

# Updates to Michigan's fish screening levels using references doses, starting with toxaphene

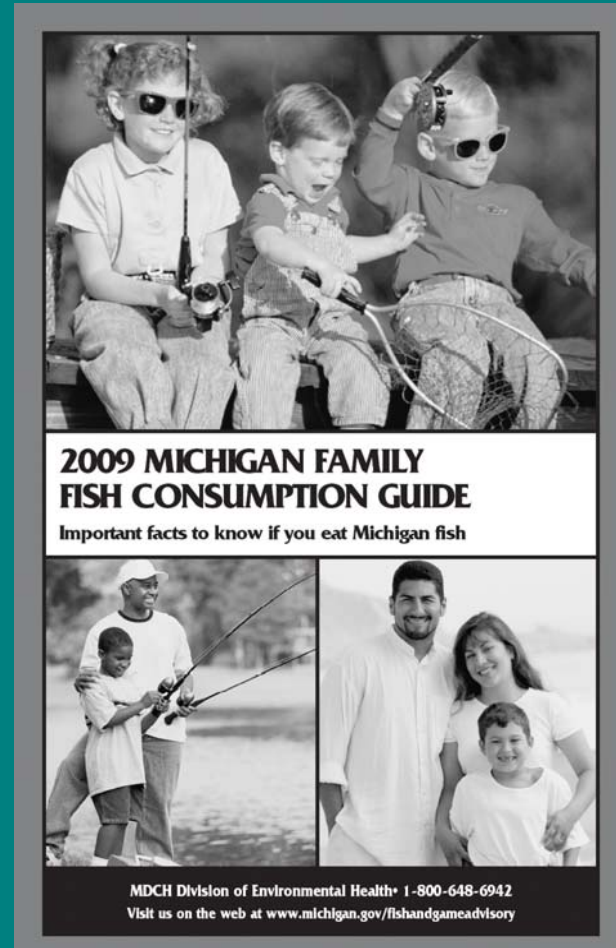
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# MDCH's overall goals

- Standardization of advisories
  - Meal categories
  - Comparison methods
- Less complexity
  - Easier to explain/less mystery



[www.michigan.gov/fishandgameadvisory](http://www.michigan.gov/fishandgameadvisory)

# Updating Michigan's fish advisory

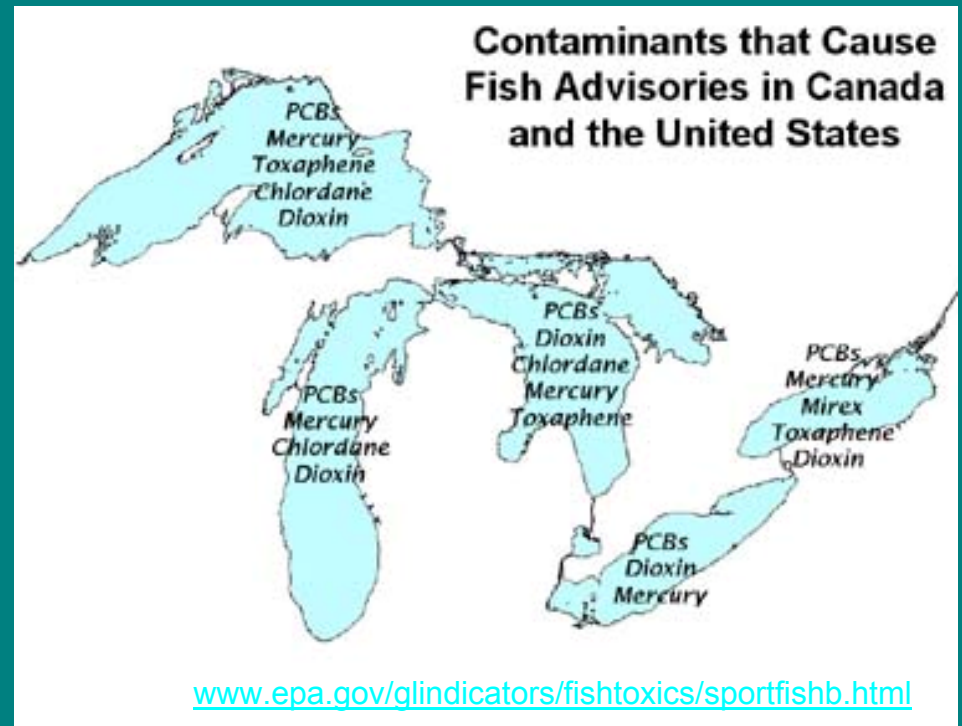
- Provide scientific support for screening levels
  - Some trigger levels are based on FDA values
- Provide written technical support documents (for future updates)
  - Michigan's fish advisories began in the 1970s with mercury



