NEW YORK STATE OF OPPORTUNITY. | Department of Environmental Conservation

NIAGARA RIVER AREA OF CONCERN BENEFICIAL USE IMPAIRMENT REMOVAL

Fish Tumors or Other Deformities

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Cover photo: setting a modified fyke net in the Niagara River during 2011 brown bullhead sampling efforts. U.S. Fish and Wildlife Service Photo.

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I. Executive Summary

Based on the results of a U.S. Fish and Wildlife Service (USFWS) study of the prevalence of liver tumors in Niagara River brown bullhead, the New York State Department of Environmental Conservation (NYSDEC), with the support of the Niagara River Remedial Advisory Committee, is recommending a change in the status of the Fish Tumors or Other Deformities beneficial use impairment (BUI) from “impaired” to “not impaired” for the U.S. side of the Niagara River Area of Concern (AOC). This report explains the background and history of the Niagara River fish tumors BUI, and discusses the strategy and rationale for the USFWS study along with its results.

In the Great Lakes Water Quality Agreement, the United States and Canada defined a set of 14 BUIs that may exist in the Great Lakes AOCs as a result of chemical, physical or biological disturbances to the ecosystem. Fish Tumors or Other Deformities is one of the 14 potential BUIs. Ontario and New York State independently manage their respective portions of the Niagara River AOC. On the U.S. side, the BUI was originally given the status of “impaired” based on evidence from studies conducted in the 1980s of higher than normal tumor rates in the river’s fish. On the Canadian side, the BUI was originally given a status of “requiring further assessment.” Based on the results of a Canadian study completed in 2010, also focused on the prevalence of liver tumors in brown bullhead, the Canadian RAP Coordinating Committee changed the status of the BUI to “not impaired” for the Canadian side.

Re-designation of a BUI’s status from impaired to not impaired may occur when conditions within the AOC meet the approved delisting criteria for that BUI. In the case of the Fish Tumors or Other Deformities BUI, the Niagara River Remedial Advisory Committee approved a single delisting criterion. Based on the recommendations of experts, the criterion requires that the prevalence of liver tumors in brown bullhead in the AOC be statistically equivalent to or lower than the prevalence at a control site, Long Point Inner Bay in Ontario. The selection of the control site and the methodology of the USFWS study were based on the extensive efforts of a number of parties in addressing this BUI for the Presque Isle Bay AOC in Pennsylvania.

The USFWS carried out its study specifically to evaluate whether Fish Tumors or Other Deformities continues to be an impairment on the U.S. side of the Niagara River AOC. The study began in 2011. USFWS conducted sampling over three years, collecting 50 fish each from upper, middle and lower zones of the AOC. Examination of livers at the U.S. Geological Survey’s National Fish Health Research Laboratory showed that five of the 150 fish collected for the study had liver tumors, for an overall uncorrected tumor prevalence of 3.3 percent.

Because the probability of an individual fish having a tumor depends on its age and gender, an accurate comparison of tumor prevalence between the AOC and the control site required the use of a statistical model. The model took into account the age and gender of the sampled fish, as well as effects caused by sampling in multiple years and multiple locations within the AOC. Statistical analysis using this model showed that the tumor prevalence within the Niagara River AOC is statistically equivalent to the prevalence at Long Point Inner Bay.

Based on this result, the delisting criterion for the Fish Tumors or Other Deformities BUI has been met. Accordingly, NYSDEC and the Remedial Advisory Committee fully support the re-designation of its status from “impaired” to “not impaired.”

II. Background

The Niagara River is an AOC as defined in the Great Lakes Water Quality Agreement (GLWQA) between the United States and Canada. The binational AOC encompasses the entire River on both sides of the international border. Along New York's coast, the AOC extends from the mouth of Smoke Creek near the southern end of Buffalo Harbor north to the mouth of the Niagara River at Lake Ontario (Figure 1). It also includes the lower reaches of five tributaries: Smoke Creek, South Branch Smoke Creek, Scajaquada Creek, Cayuga Creek and Gill Creek. Ontario and New York State independently developed Remedial Action Plans (RAPs) for their respective portions of the River.

In the GLWQA, the United States and Canada defined 14 potential BUIs for AOCs that could result from changes in the chemical, physical or biological integrity of the Great Lakes System. In order for the United States or Canada to delist an AOC, it must first document the restoration of each of the BUIs.

One of the 14 potential impairments that is present in the Niagara River is Fish Tumors or Other Deformities. This report outlines the available data addressing the status of this BUI, and documents the Remedial Advisory Committee's evaluation of the data and its recommendation to re-designate the status of this BUI from “Impaired” to “Not Impaired” (also referred to as removing the BUI).

A. Delisting Criterion

As approved by the Remedial Advisory Committee in December 2012, the delisting criterion for the Fish Tumors or Other Deformities BUI is:

> The prevalence of neoplastic liver tumors in brown bullhead is statistically equivalent to or lower than the prevalence at Long Point Inner Bay (as confirmed by histopathology).

B. Endpoint

The desired endpoint is to demonstrate that the prevalence of neoplastic liver tumors in brown bullhead throughout the Niagara River AOC is statistically equivalent to the prevalence at a least impacted control site. Long Point Inner Bay has been shown to be a least impacted control site for Lake Erie (Rutter 2010).

