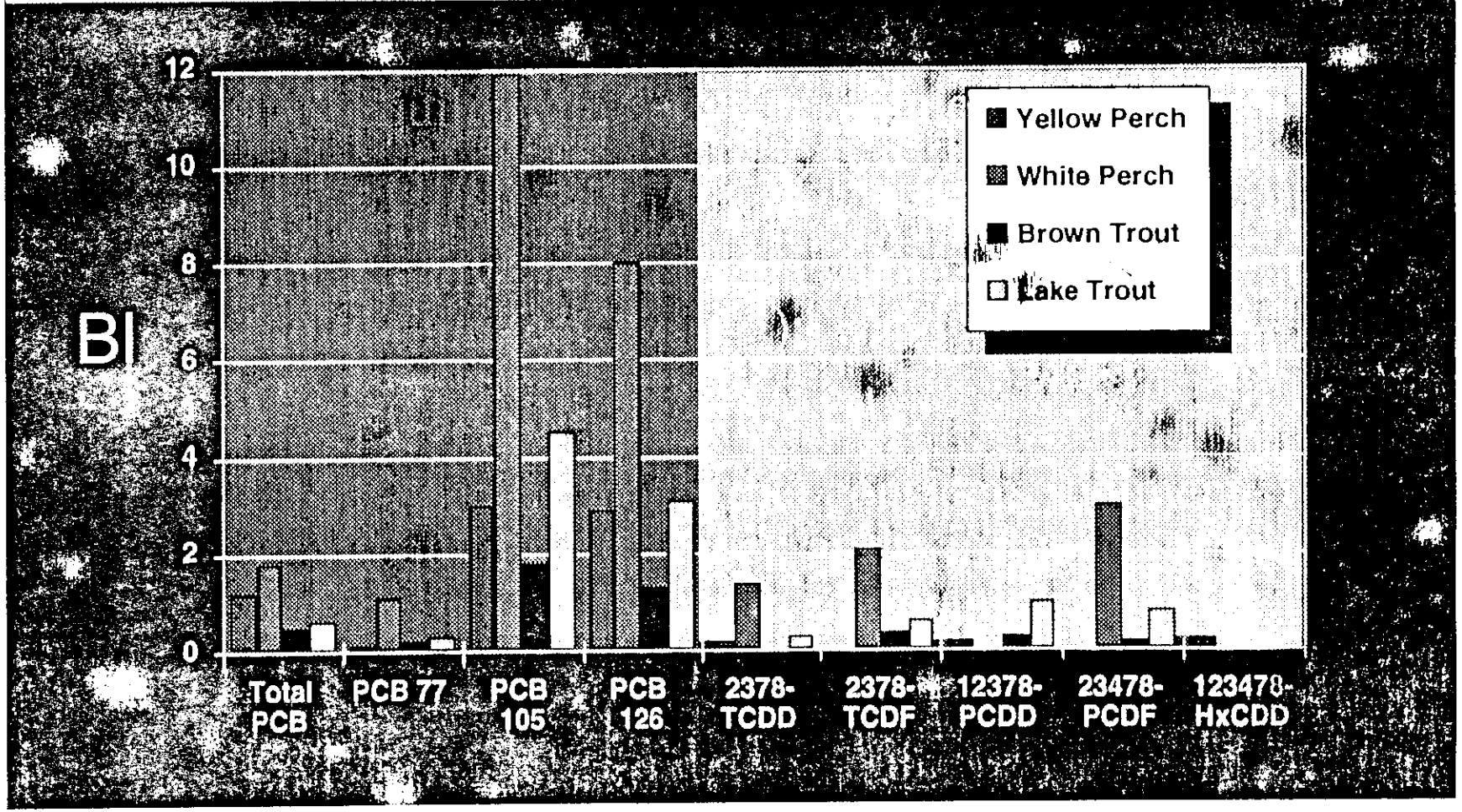
C_l = concentration of chemical in lipid

