Risk/Benefit Analysis of Great Lakes Fish for Neurodevelopmental Outcomes

Gary Ginsberg, July 30, 2016

The fact that fish contain contaminants that can have adverse effects on brain development such as mercury and PCBs have led to many species-specific and waterbody-specific advisories. In the case of mercury, this is based upon the methyl mercury (Hg) reference dose (RfD) posted on USEPA's IRIS database. However, if consumption limits are based solely upon the RfD, ingestion of fish may be limited to the extent that the beneficial effects of nutrients, particularly the omega-3 fatty acids EPA and DHA, may be lost. Therefore risk/benefit models have been used to assess commercial fish based upon the species-specific content of omega-3 fatty acids and methyl Hg. While such information is available for commercial fish, the omega-3 content of locally caught fish is less commonly available and thus fish advisories for such fish are usually based upon the mercury (or PCB) content and the USEPA RfD. This situation has recently changed with a number of Great Lakes states pooling resources to develop a database of omega-3 fatty acid levels in species which also have Hg data. This report provides the results of risk/benefit modeling of select Great Lakes species using a risk/benefit model originally published in 2009 and since updated in 2015 (Ginsberg and Toal, 2009; Ginsberg et al. 2015). The update presents modified me Hg risk and omega-3 benefit slopes so that model predictions more closely match the available epidemiology, which shows a general overall positive effect of fish on fetal neurodevelopment.

Methods

The omega-3 fatty acid database represents 900 fillet samples from fish collected between 2010 and 2013. Approximately one third of the fish were collected from the Great Lakes, while the remaining two-thirds were collected from just over 100 inland waterbodies within the Great Lakes states. Samples of a variety of fish species were collected from 34 Minnesota lakes, 17 lakes and 1 river in Wisconsin, 2 Michigan lakes, 10 Ohio lakes, 9 Pennsylvania lakes, and 15 lakes and 2 rivers in New York. A description of the omega-3 fatty acid sampling effort was presented at the 2014 National Forum on Contaminants in Fish, Alexandria, VA (Williams 2014) and has been submitted for publication. Fish were filleted after scales removed, with skin left on and whole fillets homogenized for contaminant or fish oil analysis. Hg data were provided by NY, WI and MN and included the most recent ten years of statewide data for the species in the case studies. Most samples were analyzed as individual fish.

The risk/benefit methodology described in Ginsberg et al. 2015 was used to analyze selected species which have substantial datasets for both Hg and omega-3 fatty acids. In addition, species were evaluated against standard mercury cutpoints used in fish advisories to determine if these cutpoints could be relaxed based upon the omega-3 benefit in the particular species. The Hg results were used as the mean concentration per species per waterbody directly in the model and assumed to represent methyl Hg. The omega-3 fatty acid results were presented as mg/kg of DHA or EPA. These quantities were combined to yield the total omega-3 fatty acid content of the fish (means) and this was converted to omega-3 content per 227 gram (8 oz) fish meal for 70 kg body weight for use in model calculations.

One update to the Ginsberg et al. 2015 methodology is that the calculation of maximal consumption was modified. In the published version the limit was based upon the number of fish meals needed to reach saturation of benefit (VRM score of +8.4 points) to prevent levels of consumption to increase to the point where the adverse effects of methyl Hg would be causing a decrease in benefit. However, through experience with running the model for different fish it was realized that this approach penalizes fish with high omega-3 fatty acid content as the higher the content the fewer meals it would take to saturate the benefit. Therefore, for the analyses presented in Table 2, the maximal meal frequency was based upon the number of meals it would take for the VRM score to become net neutral, in other words for the risk to catch up to the benefit after saturation of benefit is reached. This approach allows greater meal frequency because for any species reaching saturation of benefit occurs before reaching net neutral VRM, with this taking more fish consumption if the species contains less methyl Hg. As in Ginsberg et al. 2015, this approach at calculating meal frequency was used only for fish with a clearly positive VRM score. For net negative VRM fish the methyl Hg RfD is used to set meal advice.

