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Childbearing-Aged Women's Exposures to Multiple Environmental Chemicals

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Introduction

Women of childbearing age are of great public health concern because their fetuses, infants and young children are vulnerable to the health effects associated with maternal exposures to certain environmental chemicals. Twenty-eight percent of developmental disabilities in children are caused by environmental factors with annual projected costs to diagnose and treat these disabilities at $240 billion (Murray & Lopez, 1999; Pruss-Ustun, Bonjour & Corvalan, 2008; Smith, Corvalan & Kjellstrom, 1999). Three percent of these environmentally-related developmental disabilities are estimated to be caused by exposure to known neurotoxins (Boyle, Decoufle & Yeargin-Allsopp, 1994; Grandjean & Landrigan, 2006; Landrigan, et al., 2002).

Purpose

The purpose of this study was to examine pregnant and non-pregnant childbearing-aged women's exposures to specific and multiple environmental chemicals known to have neurobehavioral and neurodevelopmental consequences in animal models and/or human population studies. There were three research questions:

1. What was the prevalence of pregnant and non-pregnant childbearing-aged women's exposures to each of the following specific environmental chemicals: lead (Pb), methylmercury (MeHg) and the summed value of four polychlorinated biphenyl (PCB) congeners (118, 138/158, 153, 180) as measured by chemical-specific (xenobiotic) levels in blood samples from childbearing-aged women (16 to 49 years inclusively) who were living in the United States from 1999 through 2004 and selected as part of a national probability sample?

2. What combinations and permutations of chemical exposures were most common as evidenced by xenobiotic levels in the blood of these childbearing-aged women?

3. What, if any, subsets of childbearing-aged women were disproportionately exposed to combinations of the above environmental chemicals based on susceptibility- and exposure-related attributes, socioeconomic factors and race-ethnicity?

Background

Lead, methylmercury and PCBs are pervasive, persistent and co-occur in the environment (Choi, et al., 2008; Marshall, Clough, & Gehrels, 2009; Poissant, et al., 2008; Shotyk & LeRoux, 2005). Exposure to any one of these chemicals has been shown to have neurobehavioral and neurodevelopmental consequences in animal models and/or human population studies (Collaborative on Health and the Environment's Learning and Development Disabilities Initiative, 2008a, 2008b). Further, these epidemiologic studies have indicated that these health effects occur at concentrations below so-called "safe" levels (Grandjean, et al., 2004; Lanphear, et al., 2000) with a cumulative impact on health (Sexton & Hattis, 2007). One would expect that the effects on health from a combination of these chemicals would be more severe than the health effects from exposure to any one specific environmental chemical.

As these specific environmental chemicals bioaccumulate, the body burden from past exposures has the potential for transgenerational consequences. Therefore, childbearing-aged women – not just those who are pregnant – are of great public health concern. Also, exposure may have effects if the exposure occurs in a sensitive neurodevelopmental period during gestation. Preconceptual, periconceptual and prenatal exposures transfer to fetuses via the placenta and to infants and young children through lactation (Axelrad, et al., 2007; Bellinger, et al., 1987; Daniels, et al., 2003; Dewailly, et al., 1996; Gundacker, et al., 2002; Vreugdenhil, et al., 2004). As a result of these transfers, there may be differences in xenobiotic blood levels between pregnant, lactating and non-pregnant women.

Exposure to these specific environmental chemicals is compounded by vulnerability. It is highly likely that some subgroups of childbearing-aged women have higher exposures than others. It may be possible to identify these at-risk population subgroups by susceptibility- and exposure-related attributes as well as socioeconomic factors and race-ethnicity (Sexton, Olden & Johnson, 1993a; Turner, et al., 2003). Since the health impact of exposures to multiple environmental chemicals may be greater than the impact of exposure to a specific chemical, this impact may be magnified even more among these vulnerable population subgroups. For those who are most vulnerable, a so-called "safe" level may be zero.

Currently, interaction models evaluate chemicals with common adverse health outcomes i.e., neurotoxic and/or single exposure sources i.e., breast milk. To evaluate the influence of binary interactions on toxicity, the scientific literature is examined critically for "mechanistic" understanding for each individual chemical with attention as to whether these chemicals have the same or similar toxic action (Agency for Toxic Substances and Disease Registry, 2001). ATSDR estimated the direction of toxicological interaction to be greater-than-additive for methylmercury on PCBs and PCBs on methylmercury and additive for lead on methylmercury and methylmercury on lead (Agency for Toxic Substances and Disease Registry, 2004, 2006). To date, no mechanistic studies of PCBs on lead or lead on PCBs have been identified. Limitations

and inconsistencies with these mechanistic models may have underestimated the effects of theses chemical interactions (Callahan & Sexton, 2007; Chen, et al., 2001; Monosson, 2005; Wilkinson, et al., 2000). *In vivo* and *in vitro* mechanistic studies of these binary chemicals are limited and their findings contradictory. The contradictions may originate from differences in the outcomes evaluated as well as tissue-, time- and dose-dependent variability in bioaccumulation. Despite what is known about the hazards of exposure to these specific environmental chemicals, the health effects from exposures to multiple environmental chemicals and their corresponding biologically-effective dose are relatively unknown. Even less is known about exposures to combinations of these environmental chemicals among women of childbearing age living in the United States.

Data Collection, Analyses and Study Findings

As little is known about exposures to combinations of these environmental chemicals in both pregnant and non-pregnant childbearing-aged women, this research was a descriptive and exploratory study. However, a cross-sectional study in which a large amount of original data are collected and encoded is prohibitively time-consuming and expensive. As a result, a more practical and economical approach was to conduct a secondary analysis of existing cross-sectional data from the National Health and Nutrition Examination Survey (NHANES). NHANES is a population-based survey from the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS). Data from this survey were publicly available online. NHANES provides a probability sample of baseline information on the health and nutritional status of the non-military, non-institutionalized adults and children living in the United States. As part of this survey, biomonitoring data were collected for more than 116 environmental chemicals and their metabolites including all the chemicals of interest to this study (Centers for Disease Control and Prevention, National Center for Environmental Health, 2007). NHANES employs a four-stage, unequal probability and cluster sampling method to select study participants from the U.S. population. All NHANES protocols were approved by the Centers for Disease Control and Prevention, National Center for Health Statistics Research Ethics Review Board (Centers for Disease Control and Prevention, National Center for Health Statistics, 2010b). The proposal for this study was reviewed and approved by the Chair of the Institutional Review Board at the University of Rhode Island.