C_{oc} = concentration of chemical in surface sediment organic carbon

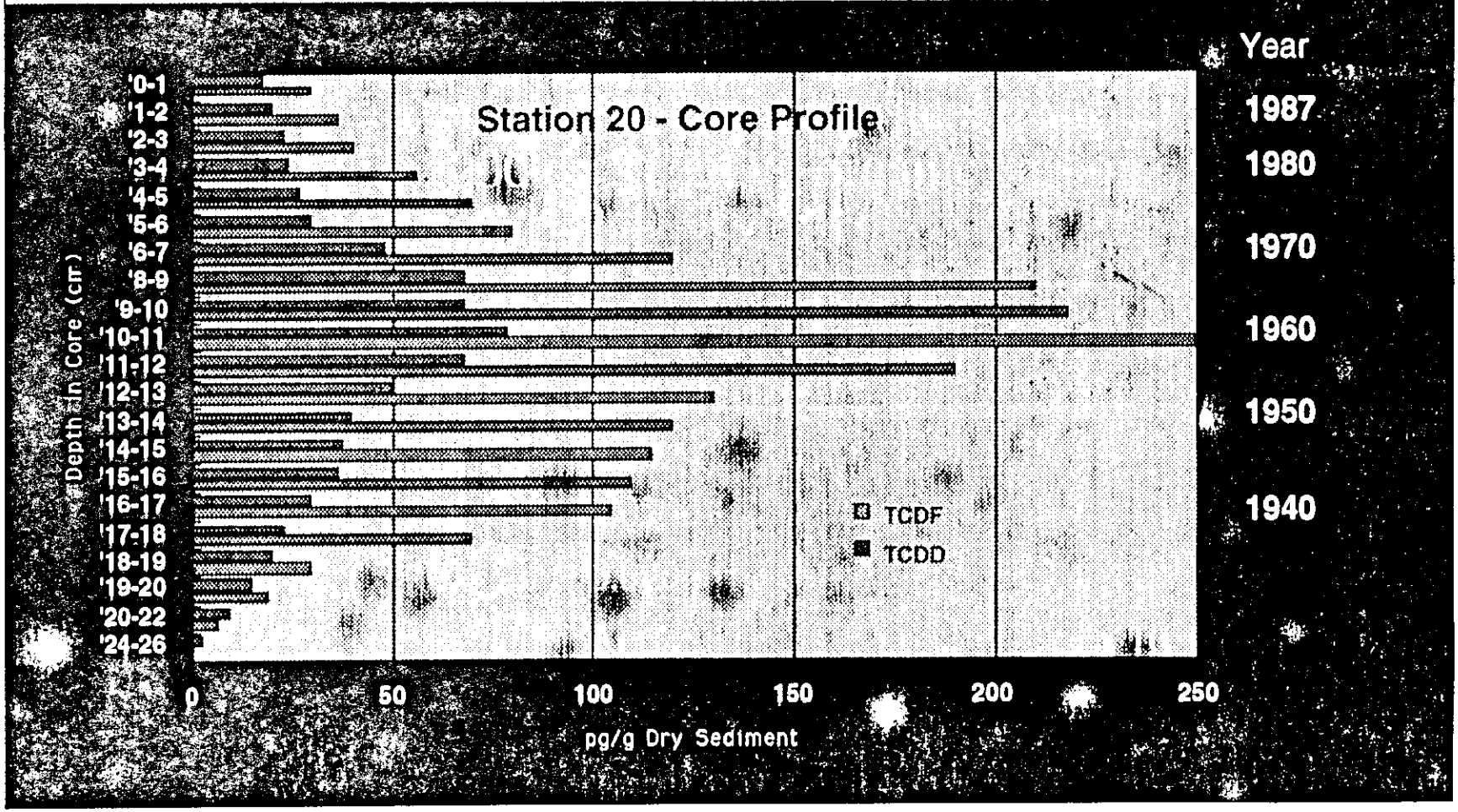
Summary of 2,3,7,8-TCDD Steady-state Bioconcentration Factor (ssBCF) Determinations for Fish