Table 1 presents risk/benefit modeling results for 8 combinations of species and waterbody prioritized as case studies based upon data availability. A positive VRM score indicates a net benefit neurodevelopmental outcome is forecast for that species, with a sensitivity analysis shown in subsequent columns to test whether uncertainty in the slope (lower bound O-3 benefit slope or upper bound Hg risk slope) would lead to a reversal of the outcome. If the original VRM score was negative, this indicates that there is a net risk to neurodevelopment from that species/waterbody combination and so further sensitivity analysis was not conducted. The analytical framework for risk/benefit modeling is to evaluate whether there is sufficient fish oil benefit to potentially offset the risk associated with the methyl Hg RfD such that consumption advice may be relaxed relative to simply using the RfD (risk with no benefit). If the VRM score is net negative there is no basis for relaxing advice and one can fall back to the standard RfD-based approach.

A further analysis was conducted in which the variability in fish oil and Hg content in each species was evaluated through a "best case" bounding scenario (25^{th} percentile Hg, 75^{th} percentile omega-3) and a "worst case" scenario (75^{th} percentile methyl Hg, 25^{th} percentile omega-3) for each species (Table 2). These bounding cases represent approximately 6% of the distribution of all possible results (0.25*0.25=0.0625). A result at this percentile which is opposite to the result when average concentrations are used would suggest that further analysis of the sources of variability in Hg and omega-3 fish content (e.g., by waterbody, fish size, etc.) might identify more specific consumption advice.

Results

Table 1 shows that when using average methyl Hg and omega-3 data for each species, a clear net benefit (positive VRM score through sensitivity analysis) was seen for cisco from Lake Superior, with this almost the case as well for lean lake trout from Lake Superior. A smaller net benefit was seen for lake trout from MN inland waters with this benefit considered marginal (VRM clearly negative on sensitivity analysis). The remaining 5 case studies in Table 1 all had negative VRM scores when using the average constituent concentrations. This includes walleye from 3 different states, lake trout from NYS and black crappie from WI.

Table 2 provides the results of a bounding sensitivity analysis of these 8 case study species by considering the variability in constituent concentrations. Best case estimates for fish whose average concentrations resulted in net risk still showed a net risk except for lake trout from NY inland waters. In this case, the VRM score was clearly beneficial (4.75 points) for 6% of the distribution of possible combined omega-3/Hg results suggesting that a full Monte Carlo analysis would find a larger percentile of the distribution of this fish species having a net positive score. Thus, this is one case in which additional sampling may identify more detailed consumption advice in which certain NY trout (e.g., from specific waterbodies, certain size cutoffs, or other variables) might be recommended to have higher consumption than the RfD-based approach. The best case analysis for walleye was explored beyond Table 2 to model the lake in the database with the best omega-3 FA to mercury ratio, Lake Winnibigoshish in MN. The omega-3 FA to mercury ratio was slightly better for walleye from that lake than in the best case variability analysis and thus the net ND score was also slightly better, but still associated with a net risk (-0.42). The reverse analysis, worst case bounding for the beneficial species indicates a positive VRM for Lake Superior cisco, providing added confidence in the beneficial effects of this species. For Lake Superior trout and trout from MN inland lakes the worst case analysis indicated a net risk suggesting that some percentile of fish (>6%) would yield a net risk in spite of a beneficial VRM score in the average case. Thus, additional sampling of these fish may be warranted to further explore this variability.

Table 3 shows the implications of these results for consumption advisories, focusing upon the average constituent concentrations in each species and the uncertainty analysis based upon bounding slopes as shown in Table 1. The columns are laid out in order of the sequential decision-making process when risk/benefit information along with the RfD to establish consumption advice (Ginsberg et al. 2015). Those Great Lakes states species with a clear benefit at Step 2 can have consumption rise above the RfD-based meal frequency (Step 1), with the recommendation then based on the maximum meal frequency that would still be beneficial when considering the saturation of benefit. Lake Superior cisco is the only species for which unrestricted advice is suggested as the RfD-based advice is already at nearly 3 meals/week and when factoring in beneficial fish oils in cisco, the advice is further relaxed to a maximum of nearly 1 meal/day. Two other species with marginal benefit are recommended to have their consumption advice rounded up from less than 1 meal/week based upon the RfD to 1 meal/week (Lake Superior trout, MN inland waters trout, Table 3). All other case example species had net negative VRM scores on average concentration basis with RfD-based advice at less than one meal/week. The recommendation for these species is generally 1-2 meal/month.