Study Population

The subjects of this research were childbearing-aged women (16-49 years inclusively) of all races and ethnicities who were living in the United States from 1999 through 2004 and selected as part of this national probability sample. For this study, women were required to have all xenobiotic blood tests and a reliable dietary recall. There were 3,173 childbearing-aged female study participants selected of whom 391 were pregnant. Since NHANES was a nationally representative sample, weighted data allowed for estimation of true variance and generalizability to the U.S. population (Centers for Disease Control and Prevention, National Center for Health Statistics, 2006). To obtain weighted estimates for 1999-2004, a six-year weight variable was created. This is possible because the 2003-2004 weights were comparable on a population basis to the combined 1999-2002 four-year weights (Centers for Disease Control and Prevention, National Center for Health Statistics, 2006). As a result, there were approximately 134.5 million childbearing-aged women in this study of whom 4.8 million were pregnant.

Dependent Variables

For this study, exposure was the concept of interest, because it is believed that "exposure, not toxicity, is the ultimate means by which we regulate the use or release of hazardous agents" (Graham, et al., 1992, p. 409). Existing definitions and measurements of exposure in five disciplines central to environmental health were explored. For this study, the definition of exposure is "contact between an agent and a target with contact taking place at an exposure surface over an exposure period by an exposure route" (International Programme on Chemical Safety, 2000, p.21). This definition was published in a comprehensive criteria document on human exposure assessment by the International Programme on Chemical Safety under the auspices of World Health Organization, the United Nations Environment Programme and the International Labour Organization. This transdisciplinary definition of exposure is aligned with current principles and practices in environmental health.

The outcome of interest was based on evidence of biological uptake of two or more neurotoxic chemicals, specifically, lead, methylmercury and the summed value of four polychlorinated biphenyl congeners (118, 138/158, 153 and 180). These congeners were selected because they are most prevalent in humans. Thus, they serve as an indicator of total PCB exposure. Exposures were measured by the presence of these xenobiotics in the blood of study participants. A biomarker of exposure reflects the relationship between external contaminant (amount available for contact from all potential sources) and body burden (internal dose). The large sample size compensated for intra-individual exposure variability associated with intermittent exposures (Needham, et al., 2005; Phillips, et al. 1989). Differences in survey participation by season, time of day for data collection, fasting time and usual/unusual food consumption were not correlated (p = 0.18 to 0.63) with exposure. For the purposes of this study, an "elevated level" was defined as a xenobiotic blood level at or above geometric mean; "concurrently elevated levels" were defined as two or more xenobiotic blood levels at or above the geometric mean.

All specimens with a level at or above the upper limit of detection were diluted prior to reanalysis and recalculation (Centers for Disease Control and Prevention, National Center for Health Statistics, 2010a). Lower limits of detection for PCB congeners varied as each sample had its own limit; the larger an individual sample volume, the lower the detection limit. NHANES documented all PCB values below the lower limit of detection. All PCB values were lipid-adjusted. For lead, total mercury and inorganic mercury, NHANES used the Hornung and Reed (1990) method (LoD/$\sqrt{2}$) to impute values less than the lower limit of detection (LoD) after correcting for sample weight and analyte recovery (Centers for Disease Control and Prevention, National Center for Health Statistics, 2009a, 2009c, 2010a). The Centers for Disease Control and Prevention, National Center for Environmental Health (2009) found these imputations made little difference in geometric mean estimates. Due to limits of available analytic methodology, organic mercury i.e., methylmercury could not be measured directly. As a result, methylmercury was derived by subtracting inorganic mercury from total mercury (Cernichiari, et al., 1995). Using this calculation, a negative value for methylmercury was observed in 18.4% cases among all NHANES participants and 15.1% cases among childbearing-aged female participants. Mahaffey, Clickner and Bodurow (2004, p.565) attributed these negative values to differences in detection limits and recoded all methylmercury values less than zero equal to one-half inorganic mercury's detection limit. This method of imputation was used in this study and may have underestimated total mercury and methymercury levels slightly.

Prior to data analysis, xenobiotic levels were transformed logarithmically to approximate normal distribution. A geometric mean provided a better estimate of central tendency for these data which are distributed with a long tail at the upper end. This phenomenon is found commonly among environmental chemical biomarkers. For this reason, logarithmic transformation is routinely performed in environmental health studies. The geometric mean dampens the effect of higher values which would ordinarily bias an arithmetic mean. The geometric mean represents a 50/50 distribution; half of the values are above, half of the values are below. Values at +3 SD are of greatest concern to public health so they were retained as opposed to treating them as outliers.

Independent Variables

The conceptual framework selected for this dissertation was the modified environmental health paradigm (Sexton, Olden & Johnson, 1993a) as it most aptly described the intersection of exposure and an agent's toxicity with a target's vulnerability. Initially, 55 independent variables were identified. Susceptibility-related attributes can modify the target's response to exposure. These attributes included genetics, age, gender, and measures of health status, nutritional status and reproductive status (Grassman, 1996; Sexton, 1997; Sexton, et al., 1993b). Exposure-related attributes can reflect differences in proximity, activity and behavior which increase the likelihood of exposure. These exposure sources included acculturation, dietary consumption, alcohol consumption, tobacco use, residential and workplace characteristics and occupation (Lee, 2005; Sexton, 1997). Socioeconomic factors can influence health indirectly through complex interactions with susceptibility- or exposure-related attributes or both. These factors include measures of education, employment, income and marital status (Sexton, Olden & Johnson, 1993a). Race-ethnicity was considered separately. Health disparities among racial and ethnic minorities are well known (Morello-Frosch & Lopez, 2006a; Morello-Frosch & Shenassa, 2006b; Payne-Sturges & Gee, 2006). There is considerable evidence of inequitable distribution of the costs and benefits associated with environmental regulations among vulnerable communities i.e., the placement of hazardous waste sites, landfills, incinerators and polluting industries in communities inhabited mainly by low income groups and racial and ethnic minorities (Johnson, et al., 1992; Mohai, & Bryant, 1992b; United Church of Christ Commission for Racial Justice, 1987; U.S. Government Accounting Office, 1983). Race-ethnicity may serve as proxy variables for residential segregation and social isolation (Acevedo-Garcia & Osypuk, 2008) and/or reflect institutional environmental discrimination (Gelobter, 1992). In turn, each of these factors could influence susceptibility, exposure and health (Merkin, et al., 2009).

Data Analysis

Data analysis encompassed three phases beginning with organizing the data into one large database and preparing the data for analysis. Datafiles for three contiguous two-year cycles (1999-2004) were downloaded in SAS transport file format and imported into SAS statistical software using StatTransfer. The second phase involved operationalization of the variables and constructing software instructions under SAS and SAS-callable SUDAAN for unweighted (study population) and weighted (target population) statistical analyses, respectively. Phase Three addressed the research questions. Descriptive and univariate statistics were used to estimate prevalence of exposure to each of the environmental chemicals of interest. The most common types of exposures were identified. Before performing multivariate statistical modeling, the dependent variable was created and bivariate statistical analyses (χ^2) were conducted. Logistic regression models were developed by creating a series of nested models and utilizing likelihood

ratio testing per Hosmer and Lemeshow (2001). Stepwise logistic regression analysis of exposure as outcome with two categories was performed. Variance inflation factor test for collinearity among independent variables was employed. Tests for interactions between pairs of independent variables were conducted using the best-fit exposure model. Finally, odds ratios were calculated for each variable in the best-fit logistic regression exposure model.