[visibleearth.nasa.gov/view\\_rec.php?id=1244](http://visibleearth.nasa.gov/view_rec.php?id=1244)

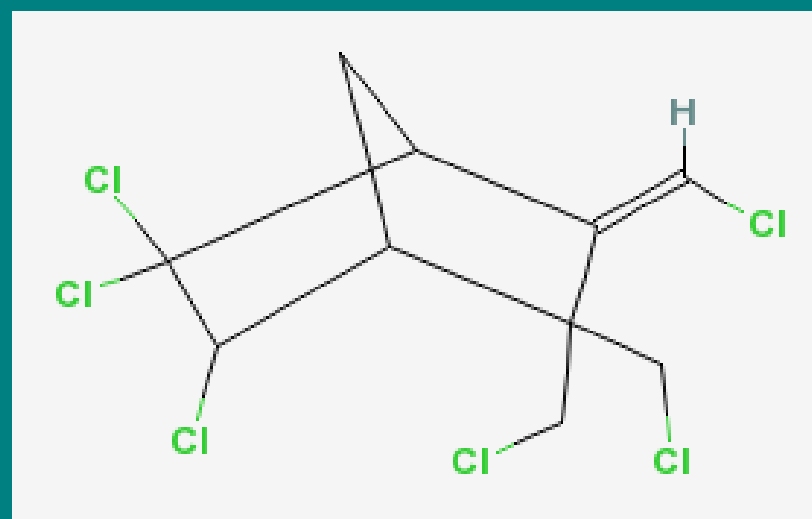
# Toxaphene first

- Letter from Michigan resident
- Still measured - detectable levels in some fish species
- Currently no advisories due to toxaphene (other chemicals are driving advisories)



# What is toxaphene?

- Polychlorinated camphenes (and bornanes)
- Technical toxaphene can have a range of congeners
  - More than 670 congeners possible (~200 in technical mix)
  - Chlorination of ~68%
  - Parlar labeling system: time off column



[pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5375921&loc=ec\\_rcs](https://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5375921&loc=ec_rcs)