Table 4 further explores modeling results by showing how the beneficial fish oil content would modify default fish consumption limits based upon Hg cutpoints. Thus, rather than taking the Hg content data gathered thus far for these species, one assumes that new data are available that shows a particular species at a particular waterbody has Hg at or between the preset cutpoints. The table shows that for fish with substantial omega-3 fatty acids, the preset cutpoints could be relaxed to allow greater fish consumption. For example, lake trout from Lake Superior could be considered for unrestricted consumption advice below a Hg cutpoint of 0.22 ppm with limitation to 1 meal/month not occurring until 0.43 ppm (rather than 0.22 ppm). A number of other fish, most notably trout from a number of waterbodies, have positive VRM scores at preset Hg cutpoints suggesting that these cutpoint limits could be relaxed somewhat (Table 4). In addition to the 8 case studies fish species analyzed in Tables 1-3, 6 additional cases are presented in Table 4. As described above for the basic case studies, risk/benefit results for a number of species suggest greater consumption allowances than indicated from the RfD approach. A cautionary note is that its advisable for the model to still be run for the exact Hg concentration detected in the fish since its possible to have a reversal in VRM result over a relatively small range as seen for smallmouth bass from Lake Ontario. In this case, VRM goes from net positive at 0.11 ppm to negative at 0.22 ppm which means that the benefit is lost somewhere in that methyl Hg range. Given that these VRM deflections are small, one can choose for simplicity to have uniform advice throughout that range for small mouth bass (i.e., unrestricted consumption through that range and jump down to 1 meal/week above that range). Table 4 provides a suggested new cutpoint for a number of species which have a net benefit at or above 0.22 ppm Hg. Since the 1 meal a month category covers a large Hg range (>0.22 ppm to 0.95 ppm), it may be helpful to have a species-specific cutpoint to make this range less generic as the advice is variable across species in this range when considered from a neurodevelopmental risk/benefit perspective.

Assessment of non-fish oil neurodevelopmental benefits

The benefit attributed to the omega-3 content of fish stems from a regression analysis of dietary recall data for fish quantity and type during pregnancy in relation to VRM results (Oken et al. 2005). However, it is possible that some percentage of the omega-3 benefit is actually due to other benefits from fish consumption such as other nutrients. A sensitivity analysis of this issue can be done by reverting to the original benefit slope for fish oil (Ginsberg and Toal 2009) rather than calibrate the slope by increasing it to match the VRM benefit seen in Oken et al. (2005) as done in Ginsberg et al. 2015. The increase in benefit seen over that predicted by the regression slope may be considered the non-omega-3 benefit from fish ingestion. Reverting to the original (non-calibrated) benefit slope decreases this slope by 48%, which leaves this as an estimate of the benefit due to non-oil fish meal benefit. This can be calibrated against the net VRM score seen in Oken et al (2005) per fish meal using the US marketshare diet to simulate the omega-3 fatty acid and methyl Hg content of the fish diet in the population studied by Oken et al. The VRM benefit not associated with fish oil is calibrated to 1.92 VRM points/fish meal. If we apply this VRM benefit per fish meal across species while also using the original omega-3 slope in these calculations there is a natural break in the data. Fish with a high omega-3 content (>5177 mg/kg, combined DHA+EPA) have a net decrease in benefit when attributing some of the benefit to a non-fish oil source. This is because the omega-3 slope has been lowered to leave room for non-fish oil nutrients, making the species with high oil content appear to be less beneficial. In contrast, species which have low fish oil content have a higher net VRM by adding 1.92 VRM points per meal without involving a loss of much benefit due to a lower omega-3 fatty acid slope. This backfit fish meal benefit is the equivalent of 0.137 ppm Hg in fish. In other words, the non-fish oil benefit is estimated to offset 0.137 ppm of mercury in the fish with the remainder of the benefit coming from the fish oil content. Thus, this estimation method predicts a net benefit for species with relatively low Hg content (<0.137 ppm) regardless of the omega-3 content and that fish with lower mercury content could be consumed without limit, at least in terms of neurodevelopmental risk/benefit.. For most species, this approach will not produce a marked change in net VRM score because some of the fish oil benefit is lost to accommodate the non-fish oil benefit. However it may be possible to define a threshold of mercury in fish below which meal advice would not be necessary because of the general benefits of a fish meal. Further research in this area is needed to further define whether such an approach is feasible and what would be the mercury threshold that begins to become a net risk against the baseline fish benefit. .