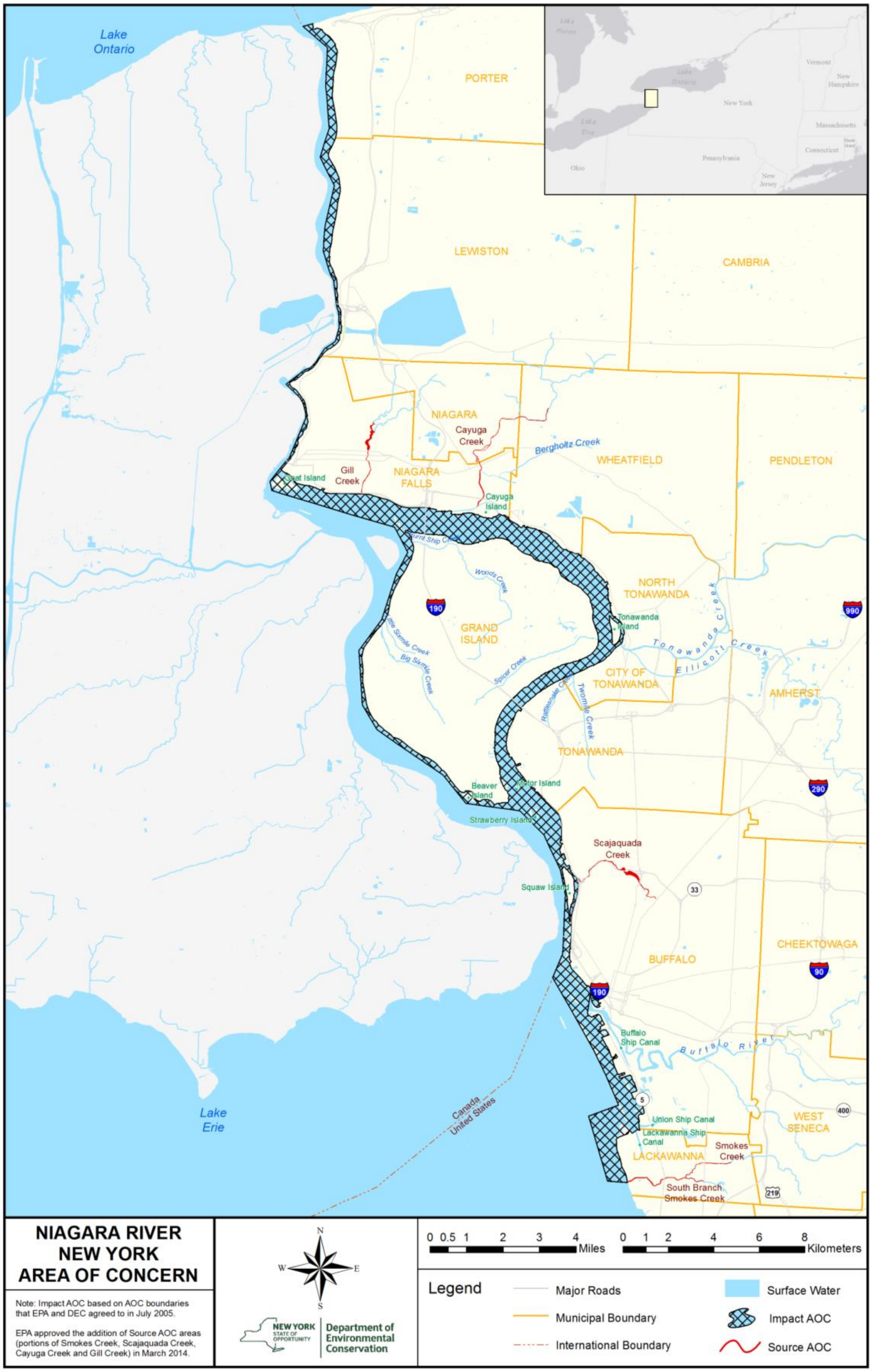

Figure 1 – U.S. Niagara River Area of Concern

III. Impairment Status Resolution

A. Strategy and Rationale

The United States Environmental Protection Agency (USEPA) Delisting Guidance document, Restoring United States Great Lakes Areas of Concern: Delisting Principles and Guidelines, adopted by the United States Policy Committee (USPC 2001) states the following:

> "Re-designation of a BUI from impaired to unimpaired can occur if it can be demonstrated that:
>
> - Approved delisting criteria for that BUI have been met;
> - The impairment is not solely of local geographic extent, but is typical of upstream conditions OR conditions outside of the AOC boundaries on a regional scale. Such re-designation would be contingent upon evidence that sources within the AOC are controlled;
> - The impairment is due to natural rather than human causes."

The strategy in this case is to demonstrate that the delisting criterion has been met. Due to the extensive efforts of a number of parties in developing a methodology to address the Fish Tumors or Other Deformities BUI for the Presque Isle Bay AOC, NYSDEC and USFWS elected to adopt the same methodology for the Niagara River AOC.

Development of Presque Isle Bay Methodology

International Joint Commission (IJC) delisting guidelines state that Fish Tumors or Other Deformities may be deemed to be not impaired "when the incidence rates of fish tumors or other deformities do not exceed rates at unimpacted control sites or when survey data confirm the absence of neoplastic or pre-neoplastic liver lesions in bullheads or suckers" (IJC 1991). However, these early guidelines did not address the definitions of "unimpacted control sites" and "pre-neoplastic liver tumors," or how to determine background tumor rates.

The status of the fish tumor BUI for the Presque Isle Bay AOC was changed to "in recovery" in 2002 based on studies showing declining rates of liver and skin tumors in brown bullhead. This meant that all necessary remedial activities were thought to be complete and the focus would turn to monitoring and determining when removal of the BUI would be appropriate. As the Pennsylvania Department of Environmental Protection

(DEP), Pennsylvania Sea Grant, the Public Advisory Committee, and other involved parties considered the issue of when to remove the BUI, more questions arose that the studies done in Presque Isle Bay or elsewhere in the Great Lakes could not answer (Rafferty et al. 2009).

To begin answering these questions and to address past inconsistencies in the evaluation of the fish tumor impairment across the Great Lakes, the Pennsylvania DEP, U.S. Environmental Protection Agency Great Lakes National Program Office (GLNPO), and Pennsylvania Sea Grant sponsored three conferences related to fish tumors in Great Lakes AOCs during 2003 through 2006. Pennsylvania Sea Grant recruited a panel of national experts in fish pathology and biological assessment to form a core group for development of criteria and sampling methods. Subcommittees of the conference participants developed a field manual on collecting and processing brown bullhead (Rafferty and Grazio 2006) and a manual on diagnosing tumors in brown bullhead (Blazer et al. 2007). The purpose of the latter manual was to describe neoplastic and non-neoplastic proliferative lesions of the liver and skin of the brown bullhead and suggest terminology that could be consistently used at AOCs throughout the Great Lakes and in other areas.

Experts also published recommendations on sampling frequency and distribution within an AOC for studies to determine tumor prevalence (Blazer et al. 2009). They noted that localized differences in tumor prevalence were found in the Presque Isle Bay and Cuyahoga River AOCs, and suggested that areas of high sediment, water or dietary contaminant loads may be important. They also noted annual variation in liver neoplasms at Presque Isle Bay and at some potential reference sites. The reasons for the variation were not identified, but could include sample size, the particular location within an AOC or reference site at which fish were collected, age of fish collected, and environmental factors (both recent and early life stage exposures). Based on these observations, they recommended that sampling should be conducted during more than one year and at multiple sites within a large AOC to obtain an accurate estimate of tumor prevalence. These recommendations, together with the field and diagnostic manuals, provide the rationale for the design of the USFWS study of tumor prevalence in the Niagara River AOC.

Identification of a Least Impacted Control Site

In order to identify a least-impacted control site, the Pennsylvania DEP sampled brown bullhead from a number of candidate sites across Lake Erie. In addition to having a resident bullhead population, candidate sites had to be outside any AOC and could not have point-source discharges of pollutants or known sediment contamination. Based on these criteria, the DEP collected samples in 2004, 2005, and 2007 from Dunkirk Harbor (New York), Long Point Inner Bay (Ontario), Old Woman's Creek (Ohio), and Sandusky Bay (Ohio) (PADEP 2012).

The evaluation of the candidate sites considered prevalence of both liver and skin tumors. Dunkirk Harbor had the lowest estimated liver tumor prevalence (0.0%), while Long Point Inner Bay (LPIB) had the lowest estimated skin tumor prevalence (6.4%). However, the estimate for the Dunkirk Harbor liver tumor prevalence had a high level of uncertainty, with the 95% confidence interval ranging from 0.0% to 56.0%. Dunkirk Harbor also had the highest estimated prevalence of skin tumors (22.5%). LPIB had the second lowest estimated liver tumor prevalence (1.2%) and the 95% confidence interval was much narrower (0.0% to 14.9%), indicating less uncertainty in the estimate. Therefore, LPIB was selected as the least-impacted Lake Erie control site (Rutter 2010).

Tumors in Bullhead as an Environmental Indicator

Brown bullhead catfish are commonly accepted as good indicators of local environmental conditions because they are a bottom-dwelling fish and are considered to have a limited home range. Of tumors that occur in brown bullhead, the types that experts have most commonly associated with exposure to contaminants are liver tumors and, to a lesser extent, skin tumors (Rafferty et al. 2009).

Numerous studies have provided evidence for a link between exposure to chemicals, most often polycyclic aromatic hydrocarbons (PAHs), in the sediment of lakes and rivers and an increased prevalence of liver tumors in brown bullhead (Rafferty et al. 2009). However, these studies cannot prove a definite cause and effect relationship. In fact, bullheads with tumors have been found in both contaminated and uncontaminated waterbodies throughout the northeastern United States (PADEP 2012). However, Rafferty et al. (2009) concluded that the weight of evidence does suggest an association between exposure to PAHs and liver tumors in brown bullhead. They added that PAHs may not be the only class of chemicals responsible for such tumors, though more research is needed regarding other chemicals.

Rafferty et al. (2009) also concluded that the weight of evidence for an association between exposure to PAHs and skin tumors is “much more problematic.” The Pennsylvania DEP later conducted its own investigation into the cause of skin tumors while in the process of determining whether to delist the Presque Isle Bay AOC. Their goal was to evaluate whether skin tumors are an appropriate indicator of environmental contamination. Their efforts included an investigation of pathogens as potential natural causes of the tumors, an evaluation of the possible role of genetics, an experimental investigation for any relationship between exposure to Bay sediment and the development of tumors, and an extensive literature review. These efforts were unable to isolate any factors responsible for the development of skin tumors. This result, coupled with the fact that their studies at multiple locations had not shown a correlation between high liver tumor prevalence and high skin tumor prevalence, led to the conclusion that skin tumors are not a reliable indicator of environmental contamination (PADEP 2012).

