Review of Statistical Modeling Methods, Analysis, and Interpretation

University of Michigan Dioxin Exposure Study

March 30, 2009

KERN
STATISTICAL SERVICES

Presentation Draft

DEQ

Introduction

- The UMDES is a very large study with primary objective to

"*identify factors that explained variation in serum dioxin concentrations among residents in Midland and Saginaw Counties.*"

- Complex sampling and analysis methods
- Confidentiality renders peer review difficult
- The science advisory board (SAB) has not included a PhD statistician since 2006
- As a result MDEQ requested a review by professional statisticians with national experience at large contaminated sediment mega sites
- Desired outcome is a collaborative technical process to develop results applicable to risk management decisions

Objectives of the Review

- Evaluate experimental design and statistical methods to aid MDEQ to:
  - Insure understanding of study conclusions and their strengths and limitations
  - Evaluate the utility and applicability of the UMDES data for risk management decisions
  - If appropriate, determine if modifications to analyses are necessary to improve applicability to risk management decisions
  - Insure that results and interpretations are properly and accurately stated to the public

Presentation Overview

- Summary of primary findings
- Brief discussion of risk assessment components
- Catalog of experimental designs and their strengths and limitations
- Nature of the UMDES design
- Discussion of statistical methods appropriate to UMDES
- Findings
- Recommendations

Primary Findings

- Data are not publicly available beyond UM research team
- Study design is observational which limits the potential to make causal inference
- Statistical modeling—Variable selection by significance tests and stepwise procedures lead to unreliable models (Harrell, 1996)
- Sampling design and selection of subjects may under represent critical target populations

Typical Application of Human Health Risk Assessments for Remedial Decisions

- Michigan DEQ
  - Develop generic cleanup criteria
  - Determine need for and develop site-specific cleanup criteria
- U.S. EPA CERCLA/RCRA Programs
  - Baseline HHRA to evaluate need for remediation/corrective action
  - Use for developing preliminary and final remediation/corrective action goals

Risk Assessment Overview

- Identify concerns = **hazard identification**
  - What chemicals and what levels?
  - Where are they?
- Determine potential for contact with contamination = **exposure assessment**

$$Exposure \propto Intensity \times Frequency \times Duration$$

- Potential for health effects from contamination = **toxicity assessment**
  - How much (dose)?
- Potential risk = **risk characterization**
  - Combine information on exposure and toxicity to determine risk

Exposure Pathway:

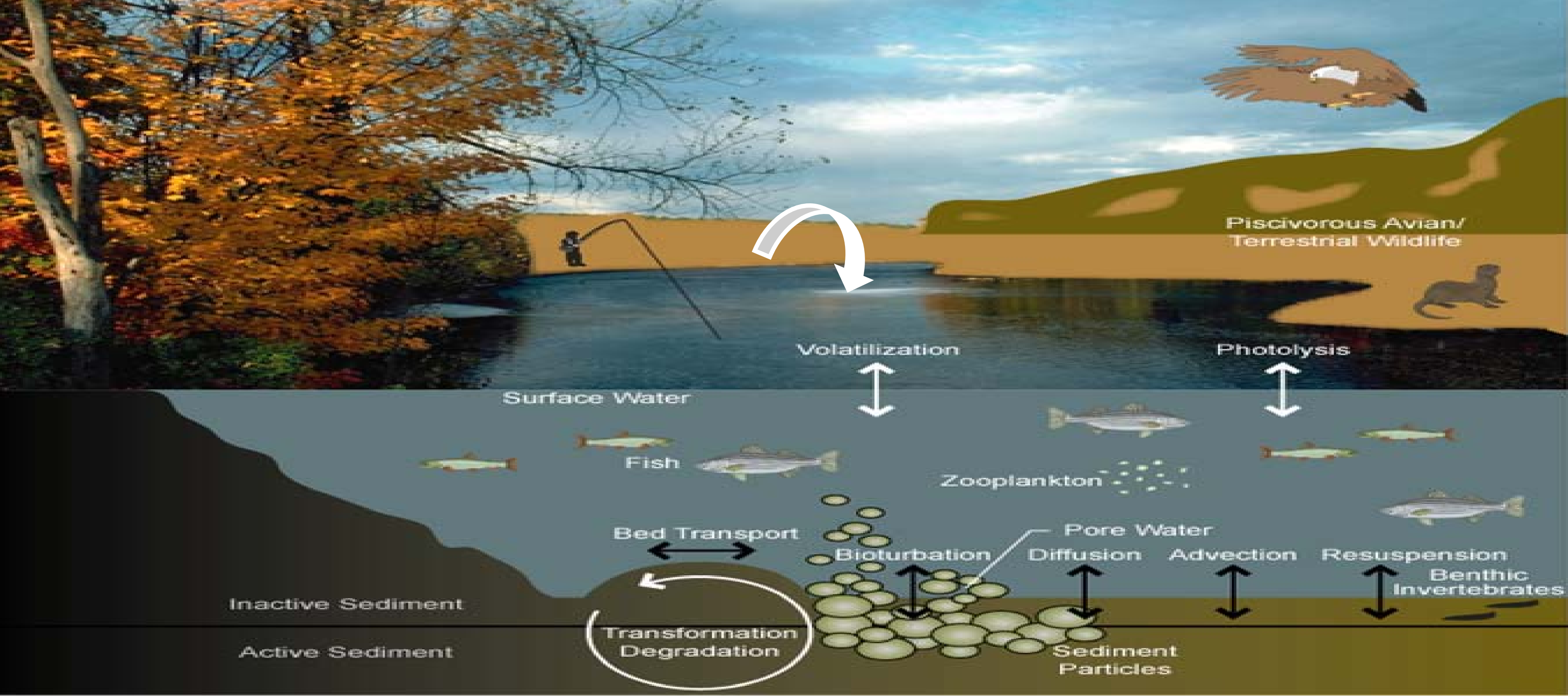
- The route a substance takes from its source (where it began) to its end point (where it ends), and how people can come into contact with (or get exposed to) it. An exposure pathway has five parts:
  - a source of contamination (such as an abandoned business);
  - an environmental media and transport mechanism (such with surface water and sediment);
  - a point of exposure (such as a residential property);
  - a route of exposure (eating, drinking, breathing, or touching),
  - a receptor population (people potentially or actually exposed).