Findings

The first research question addressed the prevalence of childbearing-aged women's and pregnant childbearing-aged women's exposures to individual chemicals of interest. (See Tables One and Two.) The large number of childbearing-aged and pregnant childbearing-aged females who had the highest xenobiotic blood levels i.e., at and above the 95th percentile, illustrates the degree to which exposures to these chemicals are ubiquitous.

The second research question addressed the most common combinations and permutations of these three chemicals. (See Graphs One and Two.) Concurrently elevated blood levels of PCBs and lead were found in 17% of childbearing-aged women. This finding highlights the need for mechanistic studies on this chemical pair, particularly since the study by Denham, et al. (2005) reported a statistically significant interaction between PCBs and lead ($p<0.05$). Concurrently elevated blood levels of PCBs and methylmercury were identified in 27% of pregnant women and 17% of childbearing-aged women. As discussed previously, the Agency for Toxic Substances and Disease Registry (2004) predicted a greater-than-additive interaction between these two chemicals; results from *in vitro* and *in vivo* studies were conflicting. Further mechanistic studies on the interactions of these two chemicals are indicated. Approximately 20% – one-fifth – of childbearing-aged females had concurrently elevated xenobiotic blood levels of all three chemicals; 16% had none. Six percent of pregnant childbearing-aged females had concurrently elevated xenobiotic blood levels of all three chemicals, 33% had none.

The third research question addressed subsets of childbearing-aged women who may be disproportionately exposed to combinations of these three environmental chemicals based on susceptibility-related attributes, exposure-related attributes, socioeconomic factors and race-ethnicity. Of the original 55 independent variables, the following 13 independent variables were included in the best fit logistic regression exposure model (in order of ascending p values and descending χ^2 values): fish consumption in past 30 days, age, food security, ever breastfed, highest education, shellfish consumption in past 30 days, marital status, selenium intake, time in longest employment, alcohol consumption, household size, serum cotinine and race-ethnicity. Overparameterization occurred after three sequential nested model operations because data were too sparse for the total number of possible interactions. Rather than introduce prejudice to the model, efforts were redirected to identify all statistically relevant two-way interactions for future analyses. Ten variable pairs could not be tested due to overparameterization. Nineteen pairs were not statistically significant ($p>0.20$). For the remaining 48 pairs, 40% showed strong statistically significant interactions ($p<0.001$). For the exposure model with no interactions, the odds of having two or more concurrently elevated xenobiotic blood levels rose non-linearly with age. (See Graph 3.) The oldest cohort of women (40-49) had an exponential risk for exposure to multiple environmental chemicals. If historical emissions is a valid explanation, one would expect equally high or higher xenobiotic levels in women older than 49 and conversely, ever decreasing xenobiotic levels among successive cohorts of childbearing-aged women in subsequent survey years; additional data are needed. Any fish consumption in the past 30 days multiplied the odds of exposure by three when compared to no fish consumption. Domestic and imported seafood and

freshwater fish are primary sources of methylmercury and PCBs for adults. These findings may indicate a need for federal and state agencies to examine the effectiveness of their educational efforts to educate women and in particular pregnant women about avoiding predatory species of fish in which biomagnification of methylmercury and PCBs is greatest. On the other hand, breastfeeding appeared to be protective for childbearing-aged women. Those who were currently breastfeeding or had ever breastfed a child for more than one month were 44% less likely to have two or more concurrently elevated xenobiotic levels than those who had never breastfed. (See Graph 4.) All three chemicals have been measured in breast milk (Agency for Toxic Substances and Disease Registry, 2004). There was no statistically significant interaction found between ever breastfed and age with the best-fit exposure model.

The best-fit logistic regression exposure model with no interactions was compared to the best-fit models with no interactions for lead, methylmercury and PCBs. Variable by variable, there appeared to be no discernable pattern(s) across models, a possible indication that factors contributing to individual chemical exposures should not be used to predict multiple chemical exposures. For example, education was associated with concurrently elevated xenobiotic blood levels but not each chemical. The odds of having two or more concurrently elevated blood levels were twice more likely if a childbearing-aged woman did not have a high school diploma or GED. The opposite occurred with current pregnancy. While current pregnancy was only statistically significant with exposure as outcome with two categories prior to multivariate analyses, current pregnancy was strongly protective in the lead, methylmercury, and PCB best-fit logistic regression models. (See Graph 5.) There are three possible explanations to consider: those who were pregnant modified their lifestyles to decrease their exposures; chemicals were transferred from the women to their fetuses; and age acted as an effect modifier for current pregnancy. This study could not test for interaction between age and pregnancy due to overparameterization; additional data are needed.

Limitations of the Study

1. Since data on individuals were collected at one time, only associations – not causations – can be made in describing the relationships between dependent and independent variables.

2. Uncertainty was inevitable when addressing complex, dynamic systems such as exposures to multiple environmental chemicals. Uncertainty increases when agents and exposure pathways are less defined and their sources are remote from the target's micro-environment (Price & Chaisson, 2005). Not all known and unknown contributing factors were addressed in this model. Over-parameterization occurred after three sequential nested model operations because data were too sparse to test for all possible interactions.

3. Not all toxicokinetic and toxicodynamic processes are known or understood fully and even less is known about multiple environmental chemical exposures. However, measurements of xenobiotics in blood estimated body burden most closely.

4. For each dose response, there should be a corresponding conceptual biological plausibility that may or may not be understood fully. The presence of a xenobiotic in blood does not by itself cause or infer disease causation; equal xenobiotic values across chemicals do not infer relative equality in toxicity (National Research Council, 2006). Toxic equivalency across chemicals was not considered because this study examined exposures and not outcomes of

said exposures. However, xenobiotic levels in blood provided unequivocal evidence that exposure and uptake had occurred (Sexton, Callahan, & Bryan, 1995).