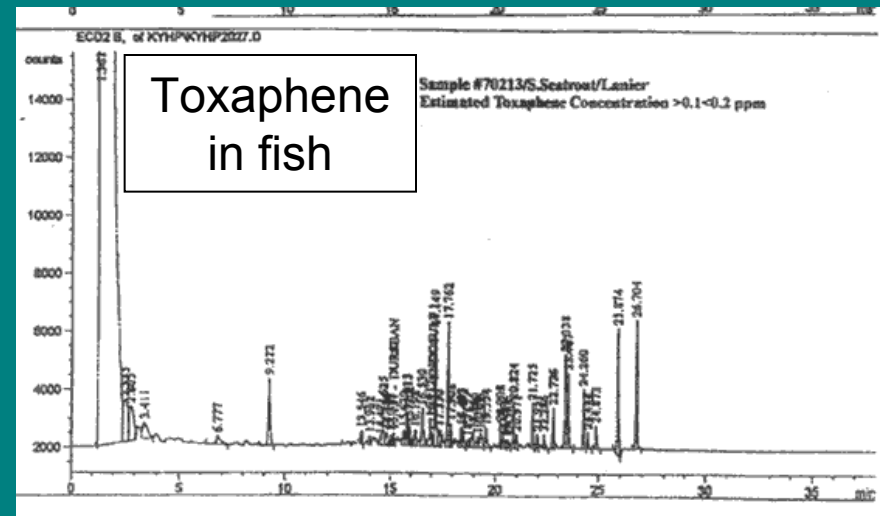
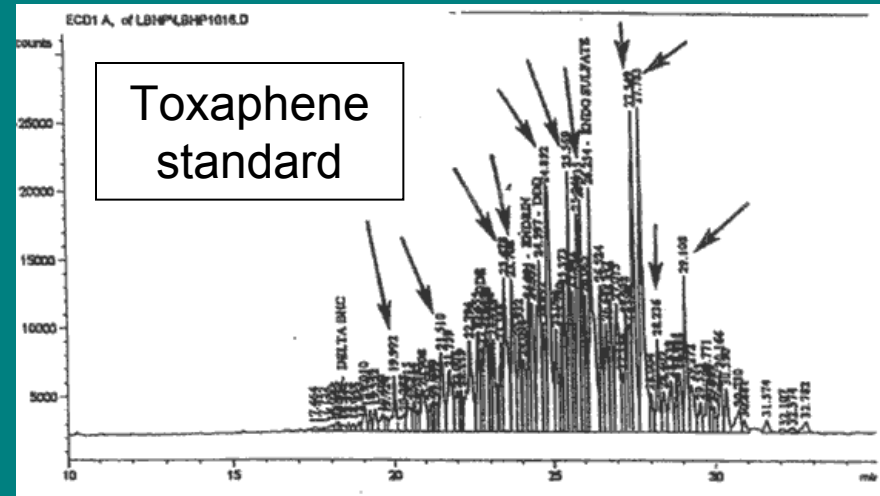
# Toxaphene is a pesticide

- Insecticide and accicide (mites)
  - Agricultural use
- Used to kill unwanted fish in lakes before stocking with sports fish (1950s-1970s)
  - Killed sports fish too
- Indirect source to Great Lakes (Southeastern U.S. agricultural fields; Ma et al. 2005)



# Weathering of toxaphene

- Technical toxaphene
  - Originally produced toxaphene
- Weathered toxaphene
  - Results in reduction in number of congeners (Parlars) present and amount of chlorine



<http://www.atsdr.cdc.gov/hac/PHA/terrycreek/tcd> fe1.gif



# Weathered toxaphene

- Degradation products
  - Major: Hx-Sed and Hp-Sed
    - Large proportion in soil
  - Minor: Parlars 26, 40, 41, 44, 50, and 62, and more
    - Large proportion in animals
- Bioaccumulation of the minor products



Dechlorination in:

- UV light
- High temperatures (>120°C)
- High pH



# Measuring toxaphene in Michigan fish

- MDCH Analytical Chemistry Laboratory
  - “Apparent” toxaphene measured in fish tissue
  - Technical standard
  - Less than 32 minute retention time not included in the value (interference)
- Compared to 5 ppm toxaphene trigger level

# Toxaphene in Michigan fish

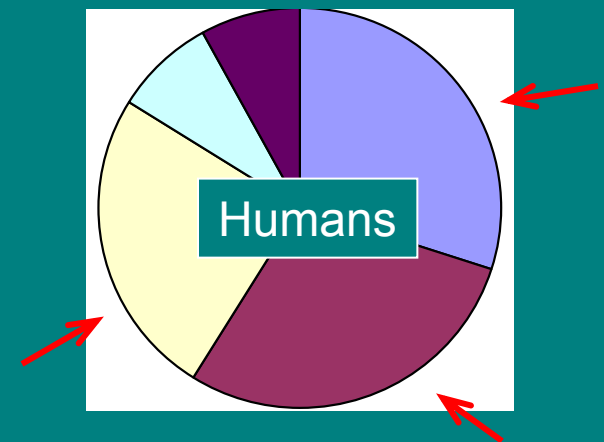
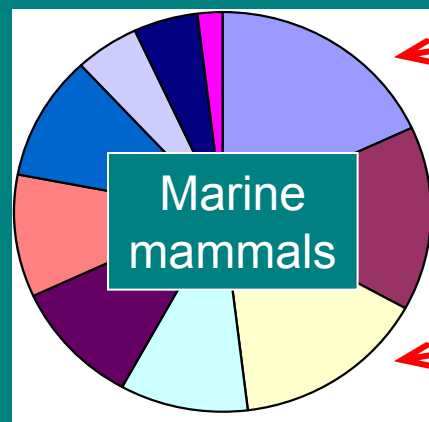
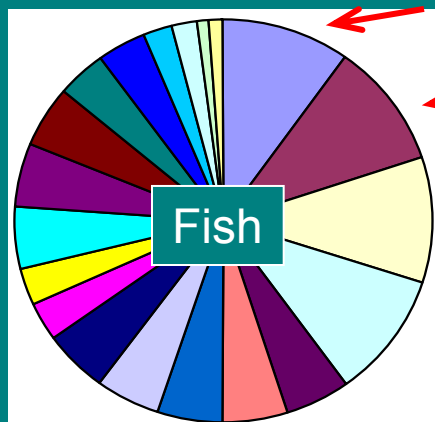
- Siscowet trout from Lake Superior
  - 1984 to 1999:  $2.63 \pm 0.23$  ppm (n = 100; range 0.05 to 10 ppm)
  - 2000 to 2006:  $0.41 \pm 0.10$  ppm (n = 30; range 0.05 to 2.264 ppm)