- When all five parts are present, the exposure pathway is termed a **completed exposure pathway**

Definitions provided by ATSDR Glossary of Terms, http://www.atsdr.cdc.gov/glossary.html; last accessed March 26, 2009

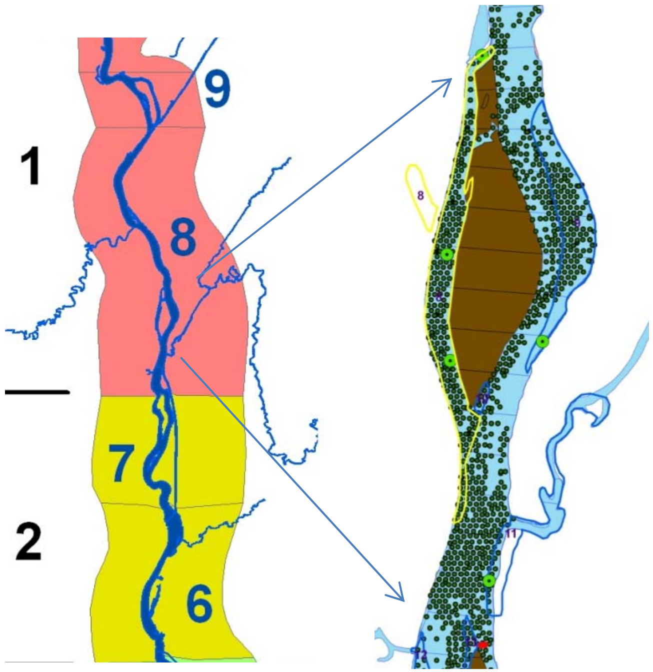
Background

- A central goal of the study is to determine which factors explain variation in serum dioxin congener levels, and to quantify how much variation each factor explains.
- In particular, does living on contaminated soil, or living in a house with contaminated house dust lead to increased serum dioxin levels?
- The study is a human exposure pathway study
  - It is not a study of health outcomes.
  - It is not intended to provide information on the geographic distribution of soil contamination with dioxins, furans and PCBs in Midland and Saginaw Counties or elsewhere.
  - The study does not address potential economic consequences of dioxin contamination or exposures.

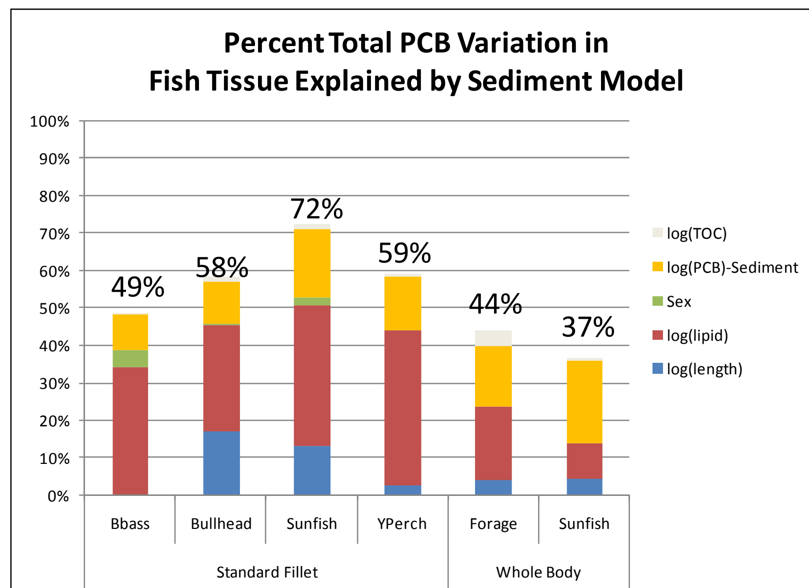


- **Bottom Up (Mechanistic)**
  - Mechanistic "models"
  - Measurements in soil, sediment and lower trophic levels
  - Models predict receptor exposures
- **Top Down (Empirical)**
  - Receptor and source concentrations are measured
  - Empirical relationships developed
  - Common in ecological studies
  - Biota to sediment or soil accumulation factors (BSAFs)

Hudson River Fish Exposure Model
A Top Down Example



- 80 foot spacing for sediment samples
- 300 to 500 fish per species
- Collocated fish and sediment samples at multiple scales
- Biological parameters explain majority of variance
- Adjusted R-squared values are generally low
- Sediment explains less than 10% of variation



$$Log\left(C_{fish}\right) = \beta_0 + \beta_1 Log\left(Lipid\right) + \beta_2 Log\left(Length\right) + \beta_3 Log\left(TOC\right) + \beta_4 Log\left(C_{sediment}\right)$$

Regression model is identical in **form** to the UMDES regression models

EXPERIMENTAL DESIGN

Specification of Research Questions

- Stepwise variable selection implicitly creates many research questions (thousands of them)
- Important research questions should be specified *a priori* and tested by careful specification of individual models
- Results should be provided in such a way that competing hypotheses can be ranked

Research vs. Risk Management

- Research conducted according to **"the scientific method"** is an iterative process consisting of:
  - *A priori* formulation of research questions
  - Study design and sample selection
  - Careful and detailed statistical analyses
  - Formulation of new research questions and insights
- **Risk management** is a process of integration of diverse sources of information for selection among remedial alternatives
  - unlike academic research findings, remedial selection is often not reversible
- This distinction influences how users of the UMDES must **interpret** study results
  - **Risk managers have fewer iterative cycles** with which to refine research questions and to answer them, and false positive (negative) interpretations have costly and, at times, immediate consequences