In summary, while some debate continues regarding the association between liver tumors and environmental contamination, liver tumors have become widely accepted as an indicator for the purpose of evaluating the Fish Tumors BUI. Skin tumors, however, are not generally accepted as an appropriate indicator. As previously noted, the Niagara River Remedial Advisory Committee has approved a delisting criterion that considers only liver tumors.

B. Supporting Data and Assessment

Finding of Impairment

Fish Tumors or Other Deformities was found to be an impairment on the U.S. side of the Niagara River AOC based on limited evidence. The Niagara River Remedial Action Plan (RAP) states that this finding is based on the results of two studies of tumor incidence in fish from the upper river (NYSDEC 1994). A freshwater drum skin tumor study indicated a skin tumor rate of 11.7% in fish collected from a location just downstream of Black Rock Canal, higher than the Lake Erie-wide incidence level of 1.5% (Black 1983).

The second study compared the incidence of several types of abnormalities, including neoplastic and pre-neoplastic liver tumors, in brown bullhead from the 102nd Street embayment and a reference site on Black Creek, Ontario, a tributary to the Niagara River (Hickey et al. 1990). Of 101 fish collected from the 102nd Street embayment, three showed pre-neoplastic liver tumors and two had neoplastic liver tumors (Table 1). (Contaminated sediment was removed from the embayment in 1996.) The RAP states that these five tumors indicate “elevated conditions above the suggested zero rate of this indicator of impairment.” The RAP also notes that due to some limitations of the Hickey et al. (1990) study, further research would be necessary to comprehensively define the extent of this impairment in the Niagara River.

The “suggested zero rate” for liver tumors mentioned in the RAP is no longer consistent with scientific consensus. The background neoplastic liver tumor prevalence in brown bullhead is now considered to range from two to five percent in fish age 3 and older

(Baumann 2010). Therefore, by current standards the Hickey et al. (1990) study does not provide strong evidence of a fish tumor beneficial use impairment.

Table 1 – Historical Liver Neoplasm Prevalence in Niagara River Brown Bullhead

Year of Sampling	Sample Size	Location	Percentage with Liver Tumors	Source
1987	101	102nd Street embayment	2.0	Hickey et al. 1990
1998	40	102nd Street embayment	7.5	Blazer et al. 2009
2004	43	Queenston	0.0	Baumann 2010
2004 & 2008	101	Black Creek (Ontario)	3.0	Baumann 2010

Canadian Evaluation of Impairment

In the Canadian RAP, the Fish Tumors or Other Deformities BUI was originally given a status of "Requiring Further Assessment." In 2009, Environment Canada commissioned a study by Dr. Paul Baumann to evaluate the status of this BUI for all of the Canadian AOCs. The evaluation was based on the prevalence of liver tumors in brown bullhead. For the Niagara River AOC, a total sample of 101 bullhead had been collected during 2004 and 2008 near Black Creek (Figure 2). Three of these fish had liver tumors (Table 1). This prevalence was not significantly different from the background prevalence that Dr. Baumann had calculated based on data from a number of reference sites (Baumann 2010). Therefore, the Canadian RAP Coordinating Committee changed the status of the Fish Tumors BUI to "Not Impaired" for the Canadian side.

U.S. Fish and Wildlife Service Study

The USFWS began a study of tumor prevalence in U.S. Niagara River AOC brown bullhead in June 2011. For purposes of sampling, the river was divided into upper, middle and lower zones with a planned sample size of 50 fish from each zone (Table 2).

The upper zone was separated into two sites, the developed shoreline (Buffalo Outer Harbor and Black Rock Canal) and undeveloped shoreline (Strawberry Island and East River Marsh). The middle zone was also divided into two sites, an area near the mouth of Gun Creek at the northeast end of Grand Island and an area around Cayuga Island that is in the vicinity of the Love Canal and 102nd Street Landfill hazardous waste sites (Figure 2).

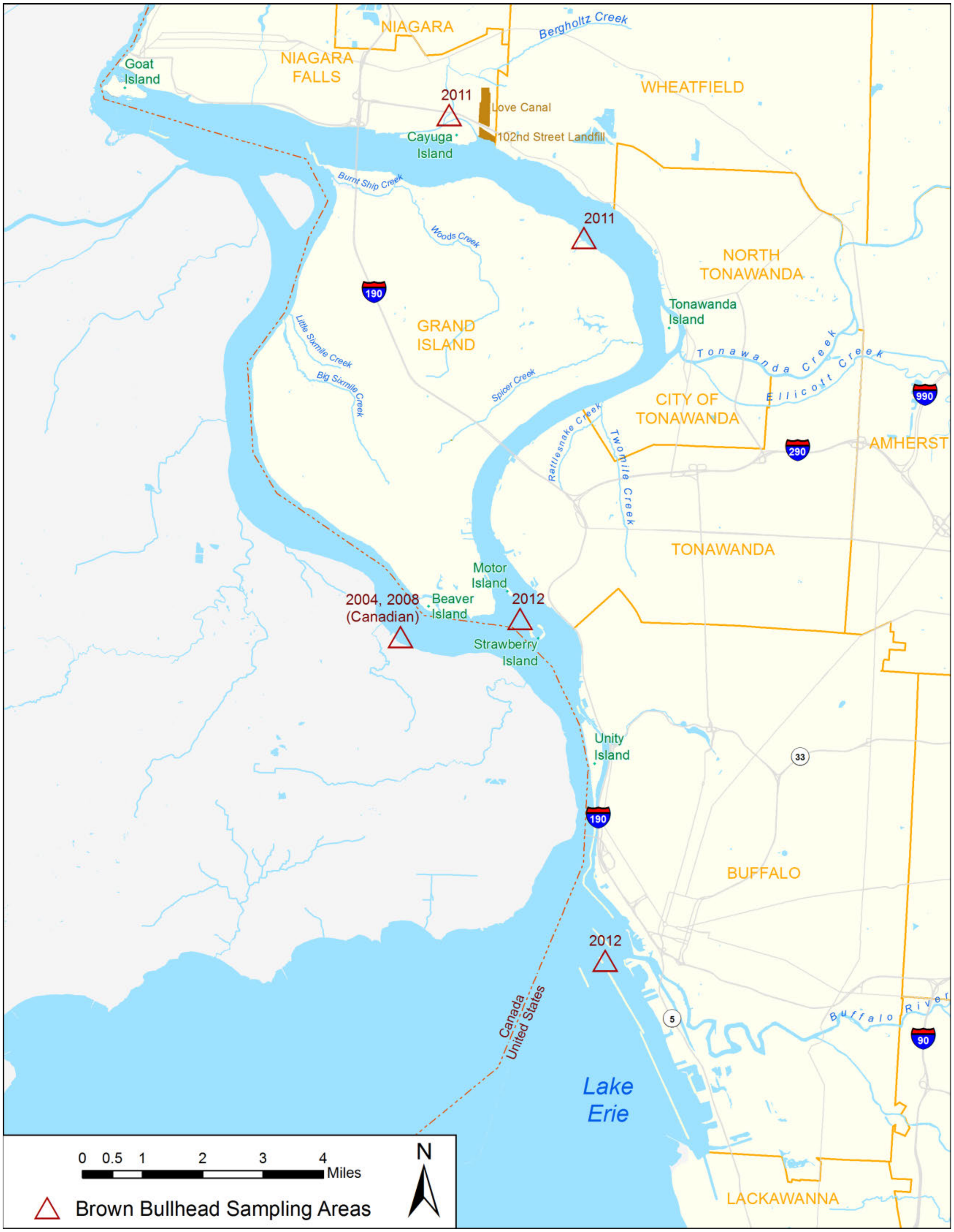

Figure 2 – Upper River Sampling Areas

Table 2 – Sampling Sites

Location	Sampling Date	Sample Size
Middle Zone		
Near mouth of Gun Creek, Grand Island	6/14/2011	26
Cayuga Island area	6/21/2011	24
Upper Zone		
Developed areas	6/12/2012	25
Undeveloped areas	6/13/2012	25
Lower Zone	7/23/2013	50

The lower zone included the portion of the river between Lewiston and Fort Niagara. Shoreline along this approximately 6.7 mile reach is not heavily developed. Although samples were collected in four distinct areas of the reach (Figure 3), the fish were not kept separate for analysis because the habitat and the degree of shoreline development were not remarkably different among the four areas.

