

POTENTIAL FOR HUMAN EXPOSURE TO TOXAPHENE THROUGH CONSUMPTION OF GREAT LAKES FISH

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Abstract

Concerns have been raised about the presence of the bioaccumulating pesticide toxaphene in the tissues of Great Lakes fish. Toxaphene, banned in the U.S. since 1990, is an environmentally persistent chlorinated hydrocarbon mixture of over 670 chemical congeners. Current fish consumption advisories issued in the Great Lakes states focus on concentrations of PCBs and mercury in fish. The Great Lakes Consortium is now considering whether toxaphene should also influence fish consumption advisories. In this report, an exposure assessment was conducted using toxaphene concentrations in Great Lakes fish tissue collected and analyzed from 2010-2012 by the Departments of Natural Resources of Michigan, Minnesota, and Wisconsin. The exposure assessment addressed several consumption frequencies used to issue consumption advice (unrestricted, 1 meal/week, 1 meal/month, 6 meals/year, and no consumption). Scenarios assumed a 70 kg adult and proper fish cleaning and cooking techniques. Due to the absence of an EPA-issued reference dose (RfD) for toxaphene, toxicology studies were reviewed and used to calculate a comparable value of 1.11×10^{-4} mg/kg-day. Highest toxaphene exposures resulted from consumption of siscowett lake trout from Lake Superior, which should be restricted to 1 meal/week. No other type of fish from either Lake Superior or Lake Michigan required toxaphene-driven restrictions. It was concluded that fish consumption advisories currently in place to address exposures to mercury and PCBs would also be protective of toxaphene exposures. Therefore, no revisions to current consumption advisories are recommended.

Purpose

Toxaphene is a mixture of over 670 chemical compounds, and was commonly used as a pesticide in the United States during the mid to late 20th century. Due to evidence of high environmental persistence and toxicity, the EPA restricted use of toxaphene in 1987 before completely banning it in 1990.

Although usage of toxaphene as a pesticide occurred primarily in the southern United States (U.S.), its persistence in the atmosphere allows for continued aerial transport and deposition into water bodies across the U.S., including those in the Great Lakes region. Consumption of locally-caught fish from the Great Lakes is the primary route of exposure to toxaphene for people living in this region (80-90% contribution), with a much smaller contribution (10%) from ingestion of contaminated drinking and surface water (EPA 2005). Toxicology studies have shown that chronic oral exposure to toxaphene may cause a wide array of adverse health outcomes, affecting the liver, kidney, spleen, adrenal, and thyroid glands, as well as the immune and central nervous systems and development (ATSDR 2014b). There is also some evidence that toxaphene may be carcinogenic (IARC group 2B). Therefore, unrestricted consumption of Great Lakes fish contaminated with toxaphene may pose a public health hazard.

At the request of the Great Lakes Consortium, this report estimates human exposure to toxaphene through consumption of locally-caught fish from the Great Lakes. This assessment was conducted as part of the EPA Great Lakes Restoration Initiative (GLRI) grant.

Methods

Fish Tissue Sample Analysis:

Fish tissue samples were collected from various locations in both Lake Michigan and Lake Superior, and included the following species: lake trout, siscowett lake trout, cisco, coho salmon, chinook salmon, pink salmon, lake whitefish, and walleye. The Michigan Department of Natural Resources (DNR) collected samples from Lake Michigan during 2012, while the Minnesota and Wisconsin DNRs collected samples from Lake Superior during 2010 and 2011, respectively.

The Michigan Department of Community Health Laboratories analyzed fish samples for the following toxaphene congeners: Hex-Sed, Hep-Sed, P26, P41, P40, P44, P50, and P62. The sum of these was used to represent total toxaphene for these analyses.