OUR INTERPRETATION OF UMDES DESIGN AND WHERE IT FITS IN

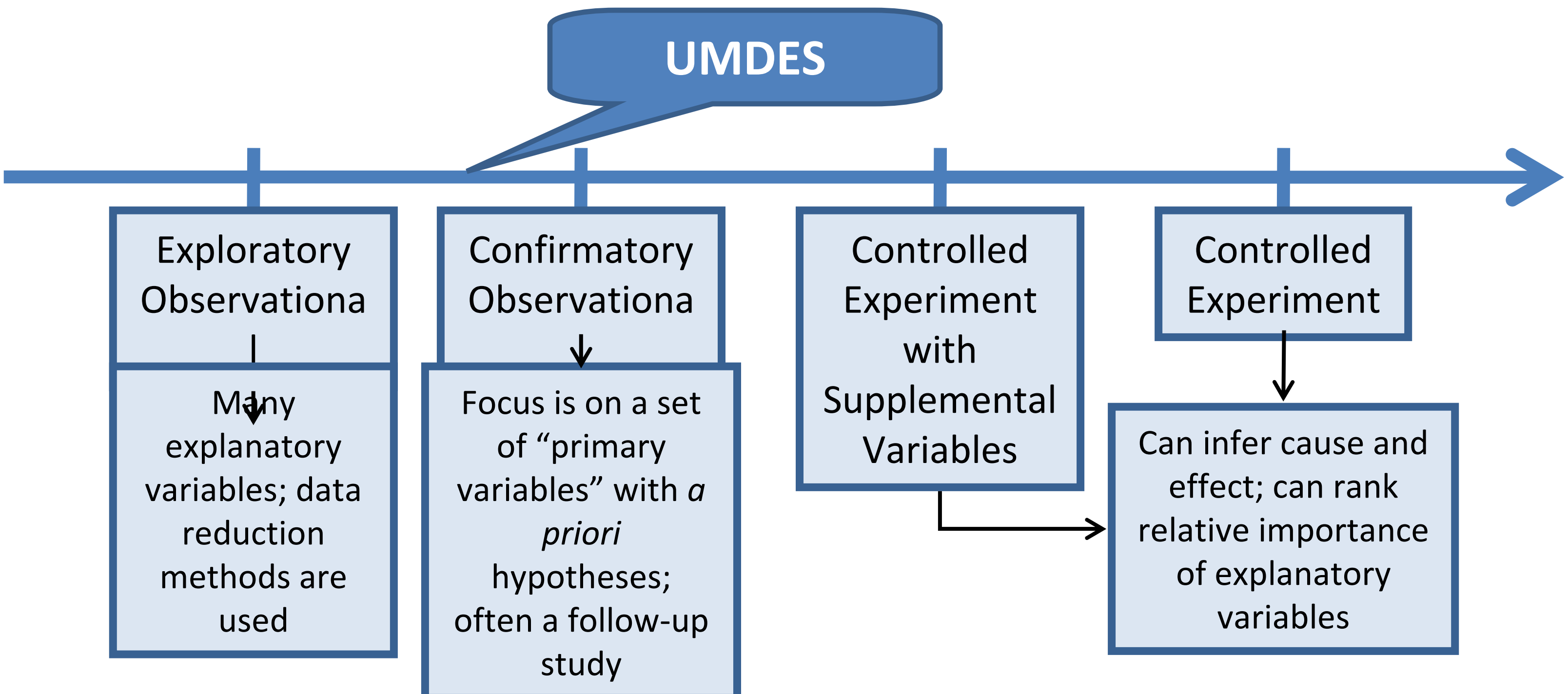
Types of Study Designs

Observational

- Hypothesis generating
- Unbalanced sampling
- Correlated explanatory variables
- Data reduction
- Confirmatory studies needed to verify results
- Arbitrary partitioning of R^2

Designed Experiment

- Hypothesis testing
- Research questions fully formed
- Independence of variables assured through random assignment of subjects to treatments
- Balanced representation of study
- Unique partitioning of R^2



Observational Studies

- In observational studies, treatments are observed, rather than assigned
- It is not reasonable to consider the observed data under different treatments as random samples from a common population
- Systematic differences in populations may exist that effect the response variables
- Designs become unbalanced with respect to treatment combinations
- Controlling for confounding factors is recommended through regression model building
- Model building for causal inference is more difficult than for prediction

Gelman and Hill (2007) *Data Analysis Using Regression and Multilevel/Hierarchical Models*

Model Building Strategies Prediction

- Include any variables known a-priori to be important
  - Age, BMI, sex, etc.
- For variables with large effects consider interactions
- Data Reduction:
  - Predictors with interpretable signs can be included regardless of statistical significance
  - Predictors that are non-significant and have the wrong signs should be discarded
  - Predictors that are significant with the wrong signs should be carefully considered and justified with new mechanisms or theories
  - Covariate relationships should be carefully investigated
  - Predictors that are significant with the expected sign are included
- These are recommendations from Gelman and Hill (2007)
- Burnham and Anderson (1998) would follow a similar strategy with the exception that statistical significance would be replaced with information theoretic measures such as the Akaike Information Criterion (Akaike 1974)
- These strategies provide basis for prediction of the response, but not for estimating the effects of manipulating the predictors (i.e. causation)

Three Primary Goals

(stated in the UMDES)

- *Evaluate concern that people's body burdens of dioxins, furans and PCBs are elevated **because** of environmental contamination*
- *Determine which factors explain variation in serum congener levels, and to quantify how much variation each factor explains*
- *Find out whether the elevated levels of dioxins in the soil in the city of Midland, and in the Tittabawassee River flood plain between Midland and Saginaw, have also caused elevated levels of dioxins in residents' bodies*

Causal Inference

- The primary goals of the UMDES are best described as causal investigations
- The UMDES is an observational study which limits potential for causal inference
- Careful consideration of balance, overlap, and distribution of the response among covariate combinations is necessary to determine the limits of causal vs. predictive statements

Signs of Trouble

- Nonsensical model results
- Coefficients that change in magnitude and even direction when variables are added or removed from models
- High pairwise correlations among continuous variables
- Significant differences in means of continuous variables among levels of discrete covariates
- Significant multiple regression relationships among predictors
- Large standard errors for regression coefficients
- High variance inflation factors
- Lack of overlap in covariate distributions
- Sample size imbalance among subgroups
- Differences in central tendency and shape of covariate distributions across subgroups

An Example

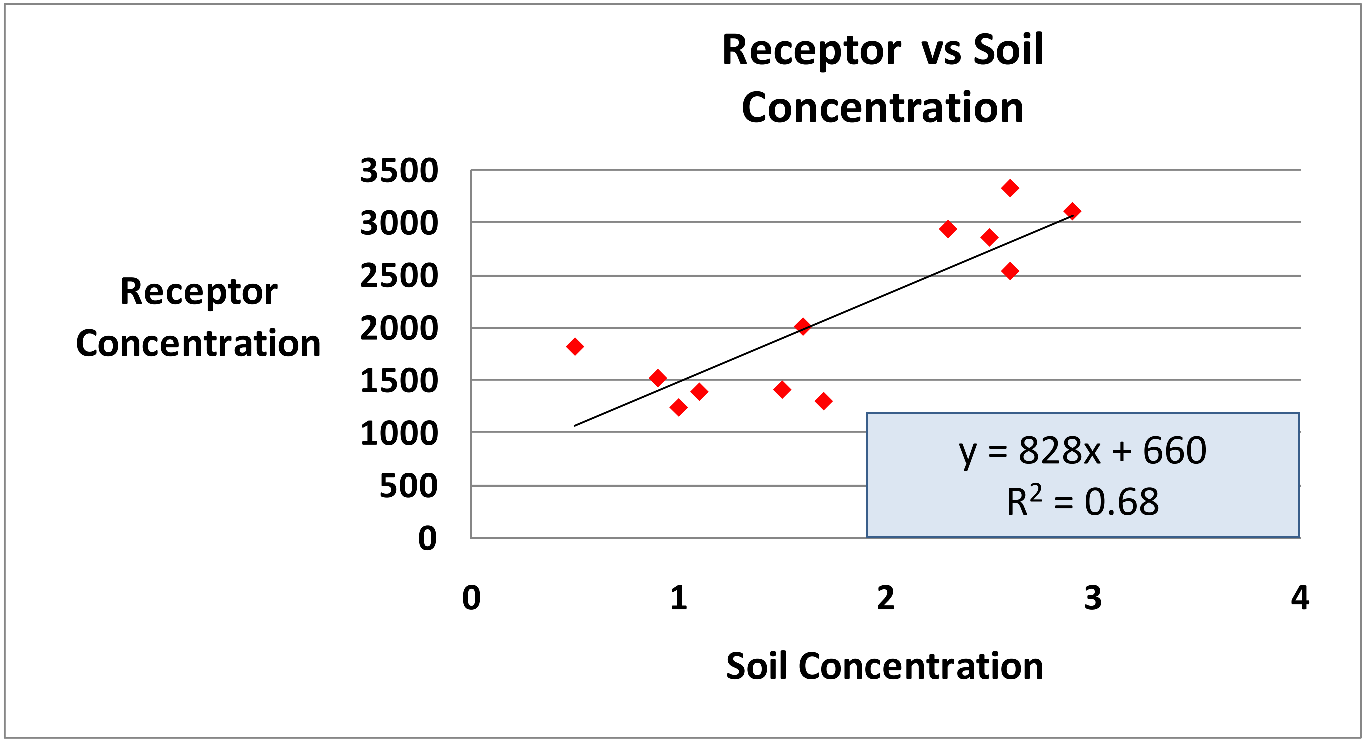
Objective: Select among two predictors of contaminant concentration in a receptor