Recommendations for Progress in Research, Education, Practice and Policy

Research

This study has revealed a number of useful avenues for new research. Recommendations for progress in research include:

1. Establish best-fit logistical regression models for binary chemical combinations using these same datasets. This would allow for further illumination of the exposure model developed in this study.
2. Add data from survey years (2005-2010) so that interactions among independent variables with the best-fit logistic regression exposure model may be fully described.
3. Reanalyze these data using structural equation modeling for factor analyses.
4. Include PCB 126 in future studies. CDC Healthy People 2020 objective EH-20.12 designated PCB 153 and PCB 126 as representatives of the non-dioxin-like and dioxin-like PCBs, respectively (Centers for Disease Control and Prevention, 2010). Consideration should be given to adjusting estimation of total PCB exposures with regard to using PCB 153 only (Grandjean, et al., 2001).
5. Mechanistic studies on the interaction of PCBs and lead.
6. Mechanistic studies on interactions of binary chemical combinations and all three chemicals that measure more sensitive outcomes using *in vitro* toxicity assays to predict cellular level effects.
7. Establish the prevalence of exposures to these environmental chemicals among females older than 49.
8. Examine how individual women's xenobiotic blood levels differ through their life stages.
9. Replicate this study among identified vulnerable subpopulations.
10. Examine exposures to other environmental chemicals e.g., cadmium or manganese and how the best-fit logistic regression exposure model varies, if at all.
11. Establish the prevalence of men's exposures to these chemicals and identify vulnerable subgroups at increased risk for exposures to multiple environmental chemicals.
12. Study how the genetic pattern varies with exposures to these environmental chemicals individually and in combinations. Determine whether there are specific genetic polymorphisms associated with increased risk of adverse outcomes associated with exposures to these environmental chemicals.

Education

This study facilitated efforts regarding risk communication with this population about their exposures to multiple environmental chemicals. Recommendations for progress in education include:

1. Increase awareness and recognition of environmental exposures and transgenerational consequences of bioaccumulation among childbearing-aged women and prepubescent girls, especially those demographic groups who were disproportionately represented in at-risk categories.
2. Re-evaluate the effectiveness of ongoing public health efforts aimed at pregnant women and their fish consumption.
3. Integrate awareness and recognition of environmental exposures and transgenerational consequences of bioaccumulation with undergraduate and graduate curricula of all environmentally- and health-related professionals especially those in maternal and child health.

Practice

Precautionary-level interventions should be designed and implemented to prevent or mitigate sources of exposures to these chemicals particularly among those women identified with increased risk for concurrently elevated xenobiotic blood levels. Recommendations for progress in practice include:

1. Escalate public health efforts at international, national, state and local levels to eradicate sources of exposure to lead, methylmercury and PCBs. *Think global, act local* (Dubos, 1980).
2. Promote discussion among EHS professionals and healthcare practitioners regarding interpretation of biomonitoring data in terms of their clinical practice and their clients' health literacy vis à vis risk communication.

Policy

This study raises two policy-related questions about transgenerational consequences of maternal exposures to multiple environmental chemicals and the exponential bioaccumulation that accompanies aging.

Is it safe? Current environmental health policy has not addressed adequately the potential health effects of exposures to multiple environmental chemicals. Demand for strong empirical justification has led to a regulatory process that responds only when a high certainty of severe harm exists. In the meanwhile, the magnitude of harm is larger than once thought and the severity of harm – irreversible (Barker, 2004; Barker, et al., 2002). For those who are most vulnerable, a so-called "safe" level may be zero. There is need for paradigmatic change from one of risk to one of "*if precaution, then proaction*". "The Precautionary Principle urges precaution when the magnitude of the potential adverse event is large or the adverse outcome is severe, even if its probability is small" (Ricci, et al., 2003, p.3).

Is it safe enough? Protecting the next generation by regulating environmental exposures of the current generation must be seriously considered. However, a fetal protection policy is neither acceptable nor legal (Automobile Workers v. Johnson Controls, Inc., 499 U.S. 187, 1991). An open dialogue should commence with federal/state agencies and key stakeholders. Pivotal issues should include consideration of lifetime cumulative exposures from all sources and uniform application of the ALARA principle (As Low As Reasonably Achieveable) in establishing permissible exposure levels (PELs) with a goal of zero harm through a cleaner environment, safer workplaces and healthier homes.

Concluding Thoughts

When will we ever learn? On May 1, 1956 in Minamata Japan, Dr. Hosokawa and his associates documented a strange new disease with a 37% mortality rate. Autopsies revealed cerebellar deterioration. Those who survived remained severely incapacitated. They concluded that the source of Minamata disease was mercury contamination of fish and shellfish from Minamata Bay; its source, effluent from a factory (Harada, 2004). There were three significant phenomena that had never been experienced or recognized previously: biotransformation of elemental mercury to methylmercury by aquatic species with resulting biomagnification; methylmercury poisoning resulted from secondary ingestion of contaminated seafood; and congenital anomalies resulting from maternal-to-fetal transfer of methylmercury through the placenta. Even today, many perpetuate the fallacy that Minamata was a poisoning "incident" that occurred in the mid-1950s. In actuality, the poisoning of Minamata and its neighboring communities occurred over a period of several decades. The factory continued to discharge methylmercury until 1971 and contaminated sediment in Minamata Bay was not removed until the 1980s. For the people of Minamata, the long term consequences of their lifetime of exposures are not yet known. Tragically, the victims in Minamata have been replaced repeatedly by the victims of other global environmental disasters.

Just think how smart we all could have been. In a 1989 commentary on lead poisoning, Dr. Herbert L. Needleman discussed a study's finding of a difference in mean IQ scores between children exposed to lead and those who were not (exposed). He wrote: "This four-to-seven point difference in means has been taken by some as a small effect. This is deceptive. The cumulative frequency distribution for IQ, typical for many distributions is sigmoid. When cumulative distributions between groups are plotted and compared, a shift in the curve resulting in a difference in medians of six points results in a four-fold increase in the rate of severe deficit (IQ<80). The same shift in distribution truncates the upper end of the curve, where superior function is displayed by 16 points. This means that five percent of lead-exposed children are prevented from achieving truly superior function (IQ>125). The costs of this effect at the high end of the distribution have received no attention; they may be extraordinarily important to our society" (Needleman, 1989, p. 643).