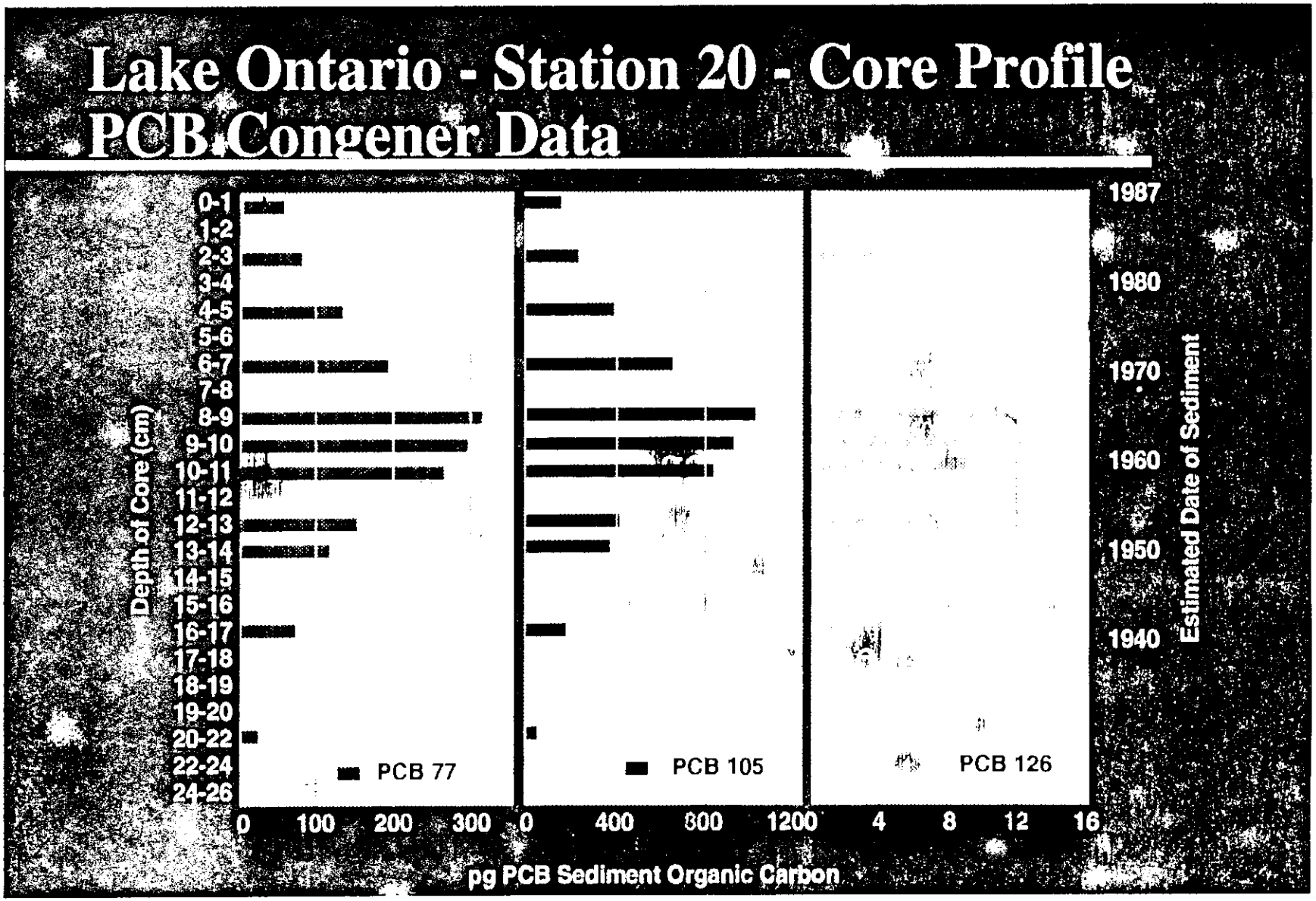
Study	Species	% Lipid	TCDD Conc. (pg/liter)	Exposure Period (days)	Uptake k_1	Elim. k_2	ssBCF[1]
Branson et al. (1985)	Rainbow Trout	11	320,000	0.25 Static	108	0.0120	81,300
Mehrle et al. (1988)	Rainbow Trout	N.R. (est. 5)	38	28 Flow-Through	1852	0.0470	780,000
Adams et al. (1986)	Fathead Minnow	N.R. (est. 7)	1,000	28 Static Renewal	381	0.0480	113,000
Cook et al. (1991)	Fathead Minnow	19	49-67	71 Flow-Through	1280	0.012-0.013	510,000
Cook et al. (1991)	Carp	9	62	71 Flow-Through	700	0.0100	733,000
Schmieder et al. (1992)	Medaka	8	101	12 Flow-Through	2306	0.0067	4,300,000