[http://www.nps.gov/archive/isro/NR\\_Profile\\_Internal/NR\\_stills/fish\\_imag/pages/siscowet\\_gif.htm](http://www.nps.gov/archive/isro/NR_Profile_Internal/NR_stills/fish_imag/pages/siscowet_gif.htm)

# Biomonitoring data

- 8-25% total toxaphene in fish was Parlar 26, 50, 62 – profiles varied by species (Chen & Yeboah 2000)



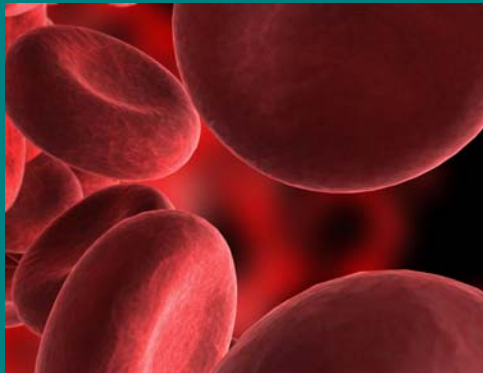
- Parlars 26 and 50
  - Approximately 50 to 90% of total toxaphene (Skopp et al. 2002, Newsome and Ryan 1999, Gill et al. 1996)

# Toxicology of technical toxaphene in non-human primates

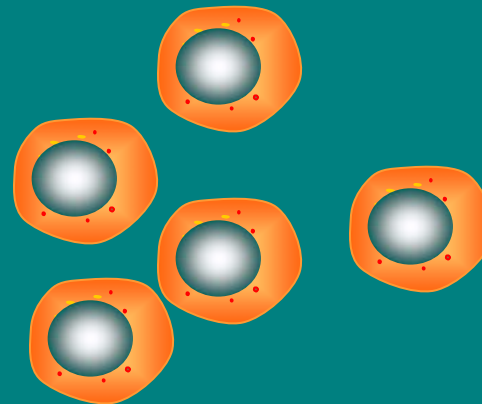
- Feeding study with technical toxaphene for 52 weeks in non-human primates (Bryce et al. 2001)
  - Effects: increased relative organ weights, increased hepatic microsomal activity, inflammation/enlargement of tarsal glands (LOAEL = 1.0 mg/kg/day)
  - Four toxaphene congeners representing a majority of the total: Parlars 26, 44, 50, and 62 (Andrews et al. 1996)
    - Leveled off at 10 weeks (blood) and between 15 to 20 weeks (adipose)

# Immunotoxicity of technical toxaphene in non-human primates

- Feeding study with technical toxaphene for 75 weeks in non-human primates (Tryphonas et al. 2001)
  - Immune function testing after 33 weeks (NOAEL = 0.1 mg/kg/day)