- Consider a two variable regression model of the form:

$$\log_{10}(C_{Receptor}) = \beta_0 + \beta_1 X_{soil} + \beta_2 X_{residence}$$

- $X_{residence}$ is a binary indicator
- Forward selection will be used to select the "important" predictor(s)

Soil Only Model (Adjusted R^2= 0.68)						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	660	325	2.03	0.07	-65	1385
Soil Conc	**828**	169	4.90	**<0.001**	451	1205



Forward Stepwise Procedure

Start with either of the two variables

Residence Only Model (Adjusted R^2 = 0.87)						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	1527	109	14.01	<0.001	1284	1770
Residence	1429	169	8.46	<0.001	1053	1805

Remove and Try Again

Add variables and test for significance

Analysis of Full Model (Adjusted R^2 = 0.85)						
	Coefficients	*Standard Error*	*t Stat*	*Significance Level (P-value)*	*Lower 95%*	*Upper 95%*
Intercept	1551	334	4.64	0.00	795	2308
Residence	1457	410	3.55	0.01	530	2384
Soil Conc	**-20**	265	-0.08	**0.94**	-619	579

Negative coefficient

Backward Elimination Procedure: Same results in this instance

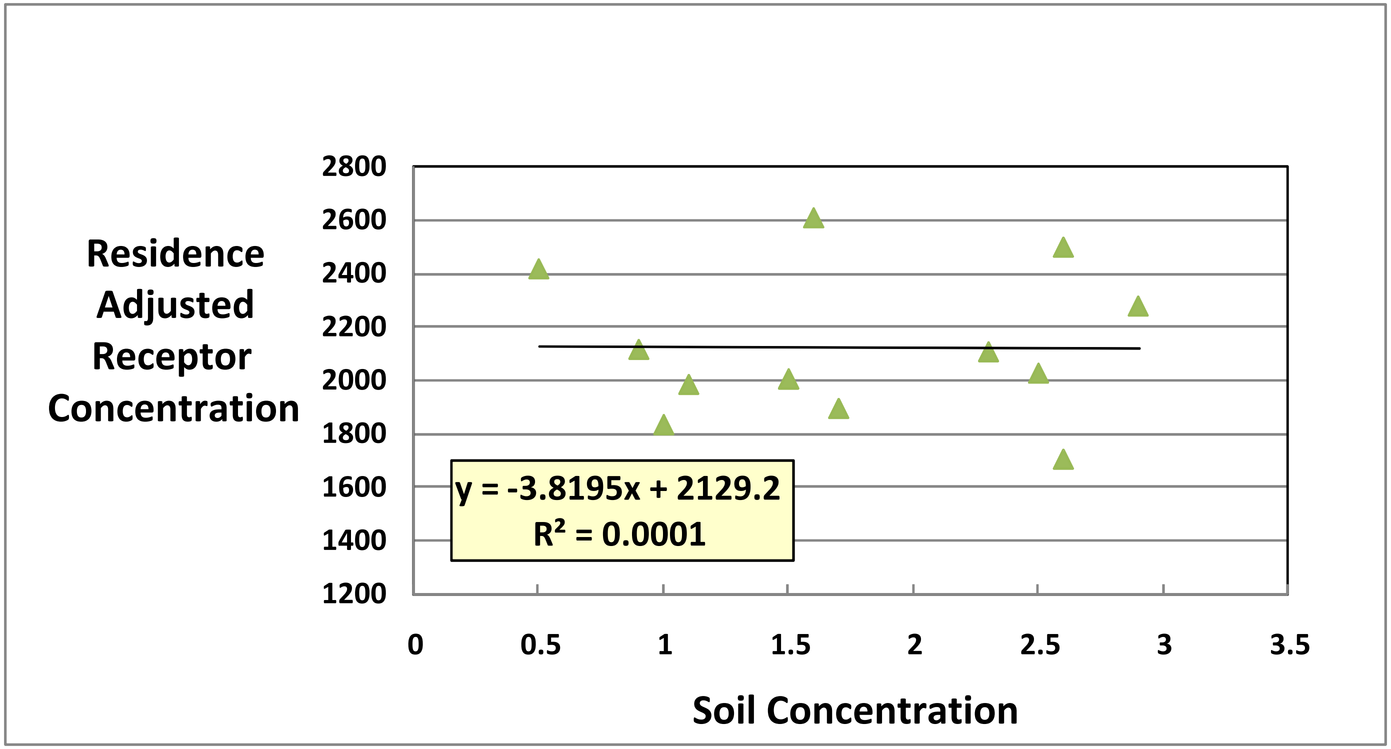
Analysis of Full Model (Adjusted R^2 = 0.85)						
	Coefficients	***Standard Error***	***t Stat***	***Significance Level (P-value)***	***Lower 95%***	***Upper 95%***
Intercept	1551	334	4.64	0.00	795	2308
Residence	1457	410	3.55	0.01	530	2384
Soil Conc	**-20**	265	-0.08	**0.94**	-619	579