Derivation of Reference Dose (RfD):

The EPA has not established an oral reference dose (RfD) for toxaphene; however, several toxicology studies are available and have been used to derive RfDs in similar assessments. For example, Health Canada has published a tolerable daily intake (TDI; conceptually similar to a RfD) of 0.2 µg/kg-day, based on a subchronic exposure toxicology study conducted in rats and dogs (Health Canada 2003). Typically, these calculated RfDs range from 0.1 to 1.0 mg/kg-d, but some studies have produced more conservative estimates.

The literature on health effects of toxaphene has been recently reviewed (ATSDR 2009, 2014b). Based upon these reviews, two animal toxicology studies were selected from the literature for further evaluation as candidates for critical studies to develop an oral RfD. The first, described in Simon and Manning (2006) is based on data reported in Besselink et al. (2000) for a sub-chronic study performed in female Sprague-Dawley rats. Animals were dosed with a weathered mixture of toxaphene for 20 weeks (subchronic duration), administered sub-cutaneously in corn oil vehicle. Doses ranged from 0.46 to 12.5 mg/week for the total mixture; Simon and Manning also note that the dose may be converted to represent the sum of the three constituent parlars (p-26, p-50, p-62, expressed as Σ 3PC) thought to be responsible for toxic effects. Besselink et al. (2000) reported as the critical effect the occurrence of altered hepatic foci (AHF) expressing placental glutathione-S-transferase (GSTp-AHF); these foci are indicators of tumor promotion and was considered by Simon and Manning (2006) to be protective of other health endpoints, both cancer and non-cancer. The No Observed Adverse Effect Level (NOAEL) for this endpoint was seen at the second highest dose group (4.17 mg/kg-week), or 0.0021 mg/kg-day of Σ 3PC. It is important to note that at this level of exposure, the individual parlars included in the Σ 3PC metric were not detectable in rat liver tissue samples. Based on the NOAEL, Simon and Manning suggest an RfD of 2.1×10^{-5} mg/kg-day, based upon application of uncertainty factors for interspecies (10-fold) and intraspecies (10-fold) variability (total uncertainty factor of 100). Since the RfD is meant to represent a level of chronic exposure at which no adverse health effects may be expected, an additional 10-fold uncertainty factor for the subchronic exposure duration of the Besselink et al. (2000) study may be warranted. In this case, the total uncertainty factor would be increased to 1000, for an RfD of 2.1×10^{-6} mg/kg-day.

The second animal toxicology study considered was conducted by Tryphonas et al. (2001). Tryphonas et al. treated cynomolgus monkeys with technical-grade toxaphene at levels of 0 (control group), 0.1, 0.4 or 0.8 mg/kg-day dissolved in glycerol/corn oil; dosing lasted for 75 weeks (subchronic duration). Immune system function was assessed using multiple markers, including antibody titres

(sheep red blood cells, tetanus toxoid, pneumococcus); flow cytometry indicators; hypersensitive response to dinitrochlorobenzene; lymphocyte transformation; natural killer cell level; and cortisol level. The final NOAEL was determined to be 0.1 mg/kg-day, based on statistically significant depression of humoral immunity at the higher doses evaluated. Several uncertainty factors were applied to the NOAEL to obtain an RfD, beginning with those typically applied by ATSDR when calculating intermediate oral minimal risk levels (MRLs): 3 for interspecies uncertainty (nonhuman primate to human) (OEHHA, 2008), 10 for intraspecies uncertainty (human to human), and a modifying factor of 3 for the potential that developmental effects may occur at even lower levels of exposure (i.e., database uncertainty). A further uncertainty factor of 10 was applied to convert the subchronic exposure duration to the desired chronic exposure duration. This results in a total uncertainty factor of 900 (3x10x3x10).

In considering these two studies, each has its strengths and weaknesses. The study by Tryphonas et al. (2001) was ultimately selected for the basis of the RfD due to the following strengths:

- oral administration of toxaphene (as opposed to injection) mirrors human exposure route of interest;
- use of monkeys may be a better model for human exposure than use of rat models;
- suitable exposure duration (75 weeks); and
- immune system effects represent a sensitive endpoint.