U.S. Geological Survey (USGS) fishery biologist Dr. Vicki Blazer was responsible for the examination of the fish for the presence of tumors. Necropsy teams visited the AOC to process the brown bullhead samples. The histopathology work took place at the USGS's National Fish Health Research Laboratory in West Virginia.

Five of the 150 fish collected for the study were found to have neoplastic liver tumors (Blazer et al. 2014). Three of these fish were collected in the middle zone and two in the upper zone. The incidence of liver tumors ranged from 0% for the 2013 lower zone sample to 7.7% for the 2011 Gun Creek sample (Table 3). The overall uncorrected incidence was 3.3%. The mean age of the samples by location ranged from 4.2 to 6.8 years.

Table 3 – Liver Tumors by Site

Location	Sample Size		Number with Liver Tumors		Percentage with Liver Tumors		
	Male	Female	Male	Female	Male	Female	Combined
Middle Zone							
Gun Creek area	18	8	2	0	11.1%	0	7.7%
Cayuga Island area	14	10	0	1	0	10%	4.2%
Upper Zone							
Developed areas	13	12	0	1	0	8.3%	4.0%
Undeveloped areas	16	9	0	1	0	11.1%	4.0%
Lower Zone	36	14	0	0	0	0	0
Total	97	53	2	3	2.1%	5.7%	3.3%

Figure 3 – Lower River Sampling Areas

Statistical Analysis

The statistical methodology used to compare the Niagara River AOC tumor prevalence to that of the control site (LPIB) follows the methodology used for the Presque Isle Bay analysis (Rutter 2010). The full statistical analysis report can be found in Appendix D.

The methodology is complex, but a simple comparison of overall tumor prevalence percentage between the AOC and the control site is not appropriate for two reasons:

- It would involve an assumption that every fish collected for analysis has an equal probability of having a tumor, which is not the case. The probability will vary with one or more characteristics such as the age, length, weight and gender of individual fish.

- It would also involve an assumption of having a "simple random sample" of fish from each site. Almost all statistical techniques assume a simple random sample. However, because sampling occurred in multiple locations within the AOC and in multiple years, this assumption is violated. As a result, true confidence intervals for estimates of tumor prevalence become larger than one would calculate under the simple random sample assumption. (Note that for the control site, fish were sampled in the same location, but over multiple years.)

To address the first concern, creation of a model that accounts for the impact of the demographics (age, length, gender and weight of fish) on the probability of a fish having a tumor is necessary. In this case, a logistic regression model is appropriate because the response variable in the analysis has only two possible outcomes, the presence or absence of a tumor. Logistic regression can incorporate the effects of any number of demographic characteristics (called predictor variables) on the probability of a fish having a tumor.

Addressing the second concern requires the use of a hierarchical modelling approach to represent the sampling design. The hierarchical approach accounts for the (slight) correlation among fish sampled in the same location and year. The overall effect of a predictor variable (e.g. age) on the probability of a fish having a tumor for the Niagara River is modelled as a combination of the effect of that variable specific to each sampling year (2011 – 2013). For 2011 and 2012, the year-specific effects are modelled as a combination of the effects specific to each sampling location within those years. Therefore, the hierarchy has an overall Niagara River effect at the top, which depends on year-specific effects at the next level, some of which depend on location specific effects at the bottom level (Figure 4).

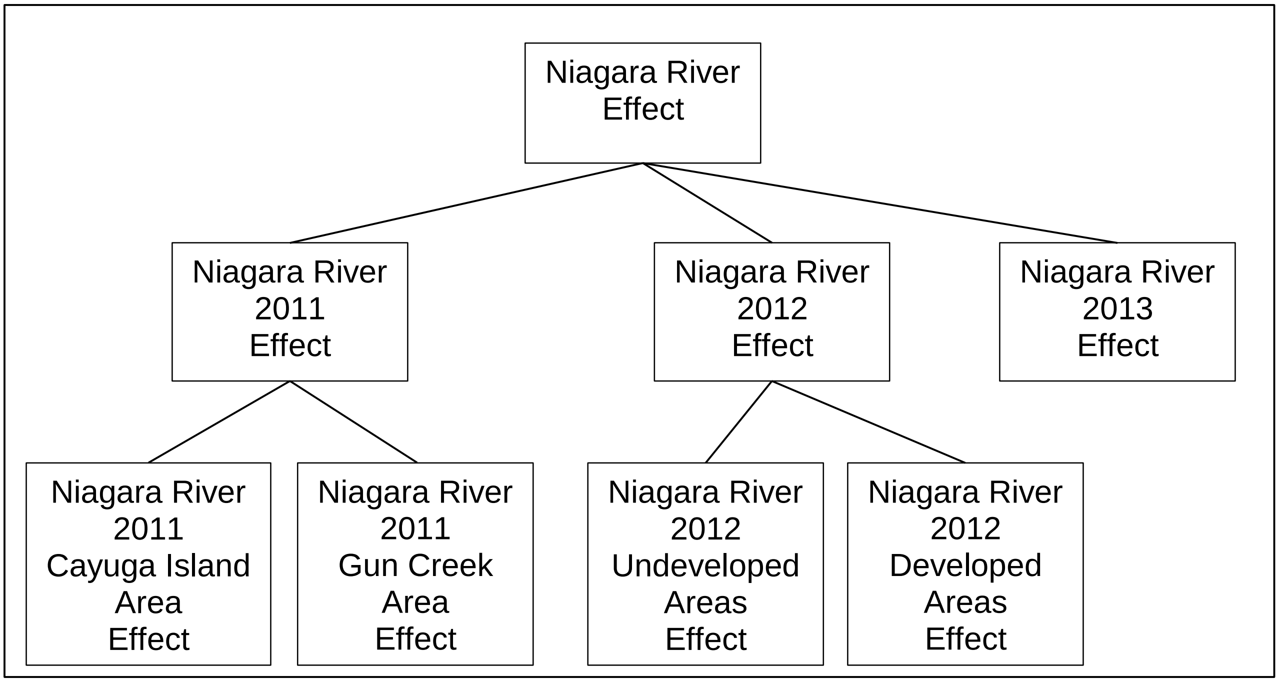

Figure 4 – Graphical Representation of the Hierarchical Model

Statistical modelling involves using observed data to estimate the model's unknown parameters, which are measures of the effects of the predictor variables (or demographic characteristics in this case). This is known as "fitting" the model. In other words, the goal is to find the set of parameter values that result in the closest match between the model's predictions and the observed data.

For technical reasons, the model parameters in this analysis were estimated using a Bayesian framework. For each of the Niagara River areas sampled, no tumors were found in fish of at least one gender (Table 3). The mathematics of the logistic regression model are not workable for cases where no tumors are observed in a sample. While at least one non-Bayesian method can address this problem, no available statistical software can apply that method together with a traditional "mixed model" to account for the sampling design. The Bayesian approach easily overcomes the problem with logistic regression.

When comparing tumor prevalence between two sites, ensuring that the amount of data is sufficient to detect meaningful differences is important; this is the "power" of the statistical procedure. Power is a measure of the ability of a method to find a statistical difference when a difference actually exists (i.e. to avoid a "false negative" result). Greater statistical power is associated with larger sample sizes. Ensuring sufficient power is important in this analysis so that a finding of no statistical difference in tumor prevalence between the AOC and control site will be due to an actual small difference in tumor prevalence and not due simply to small sample sizes. No available statistical software can perform a power analysis for a traditional mixed-model logistic regression. Use of the Bayesian framework essentially transforms the power measurement into the width of a confidence interval, with a smaller interval width indicating greater statistical power. So specifying a maximum acceptable width of a confidence interval is equivalent to requiring sufficient power.