Negative regression coefficient would go unnoticed in automated procedure

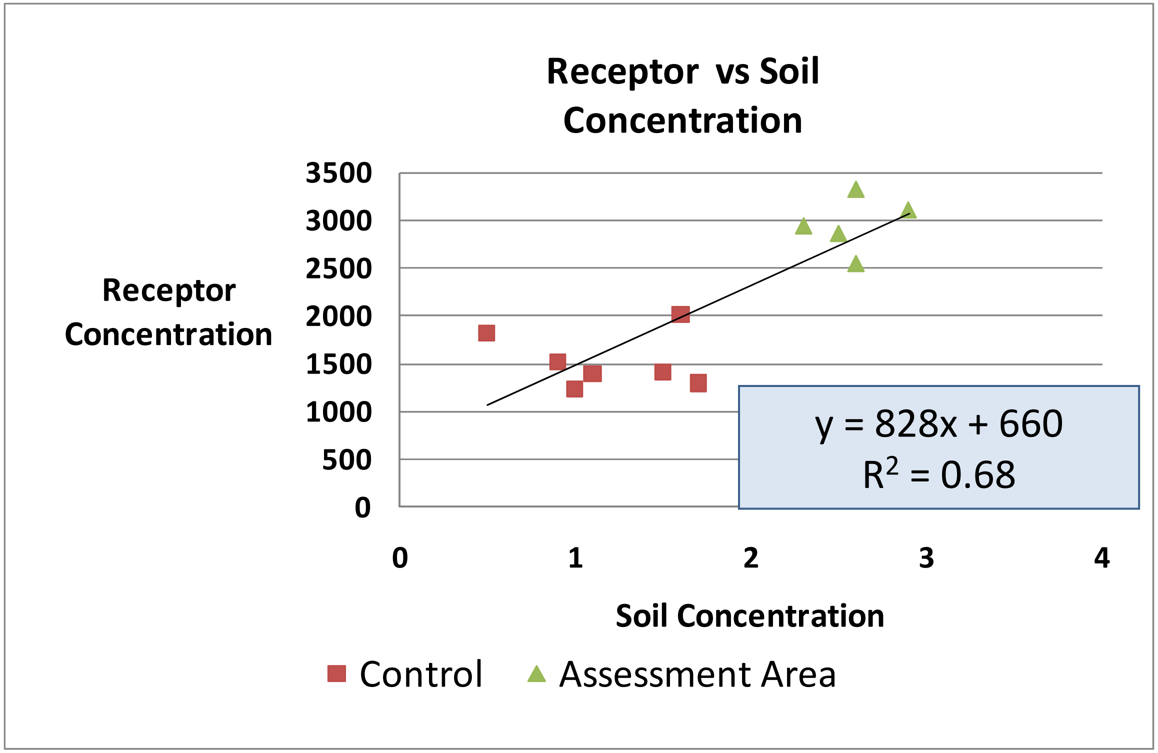
Remove Non-Significant Variables

Residence Only Model (Adjusted R^2 = 0.87)						
	Coefficients	***Standard Error***	***t Stat***	***P-value***	***Lower 95%***	***Upper 95%***
Intercept	1527	109	14.01	<0.001	1284	1770
Residence	1429	169	8.46	<0.001	1053	1805

Residence Adjusted Receptor Concentrations vs. Soil Concentration



Soil and Place of Residence are Confounded



- The sampling design is unbalanced relative to the predictors
- No overlap in the predictors
- Effects of soil and residence cannot be separated
- Residence may be acting as a surrogate for soil concentrations
- Results should be reported for both variables separately, including confidence intervals and adjusted R^2

Implications of Example

- The effect of soil exposure is conditional on other variables in the model due to confounding
- Variation cannot be partitioned into independent components
- Coefficients cannot be interpreted unconditionally
- The contribution to serum contaminant concentration is a function of other variables in, or out, of the model
- In this example, no conclusion can be drawn regarding importance of soil as opposed to place of residence
- Adjusted R^2 is not an indicator of importance of predictors in observational studies because covariates are not independent
- Demond et al. (2008) showed that soil and place of residence are confounded similarly to this example

Selection of Research Subjects - UMDES

- Representation of critical target populations defined by MDEQ (2004) not adequate
  - Critical target populations are those “most likely to have the highest exposures to DLC contamination from Dow”
- Subjects not adequately represented include:
  - Floodplain population
  - High end fish consumers
  - Game consumers
  - Consumers of other animal products associated with the Tittabawassee River, Saginaw River, or Saginaw Bay
  - These critical food chain exposure factors are not necessarily related to the geographically-based study groups identified in the UMDES

Floodplain Example

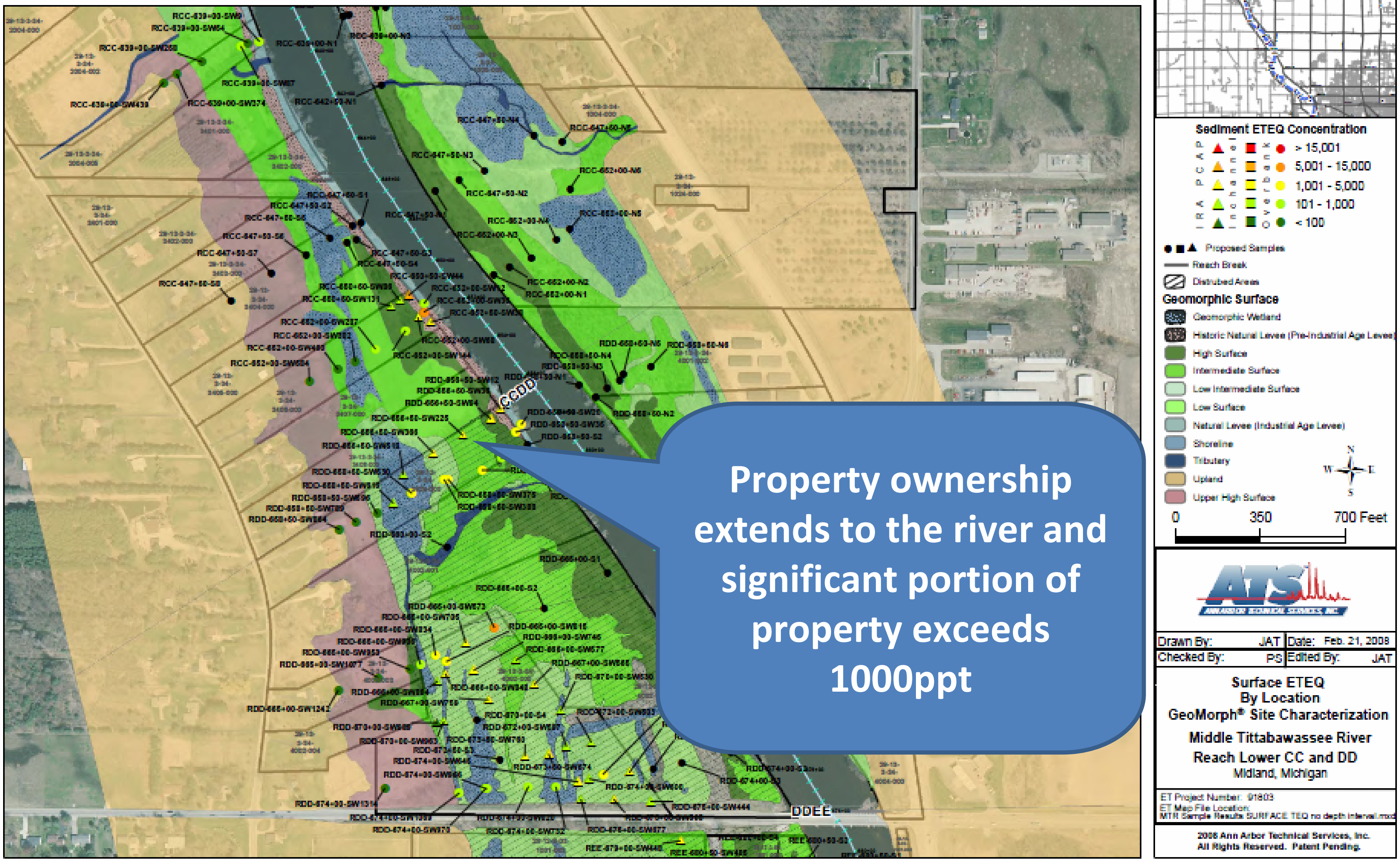
- Representation of the Floodplain population is not adequate
  - Consists of people who live **on or near** the 100-year floodplain of the Tittabawassee River
- The portion of the Floodplain population most likely to have elevated body burdens of DLCs live and or use **frequently-flooded portions** of the Tittabawassee River floodplain (MDEQ 2004)