Therefore, the final RfD used in this assessment is based on the data presented in Tryphonas et al. (2001): $\text{NOAEL/UF} = (0.1\text{mg/kg/d})/900 = 0.000111 \text{ mg/kg/day}$, or $1.11 \times 10^{-4} \text{ mg/kg/day}$.

Risk characterization using Great Lakes Consortium consumption categories:

Risk from toxaphene exposure through consumption of contaminated fish is evaluated using consumption categories outlined in the Great Lakes Consortium risk advisory protocols (available at: <http://www.health.state.mn.us/divs/eh/fish/consortium/pastprojects/index.html>). The maximum concentration of toxaphene in fish tissue for each category of consumption, is estimated using a standard bodyweight along with the RfD, as shown in **Equation 1**. These estimated concentration ranges are compared against observed toxaphene concentrations in fish samples to determine which consumption categories are most appropriate for toxaphene-containing fish.

Equation 1.

$$\text{Toxaphene concentration in fish} = \frac{\text{body weight} \times \text{RfD}}{\text{daily intake}}$$

Standard values for body weight, meal size, preparation method adjustment, and consumption frequencies, are specified in the Great Lakes Consortium advisory protocol developed by the Great Lakes Sport Fish Advisory Task Force (1993). The target consumer is assumed to be a 70 kg adult, consuming a uniform meal size of ½ pound of raw fish (227 g), with the understanding that for other consumers, meal size will change proportionally with body weight. Regarding the effect of preparation of fish (e.g., trimming fat, removing skin, and cooking) on contaminant concentrations, the Task Force reviewed the literature and concluded that a contaminant reduction factor of 50% is a realistic expectation for all the lipophilic contaminants of concern in the Great Lakes. Thus, the ingested toxaphene dose is assumed to be half of the amount present in raw, unprocessed fish. Maximum concentration ranges are estimated for the following consumption frequency scenarios: unrestricted consumption (>140 g/day fish fillet), one meal per week (32 g/day), one meal per month (7.4 g/day), one meal every two months (i.e., six meals per year, 3.73 g/day), or no consumption ('do not eat'; <3.7 g/day).

Risk Characterization using calculated chronic exposures and Hazard Quotients:

Risk may also be characterized by estimating chronic exposures to toxaphene from consuming different quantities of fish. This method will result in the same conclusions as above, but will present estimated human doses and hazard associated with various categories of consumption, as opposed to fish tissue concentrations ranges associated with these categories. Estimated chronic toxaphene dose for a given level of consumption can be estimated by **Equation 2**. Toxaphene concentration in fish is halved to account for fat removal during fish preparation (Great Lakes Sport Fish Advisory Task Force, 1993).

Equation 2.

$$\text{Chronic toxaphene dose} = \frac{(\text{mg Toxaphene/kg fish} \times 0.5) \times (\text{kg fish consumed/day})}{\text{kg bodyweight}}$$

Toxaphene concentration in fish (mg Toxaphene/kg fish) is estimated by computing the average concentration recorded during sampling activities conducted in 2010-2012 by the Wisconsin, Michigan and Minnesota DNRs, as described previously in the methods section. Average concentrations by species and water body are reported in Table 1, below. The total toxaphene in fish was estimated as the sum of

the following measured congeners: Hex-Sed, Hep-Sed, P26, P41, P40, P44, P50, and P62. Multiple species and sampling locations are represented; exposure for each of the two main water bodies (Lakes Michigan and Superior) and for each species is calculated separately to assess the need for species- or location-specific restrictions or advisories.

The Great Lakes consortium standard fish meal size (227g fish/meal) and body weight (70 kg) were used when estimating chronic doses under the previously defined consumption frequency scenarios (unrestricted consumption, 1 meal per week, 1 meal per month, 6 meals per year, and no consumption ['do not eat']).