References

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Table 1. Risk Benefit Modeling of Selected Species from the Great Lakes and Minnesota Inland Waters Considering Uncertainty in VRM Slopes

Waterbody	Species	Mean O-3 Content mg/227 g meal	Mean Hg Content (ug/g)	O-3/Hg Ratio (mg/ug)	Net VRM Score	Net VRM Upperbound Hg Slope[1]	Net VRM Lowerbound O-3 Slope[1]
Lake Superior	Lean Lk Trout	2061	0.319	28.5	2.45	-0.11	-0.10
Lake Superior	Herring Cisco	966	0.078	54.5	2.74	2.11	1.29
MN inland	Lake Trout	1455	0.298	21.5	0.76	-1.60	-1.40
MN inland	Walleye	421	0.311	5.96	-3.98	---	---
WI inland	Black crappie	252	0.245	4.92	-3.48	---	---
WI inland	Walleye	421	0.403	4.6	-5.69	---	---
NY inland	Lake Trout	1455	0.375	17.1	-0.68	---	---
NY inland	Walleye	421	0.566	3,28	-8.74	---	---

[1]See Ginsberg et al. 2015 for information of upperbound slopes and other details of this analysis.

Table 2. Risk Benefit Modeling of Great Lakes Species Considering Variability in methyl Hg and Fish Oil Content

Waterbody	Species	Net VRM Score	Net VRM 25^{th}% O-3, 75^{th}% Hg	Net VRM 75^{th}% O-3, 25^{th}% Hg	**Overall Result**
Lake Superior	Lean Lk Trout	2.45	-3.0162	10.08824	Net risk in at least 6% of fish
Lake Superior	Herring Cisco	2.74	1.516877	4.096868	VRM positive even in worst case
MN inland	Lake Trout	0.76	-3.75776	6.229333	Net risk in at least 6% of fish
MN inland	Walleye	-3.98	-6.2084	-0.69916	Net risk even in best case
WI inland	Black crappie	-3.48	-4.56663	-1.3281	Net risk even in best case
WI inland	Walleye	-5.69	-8.7284	-1.85649	Net risk even in best case
NY inland	Lake Trout	-0.68	-5.75509	4.754666	Net benefit in at least 6% of fish
NY inland	Walleye	-8.74	-12.4244	-0.53116	Net risk even in best case

Table 3. Derivation of Risk Specific Advice for Great Lakes Case Studies Species

Species/ Waterbody	Step 1. Meal Freq/Wk at Rfd[a]	Step 2. Net VRM Score	OK to Exceed RfD?	Step 3. Max Meal Frequency[b]	Suggested Advice
Lean Lake Trout (Superior)	0.676674	2.5, Marginal benefit	By rounding up only	1.4/wk	1/wk
Cisco (Superior)	2.767423	2.74, Clear benefit	Yes	5.8/wk	Unrestricted
Lake trout (MN)	0.724359	0.8, Marginal benefit	By rounding up only	1.51/wk	1/wk
Walleye (MN)	0.69408	-3.98, Clear risk	No	---	1-2/month
Black Crappie (WI)	0.881057	-3.48, Clear risk	No	---	1-2/month
Walleye (WI)	0.53563	-5.69, Clear risk	No	---	1-2/month
Lake Trout (NY)	0.575624	-0.68, Marginal risk	No	---	1-2/month
Walleye (NY)	0.381376	-8.74, Clear risk	No	---	1/month

[a]Step 1 meal frequency based upon default approach for setting risk-based consumption limits (USEPA, 2000)which utilizes the following equation: #meals/day = (RfD*body wt - kg)/(Meal size*Hg conc) where mercury concentrations are listed in Table 4, RfD = 0.1 ug/kg/d, body wt = 70 kg, meal size = 8oz or 227g. This gets multiplied by 7 to get meals/week.

[b]Calculated as the meal frequency at which mercury VRM decrease exceeds saturation of O-3 benefit (8.4 VRM points) for species which have a net benefit. For species with a net risk, maximum meal frequency defaults to RfD-based frequency.