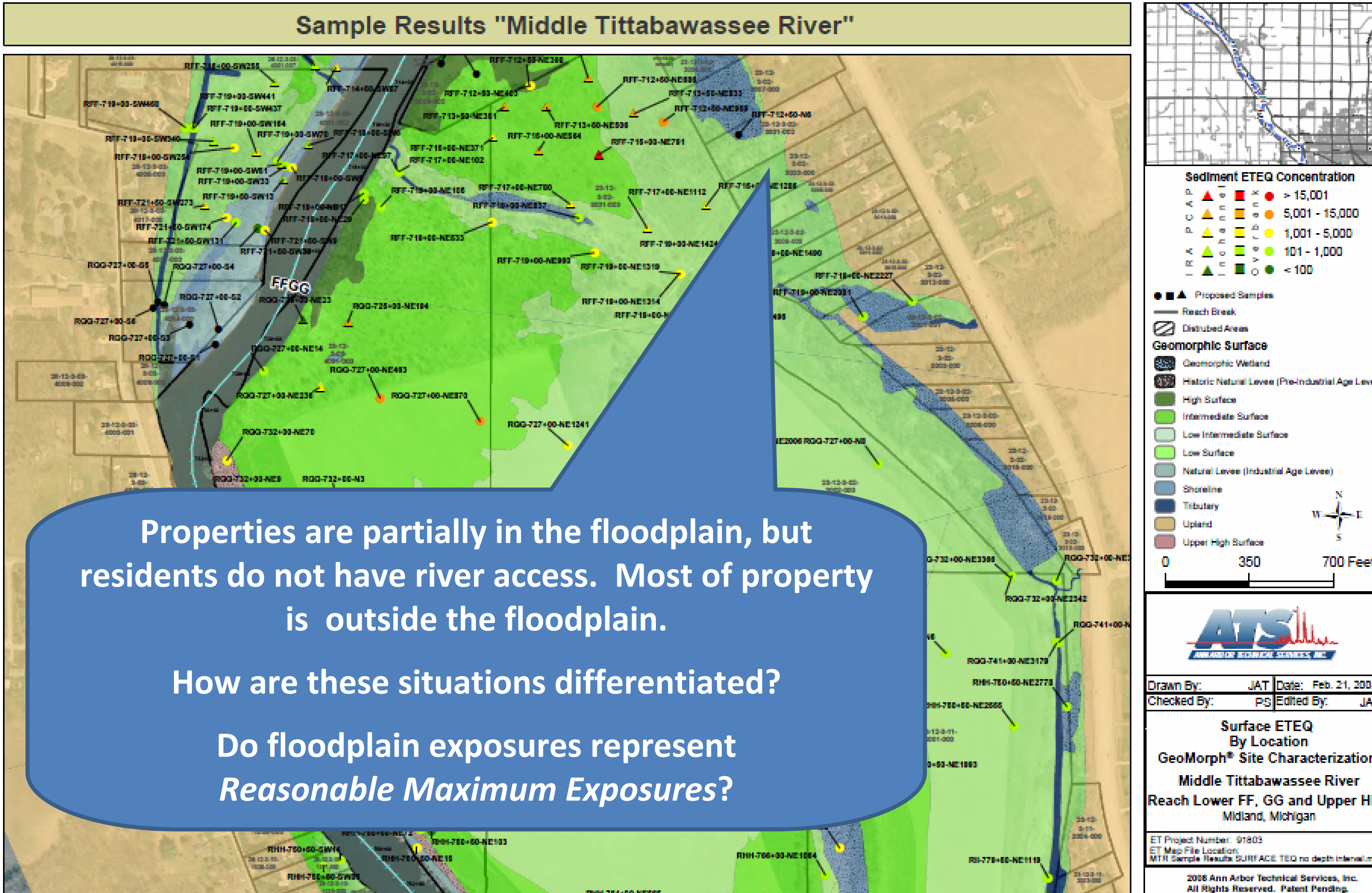
Definition of the Floodplain Population

1) *[Census] blocks in Midland and Saginaw counties which contained any land area in the Federal Emergency Management Administration-defined 100 year flood plain of the Tittabawassee River below the Dow Chemical Company facility in Midland, and above the point where the Tittabawassee and Shiawassee Rivers join and have a mixed flood plain; (Garabrandt 2008a).*

Garabrandt et al 2008a. The University of Michigan Dioxin Exposure Study: Methods for an Environmental Exposure Study of Polychlorinated dioxins, Furans and Biphenyls. **doi: 10.1289/ehp.11777 (available at http://dx.doi.org/) Online 22 December 2008**

Sample Results "Middle Tittabawassee River"





Properties are partially in the floodplain, but residents do not have river access. Most of property is outside the floodplain.

How are these situations differentiated?

Do floodplain exposures represent *Reasonable Maximum Exposures*?

UMDES Soil TEQ Summary

Soil Composites HP 0-1 Inch	N	TEQ$_{DFP29-2005}$ (pg/g)						
		Mean	S.E.	Median	75th%ile	95th%ile	Min	Max
Floodplain	203	56.5	9.7	11.4	35.4	223.1	1.1	1881.4
Near Floodplain	164	52.0	36.7	3.9	10.4	102.9	0.8	2299.8
Other M/S	168	13.5	2.0	5.3	13.2	59.4	0.8	157.7
Plume	37	109.2	31.0	58.2	111.9	257.2	6.3	745.5
Jackson/Calhoun	194	6.9	0.8	3.6	7.6	22.6	0.4	186.2

Vegetation Composites House Perimeter	N	TEQ$_{DFP29-2005}$ (pg/g dry wt)						
		Mean	S.E.	Median	75th%ile	95th%ile	Min	Max
Floodplain	188	14.2	3.4	3.4	7.4	50.2	0.4	1427.2
Near Floodplain	69	376.6	354.1	3.3	10.1	152.0	0.6	7994.9
Other M/S	71	4.2	0.4	3.3	5.1	10.1	1.0	27.5
Plume	36	37.5	12.7	18.3	31.1	125.4	0.8	268.9
Jackson/Calhoun	52	4.5	0.6	3.3	6.7	8.7	0.6	25.9

Environmental Health Perspectives Publication (2008):

1. Start with over 100 predictors
2. Variable groupings have many similar variables that are expected to be interrelated
3. Automated selection may obscure confounding

COMPARISON OF MACHINE LEARNING METHOD AND LINEAR REGRESSION MODEL IN IDENTIFYING IMPORTANT PREDICTOR VARIABLES FOR SERUM DIOXIN TEQ FOR A COMMUNITY IN MICHIGAN, USA