Hazard quotients (HQs) are calculated as the ratio of the potential exposure (i.e., chronic toxaphene dose) to a level at which no adverse health effects are expected to occur (i.e., the RfD). If the HQ is <1, no adverse health effects are expected to occur at the given level of exposure, while a HQ ≥1 indicates the possibility that adverse health effects may occur. HQs are computed for each chronic exposure scenario described above, using **Equation 3** and the RfD estimated from Tryphonas et al. as the screening benchmark.

Equation 3.

$$HQ = \frac{\text{Dose(toxaphene)}}{\text{Screening Benchmark}}$$

Results

Toxaphene concentrations in fish tissue

Average toxaphene concentration for each combination of fish species and sampling location is shown in **Table 1**. Lake trout sampled at FPT in Lake Superior (average concentration of 0.18 mg/kg fish fillet), and siscowett lake trout sampled at grid 1311 in Lake Superior (average concentration of 0.17 mg/kg) had the highest average toxaphene concentrations while walleye sampled from Little Bay de Noc in Lake Michigan had the lowest average concentration (~185-fold lower).

TABLE 1. Toxaphene concentrations in Lake Michigan and Lake Superior fish samples				
Species	Water body	Sampling Location	Average concentration (ppt)	Average concentration (mg/kg fish fillet)
Lake Trout	Lake Michigan	Grand Traverse Bay	5558.72	0.006
Walleye	Lake Michigan	Little Bay De Noc	970.90	0.001
Chinook	Lake Superior	French River	26353.00	0.026
Chinook	Lake Superior	Grand Marais	3112.00	0.003
Chinook	Lake Superior (All locations)		18606.00	0.019
Cisco	Lake Superior	ECI	8266.06	0.008
Cisco	Lake Superior	Larsmont	4952.00	0.005
Cisco	Lake Superior	LBB	26584.85	0.027
Cisco	Lake Superior	Silver Bay	7077.00	0.007
Cisco	Lake Superior (All locations)		10877.92	0.011
Coho	Lake Superior	Grand Marais	2111.50	0.002
Coho	Lake Superior	Sioux River	6889.33	0.007
Coho	Lake Superior (All locations)		3704.11	0.004
Lake Trout	Lake Superior	ECI	12617.00	0.013
Lake Trout	Lake Superior	FPT	21347.23	0.021
Lake Trout	Lake Superior	Grid 1311	174393.60	0.174
Lake Trout	Lake Superior	Grid 1401	28086.10	0.028
Lake Trout	Lake Superior	Silver Bay	13381.00	0.013
Lake Trout	Lake Superior	Split Rock Reef	10481.00	0.010
Lake Trout	Lake Superior (All locations)		69557.45	0.070
Lake Whitefish	Lake Superior	Larsmont	52504.30	0.053

Species	Water body	Sampling Location	Average concentration (ppt)	Average concentration (mg/kg fish fillet)
Pink Salmon	Lake Superior	French River	3510.04	0.004
Siscowett Lake Trout	Lake Superior	FPT	182094.80	0.182
Siscowett Lake Trout	Lake Superior	Grid 1410	140490.20	0.140
Siscowett Lake Trout	Lake Superior (All locations)		163183.61	0.163
<i>Total toxaphene is the sum of: Hex-Sed, Hep-Sed, P26, P41, P40, P44, P50, P62</i>				

Estimated toxaphene dose and Great Lakes Consortium consumption advisory categories:

The Great Lakes Consortium uses consumption categories of unrestricted consumption, one meal per week, one meal per month, one meal every two months, and no consumption (do not eat) when considering fish consumption advisories. The RfD was used to derive toxaphene concentration ranges associated with safe exposures, which apply to the fish tissue consumed. As described above, the observed concentration of toxaphene in fish samples was reduced by 50% when calculating ingested toxaphene dose, under the assumption that consumers are properly preparing and cooking fish before eating.