Lake Ontario - Lakewide Average Bls



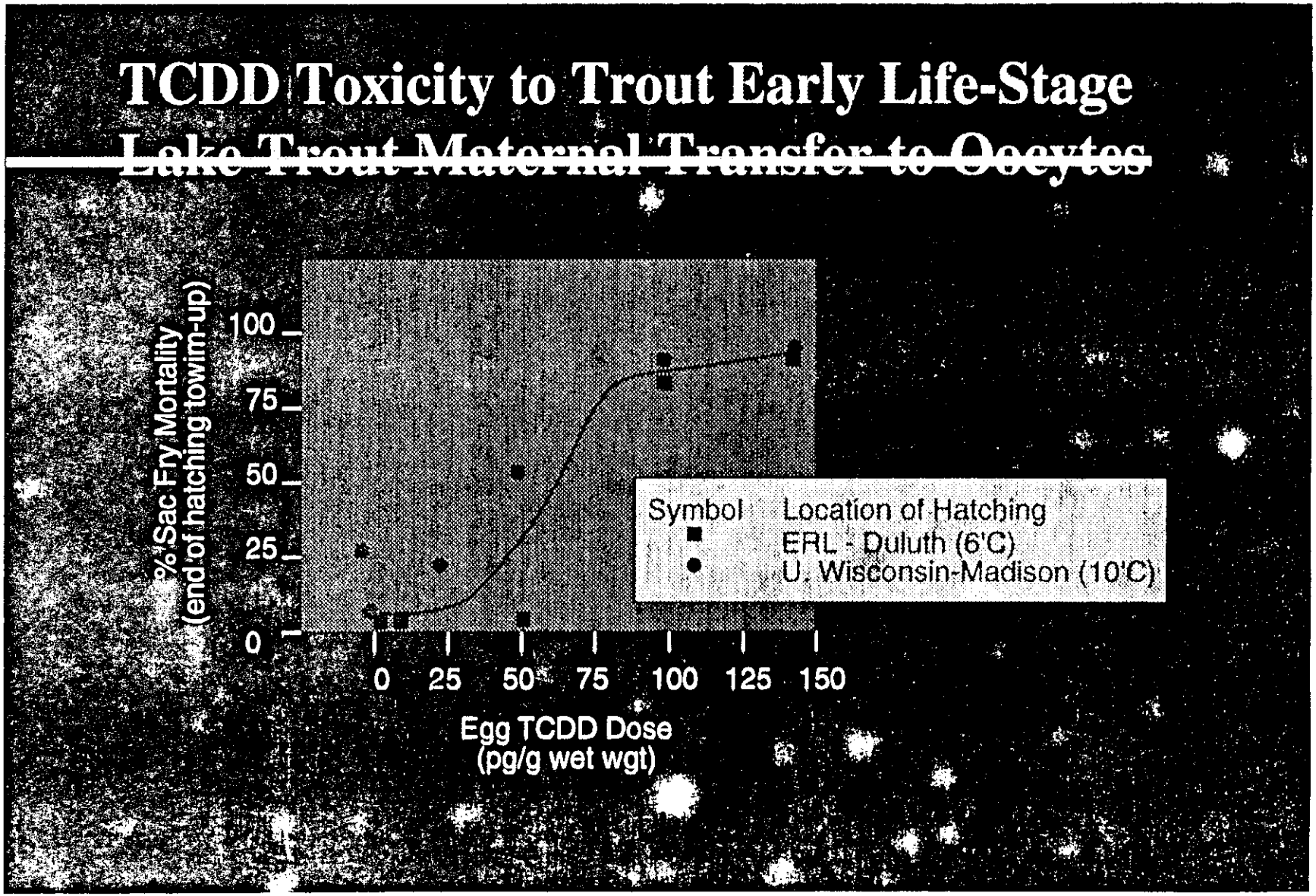
Lake Ontario Sediment
Estimated Date of Sedimentation




Lake Ontario - Station 20 - Core Profile
PCB Congener Data
Depth of Core (cm)
0-1
1-2
2-3
3-4
4-5
5-6
6-7
7-8
8-9
9-10
10-11
11-12
12-13
13-14
14-15
15-16
16-17
17-18
18-19
19-20
20-22
22-24
24-26
PCB 77
PCB 105
PCB 126
0
100
200
300
0
400
800
1200
4
8
12
16
pg PCB Sediment Organic Carbon
1987
1980
1970
1960
1950
1940
Estimated Date of Sediment

TCDD Toxicity to Trout Early Life-Stage

~~Lake Trout Maternal Transfer to Oocytes~~



Examples of Calculations for a Proposed Safe Water Concentration of TCDD for Great Lakes Wildlife

$$\text{Wildlife value (WV)} = \frac{\text{NOAEL} \cdot \text{SSF} \cdot \text{M}}{\text{F} \cdot \text{BAF}}$$