Qixuan Chen, Shih-Yuan Lee , Brenda Gillespie, Debashis Ghosh, Biling Hong, Elizabeth Hedgeman, James Lepkowski, David Garabrant; University of Michigan, Ann Arbor, Michigan, USA

Domain	Effect	BWD[1]	RF[2]	Final[3]
Demo/Health	smoking	X	X	X
	breast feeding	X	X	X
	body mass index change	X	X	X
	pregnancies and childbearing	X	X	X
	female		X	X
	income		X	
Soil	soil		X	X
Residence	region (live in Midland)		X	X
Property Use	live on a property raising any of crops, livestock or poultry	X	X	X
	use weed killers on the property	X	X	X
	live in property ever damaged by fire	X		X
	live in property burning trash		X	
	live on a property using wood burning stove regularly		X	
Work	work in the paper industry	X		
	work involving spraying chemicals to kill plants or weeds	X		X
	work in the production, formulation, use or disposal of herbicide	X		X
	work at Dow Chemical Company	X		X
	work in a foundry	X		
	serve as an emergency responder	X		X
	live with people working for chemical company	X	X	X
Food	eating game meat		X	X
	eating the liver of game meat		X	
	eating fish	X	X	X
	eating sport caught fish from Saginaw River or Bay, Tittabawassee River		X	X
	eating bottom fish	X		X
	eating walleye or perch	X		X
	eating squirrel or wild rabbit	X	X	
	eating wild turkey, pheasant, grouse, quail or woodcock		X	X
	eating eggs	X	X	X
Activities	fishing activities in Saginaw River	X		
	water activities in Tittabawassee River	X	X	X
	water activities in Saginaw River and Saginaw Bay		X	

(1) Significant variables in the backward selected model; (2) The 30 most important variables identified using the Random Forest method; (3) Index for significance of the given variables in the final model[4].

Garabrandt et al 2008. The University of Michigan Dioxin Exposure Study: Predictors of Human Serum Dioxin Concentrations in Midland and Saginaw, Michigan. *Environmental Health Perspectives.* **doi: 10.1289/ehp.11779 (available at http://dx.doi.org/) Online 22 December 2008**

Table 1. Adjusted R^2 indicating the percentage of the variation in serum dioxin explained by the full regression model and by categories of variables. The adjusted R^2 would be decreased by the amount listed in the table if the factor was removed from the full regression model.

Contribution to Adjusted R^2 (%)	TEQ-WHO_{05}	2378-TCDD	12378-PeCDD	123678-HxCDD	23478-PeCDF	PCB 126
Overall (Full Model)	70.26	63.68	67.13	63.07	65.10	48.90
Demographic factors[a]	39.63	30.48	44.24	36.52	40.13	31.23
Residence factors[a]	0.55	3.40	1.09	0.00	0.00	0.37
Soil/Household dust[a]	0.00	0.51	0.00	0.00	0.00	0.96
Property use factors[a]	1.34	1.00	0.21	0.34	2.24	2.35
Work history factors[a]	0.18	1.82	0.92	0.74	0.78	0.68
Water activities factors[a]	0.42	0.57	0.00	0.61	0.70	0.77
Fish consumption and fishing[a]	1.02	0.47	0.92	1.09	2.78	2.04
Meat and dairy consumption and hunting[a]	0.00	0.34	0.82	0.18	0.17	0.16

[a]See Table 2 for a list of the factors included in each category

Variance partitioning results are reported unconditionally in spite of the likely correlations.

Three pages of model coefficients distilled into one primary conclusion

Conclusions: The study provides valuable insights into the relationships between serum dioxins and environmental factors, **age, sex, BMI, smoking, and breast feeding**. These factors together explain a substantial proportion of the variation in serum dioxin concentrations in the general population. **Historic exposures to environmental contamination appeared to be of greater importance than recent exposures for dioxins.**

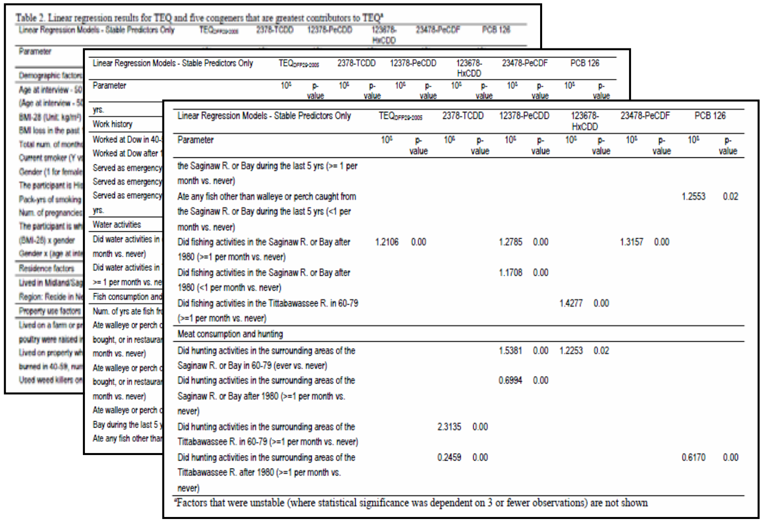


Table 2. Linear regression results for TEQ and five congeners that are greatest contributors to TEQ[a]

Linear Regression Models - Stable Predictors Only	$TEQ_{DFP29-2005}$		2378-TCDD		12378-PeCDD		123678-HxCDD		23478-PeCDF		PCB 126	
Parameter	10^{β}	p-value	10^{β}	p-value	10^{β}	p-value	10^{β}	p-value	10^{β}	p-value	10^{β}	p-value
the Saginaw R. or Bay during the last 5 yrs (>= 1 per month vs. never)												
Ate any fish other than walleye or perch caught from the Saginaw R. or Bay during the last 5 yrs (<1 per month vs. never)											1.2553	0.02
Did fishing activities in the Saginaw R. or Bay after 1980 (>=1 per month vs. never)	1.2106	0.00			1.2785	0.00			1.3157	0.00		
Did fishing activities in the Saginaw R. or Bay after 1980 (<1 per month vs. never)					1.1708	0.00						
Did fishing activities in the Tittabawassee R. in 60-79 (>=1 per month vs. never)							1.4277	0.00				
Meat consumption and hunting												
Did hunting activities in the surrounding areas of the Saginaw R. or Bay in 60-79 (ever vs. never)					1.5381	0.00	1.2253	0.02				
Did hunting activities in the surrounding areas of the Saginaw R. or Bay after 1980 (>=1 per month vs. never)					0.6994	0.00						
Did hunting activities in the surrounding areas of the Tittabawassee R. in 60-79 (>=1 per month vs. never)			2.3135	0.00								
Did hunting activities in the surrounding areas of the Tittabawassee R. after 1980 (>=1 per month vs. never)			0.2459	0.00							0.6170	0.00

[a]Factors that were unstable (where statistical significance was dependent on 3 or fewer observations) are not shown

Garabrandt et al 2008. The University of Michigan Dioxin Exposure Study: Predictors of Human Serum Dioxin Concentrations in Midland and Saginaw, Michigan. *Environmental Health Perspectives.* **doi: 10.1289/ehp.11779 (available at http://dx.doi.org/) Online 22 December 2008**