The first phase of carrying out the analysis was to determine which combination of predictor variables best described the observed tumor prevalence. Hierarchical logistic regression models using all possible combinations of the four predictor variables (age, length, weight and gender) were tested using the Bayesian framework. The best model of those examined included age and gender as predictor variables.

The tumor prevalence for the control site and the Niagara River were then estimated. All the sampling sites for the Niagara River were combined over all the years to arrive at a single estimate of the AOC tumor prevalence. Similarly, a single tumor prevalence estimate was generated for the control site, combining over years. Because the probability of having a tumor varies with the age of the fish, it was necessary to choose an age at which to calculate the estimates. The average age of bullhead in the data set was 6.4 years, so all tumor prevalence estimates were calculated for age 6 bullhead. Gender was the other important predictor variable, so estimates for both male and female bullhead were calculated.

While a traditional statistical method would generate a point estimate for the desired result, Bayesian analysis generates a probability distribution over the range of possible result values. For this analysis, each probability distribution was summarized by finding its median and the 95% highest probability density interval (HPDI), which is the smallest interval within the range of possible result values that is associated with a total probability of 95%. Figure 5 provides an illustration for an arbitrary probability distribution. The horizontal axis represents possible result values and the vertical axis represents probability. The median is the result value for which the total probability associated with all lower values and the total probability associated with all higher values are both equal to 50%. The 95% HPDI, which is shaded, is denoted as (a, b).

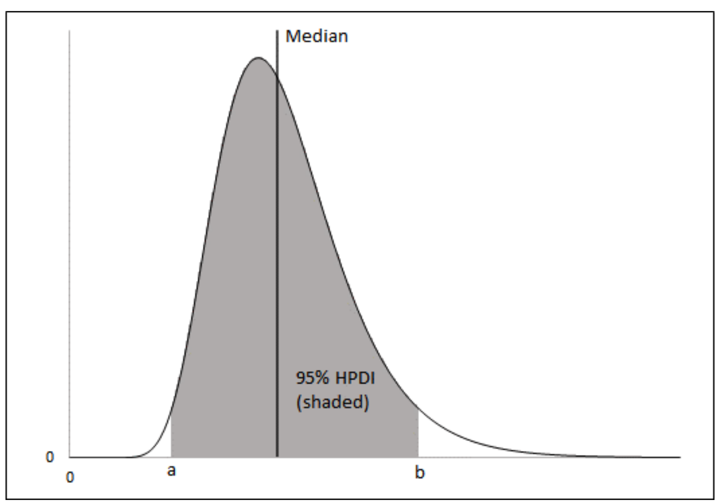

Figure 5 – Example Probability Distribution

In this analysis, the median of the probability distribution is used as a point estimate of tumor prevalence while the 95% HPDI is a Bayesian analogue of a 95% confidence interval. The resulting point estimates of Niagara River AOC tumor prevalence (Table 4) for both female fish (2.0%) and male fish (1.9%) compare favorably with the generally accepted background prevalence mentioned earlier of two to five percent for fish age 3 and older.

Table 4 – Tumor Prevalence Estimates for Age 6 Fish

Location and Gender	95% HPDI	Median
Niagara River: Female	(0.0%, 25.5%)	2.0%
Niagara River: Male	(0.0%, 35.2%)	1.9%
Long Point: Female	(0.0%, 4.4%)	0.4%
Long Point: Male	(0.0%, 5.1%)	0.3%

The final step of the analysis was to conduct a statistical test for equivalency between the tumor prevalence at the AOC and at LPIB using a Two One-Sided Tests (TOSTs) procedure, which is accepted by the U.S. Food and Drug Administration for evaluating the comparability between two groups. Hypothesis testing commonly involves a null hypothesis that no difference exists in some quantity measured for two groups and an alternative hypothesis that a difference does exist. However, for the TOST procedure, the null hypothesis is that the measurements for two groups are not equivalent or, stated another way, that the difference in the measurements exceeds some pre-defined tolerance level. For this analysis, the null hypothesis can be stated as

$$H_0: PREV_{LPIB} - PREV_{AOC} \leq -\theta \text{ or } PREV_{LPIB} - PREV_{AOC} \geq \theta$$

where $PREV_{LPIB}$ and $PREV_{AOC}$ are the tumor prevalence at LPIB and the AOC respectively and θ is the tolerance level. The alternative hypothesis is

$$H_A: -\theta < PREV_{LPIB} - PREV_{AOC} < \theta$$

The TOST procedure is performed as two separate one-sided tests having null and alternative hypotheses:

$H_0: PREV_{LPIB} - PREV_{AOC} \leq -\theta$	$H_0: PREV_{LPIB} - PREV_{AOC} \geq \theta$
$H_A: PREV_{LPIB} - PREV_{AOC} > -\theta$	$H_A: PREV_{LPIB} - PREV_{AOC} < \theta$

The p-value is the larger of those obtained for the two one sided tests. If the p-value is less than an acceptable significance value (chosen to be 0.05) then sufficient evidence exists to suggest the tumor prevalences are equivalent at the θ tolerance level.

An equivalent approach to the TOST procedure is to construct a 90% confidence interval for the difference in tumor prevalence between the AOC and control site. (Under the Bayesian framework, the analogous 90% HPDI for the difference in tumor prevalences was determined.) If this interval is entirely between the tolerance limits $-\theta$ and θ, then the prevalences can be considered to be equivalent. If the interval is too large or does not contain zero, then the prevalences are statistically significantly different. The tolerance is determined essentially by applying the TOST procedure to compare the AOC to itself.

The Niagara River AOC tolerance intervals were determined to be ±24% for female fish and ±34% for male fish. Comparing Niagara River to LPIB, the calculated 90% TOST HPDI interval for tumor prevalence in females is (-5.4%, 18.8%) and in males is (-5.5%, 25.5%). Both of these results are within the corresponding tolerance intervals, indicating statistical equivalency between the two sites.

C. Criteria, Principles and Guidance Application

The intent of the RAP process is to assess the status of each BUI and, if existence of an impairment is indicated, to remedy the source of the impairment and subsequently demonstrate that the beneficial use has been restored. In this case, initial evidence for an impairment was limited. Also, contaminant concentrations in the Niagara River have fallen significantly since the time of the two studies that indicated an impairment. However, the relationship between contaminants found in the Niagara River and brown bullhead tumors is uncertain. Therefore, conducting a new study to determine whether tumor prevalence is elevated in comparison to a control site was appropriate.

The delisting criterion for the Fish Tumors or Other Deformities impairment is met because the USFWS fish tumor study, conducted according to the guidance prepared by experts in the fields of fish pathology and biological assessment, has shown statistical equivalency between the tumor prevalence within the Niagara River AOC and the LPIB control site.

D. Removal Statement

Based on the demonstrated equivalency between the prevalence of liver tumors in the Niagara River and the prevalence in a least impacted control site, the endpoint for the Fish Tumors or Other Deformities BUI has been met. Accordingly, NYSDEC and the Remedial Advisory Committee fully support the re-designation of its status from "impaired" to "not impaired."

IV. BUI Removal Steps and Follow-up

A. BUI Removal Steps

	Completed	*Date*	*Action*
1.	✓	12/2008	Delisting criteria completed and finalized with USEPA
2.	✓	2/2010	USFWS proposed a multi-year study to measure the prevalence of tumors in brown bullhead in the U.S. portion of the Niagara River AOC
3.	✓	1/2012	Original impaired condition reviewed to identify causes and sources
4.	✓	12/2012	Remedial Advisory Committee endorsed a change to the BUI delisting criterion for consistency with the Pennsylvania Department of Environmental Protection's approach for the Presque Isle Bay AOC
5.	✓	5/2014	USGS issued a report on the Niagara River brown bullhead analysis
6.	✓	11/2014	Dr. Rutter completed a preliminary statistical analysis showing that tumor prevalence in the AOC is equivalent to that in the control site
7.	✓	7/2015	Discussion of removal by the Remedial Advisory Committee
8.	✓	7/2015	NYSDEC collaborated with USEPA to revise the draft BUI removal proposal document
9.	✓	8/2015 - 9/2015	NYSDEC conducted outreach and held a public meeting to solicit comments on the draft removal proposal (30-day public comment period)
10.	✓	10/2015	NYSDEC assembles comments, prepares responsiveness summary and completes final modifications to the BUI removal document
11.		11/2015	Coordinate the formal transmittal of the BUI removal with USEPA GLNPO. Communicate result with IJC
12.		11/2015	Communicate results to local RAP Coordination for appropriate recognition and follow-up

B. Post-Removal Responsibilities

Following removal of the Fish Tumors or Other Deformities BUI, NYSDEC and USEPA will continue ongoing environmental programs that will ensure that the BUI's status remains "not impaired." These programs include hazardous waste site remediation, contaminated sediment remediation, monitoring of permitted wastewater discharges, water quality monitoring, and coordination of the Niagara River Remedial Advisory Committee.