As seen in **Table 2**, unprepared fish with toxaphene concentrations less than 0.033 mg/kg may be eaten without restriction and result in chronic doses less than the RfD. Concentrations ranging from 0.033 up to 0.146 mg/kg may be eaten once per week; 0.146 up to 0.630 mg/kg may be eaten once per month; 0.630 up to 1.26 mg/kg may be eaten 6 times per year; and fish containing more than 1.26 mg/kg should not be eaten at all.

Consumption advice may be derived by comparing these ranges in unprepared fish with the water body and species specific average toxaphene concentrations, presented in **Table 1**. As summarized in **Table 2**, lake trout and walleye from Lake Michigan, and chinook salmon, cisco, coho salmon, lake trout, lake whitefish, and pink salmon from Lake Superior may be eaten without restriction. Siscowett lake trout from Lake Superior should not be eaten more than once per week.

TABLE 2. Maximum allowable toxaphene concentration ranges in fish tissue			
Consumption Category	Concentration in edible tissue after preparation (mg/kg)	Concentration in fish before preparation (mg/kg)	Advice
Unrestricted	<0.056	<0.111	Lake Michigan lake trout, walleye; Lake Superior cisco, coho salmon, chinook salmon, , lake trout, lake whitefish, and pink salmon.
1 meal/week	0.056 to 0.243	0.11 to 0.486	Lake Superior siscowett lake trout
1 meal/month	0.243 to 1.05	0.485 to 2.1	--
6 meals/year	1.05 to 2.08	2.1 to 4.17	--
Do Not Eat	>2.08	>4.17	--

Estimated chronic toxaphene exposure and hazard quotient values

Table 3 shows the estimated chronic toxaphene dose to a 70 kg adult under the five exposure frequency scenarios, assuming appropriate fish preparation techniques. Unrestricted consumption of Lake Michigan species (lake trout and walleye), along with coho salmon, chinook salmon, cisco, lake trout, lake whitefish and pink salmon from Lake Superior would not result in doses exceeding the RfD for toxaphene. Siscowett lake trout from Lake Superior should not be consumed more than once per week.

TABLE 3. Estimated chronic toxaphene dose to a 70 kg adult consumer (mg/kg-day)										
Species	Unrestricted		1 meal/week		1 meal/month		6 meals/year		No consumption	
	Chronic Dose	HQ	Chronic Dose	HQ						
<i>Lake Michigan</i>										
Lake trout	5.56E-06	0.05	1.27E-06	0.01	2.94E-07	0.003	1.48E-07	0.001	1.47E-07	0.001
Walleye	9.71E-07	0.009	2.22E-07	0.002	5.13E-08	0.0005	2.59E-08	0.0002	2.57E-08	0.0002
<i>Lake Superior</i>										
Coho	3.70E-06	0.17	8.47E-07	0.04	1.96E-07	0.009	9.87E-08	0.004	9.79E-08	0.004
Chinook	1.86E-05	0.1	4.25E-06	0.02	9.83E-07	0.005	4.96E-07	0.003	4.92E-07	0.003
Cisco	1.10E-05	0.03	2.51E-06	0.008	5.81E-07	0.002	2.93E-07	0.0009	2.91E-07	0.0009
Lake Trout	6.96E-05	0.63	1.59E-05	0.14	3.68E-06	0.03	1.85E-06	0.02	1.84E-06	0.02
Lake Whitefish	5.25E-05	0.47	1.20E-05	0.11	2.78E-06	0.03	1.40E-06	0.01	1.39E-06	0.01
Pink Salmon	3.51E-06	0.03	8.02E-07	0.007	1.86E-07	0.002	9.35E-08	0.0008	9.28E-08	0.0008
Siscowett Lake Trout	1.63E-04	1.5	3.73E-05	0.34	8.63E-06	0.08	4.35E-06	0.04	4.31E-06	0.04

Shading indicates exposure level exceeding the calculated chronic RfD for toxaphene.