NOAEL = mammalian or avian no observable adverse reproductive effect level

SSF = Species sensitivity factor = 0.1

M = Mass of animal

F = Feeding rate

BAF = Bioaccumulation factor for food = 90,000

Species	*NOAEL (µg/kg/d)*	*F (kg/d)*	*M (kg)*	*WV (pg/l)*
Mink	0.001	0.1500	1.00	0.0074
Otter	0.001	0.9000	8.00	0.0099
Kingfisher	0.014	0.0750	0.15	0.0310
Osprey	0.014	0.3000	1.50	0.0780
Eagle	0.014	0.5000	4.50	0.1400
Man	10^{-6} cancer risk (WOC)	0.0065	70.00	0.0130

Calculation of a Lipid-Normalized Bioaccumulation Factor (BAF_l^d)

1. Assume equilibrium between sediment and water:

$$BAF_l^d = C_l / C_l^d = (C_l / C_{oc}) K_{oc} = (C_l / C_{oc}) K_{ow}$$

2. Assume steady-state between sediment and water at disequilibrium (eqC_w^d / ssC_w^d):

$$BAF_l^d = (C_l / C_{oc}) K_{ow} (eqC_w^d / ssC_w^d)$$

3. Use a site-specific model that considers sediment-water disequilibrium as well as the influence of total suspended solids and dissolved organic carbon on the fraction of chemical dissolved in the water (f_d)

TCDD BAF_l Estimates: Lake Ontario

$BAF_l^d = C_l / C_w^d$, $BAF_l^t = C_l / C_w^t$

C_l = 194 pg TCDD/g lipid (lake trout)

C_{oc} = 2000 pg TCDD/g organic carbon

$eqC_w^d / ssC_w^d = 2.4$

Estimation Method	Log Kow	C_w^d (pg/l)	C_w^t (pg/l)	f_d	BAF_l^d	BAF_l^t
Sed/Water Equil.	7	0.2000			9.7×10^5	
Sed/Water Equil.	8	0.0200			9.7×10^6	
Steady State	7	0.0800			2.4×10^6	
Steady State	8	0.0080			2.4×10^7	
L.C. Model	7	0.0220	0.102	0.220	8.8×10^6	1.9×10^6
L.O. Model	8	0.0026	0.095	0.027	7.5×10^7	2.0×10^6

Research for Development of Dioxin Mode-of-Action Hazard Assessment Capability

Complex Mixtures

- Measure bioaccumulation potential of PCDDs, PCDFs, PCBs including pharmacokinetic models for distribution
- Measure TCDD Toxic Equivalencies (LR_{50}, ER_{50}) of key PCDD, PCDF and PCB congeners
  - trout egg model
  - medaka
- Test TCDD Toxic Equivalence Hypothesis with Binary Mixtures
- Validate TEC model for exposure of fish to mixtures
- Compare TEC model to field epidemiology