Regular monitoring of water quality will continue under the Niagara River Toxics Management Plan, operated by a partnership of USEPA, NYSDEC, Environment Canada and Ontario Ministry of the Environment and Climate Change. This monitoring includes biweekly sampling at both Fort Erie and Niagara-on-the-Lake to check concentrations of a range of potential contaminants.

New York State Department of Environmental Conservation

- Under the State Superfund Program, NYSDEC will continue working to complete the remediation of hazardous waste sites. Remediation is complete at 37 of 44 sites originally found to have the potential to impact the Niagara River. Remedial activities are under way at the seven remaining sites.

- Through the State Pollutant Discharge Elimination System, NYSDEC will continue to regulate point source discharges of industrial and municipal wastewater and storm water in accordance with the federal Clean Water Act.

- NYSDEC will continue to monitor water quality in the AOC through its statewide Rotating Integrated Basin Studies (RIBS) ambient water quality monitoring program. NYSDEC collects biological samples every five years at several Niagara River tributary locations, and conducts routine monitoring on the Niagara River near Fort Niagara 5 – 6 times per year in spring, summer, and fall. The samples are analyzed for a wide range of potential contaminants and toxicity bioassays using *C. dubia* are conducted every five years.

- NYSDEC will continue to provide a coordinator for the Niagara River AOC whose responsibilities include coordination of the Remedial Advisory Committee.

United States Environmental Protection Agency

- Under the Great Lakes Legacy Act Program, USEPA will continue to lead efforts to characterize sediment within the AOC, and to conduct remediation where necessary.

- USEPA will also continue to provide funding for technical assistance on AOC projects to the extent that resources are available.

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Appendix A – List of Remedial Advisory Committee Members

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Appendix B – Public Meeting Notes

Meeting Summary

Niagara River Area of Concern
Fish Tumors or Other Deformities Beneficial Use Impairment Removal Proposal
Public Meeting
Tuesday, August 25, 2015
6:00 – 8:00 p.m.
Grand Island Memorial Library, Grand Island, New York

Participants:

NYSDEC – Shannon Dougherty, Don Einhouse, Mark Filipski, Jim Lehnen, Paul McKeown, Don Zelazny

Public – Ron Rezabek (Niagara River Station Fishing Club)

Introduction:

Mr. Zelazny, NYSDEC Great Lakes Programs Coordinator, introduced himself as well as Mr. Filipski, NYSDEC Niagara River Area of Concern Coordinator, and Mr. Einhouse, Senior Great Lakes Fisheries Biologist for Lake Erie. He mentioned that this is NYSDEC's first public meeting on a beneficial use impairment removal proposal for the Niagara River Area of Concern.

Presentation:

Mr. Filipski gave a presentation that included a brief overview of the Great Lakes Areas of Concern program and the Niagara River Area of Concern in particular, followed by specific information regarding the proposal to remove the fish tumors beneficial use impairment (BUI). A summary of the presentation follows.

Areas of Concern and the Niagara River

In 1987, the United States and Canada agreed to give the most polluted areas of the Great Lakes priority attention for restoration. They designated a total of 43 such areas as "Areas of Concern" because they had serious pollution problems to a greater degree than in the rest of the Great Lakes. The problems in these areas seriously restricted beneficial uses of the water. Twenty-six Areas of Concern were located entirely within the United States, 12 within Canada, and five, including the Niagara River, were binational waterways.

In the Great Lakes Water Quality Agreement, the United States and Canada defined 14 potential beneficial use impairments for Areas of Concern that could result from changes in the chemical, physical or biological integrity of Great Lakes waters. The U.S. side of the Niagara River AOC has 7 of the 14 possible BUIs. With the exception of habitat loss, all of the Niagara River BUIs are caused at least in part by pollutants. The habitat loss BUI is the result of physical changes to the river that accompanied urbanization, and water level fluctuations associated with power production.

The Area of Concern includes the entire River. On the U.S. side, it extends from Smoke Creek near the southern part of the Buffalo Harbor north to the mouth of the River at Lake Ontario. It does not extend inland to include the watershed. Ontario and New York developed separate Remedial Action Plans for the Canadian and U.S. sides of the River. New York published its plan in 1994. The goal of the remedial action plan is to restore all of the beneficial use impairments.

Sources of contaminants to the Niagara River include contaminated sediments, hazardous waste sites, groundwater, wastewater discharges, sewer overflows, other nonpoint sources and inflow from Lake Erie. Progress on addressing these sources includes:

- A total of 44 U.S. hazardous waste sites were found to have the potential to release contaminants to the River. Today, measures to address the contamination are complete for 37 of the 44 sites. Actions are under way at all 7 remaining sites.

- Projects addressing sediment contamination have been completed at 14 locations, with a few of those locations having multiple projects. These projects were generally components of a hazardous waste site cleanup and in total they removed over 300,000 cubic yards.

- Upgrades to WWTPs have reduced the amount of contaminants entering the river, especially from the City of Niagara Falls.

- Within the Niagara River watershed, the cities of Buffalo, Lockport and Niagara Falls are implementing long-term control plans to reduce the frequency, duration, and intensity of combined sewer overflows. Implementation of these plans is quite expensive and is therefore spread over a number of years, but the plans are enforceable so they do guarantee reductions in this source of contaminants.

Fish Tumors or Other Deformities Impairment

A group of experts has been studying tumors in brown bullhead catfish for a number of years. They have concluded that the weight of evidence suggests an association between exposure to polycyclic aromatic hydrocarbons (PAHs) and liver tumors in brown bullhead. The evidence for an association between exposure to PAHs and skin tumors is much weaker. Liver tumors have become widely accepted as an indicator for the purpose of evaluating the Fish Tumors BUI. Skin tumors, however, are not generally accepted as an appropriate indicator. Therefore, although skin tumors played a role in the original finding of a fish tumor impairment for the Niagara River, only liver tumors are considered in the current evaluation of the impairment.

The original finding of an impairment on the U.S. side of the Niagara River was based on limited evidence. The Niagara River Remedial Action Plan (RAP) states that this finding is based on the results of two studies of tumor incidence in fish from the upper river.

- A freshwater drum skin tumor study indicated a skin tumor rate of 11.7% in fish collected from a location just downstream of Black Rock Canal, higher than the Lake Erie-wide incidence level of 1.5%.

- The second study focused on brown bullhead from the 102nd Street embayment. Of 101 fish collected, three showed pre-neoplastic liver tumors and two had neoplastic liver tumors. The RAP states that these five tumors indicate “elevated conditions above the suggested zero rate of this indicator of impairment.”

The “suggested zero rate” for liver tumors mentioned in the RAP is no longer consistent with scientific consensus. The background liver tumor prevalence in brown bullhead is now considered to range from two to five percent in fish age 3 and older.

In the Canadian RAP, the Fish Tumors BUI was originally given a status of “Requiring Further Assessment.” In 2009, Environment Canada commissioned a study to evaluate the status of this BUI for all of the Canadian AOCs. The evaluation was based on the prevalence of liver tumors in brown bullhead. For the Niagara River AOC, a total sample of 101 bullhead had been collected during 2004 and 2008 near Black Creek. Three of these fish had liver tumors. This prevalence was not significantly different from the background prevalence calculated based on data from a number of reference sites.