Discussion

Toxaphene-driven fish consumption advisories were evaluated using observed concentrations of toxaphene concentrations in fish tissue collected in the Great Lakes region. Assuming recommended protocol for cleaning and cooking of fish is followed, no restrictions are needed for lake trout or walleye from Lake Michigan, or for cisco, coho salmon, chinook salmon, lake trout, lake whitefish, and pink salmon from Lake Superior. Consumption of Lake Superior sicsowett lake trout should be limited to one meal per week to avoid chronic toxaphene doses exceeding the RfD 1.11×10^{-4} mg/kg/day. None of the species fall into more restrictive categories.

As noted in a previous study by Gandhi et al. (2013), any consumption advisory based on toxaphene concentrations in fish must be considered in the context of other contaminants such as mercury and PCBs, and that risks posed by these latter contaminants will frequently overshadow the risk conferred by toxaphene. As seen in **Table 4**, existing advisories for fish consumption driven by mercury and PCB exposures are more restrictive than those estimated in this assessment. Therefore, risks associated with exposures to toxaphene should be considered along with existing consumption advisories for the species examined in this analysis. Furthermore, consumption advice generated using toxaphene as the driving contaminant should not be used over existing advice based on mercury and PCBs as this may result in unacceptable risks associated with exposures to these contaminants.

The study by Tryphonas et al. was used to derive the RfD for toxaphene used in this assessment due to several study strengths mentioned previously. Several other toxicology studies are available in the literature; many of these would lead to calculated toxaphene RfD values that are less stringent than that calculated by Tryphonas et al., ranging from 0.1 to 1.0 mg/kg-d (ATSDR 2009). Overall, the conclusions of this assessment would not change if a less conservative RfD had been used.

Other studies, such as that described by Simon and Manning (2006), could lead to a lower RfD (if applying an additional adjustment for subchronic duration of exposure) of 2.1×10^{-6} mg/kg-d. In this case, the estimated HQs would exceed one under more scenarios. As noted earlier, a HQ above one indicates that the RfD has been exceeded, but does not imply that adverse health effects will necessarily occur. Such exceedances of the RfD do, however, indicate a potential area of further investigation and may lead to different advice for fish consumers. Furthermore, as stated above, the study by Tryphonas et al. has many strengths and may be a more appropriate study for use in developing an oral RfD for toxaphene.

Consumption Category	Mercury and PCB driven advice, general population	Mercury and PCB driven advice, sensitive populations
Unrestricted	Lake Superior coho salmon	--
1 meal/week	Lake Superior chinook <32", lake trout <22", lake whitefish, walleye	Lake Superior chinook <32", coho salmon, lake trout <22", lake whitefish
1 meal/month	Lake Michigan lake trout <27"; Lake Superior chinook >32", lake trout 22"-37", siscowett <29"	Lake Michigan lake trout <27"; Lake Superior chinook >32", lake trout 22"-37", siscowett <29", walleye
6 meals/year	Lake Superior lake trout >37", siscowett 29"-36"	Lake Superior lake trout >37", siscowett 29"-36"
Do Not Eat	Lake Michigan lake trout >27"; Lake Superior siscowett >36"	Lake Michigan lake trout >27"; Lake Superior siscowett >36"

<http://dnr.wi.gov/FCSExternalAdvQry/FishAdvisorySrch.aspx>

Conclusion

Based on this assessment, no toxaphene-driven fish consumption restrictions would be recommended for lake trout or walleye caught in Lake Michigan, or for cisco, coho salmon, lake trout, lake whitefish, and pink salmon caught in Lake Superior, assuming fish are properly cleaned of fatty tissues. Siscowett lake trout from Lake Superior should not be consumed more than once per week. Existing consumption advisories driven by mercury and PCBs are protective of chronic exposures to toxaphene. However, consumption advisories should not be adjusted to reflect toxaphene-driven estimates derived in this analysis as this could result in exposure to mercury and PCB reaching unacceptable levels.

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