Table 4. Evaluation of Advisory Cutpoints for Consumption of Various Great Lakes Species

Species	Net VRM Score using Species-Specific Hg Data	Mercury Cutpoint, default advice	Net VRM at Cutpoint, modified advice
Lean Lake Trout, Superior	2.5, marginal benefit	0.11 ppm – 2 meals/wk	6.4 – clear benefit Unlimited consumption
		0.22 ppm – 1 meal/wk	4.3 – clear benefit Unlimited consumption
		>0.22 ppm – 1 meal/month	0.3 ppm benefit becomes marginal, 0.44 ppm VRM neutral, thus 1 meal/wk 0.3-0.43 ppm; >0.43 ppm follow default of 1meal/month
Cisco, Inland	2.74, clear benefit	0.11 ppm – 2 meals/wk	2.14 – clear benefit Unlimited consumption
		0.22 ppm – 1 meal/wk	0.087 – marginal benefit

			Leave as 1 meal/wk
		>0.22 ppm – 1 meal/month	VRM negative >0.23 ppm thus stay with default 1/mth
Lake Trout (MN)	0.76, marginal benefit	0.11 – 2 meals/wk	4.6 – clear benefit, unlimited consumption
		0.22 ppm – 1 meal/wk	2.21 – clear benefit, unlimited consumption
		>0.22 ppm – 1 meal/month	0.23 benefit becomes marginal, VRM neutral at 0.34 ppm; thus 1/wk from 0.23-0.33, 1/month > 0.33
Walleye (MN)	-3.98, clear risk	0.11 ppm – 2 meals/wk	-0.22 – net risk, follow Default advice
Black crappie (WI)	-3.48, clear risk	0.11 ppm – 2 meal/wk	-0.96 – net risk – retain default advice
Walleye (WI)	-5.69, clear risk	0.11 – 2 meals/wk	-0.23 – net risk, retain default advice
Lake trout (NY)	-0.68, marginal risk	0.11 ppm – 2 meal/wk	4.27 – clear benefit, unlimited consumption
		0.22 – 1 meal/wk	2.21, clear benefit, unlimited consumption
		>0.22 – 1 meal/month	0.23 ppm benefit becomes marginal, VRM neutral at 0.34 ppm; thus 1/wk at 0.23-0.33, 1/month > 0.33ppm
Walleye (NY)	-8.74, clear risk	0.11 – 2 meal/wk	-0.23 – net risk, follow default advice
Additional Species for Hg Cutoff Evaluation			
Walleye (Erie)	---	0.11 – 2 meal/wk	0.34 – marginal benefit, follow default advice
Lean Lake Trout (Huron)	---	0.11 – 2 meal/wk	7.7 – clear benefit, unlimited consumption
		0.22 – 1 meal/wk	4.1 – clear benefit, unlimited consumption
		>0.22 – 1 meal/month	0.36 ppm benefit becomes marginal, VRM neutral at 0.52 ppm; thus 1/wk from 0.36-0.51, 1/month > 0.51
Rainbow trout (Huron)	---	0.11 – 2 meal/wk	3.64 – clear benefit, unlimited consumption
		0.22 – 1 meal/wk	1.58 – marginal benefit, 2 meals/wk
		>0.22 – 1 meal/wk	0.30 ppm – VRM Neutral – 1 meal/wk from 0.23 to 0.29 ppm; 1/month >0.29 ppm
Brown trout (Michigan)	---	0.11 – 2 meal/wk	7.02 – clear benefit, unlimited consumption
		0.22 – 1 meal/wk	4.97 – clear benefit, unlimited consumption

		>0.22 – 1 meal/wk	0.34 ppm benefit becomes marginal, VRM neutral at 0.48 ppm; thus 1/wk from 0.34-0.47, 1/month > 0.47
Chinook Salmon (MI)	---	0.11 – 2 meal/wk	2.06 – clear benefit, unlimited consumption
		0.22 – 1 meal/wk	0.008 – marginal benefit, default advice
		>0.22 – 1 meal/month	Net risk – follow default advice
Smallmouth Bass (Ontario)		0.11 – 2 meal/week	1.1 clear benefit, unlimited consumption
		0.22 – 1 meal/wk	Negative VRM – follow default advice