Therefore, the Canadian RAP Coordinating Committee changed the status of the Fish Tumors BUI to “Not Impaired” for the Canadian side.

The International Joint Commission published delisting guidelines in 1991 that stated that Fish Tumors or Other Deformities may be deemed to be not impaired “when the incidence rates of fish tumors or other deformities do not exceed rates at unimpacted control sites or when survey data confirm the absence of neoplastic or pre-neoplastic liver lesions in bullheads or suckers.” However, these early guidelines did not address the definitions of “unimpacted control sites” and “pre-neoplastic liver tumors,” or how to determine background tumor rates.

The status of the fish tumor BUI for the Presque Isle Bay AOC in Pennsylvania was changed to “in recovery” in 2002 based on studies showing declining rates of liver and skin tumors in brown bullhead. As involved parties considered the issue of when to remove the BUI, more questions arose that the studies done in Presque Isle Bay or elsewhere in the Great Lakes could not answer. To begin answering these questions and to address past inconsistencies in the evaluation of the fish tumor impairment across the Great Lakes, the Pennsylvania DEP, U.S. Environmental Protection Agency Great Lakes National Program Office (GLNPO), and Pennsylvania Sea Grant sponsored three conferences related to fish tumors in Great Lakes AOCs during 2003 through 2006. Pennsylvania Sea Grant recruited a panel of national experts in fish pathology and biological assessment to form a core group for development of criteria and sampling methods. Subcommittees of the conference participants developed a field manual on collecting and processing brown bullhead and a manual on diagnosing tumors in brown bullhead.

Experts also published recommendations on sampling frequency and distribution within an AOC for studies to determine tumor prevalence. They recommended that sampling should be conducted during more than one year and at multiple sites within a large AOC to obtain an accurate estimate of tumor prevalence. These recommendations, together with the field and diagnostic manuals, provided the rationale for the design of the USFWS study of tumor prevalence in the Niagara River AOC.

In order to identify a least-impacted control site, the Pennsylvania DEP sampled brown bullhead from a number of candidate sites across Lake Erie. The evaluation of the candidate sites considered prevalence of both liver and skin tumors. Long Point Inner Bay was selected as the least-impacted Lake Erie control site.

The Department works with a Niagara River Remedial Advisory Committee in implementing the Remedial Action Plan. The Committee approved a delisting criterion for the Fish Tumors BUI that reflects the Presque Isle Bay approach:

> "The prevalence of neoplastic liver tumors in brown bullhead is statistically equivalent to or lower than the prevalence at Long Point Inner Bay (as confirmed by histopathology)."

USFWS Niagara River Study

The USFWS began a study of tumor prevalence in U.S. Niagara River AOC brown bullhead in June 2011. For purposes of sampling, the river was divided into upper, middle and lower zones with a planned sample size of 50 fish from each zone.

The upper zone was separated into two sites, the developed shoreline (Buffalo Outer Harbor and Black Rock Canal) and undeveloped shoreline (Strawberry Island and East River Marsh). The middle zone was also divided into two sites, an area near the mouth of Gun Creek at the northeast end of Grand Island and an area around Cayuga Island that is in the vicinity of the Love Canal and 102nd Street Landfill hazardous waste sites.

The lower zone included the portion of the river between Lewiston and Fort Niagara. Shoreline along this approximately 6.7 mile reach is not heavily developed. Although samples were collected in four distinct areas of the reach, the fish were not kept separate for analysis because the habitat and the degree of shoreline development were not remarkably different among the four areas.

U.S. Geological Survey (USGS) fishery biologist Dr. Vicki Blazer was responsible for the examination of the fish for the presence of tumors. Teams visited the AOC to process the brown bullhead samples. Examination of the livers took place at the USGS's National Fish Health Research Laboratory in West Virginia.

Five of the 150 fish collected for the study were found to have liver tumors. Three of these fish were collected in the middle zone and two in the upper zone. The incidence of liver tumors ranged from 0% for the lower zone sample to 7.7% for the Gun Creek sample. The overall uncorrected incidence was 3.3%.

The statistical analysis that shows that the tumor prevalence in the Niagara River AOC and Long Point Inner Bay are equivalent is complex. The statistician who carried out the analysis was not available to attend the meeting, but Mr. Filipski gave a very brief overview of the analysis and results.

A simple comparison of overall tumor prevalence percentage between the AOC and the control site would not be an appropriate approach to the statistical analysis because it would require making assumptions about the data that are not true. The statistician used certain modelling techniques to overcome this problem.

A model in which the probability of a fish having a tumor was dependent upon the age and gender of the fish was the best match for the data. Based on this model, the analysis generated estimates for the tumor prevalence for the control site and the Niagara River. Because the probability of having a tumor varies with the age of the fish, it was necessary to choose an age at which to calculate the estimates. The average age of bullhead in the data set was 6.4 years, so all tumor prevalence estimates were calculated for age 6 bullhead. Gender was the other important factor, so estimates for both male and female bullhead were calculated. The resulting estimates of Niagara River AOC tumor prevalence for both female fish (2.0%) and male fish (1.9%) compare favorably with the generally accepted background prevalence of two to five percent for fish age 3 and older.

The final step of the analysis was to apply a statistical test for equivalency that takes into account the uncertainty in the tumor prevalence estimates. The test showed that the prevalence in the AOC is statistically equivalent to the prevalence in the control site. This outcome shows that the delisting criterion is satisfied. Therefore, both NYSDEC and the Remedial Advisory Committee fully support changing the status of the BUI to "not impaired."

Environment Canada regularly samples water at Fort Erie and Niagara-on-the-Lake to check for a variety of chemicals. The results, which show that levels of contaminants in the Niagara River have fallen since the 1980s, provide supporting evidence for the BUI removal proposal. The presentation included charts showing the changes in concentrations of PCBs and Mirex in Niagara River water over a 20 year period. Concentrations of both fell by about 80 percent over the period.

Following removal of the Fish Tumors or Other Deformities BUI, NYSDEC and USEPA will continue ongoing environmental programs that will ensure that the BUI's status remains "not impaired." These will include completing the remediation of hazardous waste sites, characterizing sediment within the AOC and conducting remediation where necessary, continuing to regulate point source discharges of industrial and municipal wastewater and storm water, regular monitoring of water quality, and coordination of the Remedial Advisory Committee.

The presentation concluded with a review of the remaining steps in the BUI removal process.

Discussion:

Mr. Rezabek asked whether all bullhead sampled in each zone of the AOC were collected on the same day. Mr. Filipski responded that they were collected over a short period of time, but not in a single day. Some fish were held in the water after being collected. The dates in the table in the presentation were the dates that the USGS scientists visited the Niagara River to process the collected fish.

Mr. Zelazny asked Mr. Rezabek whether members of the Niagara River Station Fishing Club are currently seeing tumors on fish they catch. Mr. Rezabek responded that they are seeing less than they did historically. He specifically mentioned an area near the northern end of Buffalo Outer Harbor where people historically commonly caught freshwater drum with large skin tumors and deformed mouths. He added that he was unable to recall the last report of skin tumor on a freshwater drum.

Conclusion:

Meeting participants had no objections to the removal of the Fish Tumors BUI based on the outcome of the USFWS study as detailed in NYSDEC's draft removal proposal.

Appendix C – Responsiveness Summary

NYSDEC received no substantive comments on the draft of this BUI removal proposal made available for public comment during the 30 day period from August 12 to September 11, 2015. Therefore, no responsiveness summary is required.

Appendix D – Statistical Analysis Report

Final Niagara River AOC Tumor Statistical Analysis Report

Michael A. Rutter

12/22/2015

Introduction

This is the final report of statistical analysis of the Niagara River AOC bullhead tumor data. In this analysis, I concentrate on total liver and total skin tumors. Two types of analyses were conducted for this report. The first is a Bayesian analysis using the same methodology as Rutter (2010). The second analysis looks at the same data using a chi-square test of independence, a traditional approach that assumes no other covariates, for example age, affect tumor prevalence.