Further Interpretation 2378-TCDD

- Analyses were conducted in $\log_{10}$ so regression coefficients represent ratios of concentration.
- Ratios **greater than one indicate positive relationships** while those **less than one indicate negative relationships**

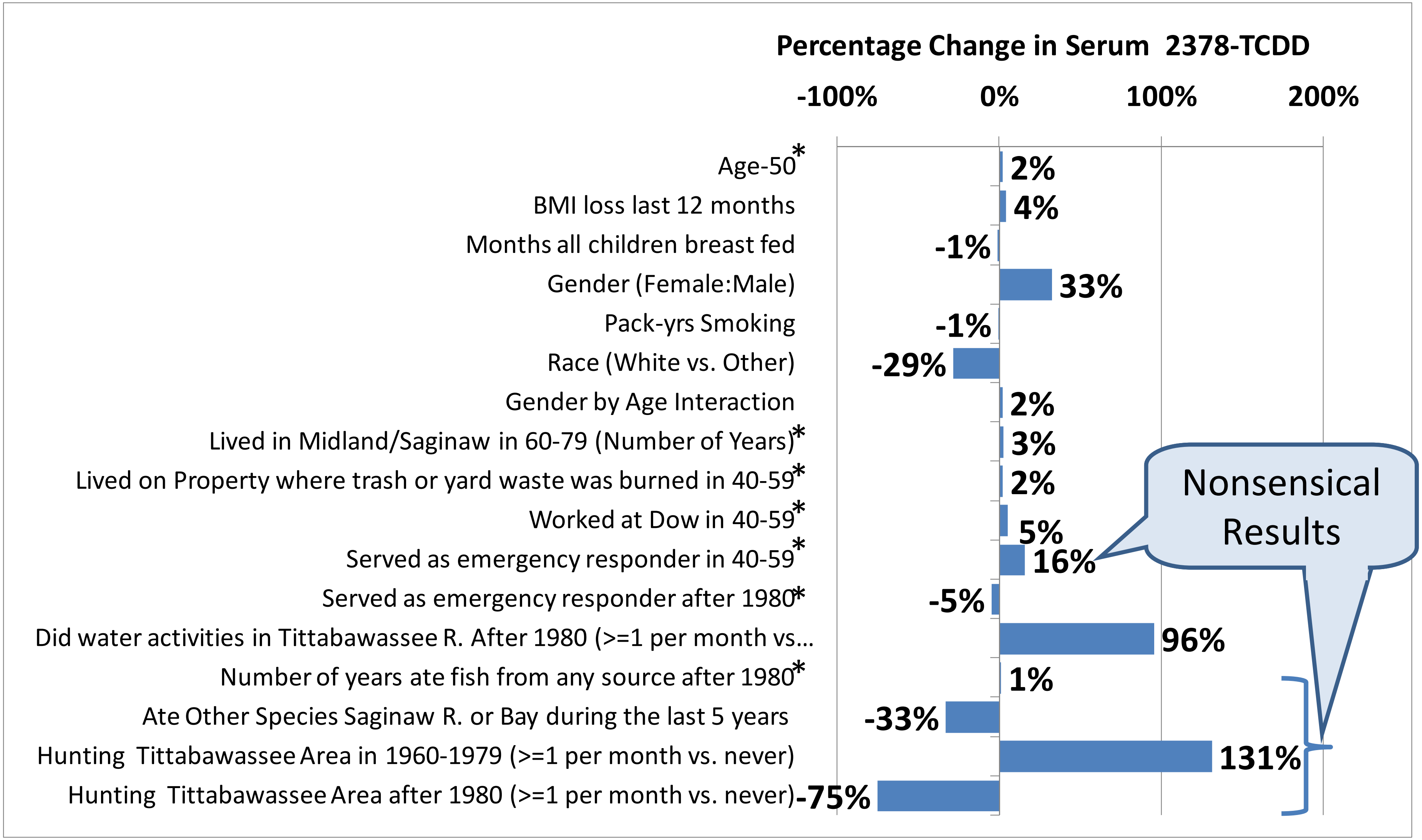
$$C(x) = 10^{\beta_0} \times 10^{\beta_1 x}$$

$$\frac{C(1)}{C(0)} = \frac{10^{\beta_0} \times 10^{\beta_1}}{10^{\beta_0}} = 10^{\beta_1}$$

$$Percentage\ Effect = \left(10^{\beta_1} - 1\right) \times 100\%$$

Estimated Effects Reported in Table 1

(Significant at $\alpha = 0.05$)



* Effect size for variable applies per year

Path Forward

- Collaborative work at the technical level
- Development of selected multiple regression models that can be used to quantify relationships between serum and critical variables reliably
- Joint development of materials to communicate mutually supportable results
- Development of materials suitable for the MDEQ to review in order to verify that issues identified herein have been addressed and that results can be relied upon for risk management decisions

Summary of Findings

- Conclusions regarding primary factors influencing serum dioxin and furan (D/F) concentrations are based on data that are over processed and under analyzed (interpreted)
- Automated model selection methods used to process data appear to have resulted in overly fitted models that very likely mask important relationships between serum and environmental D/F concentrations
- Models have apparently not been validated and likely have poor out of sample predictive power
- Partial R^2 values are incorrectly interpreted as a means to rank importance of variables with regard to D/F exposure
- Reported results fail to recognize the large proportion of variance apparently explained jointly by the collection of environmental variables

Summary of Findings

- Results are stated unconditionally, when they should be qualified as conditional on the other variables included as well as excluded from the final models
- Reported associations between serum and environmental factors are frequently nonsensical and inconsistent with mechanisms known to influence serum dioxin levels
- It appears that subjects included in the floodplain population are likely to not live in areas with elevated soil D/F concentrations
- Soil (D/F) concentrations in the floodplain are in general one to two orders of magnitude higher than those reported in the UMDES study
- Failure to test important hypotheses separately (i.e. food consumption, region of residence, soil concentration and life history) has likely caused confounding amongst critical variables of interest

Recommendations

- Results and findings for critical variables need to be based on individual models with sound theoretical underpinnings based on understood mechanisms of fate and transport and bio-uptake of D/F and PCBs
- All results should include estimates of effect sizes and standard errors and or confidence intervals
- Results that cannot be rectified with the scientific literature should be obviously identified as such and described
- Statements of results should not be released until these modifications have been undertaken and results can be thoroughly peer reviewed

Recommendations

- The science advisory board SAB should recruit and retain one or more PhD statisticians with experience in risk assessment, superfund and remedial decision making, sample survey methodology and linear models theory
  - Candidates for this position should be nominated by Dow, MDEQ, USEPA, ASTDR , NIH and other interested agencies and stakeholders
- Statistical methods need to be revised and published in an applied statistics journal such as Journal of Applied Biological and Environmental Sciences (JABES), Biometrics, Technometrics , or Journal of the American Statistical Association (JASA)

References

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