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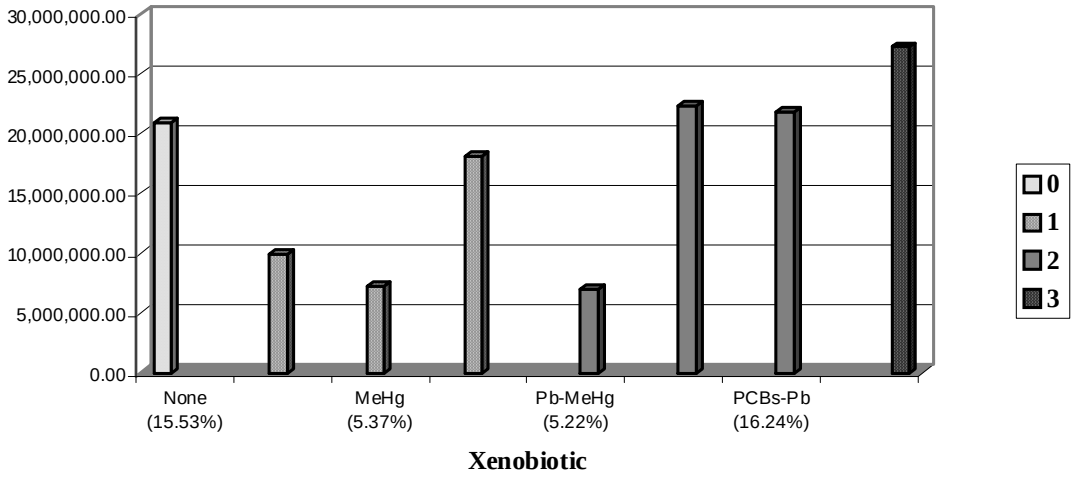
Tables and Graphs

Chemical	Childbearing-Aged Females			Pregnant Childbearing-Aged Females		
Percentile	**95th**	**99th**	**>99th**	**95th**	**99th**	**>99th**
Pb	5,231,195	4,232,471	3,087,576	405,690	145,829	433,608
MeHg	7,992,994	7,335,270	2,013,780	125,709	416,958	190,144
PCBs	9,962,451	7,044,652	1,746,100	328,088	394,968	21,192

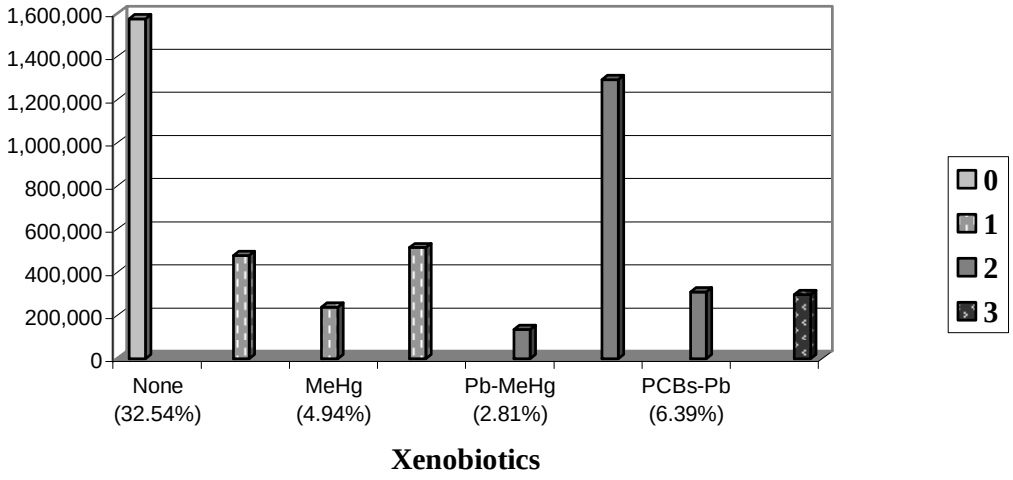
Table 1. Number of Childbearing-Aged and Pregnant Childbearing-Aged Females with Xenobiotic Blood Levels by Percentile (weighted data 1999-2004).

Chemical	Childbearing-Aged Females	Pregnant Childbearing-Aged Females
	At or Above Geometric Mean	**At or Above Geometric Mean**
Pb	49.05 per 100	25.19 per 100
MeHg	47.45 per 100	32.99 per 100
PCBs	66.54 per 100	49.85 per 100

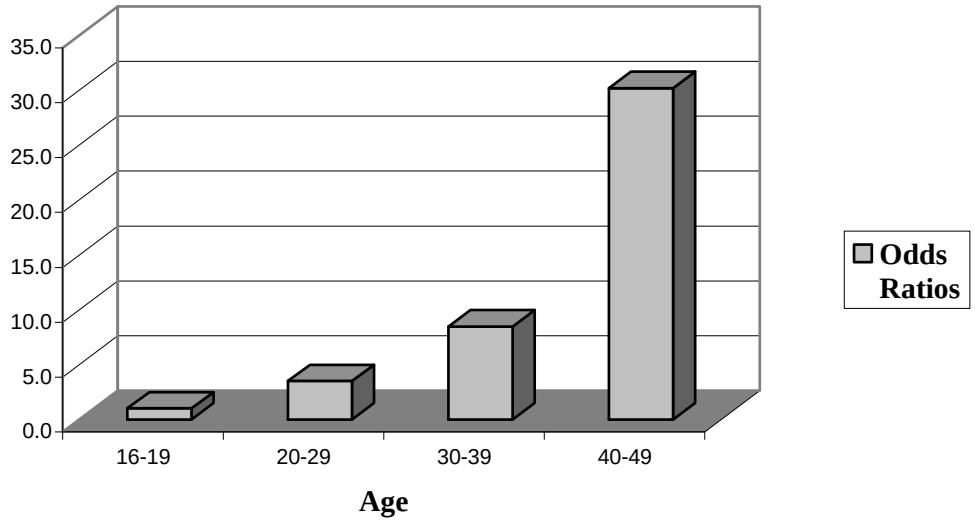
Table 2. Prevalence Rates of Childbearing-Aged and Pregnant Childbearing-Aged Females with Elevated Xenobiotic Blood Levels (weighted data 1999-2004).



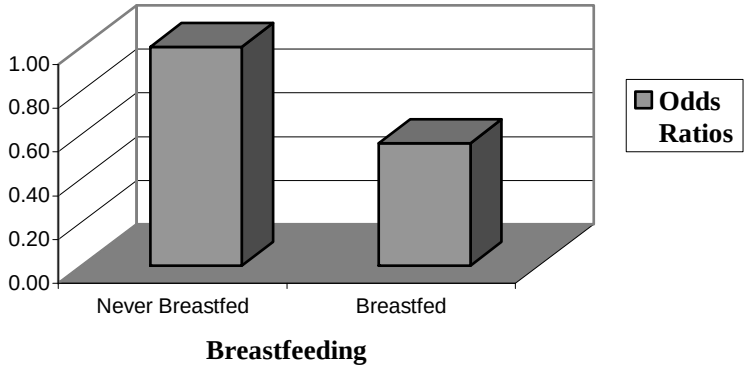
Graph 1. Number of Childbearing-Aged Females in U.S. with Xenobiotic Blood Levels At or Above the Geometric Mean (weighted data 1999-2004).