For each of these analyses, only bullhead with all covariates measured were used in the analysis. For the Niagara River data set, 146 fish out of the 150 fish sampled were utilized. Long Point (inner bay) located near Port Rowan, Ontario, was used as the Lake Erie reference site. This was the lone reference site used in Rutter (2010). Data from the Presque Isle Bay study (2002-2007) were combined with recently collected data. Of the 243 fish collected in the reference site, 241 fish were included in the analysis.

Bayesian Analysis

Methods

The Bayesian analysis utilizes a hierarchical logistic regression model to summarize tumor prevalence on bullhead in the Niagara River and compare it to tumor prevalence observed at the reference site. A logistic regression model is used when the response variable has only two possible outcomes. When analyzing tumor data, the response variable is the presence or absence of a tumor. Logistic regression also allows for the inclusion of any number of predictor variables that may affect tumor prevalence. Variables examined in this analysis include age, length, weight, and gender of brown bullhead.

An important consideration for a statistical analysis of an AOC is sampling design. Traditional statistical methods assume that fish are sampled using a simple random sample approach. That is, each fish in the AOC is equally likely to be sampled. As with many sampling designs involving fisheries, this is not the case. Only certain, pre-determined locations in an AOC are selected to be sampled, and a pre-determined number of fish are usually sampled in each location. One method to statistically account for the sampling design is to use a hierarchical modeling approach (Rutter 2010). For the Niagara River, five different sites were sampled in three different years. From a statistical perspective, since five sites were sampled, all the bullhead are not independent. By using a hierarchical approach, the correlation among brown bullhead sampled in the same location and year is accounted for. For the reference location, all the fish were sampled from Long Point (inner bay) but over multiple years. Again, the non-independence in the sampling design is accounted for with the hierarchical model. By using a hierarchical model, AOC wide tumor prevalence can be estimated by correctly combining the samples collected at each site in the AOC.

The first phase of the analysis was to determine which combination of predictor variables best describes tumor prevalence. For both liver and skin tumors, hierarchical logistic regression models were fit using all possible combinations of the four predictor variables: age, length, weight, and gender. For each model, the Deviance Information Criteria (DIC, Gelman et al. (2003)) was calculated. DIC is a measure of goodness of fit used in Bayesian hierarchical models that penalizes for the number of parameters in the model. That is, as more parameters are added to the model (age, length, and gender, for example), the DIC value will increase due to the large number of predictor variables. The model with the smallest DIC is the model out of all those examined that best fits the data.

Once the best set of predictor variables was selected for each type of tumor, the tumor prevalence for the reference site and Niagara River were compared. All the sites for the Niagara River were combined over all years for one estimate of tumor prevalence. One tumor prevalence was also estimated for the reference site, combining over years. Each point estimate is based on the median of the posterior distribution of tumor prevalence and can be thought of as the representative tumor prevalence for the site. The tumor prevalences were estimated for the average value of the predictor variables, combined over both data sets. It is important to compare tumor prevalence on a standardized, representative fish across locations, as comparing tumor prevalence on age nine fish at one site to an age three fish at another site does not make sense if tumor prevalence is influenced by age. It also is important to note that this standardized tumor prevalence on a representative fish is determined by the model using data collected on all fish, not just fish of that representative age. A 95% highest posterior density interval (HPDI, the Bayesian version of a confidence interval) for each tumor prevalence was reported as well.

The Niagara River and the reference site were compared by calculating the difference in tumor prevalence between the two sites. The sites are considered to have statistically equivalent tumor prevalence if the 90% HPDI is contained within a given tolerance level. This procedure is called a Two One-Sided Test (TOST) of equivalency (Rutter 2010).

The tolerance level for the Niagara River AOC was created by determining what tolerance level would be required for the AOC to be equivalent with itself, a similar approach to what was done for the the Presque Isle Bay AOC (Rutter 2010).

Results

Best predictor variables

For each type of tumor, 15 different hierarchical logistic regression models were fit for all combinations of the four predictor variables. Models with one, two, three, and four predictor variables were considered. No interactions of the predictor variables were considered. The results for liver tumors are given in Table 1 and the results for skin tumors are given in Table 2.

Model	DIC
age, gender	96.5
age, weight	97.9
age, weight, gender	98.3
age, length, gender	98.8
age, length, weight, gender	99.2
age	99.4
age, length	100.2
age, length, weight	100.9
gender	108.2
length	109.8
length, gender	110.5
weight, gender	111.8
weight	112.3
length, weight	113.9
length, weight, gender	114.1

Table 1 – DIC values for liver tumor models

Model	DIC
age, gender	292.2
age	293.5
age, length	296.0
age, length, gender	296.7
age, weight, gender	299.6
age, length, weight, gender	299.8
age, weight	302.1
age, length, weight	302.7
length	303.9
length, gender	305.2
length, weight	309.1
length, weight, gender	311.1
weight	311.3
weight, gender	313.1
gender	330.1

Table 2 – DIC values for skin tumor models

For both skin and liver tumors, the best model of those examined was the model that included age and gender as predictor variables. It should be noted that concerns have been raised in the past about including both age and length in fisheries related models, as the two variables can be highly correlated. However, for the Niagara River data, the correlation between age and length was $r = 0.57$ and $r = 0.45$ for the Long Point (inner bay) reference site. Given these levels of correlation, there are no statistical issues including both covariates in the model at the same time.

Tumor Prevalence Estimates

For both types of tumors, age was an important predictor. The average age of bullhead in the data set was 6.4 years, so all tumor prevalences were estimated for age 6 bullhead. Given that gender was the other important predictor variable, estimates for both male and female bullhead are given. Point estimates of tumor prevalence are based on the median of the posterior distribution of tumor prevalence.

Location and Gender	95% HPDI	Median
Niagara River: Female	(0.0%, 25.5%)	2.0%
Niagara River: Male	(0.0%, 35.2%)	1.9%
Long Point: Female	(0.0%, 4.4%)	0.4%
Long Point: Male	(0.0%, 5.1%)	0.3%

Table 3 – Liver tumor prevalence

Location and Gender	95% HPDI	Median
Niagara River: Female	(0.5%, 65.6%)	22.5%
Niagara River: Male	(0.3%, 79.3%)	26.7%
Long Point: Female	(0.0%, 12.4%)	2.2%
Long Point: Male	(0.0%, 19.2%)	2.6%

Table 4 – Skin tumor prevalence

TOST of Equivilance

In Rutter (2010), Two One Sided Tests (TOST) of equivalence were conducted to see if AOC tumor prevalence was equivalent to the reference site. In that approach, if the 90% HPDI for the difference in tumor prevalence was within a given tolerance, the locations were considered to be statistically equivalent. For the Niagara River AOC, gender was also an important predictor of tumor prevalence, so gender specific tolerances were calculated. Since liver tumor prevalences are the lower and estimated with more certainty, they were used to create TOST tolerance levels for each gender. For females, the Niagara River TOST tolerance is $\pm 24\%$. For males, the Niagara River TOST tolerance is $\pm 34\%$.

The 90% TOST HPDI interval for female liver tumors is (-5.4%, 18.8%), well within the Niagara River tolerance. Liver tumors for males [(-5.5%, 25.5%)] is also within the tolerance for the Niagara River, indicating statistical equivalence. Based on the Niagara River tolerances skin tumors for females [(-2.1%, 57.4%)], and skin tumors for males [(-3.1%, 66.9%)] exceed the the tolerance, indicating those tumor prevalences are not statistically equivalent.

Traditional Statistical Approach

The traditional statistical approach to tumor prevalences is to use a chi-square test of independence to see if location is independent of tumor prevalence. The disadvantage of such an approach is that data such as age and gender are ignored. In the case of liver tumors, the number of tumors is low enough that a Fisher's exact test is used to test for independence. For liver tumors, there is not enough evidence (Odds Ratio=0.721, p=.754) to suggest that liver tumor prevalence depends on location. Skin tumors are plentiful enough that a chi-square test indicates there is enough evidence (χ^2=50.26, p<0.0001) to suggest that skin tumor prevalence differs depending on location, with the Niagara River skin tumor prevalence being higher.

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