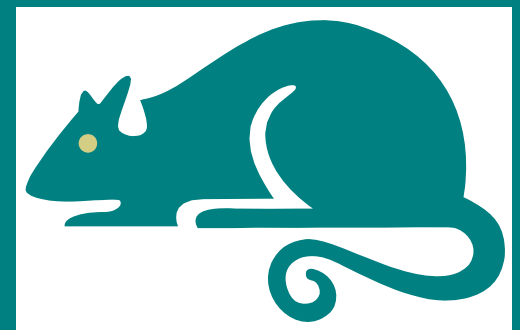
Reduced antibodies to sheep red blood cells (two of the three doses)



Reduced absolute B cell number (one of three doses)

# Toxicology of weathered toxaphene in rats

- Partially hepactomized rats treated with initiator were subcutaneously injected for 20 weeks (Besselink et al. 2008)
  - Effects: altered hepatic foci expressing placental glutathione-S-transferase (measure of tumor promotion)
  - NOAEL = 0.0021 mg/kg/day sum of three persistent congeners ( $\Sigma$ 3PC) from cod liver oil extract (weathered toxaphene)



# Carcinogenic endpoint for RfD

- Guidelines for Carcinogen Risk Assessment (EPA 2005)
- RfD if nonlinear mode of action
  - not mutagenic or genotoxic
- Toxaphene = tumor promoter
  - Interference with cell-to-cell communication
  - Not shown to be mutagenic or genotoxic in mammalian cells



# Two possibilities for an RfD:

- Technical toxaphene
  - Similar method (currently measuring apparent toxaphene)
  - Able to use previously measured fish tissue levels
- Individual Parlars - more accurate or appropriate
  - Concern is only with a few Parlars
  - Would need to adjust method and have no historic fish tissue data

# Two NOAELs selected

- Technical toxaphene
  - Altered immune system function (Tryphonas et al. 2001)
  - NOAEL = 0.1 mg/kg/day
- Weathered toxaphene (sum of Parlars 26, 50, and 62)
  - Preneoplastic foci (carcinogenic effect; Besselink et al. 2008)
  - NOAEL = 0.0021 mg/kg/day

$$\text{RfD} = \frac{\text{NOAEL or other POD}}{\text{Uncertainty and modifying factors}}$$

# Development of an RfD

- Uncertainty factors (for both NOAELS):
  - Animal to human (10), human to human (10), subchronic to chronic (10)
    - $RfD (\Sigma 3PC) = 0.0021 \mu\text{g/kg/day}$
- Additional modifying factor added for possible developmental effects (3; technical toxaphene only)
  - $RfD = 0.033 \mu\text{g/kg/day}$

# Sample screening values for technical toxaphene:

RfD = 0.033 µg/kg/day		
Population	Fish toxaphene concentration (ppm)	Fish Meals
General Population	≤ 0.019	Unrestricted
	> 0.019 to ≤ 0.081	One meal/week
	> 0.081 to ≤ 0.351	One meal/month
	> 0.351 to ≤ 0.703	Six meals/year
	> 0.703	Do not eat
Sensitive Population (women of childbearing age and children under 15)	≤ 0.016	Unrestricted
	> 0.016 to ≤ 0.069	One meal/week
	> 0.069 to ≤ 0.297	One meal/month
	> 0.297 to ≤ 0.595	Six meals/year
	> 0.595	Do not eat

# Sample screening values for sum of three Parlars (26, 50, and 62):

RfD = 0.0021 µg/kg/day		
Population	Fish Σ3PC concentration (ppb)	Fish Meals
General Population	≤ 1.2	Unrestricted
	> 1.2 to ≤ 5.1	One meal/week
	> 5.1 to ≤ 22.2	One meal/month
	> 22.2 to ≤ 44.3	Six meals/year
	> 44.3	Do not eat
Sensitive Population (women of childbearing age and children under 15)	≤ 1.0	Unrestricted
	> 1.0 to ≤ 4.3	One meal/week
	> 4.3 to ≤ 18.6	One meal/month
	> 18.6 to ≤ 37.3	Six meals/year
	> 37.3	Do not eat

# Future objectives:

- Setting screening levels
  - Proposed or different
    - Decisions: body weight, trimming and cooking, meal cutoffs, etc
- Implementation as resources are available
- Thanks to: Linda Dykema, Kory Groetsch, Joe Bohr, MDCH Analytical Lab