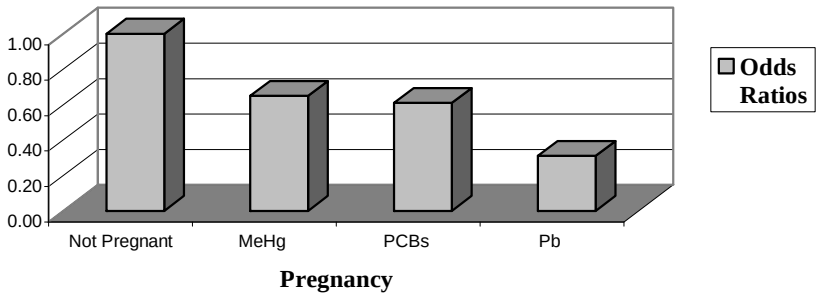
Graph 2. Number of Pregnant Childbearing-Aged Females in U.S. with Xenobiotic Blood Levels At or Above the Geometric Mean (weighted data 1999-2004).



Graph 3. Odds of Childbearing-Aged Females in U.S. Having Two or More Concurrently Elevated Xenobiotic Blood Levels Based on Age (1999-2004)



Graph 4. Odds of Childbearing-Aged Females in U.S. Having Two or More Concurrently Elevated Xenobiotic Blood Levels Based on Breastfeeding (1999-2004).



Graph 5. Odds of Childbearing-Aged Females in U.S. Having Two or More Concurrently Elevated Xenobiotic Blood Levels by Pregnancy Status (1999-2004)

Bibliography

- Acevedo-Garcia, D., & Osypuk, T. L. (2008). Residential Segregation and Health – The Complexity of Modeling Separate Social Contexts (Peer Commentary on the article "Effect of racial residential segregation on black infant mortality" by Hearst, Oakes & Johnson, 2008, December 1). *American Journal of Epidemiology, 168*(11), 1255-1258. doi:10.1093/aje/kwn290.
- Agency for Toxic Substances and Disease Registry. (2001, February). *Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures*. Atlanta, GA: Author.
- Agency for Toxic Substances and Disease Registry. (2004). Interaction Profile for Persistent Chemicals Found in Breast Milk (Chlorinated Dibenzo-p-Dioxins, Hexachlorobenzene, p,p'-DDE, Methylmercury, and Polychlorinated Biphenyls. Atlanta, GA: Author.
- Agency for Toxic Substances and Disease Registry. (2006, August). *Interaction Profile for: Chlorpyrifos, Lead, Mercury and Methylmercury*. Atlanta, GA: Author.
- Automobile Workers v. Johnson Controls, Inc., 499 U.S. 187 (1991).
- Axelrad, D. A., Bellinger, D. C., Ryan, L. M., & Woodruff, T. J. (2007). Dose-Response Relationship of Prenatal Mercury Exposure and IQ: An Integrative Analysis of Epidemiologic Data. *Environmental Health Perspectives, 115*, 609-615. doi:10.1289/ehp.9303.
- Barker, D. (2004). Developmental origins of adult health and disease. *Journal of Epidemiology and Community Health*, *58*, 114-115.
- Barker, D., Eriksson, J., Forsen, T., & Osmond, C. (2002). Fetal origins of adult disease: strength of effects and biological basis. *International Journal of Epidemiology, 31*, 1235-1239.

- Bellinger, D. C., Leviton, A., Waternaux, C., Needleman, H., & Rabinowitz, M. (1987, April 23). Longitudinal Analyses of Prenatal and Postnatal Lead Exposure and Early Cognitive Development. *The New England Journal of Medicine, 316*(17), 1037-1042.
- Boyle, C. A., Decoufle, P., & Yeargin-Allsopp, M. (1994, March). Prevalence and Health Impact of Developmental Disabilities in U.S. Children. *Pediatrics, 93*(3), 399-403.
- Callahan, M. A., & Sexton, K. (2007, May). If Cumulative Risk Assessment Is the Answer, What is the Question? *Environmental Health Perspectives, 115*(5), 799-806. doi:10.1289/ehp.9330.
- Centers for Disease Control and Prevention. (2010). *Healthy People 2020 Objective Topic Areas*. Retrieved December 7, 2010 from http://www.healthypeople.gov/2020/topicsobjectives2020/default.aspx.
- Centers for Disease Control and Prevention, National Center for Environmental Health. (2009). *Fourth National Report on Human Exposure to Environmental Chemicals.* Retrieved December 7, 2010 from http://www.cdc.gov/exposurereport/.
- Centers for Disease Control and Prevention, National Center for Health Statistics. (2006). *NHANES Homepage*. Retrieved December 7, 2010 from http://www.cdc.gov/nchs/mhanes.htm.
- Centers for Disease Control and Prevention, National Center for Health Statistics. (2009a, August). *Laboratory Methods 2001-2002*. Retrieved December 7, 2010 from http://www.cdc.gov/nchs/nhanes/nhanes2001-2002/lab_methods_01_02.htm.
- Centers for Disease Control and Prevention, National Center for Health Statistics. (2009b, July 30). *About National Health and Nutrition Examination Survey (NHANES).* Retrieved December 7, 2010 from http://www.cdc.gov/nchs/nhanes/about_nhanes.htm.
- Centers for Disease Control and Prevention, National Center for Health Statistics. (2009c, December). *Laboratory Methods 2003-2004*. Retrieved December 7, 2010 from http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/lab_methods_03_04.htm.
- Centers for Disease Control and Prevention, National Center for Health Statistics. (2010a, January). *Laboratory Methods 1999-2000*. Retrieved December 7, 2010 from http://www.cdc.gov/nchs/nhanes/nhanes1999-2000/lab_methods_99_00.htm.
- Centers for Disease Control and Prevention, National Center for Health Statistics. (2010b, May 21). *NCHS Research Ethics Review Board (ERB) Approval.* Retrieved December 7, 2010 from http://www.cdc.gov/nchs/nhanes/irba98.htm.
- Cernichiari, E., Toribara, T. Y., Liang, L., Marsh, D. O., Berlin, M. W., Myers, G. J., … Clarkson, T. W. (1995). The Biological Monitoring of Mercury in the Seychelles Study. *NeuroToxicology, 16*(4), 613-628.
- Chen, J. J., Chen, Y.-J., Rice, G., Teuschler, L. K., Hamernik, K., Protzel, A., & Kodell, R. L. (2001). Using Dose Addition to Estimate Cumulative Risks from Exposures to Multiple Chemicals. *Regulatory Toxicology and Pharmacology, 34,* 35-41. doi:10.1006/rtph.2001.1485.
- Children's Health Act of 2000, Pub. L. No. 106, §310, 1004 (2000, October 17).