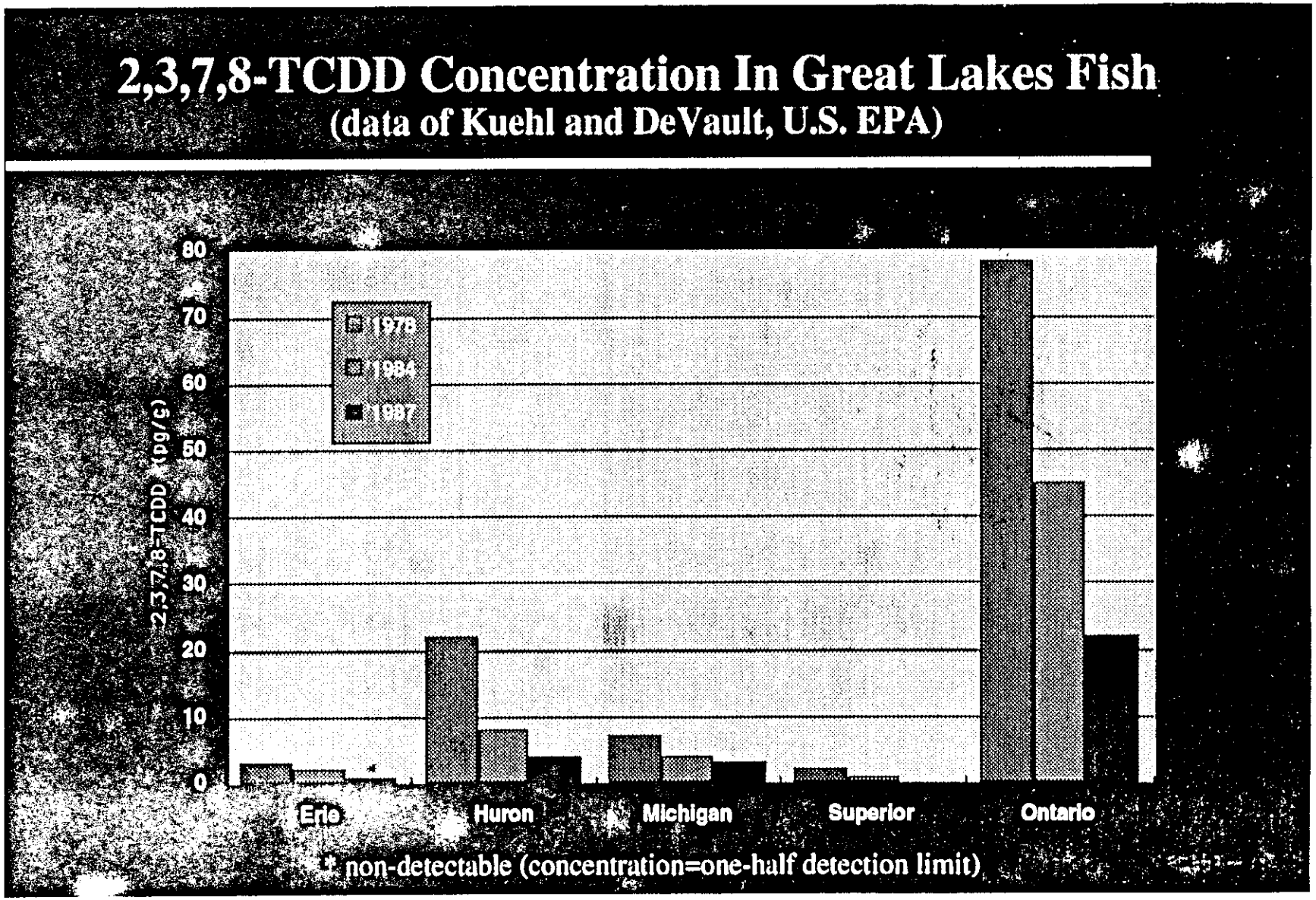
TCDD Toxicity Equivalence Concentration (TEC)

Calculated for risk of early life stage mortality/blue-sac disease in Lake Ontario lake trout due to exposure to planar chlorinated aromatic hydrocarbons.

Estimated effect threshold:	30 pg TCDD/g egg
TEC (Safe et al,):	>300 pg TCDD/g egg
TEC (U. Wisconsin/ERL-Duluth):	~20 pg TCDD/g egg

Tentative Conclusions:

1. Lake trout reproduction has been prevented in Lake Ontatio and possibly Lake Michigan due to dioxin toxicity.
2. Due to dioxin and PCB exposure reduction, residues in trout may now have been reduced sufficiently to allow reproduction (at the threshold now).
3. Research planned for FY92-FY93 will allow confirmation of this risk analysis and projection of future reduction in dioxin toxicity hazard in the Great Lakes.


2,3,7,8-TCDD Concentration In Great Lakes Fish
(data of Kuehl and DeVault, U.S. EPA)
2,3,7,8-TCDD (pg/g)
80
70
60
50
40
30
20
10
0
1978
1984
1987
Erie
Huron
Michigan
Superior
Ontario
non-detectable (concentration=one-half detection limit)

Aquatic Ecological Risk Characterization For TCDD and Related Chemicals

1. The EPA Science Advisory Board Dioxin Ecotox Subcommittee reviewed the research plan for TCDD aquatic risk charaterization and water quality criterion development on March 19-20, 1992.
2. A draft interim aquatic ecological risk characterization report for TCDD will be available for peer review in May, 1992.
3. Planar PCB congeners are 100-1000 fold less toxic to trout embryos than indicated by TCDD TEFs reported for AHH induction.

Aquatic Ecological Risk Characterization For TCDD and Related Chemicals (Cont.)

4. ORD scientists conclude that dioxin exposure alone was sufficient to result in the observed inability of lake trout to reproduce during the 1960s and 1970s in Lake Ontario.
5. Mammals and birds that feed predominantly on TCDD contaminated fish may be the aquatic food web organisms at highest risk.
6. Although reproduction by fish can be impaired by residues of TCDD as low as 30 ppt in embryos, histopathological changes and immunosuppression can occur at lower exposure levels.