- Choi, S. D., Baek, S. Y., Chang, Y. S., Wania, F., Ikonomou, M. G., Yoon, Y. J., … Hong, S. (2008, October 1). Passive air sampling of polychlorinated biphenyls and organochlorine pesticides at the Korean Arctic and Antarctic research stations: implications for long-range transport and local pollution. *Environment and Science Technology, 42*(19), 7125-7131.
- Collaborative on Health and the Environment's Learning and Development Disabilities Initiative. (2008a, July 1). *Scientific Consensus Statement on Environmental Agents Associated with Neurodevelopmental Disorders.* Retrieved December 7, 2010 from http://www.iceh.org/pdfs/LDDI/LDDIStatement.pdf.
- Collaborative on Health and the Environment's Learning and Developmental Disabilities Initiative. (2008b, September 16). Policy Implications Based on the Scientific Consensus Statement on Environmental Agents Associated with Neurodevelopmental Disorders. Retrieved December 7, 2010 from http://www.iceh.org/pdfs/LDDI/LDDIStatement.pdf.
- Daniels, J. L., Longnecker, M. P., Klebanoff, M. A., Gray, K. A., Brock, J. W., Zhou, H., … Needham, L. L. (2003). Prenatal Exposure to Low-Level Polychlorinated Biphenyls in Relation to Mental and Motor Development at 8 Months. American Journal of Epidemiology, 157(6), 485-492.
- Denham, M., Schell, L. M., Deane, G., Gallo, M. V., Ravenscroft, J., DeCaprio, A. P., & the Akwesasne Task Force on the Environment. (2005, February). Relationship of lead, mercury, mirex, dichlorodiphenyldichloroethylene, hexachlorobenzene and polychlorinated biphenyls to timing of menarche among Akwesasne Mohawk girls. *Pediatrics, 115*(2), 27-34. doi:10.1542/peds.2004-1161.
- Dewailly, É., Ayotte, P., Laliberte, C., Weber, J.-P., Gingras, S., & Nantel, A. J. (1996, September). Polychlorinated Biphenyl (PCB) and Dichlorodiphenyl Dichloroethylene (DDE) Concentrations in the Breast Milk of Women in Quebec. *American Journal of Public Health, 86*(9), 1241-1246.
- Dubos, R. (1980). *Man Adapting* (enlarged ed.). New Haven, CT: Yale University Press
- Gelobter, M. (1992). Toward a Model of "Environmental Discrimination". In B. Bryant & P. Mohai (Eds.), *Race and the Incidence of Environmental Hazards* (pp. 64-81). Boulder, CO: Westview Press.
- Graham, J., Walker, K. D., Berry, M., Bryan, E. F., Callahan, M. A., Fan, A., … Sexton, K. (1992, November-December). Role of exposure databases in risk assessment. *Archives of Environmental Health, 47*(6), 408-420.
- Grandjean, P., Budtz-Jørgensen, E., Kieding, N., & Weihe, P. (2004). Underestimation of Risk Due to Exposure Misclassification. *International Journal of Occupational Medicine and Environmental Health, 17*(1), 131-136.
- Grandjean, P., & Landrigan, P. J. (2006, December 16). Developmental neurotoxicity of industrial chemicals. *Lancet, 368,* 2167-2178. doi:10.1016/S0140-6736(06)69665-7.
- Grandjean, P., Weihe, P., Burse, V. W., Needham, L. L., Storr-Hansen, E., Heinzow, B., … White, R. F. (2001). Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *NeuroToxicology and Teratology, 23,* 305-317.

- Grassman J. (1996, July 17). Obtaining information about susceptibility from the epidemiological literature. *Toxicology, 111*(1-3), 253-270. doi:10.1016/0300-483X(96)03381-1.
- Gundacker, C., Pietschnig, B., Wittmann, K. J., Lischka, A., Salzer, H., Hohenauer, L., & Schuster, E. (2002, November). Lead and Mercury in Breast Milk. *Pediatrics, 110*(5), 873-878.
- Harada, M. (2004). *Minamata Disease* (English Ed.) Tokyo, Japan: Iwanami Shoten, Publishers.
- Hornung, R.W., & Reed, D.L. (1990). Estimation of average concentration in the presence of nondetectable values. *Applied Occupational and Environmental Hygiene, 5*, 46-51.
- Hosmer, D. W., & Lemeshow, S. (2001, January). *Applied Logistic Regression*. New York, NY: John Wiley & Sons, Incorporated.
- International Programme on Chemical Safety. (2000, June 1). *Human Exposure Assessment.* Retrieved December 7, 2010 from http://www.inchem.org/documents/ehc/ehc/ehc214.htm.
- Johnson, B. L., Harris, C. M., & Williams, R.C. (1992). *National Minority Health Conference: Focus on Environmental Contamination Proceedings, December 4-6, 1990, Atlanta, Georgia.* Atlanta, GA: Princeton Scientific Publishing Company.
- Laden, F., Collman, G., Iwamoto, K., Alberg, A., Berkowitz, G., Freudenheim, J., … Hunter, D. (2001, May 16). 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene and Polychlorinated Biphenyls and Breast Cancer: Combined Analysis of Five U.S. Studies. *Journal of the National Cancer Institute, 93*(10), 768-776.
- Landrigan, P. J., Schechter, C. B., Lipton, J. M., Fahs, M. C., & Schwartz, J. (2002). Environmental Pollutants and Disease in American Children: Estimates of Morbidity, Mortality, and Costs for Lead Poisoning, Asthma, Cancer and Developmental Disabilities. *Environmental Health Perspectives, 110,* 721-728.
- Lanphear, B. P., Dietrich, K. N., Auinger, P., & Cox, C. (2000, November-December). Cognitive Deficits Associated with Blood Lead Concentrations <10 µg/dl in U.S. Children and Adolescents. *Public Health Reports, 115,* 521-529.
- Lee, C. (2005). Environmental Justice. In H. Frumkin (Ed.), *Environmental Health: From Global to Local* (pp. 170-196). San Francisco, CA: Jossey-Bass.
- Mahaffey, K. R., Clickner, R. P., & Bodurow, C. C. (2004, April). Blood Organic Mercury and Dietary Mercury Intake: National Health and Nutrition Examination Survey, 1999 and 2000. *Environmental Health Perspectives, 112*(5), 562-570.
- Marshall, W. A., Clough, R., & Gehrels, W. R. (2009, April 1). The isotopic record of atmospheric lead fall-out on an Icelandic salt marsh since AD 50. *Science and the Total Environment,407*(8), 2734-2748. doi:10.1016/j.scitotenv.2008.12.009.
- Merkin, S., Basurto-Dávila, R., Karlamangla, A., Bird, C. E., Lurie, N., Escarce, J., & Seeman, T. (2009, March). Neighborhoods and Cumulative Biological Risk Profiles by Race-Ethnicity in a National Sample of U.S. Adults: NHANES III. *Annals of Epidemiology, 19*(3), 194-201. doi:10.1016/j.annepidem.2008.12.006.

- Mohai, P., & Bryant, B. (1992, March-April). Race, poverty and the environment. *EPA Journal, 18*(1), 6-9.
- Monosson, E. (2005, April). Chemical Mixtures: Considering the Evolution of Toxicology and Chemical Assessment. *Environmental Health Perspectives, 113*(4), 383-390.
- Morello-Frosch, R., & Lopez, R. (2006a, October). The riskscape and the color line: examining the role of segregation in environmental health disparities. *Environmental Research, 102*(2), 181-196. doi:10.1016/j.envres.2006.05.007.
- Morello-Frosch, R., & Shenassa, E. D. (2006b, August). The Environmental 'Riskscape' and Social Inequality: Implications for Explaining Maternal and Child Health Disparities. *Environmental Health Perspectives, 114*(8), 1150-1153. doi:10.1289/ehp.8930.
- Murray, C. J., & Lopez, A. D. (1999, September). On the Comparable Quantification of Health Risks: Lessons from the Global Burden of Disease Study. *Epidemiology, 10*(5), 594-605.
- National Research Council. (2006). *Human Biomonitoring for Environmental Chemicals*. Washington, DC: The National Academies Press.
- Needham, L. L., Ozkaynak, H., Whyatt, R. M., Barr, D. B., Wang, R. Y., … Zartarian, V. (2005, August). Exposure Assessment in the National Children's Study: Introduction. *Environmental Health Perspectives, 113*(8), 1076-1082.
- Needleman, H. L. (1989, May). The Persistent Threat of Lead: A Singular Opportunity. *American Journal of Public Health, 79*(5), 643-645.
- Ogata, M., & Oiwa, K. (2001). *Rowing the Eternal Sea: The Story of a Minamata Fisherman*. Lanham, MD: Rowman & Littlefield Publishers, Inc.
- Payne-Sturges, D., & Gee, G. C. (2006). National environmental health measures for minority and low-income populations: tracking social disparities in environmental health. *Environmental Research, 102*, 154-171. doi:10.1016/j.envres.2006.05.014.
- Phillips, D. L., Pirkle, J. L., Burse, V. W., Bernert, J. T. Jr., Henderson, L. O., & Needham, L. L. (1989, July-August). Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. *Archives of Environmental Contaminant Toxicology, 18*(4), 495-500.
- Poissant, L., Zhang, H. H., Canario, J., & Constant, P. (2008, August). Critical review of mercury fates and contamination in the Arctic tundra ecosystem. *Science and the Total Environment, 400*(1-3), 173-211. doi:10.1016/j.scitotenv.2008.06.050.
- Price, P. S., & Chaisson, C. F. (2005). A conceptual framework for modeling aggregate and cumulative exposures to chemicals. *Journal of Exposure Analysis and Environmental Epidemiology, 15,* 473-481. doi:10.1038/sj.jea.7500425.
- Pruss-Ustun, A., Bonjour, S., & Corvalan, C. (2008). The impact of the environment on health by country: a meta-synthesis. *Environmental Health, 7*(7), 1-25. doi:10.1186/1476-069X-7-7.
- Ricci, P. F., Rice, D., Ziagos, J., & Cox Jr., L. A. (2003). Precaution, uncertainty and causation in environmental decisions. *Environment International, 29,* 1-19.

- Rosenblatt, P. (2007, July). *Internal Organs*. Retrieved December 7, 2010 from http://www.merckmanuals.com/home/sec22/ch241/ch241c.htm
- Sexton, K. (1997). Sociodemographic aspects of human susceptibility to toxic chemicals: Do class and race matter for realistic risk assessment? *Environmental Toxicology and Pharmacology, 4*, 261-269.
- Sexton, K., Callahan, M., & Bryan, E. (1995, April). Estimating exposure and dose to characterize health risks: the role of human tissue monitoring in exposure assessment. *Environmental Health Perspectives 103*(Supplement 3), S13-S29.
- Sexton, K., Gong, H., Jr., Bailar, J. C., Ford, J. G., Gold, D. R., Lambert, W. E., & Utell, M. J. (1993b). Air Pollution Health Risks: Do Class and Race Matter? *Toxicology and Industrial Health, 9*(5), 843-878.
- Sexton, K., & Hattis, D. (2007, May). Assessing Cumulative Health Risks from Exposure to Environmental Mixtures – Three Fundamental Questions. *Environmental Health Perspectives, 115*(5), 825-832. doi:10.1289/ehp.9333.
- Sexton, K., Olden, K., & Johnson, B. (1993a). "Environmental Justice": The Central Role of Research in Establishing a Credible Scientific Foundation for Informed Decision Making. *Toxicology and Industrial Health, 9*(5), 685-727.
- Shotyk, W., & LeRoux, G. (2005). Biogeochemistry and cycling of lead. *Metal Ions and Biological Systems, 43,* 239-275.
- Smith, K. R., Corvalan, C. F., & Kjellstrom, T. (1999, September). How Much Global Ill Health Is Attributable to Environmental Factors? *Epidemiology, 10*(5), 573-584.
- Turner, B. L., II, Kasperson, R. E., Matson, P. A., McCarthy, J. J., Corell, R. W., Christensen, L., … Schiller, A. (2003, July 8). A framework for vulnerability analysis in sustainability science. *Proceedings of the National Academy of Sciences of the United States of America, 100*(14), 8074-8079. doi:10.1073/pnas.1231335100.
- United Church of Christ Commission for Racial Justice. (1987). Toxic Waste and Race in the United States: A National Report on the Racial and Socioeconomic Characteristics of Communities with Hazardous Wastes Sites. Retrieved December 7, 2010 from http://www.ucc.org/about-us/archives/pdfs/toxwrace87.pdf.
- U.S. Government Accounting Office. (1983, June 1). *Siting of Hazardous Waste Landfills and Their Correspondence with Racial and Economic Status of Surrounding Communities*. (GAO-RCED-83-168.) Retrieved December 7, 2010 from http://archive.gao.gov/d48t13/121648.pdf.
- Vreugdenhil, H. J., Van Zanten, G. A., Brocaar, M. P., Mulder, P. G., & Weisglas-Kuperus, N. (2004). Prenatal exposure to polychlorinated biphenyls and breastfeeding: opposing effects on auditory P300 latencies in 9-year-old Dutch children. *Developmental Medicine & Child Neurology, 46,* 398-405.
- Wilkinson, C. F., Christoph, G. R., Julien, E., Kelley, J. M., Kronenberg, J., McCarthy, J., & Reiss, R. (2000). Assessing the Risks of Exposures to Multiple Chemicals with a Common Mechanism of Toxicity: How to Cumulate? *Regulatory Toxicology and Pharmacology, 31,* 30-43. doi:10.1006/rtph.1999.1361.